Regional Science Policy and the Growth of Knowledge Megacentres in Bioscience Clusters

Philip Cooke, Director, Centre for Advanced Studies, University of Wales, Cardiff

Centre for Advanced Studies
University of Wales, Cardiff
44-45 Park Place
Cardiff CF10 3BB
cookepn@cf.ac.uk

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Abstract

Changes in epistemology in biosciences are generating important spatial effects. The most notable of these is the emergence of a few 'Bioscience Megacentres' of basic and applied bioscience (molecular, post-genomic, proteomics, etc.) medical and clinical research, biotechnology research, training in these and related fields, academic entrepreneurship and commercial exploitation by clusters of 'drug discovery' start-up and spin-off companies, along with specialist venture capital and other innovation system support services. Large pharmaceutical firms that used to lead such knowledge generation and exploitation processes are becoming increasingly dependent upon innovative drug solutions produced in such clusters, and Megacentres are now the predominant source of such commercial knowledge. 'Big pharma' is seldom at the heart of Megacentres such as those the paper will argue are found in about four locations each in the USA and Europe, but remains important for some risk capital ('milestone payments'), marketing and distribution of drugs discovered. The reasons for this shift (which is also spatial to some extent) are as follows: first, bioscientific research requires the formation of 'collaboratory' relationships among hitherto cognitively dissonant disciplines – molecular biology, combinatorial chemistry, high throughput screening, genomics, proteomics and bioinformatics to name a few. Second, the canonical 'chance discovery' model of bioscientific research is being replaced by 'rational drug design' based on those technologies because of the need massively to reduce search costs and delivery timeframes. Third, the US and to some extent European 'Crusade against Cancer' and other pathologies has seen major increases in basic research budgets (e.g. to $27.3 billion in 2003 for the US National Institutes of Health) and foundation expenditure (e.g. $1billion in 2003 by the UK's Wellcome Trust; $1 billion approximately by the top ten US medical foundations, and a comparable sum from corporate foundations). Each of these tendencies weakens the knowledge generation role of 'big pharma'and strengthens that of Megacentres. But the process also creates major, new regional disparities, which some regional governances have recognised, causing them to develop responsibilities for *regional* science policy and funding to offset spatial biases intrinsic in traditional *national* (and in the EU, supranational) research funding regimes. Responses follow a variety of models ranging from market following to both regionalised (decentralising by the centre) and 'regionalist' (ground-up), but in each case the role of Megacentres is justified in health terms. But their role in assisting fulfilment of regional economic growth visions is also clearly perceived and pronounced in policy terms.

Introduction

The crucial matter of interest to this paper is the rapid decline in the capabilities of large pharmaceuticals companies ('big pharma') to develop in-house new therapeutic drug treatments, particularly those deriving from biotechnology, compared to the rapid rise in that precise capability on the part of networks of small, dedicated biotechnology firms (DBFs). This is commented upon in Orsenigo et al., (2001) but these authors remain reluctant to see the facts they observe as a weakness of 'big pharma'. Rather, the latter is seen retaining power through its control over the former through financing R&D contracts with milestone payments and licensing agreements, managing due diligence, and marketing and distributing final treatments or drugs. In this contribution we will present the shift in tacit and exploration knowledge to DBFs as signifying a crisis for multinational drug companies. For while some other kinds of multinational corporations adopted a strategy of downsizing central laboratories and decentralising R&D both to branches and to the supply chain (e.g. Dupont's major reduction in its central Wilmington facility; GE's restructuring of Schenectady's role; and the fact that aerospace firms like Bombardier of Canada routinely buy all R&D from a globally dispersed market; Niosi, 2002), such attenuation of the R&D function has not been sought by pharmaceuticals firms, but rather represents a failure to deal with a thoroughgoing paradigm shift. The paper will examine the nature of that shift and explore ways in which some 'big pharma' is seeking to manage its response.

The paper has four key sections:

- The first examines the knowledge management mechanisms by which DBFs tackle the R&D or 'drug discovery' process and determine the nature of their specific advantage,
- The second assesses the adequacy of these mechanisms and how industry and intermediaries judge they need to be strengthened,
- The third examines the future of big pharma concerning the cognitive paradigm shift linking 'Mode 2' knowledge production (Gibbons et al., 1994), the demise of 'discovery' methods and rise of 'rational drug design', and fine chemistry versus molecular biology,

- The fourth investigates regional development and management control issues arising from clustering of advanced bioscientific knowledge exploration and exploitation in a few globally significant 'megacentres'.

Reference will also be made to a previous paper's findings that the 'bioscience megacentre' process is leading to the emergence of a new type of regional policy called *regional science policy* that seeks to overcome the traditional centralising features of nationally formulated science policies (and in the EU, supranational RTD or research and *technology* policy).

2. Theoretical Approach

In the broadest terms, the theoretical approach informing the proposed paper dates at least from Marshall (1918) and more recent transaction costs theory (Coase, 1937) as developed by Penrose (1959) and Richardson (1972) with their 'resource' and 'capabilities' perspective on the firm, rather than the more orthodox neoclassical theorems of Williamson (1985). This chimes also with Piore & Sabel's (1984) 'flexible specialisation' conception of the advantages of small firm networks in successfully attacking global markets. More recently authors such as Teece & Pisano (1998) and Best (2001) have explored the 'capabilities' perspective in theoretical and empirical depth.

Marshall's initial statement was that small firms gained dynamic externalities (nowadays more commonly referred to as 'spillovers', including 'knowledge spillovers', see Audretsch, & Feldman, 1996; Feldman & Audretsch, 1999) from co-location. These gave advantage in terms of specialised skills pools, opportunities for production specialisation and technical or managerial knowledge transfer. These circulated rapidly due to socio-cultural factors like trust, customs, social ties and other institutional characteristics of 'industrial districts'. Porter's (1990; 1998) notion of 'clusters' owes much to these insights, as he readily admits.

However, through the twentieth century, such thinking became heterodox and other aspects of Marshall's contribution to economic theory, notably marginalism and equilibrium theory, resonated better with the rise to power of the large corporation and, within economics, theories explaining the superiority of economies of scale over

economies of scope (Chandler, 1990). Piore & Sabel's (1984) discovery of a Neo-Marshallian school of economic theory purporting to explain not the anachronistic but globally competitive existence of modern industrial districts in Italy (e.g. Becattini, 1989; Brusco, 1989) in terms that included superior knowledge circulation and management among small firms, caused revision to prevailing orthodoxy.

This paper will explore from a firm-capabilities and, innovatively, an institution-capabilities perspective, the modes by which DBFs mange complex types of knowledge ranging from basic scientific to financial in creating project networks to generate and exploit research to develop therapeutic treatments. The extent, and degree of formality and informality of involvement by knowledge intermediaries in this process as compared to direct contact among peers will be explored. Moreover the process management functions and problems of big pharma in the 'knowledge value chain' from research to financing and final distribution as its control shifts downstream will be of key theoretical interest. This is especially pertinent as a test of the evolving thesis of transnational corporations becoming 'hubs' buying not making key services (Stewart, 2001; Best, 2001). The role of knowledgeable intermediaries as agents in innovation interactions will also be investigated to refine theory.

Theoretically there are four links connecting the paper's key interests to the 'design space' of post-genomics (Stankiewicz, 2002). First, following Polanyi (1966) and Nonaka & Takeuchi (1995), there is the interplay of implicit (tacit) and explicit knowledge in the project networks formed among firms with distinctive expertise, like combinatorial chemistry, high throughput, target-based screening, genomics and genomic libraries. The extent this mimics Nonaka & Takeuchi's (1995) original and Stewart's (2001) recently reviewed 'SECI Process' linking 'Socialisation', 'Externalisation', 'Creation' and back to 'Internalisation' in the eliciting of implicit knowledge, its formulation as explicit or codified knowledge, followed by its re-internalisation as tacit knowledge can be explored. In particular, the question as to whether there are important differences related to types of knowledge (e.g. 'exploration' versus 'exploitation') has to be confronted.

Second, how adequate are the institutional mechanisms by which such interactions are managed? Are they largely informal and inaccurately accounted, where is formality

strongest, are 'arm's length' or market exchanges more or less pronounced than 'untraded interdependencies' (Dosi, 1988)? Third, what response does big pharma make, if any, to the shift towards 'rational drug design'? Are there instances where in-house capabilities to engage fully with 'Mode 2' knowledge production (e.g. through acquisition, partnership alliances or attempts to mimic certain conventions more commonly associated with DBFs, like stock options for innovative scientists or intra-preneurship). What distinctive strategies are being pursued? Finally, what are key barriers to control for big pharma, and what strategies are pursued to accommodate the current deficits in in-house drug discovery? What lessons have been learned from past experience and what new lessons are being learned currently to adjust to the predominant knowledge value chain relationships and interactions?

Knowledge sources, including tacit/codified, internal/external, contact/intermediary, and local/global, are key subjects of inquiry of direct relevance to regional science and notions surrounding regional *science policy*. Number and type of network partners, mechanisms for assembling partnerships, types of project and typical expertise requirements are important to assess and compare 'social capital' versus 'arm's length' kinds of interaction (Cooke, 2002a). To help move towards some concrete information about this, preliminary research within such networks will be drawn from a study being conducted in partnership with a biotechnology incubator named Oxford BioTechNet and incubators in Germany (BioM, Munich), Israel (Jerusalem Biotechnology Incubator), France (GenoPole, Paris) and Italy (Consorzo Ventuno, Sardinia), based on focus-group inquiry sessions with a variety of biotechnology project network members exploring the above and related issues in great depth, with a view to identification of the emergent knowledge exploration/exploitation model, its strengths and weaknesses, in comparative perspective, and how weaknesses or gaps might be tackled. The second source of information will be secondary information on big pharma companies. This evidence is both quantitative and qualitative, concerning R&D performance (input-output measures) drugs in development, drug approvals, in-licensing, out-licensing, patenting, sub-contracting of R&D, partnerships, alliances, project-management and knowledge-management issues. The capabilities and strategies of big pharma facing a 'Mode 2' knowledge production regime will thus be assessed.

3. The Capabilities of Dedicated Biotechnology Firms

In the 'capabilities' perspective on firms, and, it may be added, *regions* that are the knowledge-embedded platforms in which such firms are rooted, it is dynamic capabilities that are the most prized. This is helpful because in the literature on 'knowledge spillovers' it is the dynamic rather than static externalities with which they are associated that are equally highly prized (Feldman & Audretsch, 1999). There is an interesting debate, dating from the work of Jane Jacobs (1969) about whether it is the diversified or specialised nature of capabilities in knowledge spillovers that gives the basis for innovatively successful milieux. Jacobs argued in favour of diversification, new combinations of capabilities giving rise to cognitive progress, something with which Feldman & Audretsch broadly agree. But researchers such as Glaeser et al. (1992) and Griliches (1992) stressed the superiority of specialisation and the capabilities of fairly narrow 'communities of practice' (Seely Brown & Duguid, 2000), known elsewhere as 'epistemic communities' in delving deeply and reasonably rapidly into a particular scientific sub-field. Empirically both showed how relatively geographically circumscribed knowledge-exploitation, for example through patenting activity actually was. More recently though, Galison (1997) moving well beyond the narrow confines of patenting activity such as that relied upon by Griliches, showed convincingly that new developments in scientific method, broadly consistent with the emergence of 'transdisciplinarity' in Mode 2 knowledge production (Gibbons et al., 1994) are built fundamentally on diversification of knowledge.

This feature of contemporary 'complexity' in knowledge management specifically occurring in industrial clusters is the subject of a path-breaking book edited by Curzio & Fortis (2002). In a contribution that focuses precisely upon the issue at hand, the following observation is made by one contributor:

> '…. innovation, and problem solving generally, depend on disciplined comparisons of alternative solutions, and these in turn require transforming tacit knowledge into what might be called pidgin formalisations: accounts sufficiently detailed to be recognisable to those who know the situations to which they refer first hand, but sufficiently abstracted from them to be accessible to outsiders, from various disciplines,' (Sabel, 2002).

However, innovation is not the same as basic science. It can easily be seen that if a scientist is collaborating with an entrepreneur, say, in writing a paper that exploits a patent, they may or may not have to speak a kind of 'pidgin' scientific language to each other. But invention, or discovery may well be expected to require the greater cognitive precision associated with epistemic communities. Even Seely Brown & Duguid (2000) who refer to the importance of communities of practice recognise, from their long experience at Xerox PARC in Silicon Valley, that:

> 'A firm, then, will almost always intersect multiple networks of practice. In Silicon Valley, for example, some firms will have cross-cutting networks of engineering, manufacturing, sales and marketing, and customer service. Networks of computer engineers, for example, will run through all the firms manufacturing computers' (Seely Brown & Duguid, 2000)

They imply that these lateral professional links are cognitively less dissonant and more smoothly connected even than the distinctive 'capabilities' linkages within the firm. Hence the superiority of networking in a clustered environment rather than a stand-alone competitive posture:

> 'Knowledge seems to flow with particular ease where the firms involved are geographically close together. Being in the same area allowed the Apple and PARC scientists to meet and exchange ideas informally, paving the way for more formal links. Relations between PARC scientists and the Dallas engineers were in every sense far more distant' (Seely Brown & Duguid, 2000)

Thus it seems that proximity in a cluster is fundamentally important to innovation, that is, the stage at which deeply embedded knowledge is being confronted with processes of knowledge exploitation and commercialisation.

When scientific method was more disciplinary than it now seems to be, that is in the era of Mode 1 knowledge production as Gibbons et al. (1994) refer to it, it is probable that specialisation was more important than diversification. But now there is strong evidence, in biosciences at least, that it has become more transdisciplinary, as we have seen, even at the exploratory R&D point in the 'knowledge value chain' (Cooke, 2002b) let alone the exploitation point in the same chain. Thus even basic research is likely to contain a higher incidence of the need for 'pidgin' among diverse professional scientists and engineers than used to be the case. Orsenigo et al. (2001) date this shift in biosciences from about 1992. Thus Griliches and Glaeser were publishing their results about specialisation at about the same time that it seems the

knowledge development method (epistemology) was changing significantly, particularly in biosciences. This in turn, it can be shown related to technological changes consequent upon precisely the rapid diversification in cognitive skills brought about by the demands of such activities as gene sequencing and the eventual decoding of the human genome that ushered in the post-genomic era.

Thus, in a regional 'megacentre' to be discussed in more detail in Section 6, that of Northern California, it is clear that the biomedical industry relies crucially on information and communication technologies (ICT) to decode and synthesise bioscientific information. This is drawn from the knowledge-intensive ICT base in Silicon Valley, and includes sequencing and screening workstations, photonics and optical networking, low-level electrical energy instrumentation, and software among many others. This convergence between ICT and bioscience has contributed to discoveries in genomics, proteomics, therapeutic cloning and stem cell research, and these in turn enable improved treatments for high ranking disease targets like cancer, cardiovascular, AIDS, diabetes, and respiratory diseases. But the transdisciplinarity also operates within and between specific sub-fields like molecular biology, combinatorial chemistry, high throughput screening, genomics and bioinformatics. In conducting knowledge *exploration* multidisciplinary teams of researchers are more prominent than before. In conducting knowledge *exploitation* DBFs in the distinctive sub-fields form project-based networks interacting also with 'star' scientists and their teams.

As Zucker et al. (1999) see it, such projects involve no or few 'untraded interdependencies', they are strictly business transactions, with contracts, confidentiality agreements, time-limits and agreed actions (writing a patent or a paper, for example) and outcomes. Other actors will also enter this *mise-en-scène* at various points, as 'knowledgeable attorneys', consultants or venture capitalists (Suchman, 2000). So we may conclude that *bioscientific megacentres* are realised in the presence of a nurturing 'economic business environment' consisting of: (1) the quality of the inputs available to firms (e.g. human resources, physical infrastructure, availability of information); (2) the availability and sophistication of local suppliers of components, machinery and services, and the presence of clusters of related firms; (3) the sophistication of local demand for advanced products and processes, including the

stringency of regulatory environments; and (4) the rules governing the vitality of competition and the incentives for productive modes of rivalry (Porter, Sachs & Warner, 2000). The key point to derive from this analysis is that while such 'economic business environments' are not unique to Northern California, they are far from ubiquitous. Because they rely on massive sums of public funding, as will be shown, a moral dilemma arises for policy makers alert to regional disparities. Should they encourage spatial concentration to achieve global excellence or should they encourage the development of such facilities in less favoured regions too? Keep in mind that the latter are where negative health imbalance is often as pronounced as economic weakness in the official statistics. Finally, as health economists and others are coming to realise, health services and their supporting supply firms in pharmaceuticals, biotechnology and research laboratories contribute as much as one-sixth of GDP in some advanced economies (Cassidy, 2002).

In Table 1 data are presented on public and private health expenditure in a number of leading OECD countries for 1997. These statistics probably underestimate the whole

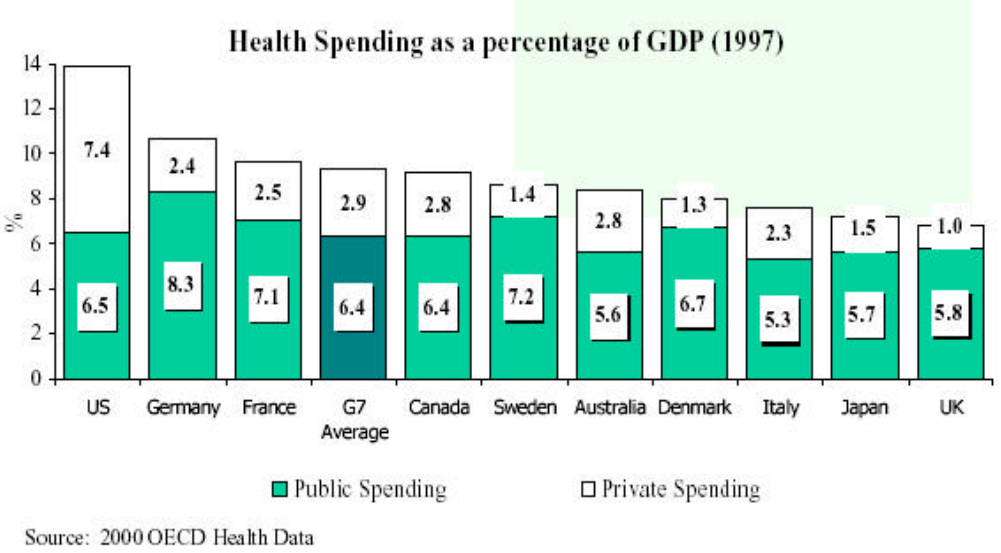

Table1: Health Expenditure in Leading OECD Countries, 1997

health economy as described above by a few percentage points. Nevertheless they demonstrate even core health expenditure running at just under 10% for the G7 countries, and much higher, at nearly 14% for the USA.

Statistical data for the USA at regional (State) level reveal just how skewed is the distribution of that element of public expenditure covered by State and Federal allocations. It should be noted that about half of US public expenditure on health is explained as follows:

> 'The system of employer-sponsored coverage emerged to restrain wage inflation during World War 2 and afterward continued when the federal courts ruled that unions could collectively bargain with employers for benefits, including health care coverage. These benefits are considered public sector 'tax expenditures' because they are excluded from workers' wages for purposes of taxation and defined as an untaxed cost of business for employers' (Milbank Memorial Fund, 2000)

Private spending occurs through private insurance taken out by individuals on top of whatever workplace-related benefits they receive. Since the 1980s there has been a growth in share of the former and a shift from 'fee-for-service' indemnity towards 'managed care' in insurance health plans. Health insurance has thus become more commoditised, suppliers are keen to raise efficiencies in treatment times, use of new technologies, and to reduce casual conduct by physicians of clinical research on patients. Companies and consumers are equally keen to achieve value for money under circumstances where information to enable assessment is at a premium. There has thus been a tendency for geographical concentration of exploration research and, due to insurance industry pressure, clinical research in specific General Clinical Research Centres. For comparable reasons under a differently funded health insurance system in the UK the same kind of concentration into Clinical Research Centres is occurring (Cooke, 2002b).

In Table 2 some illustrative data are presented regarding the regional vis à vis Federal *public* expenditure profile for direct health costs, excluding the employers' 'public tax' expenditures. Of particular note are the data pointing to California and New York States accessing 11% and 12% respectively of the US total for this item. These are, of course, large population centres, California being the larger, though it is noticeable also that while New York spends 3.9% of its GDP in this way, California only spends 2.1%. Thus demographics, politics and per capita income also play their part in explaining differences in level of expenditure. Among other large health expenditure States, but not in the same rank as California and New York, are Texas and

Pennsylvania, followed by a group spending around $8-9 billion in 1999, namely Florida, Illinois, Massachusetts, Michigan and Ohio. Of interest are the ways in

State	State Funds ($ million)	Federal Funds	S/F Ratio	GDP Share
New York	$15,009	$14,860	99%	3.9%
California	$14,412	$11,981	86%	2.1%
Texas	$ 6,993	$ 8,100	115%	2.2%
Pennsylvania	$ 6,723	$ 6,110	90%	3.3%
Florida	$ 5,080	$ 4,469	80%	2.2%
Illinois	$ 5,536	$ 3,860	70%	2.1%
Massachusetts	$ 5,125	$ 3,279	63%	3.4%
Michigan	$ 4,739	$ 4,231	89%	2.9%
Ohio	$ 6,739	$ 1,620	24%	2.3%
New Jersey	$ 4,522	$ 2,971	66%	3.9%

Table 2: State & Federal Health Expenditure, USA Top Ten, 1999
Source: Calculated from Milbank Memorial Fund & US Dept. of Commerce, Bureau of Economic Analysis

which such budgets are composed such that variance from the US mean GDP share per State (2.6%) is relatively small, including the rest, where West Virginia at 4.8% on the one hand, and Alaska at 0.6% are among the most significant outliers. With a few exceptions, such as Ohio in Table 2, Federal funding makes a significant contribution. Texas, like other southern Appalachian and south-western States receive more Federal than State disbursements.

However, calculations of such disbursements in relation to State population size show New York, at $1,572 per capita, and Massachusetts, at $1,482 to be the most generous spenders, Pennsylvania comes next, at $1,070, then New Jersey at $949, Michigan at $897 ahead of California at $800, followed by Illinois ($783), Texas ($765), Ohio ($763) and Florida ($615). Linking back to points made earlier about the increasing 'commoditisation' of health care in the US (and to a growing extent in the UK and perhaps elsewhere) States such as these are becoming active purchasers of higher quality, more technology-intensive, but also value for money health services. It should further be recalled that the statistics under discussion constitute only some 20% of total State health care budgets, but represent baseline funding. Clearly, California is

less dependent upon public funding than the East Coast States, that category accounting for only just over half the GDP share it does in New York and New Jersey. As Table 3 shows, California's 'mega-budget' for private health care expenditure easily outstrips all others among the entrants in Table 2. Hence the

State	Personal Health Care Expenditures, 1998 ($mn.)
California	$110,057
New York	$85,785
Texas	$67,750
Florida	$59,724
Pennsylvania	$51,322
Illinois	$44,305
Ohio	$42,581
Michigan	$35,647
New Jersey	$32,695
Massachusetts	$30,039

Table 3: Personal Health Care Expenditures, Top Ten US States, 1998
Source: Health Care Financing Administration (2001), Trends in State Health Care Expenditure and Funding, 1980-1998, Washington DC.

relatively low share of GDP allocated to direct public expenditure on health is compensated for by a massive figure of some 10% of GDP being expended on personal health care.

Keeping in mind that Table 2 represents one-fifth of each State's health expenditure, requiring an approximate doubling to include the employer's contribution, and that Table 3 accounts for some three-fifths we see the scale of total investment available annually in the leading States' economies. Thus California spends at least $160 billion, New York $145 billion and even modestly sized Massachusetts some $46 billion. Three key points flow from this accounting exercise. First, a few key regions, and in fact cities in those regions have the demographic, financial and scientific scale to afford the whole of the bioscientific and medical knowledge value chain. This moves from the most exploratory, fundamental research into genomics and post-genomics fields like proteomics and molecunomics. This is likely to be conducted at specialist research institutes such as the Whitehead in Cambridge, Massachusetts (partnered with the Sanger Institute, in Cambridge, UK and Washington University at St. Louis for the Human Genome project). Knowledge of this kind will likely be

applied in specalist medical research institutes at universities, like the Dana-Farber Cancer Institute at Harvard, or the New England Enzyme Centre at Tufts University, Boston. Research in other key fields noted earlier (cancer, cardiovascular, AIDS, diabetes, and respiratory diseases) will be conducted in other independent research institutes and university research centres like Harvard Medical School's pre-clinical research in Biochemical & Molecular Pharmacology, Cell Biology, Genetics, Microbial & Molecular Genetics, and Neurobiology, or affiliates like the Joslin Diabetes Centre. Second, such research institutes and centres both attract and train Life Sciences talent, giving critical mass to interactive research activity. This, in turn, strongly influences growth in funding through competitive bidding to National Institutes of Health and National Science Foundation programmes. Third, such 'megacentres' interact with the large hospitals, in which clinical research as well as patient treatment occurs along with training of physicians. Massachusetts General Hospital and the Brigham & Women's Hospital in Boston are thus important large-scale patient-bases for clinical trialling. There is, accordingly a suitable milieu also for academic entrepreneurship, which, combined with Boston's status as a top-three location for venture capital and 'knowledgeable attorneys' (Suchman, 2000), makes it a highly nurturing 'economic business environment' for *exploitation* as well as *exploration* knowledge management in the form of leading biotechnology firms like Immunex (recently acquired by Amgen), Biogen, Genzyme, Millennium, TransKaryotic Therapies, and others, recently also joined through new openings or acquisitions by the likes of Abbott Laboratories, AstraZeneca, Aventis, Pfizer and Wyeth (recently merged with American Home Products).

Thus, while scale of expenditure in general health systems clearly matters as an entry ticket to the megacentre 'tournament', it is by no means a sufficient condition. There has also to be world-class science and world-class commercialisation capability. There has to be localised 'social capital' among the actors present, which can link appropriate partners across epistemic community boundaries. Firms help themselves when they speak with a single voice on matters of common concern, something portrayed in the Boston cluster by the activities of the 280-member Massachusetts Biotechnology Council. Much of this system is portrayed in Fig. 1 below.

Fig. 1: The Cambridge, Massachusetts and Greater Boston Biosciences Megacentre

4. Rational Drug Design & DBF Networks

What are the difficulties faced by DBFs in taking advantage of such nurturing economic business environments, and in what ways are those in the USA better placed to benefit than those in Europe? One key feature that differentiates them is the estimated $20 billion per year that has been available for US biotechnology research from Federal investment in, for example, the 1994-98 period studied by Senker & Van Zwanenberg (2001). This compares with the approximately €10 billion spent by European governments over the same period. Further, it is argued, US DBFs can exploit the research findings of National Institutes of Health-funded research more swiftly and efficiently due to the existence of National Science Foundation sponsored Small Business Innovation Research grants enabling DBFs to develop ideas more quickly thus potentially influencing venture capitalists and 'big pharma' to invest in what elsewhere would appear to be more high-risk ventures. These SBIR grants arise from a requirement that R&D spending Federal government departments must spend up to 2.5% of their extra-mural research budgets on commissions from SMEs. Moreover, research-minded entrepreneurs requiring continuing interaction with other discovery firms or research institutes have more of these to choose among and thus exploit better networking opportunities.

Jaffe et al.'s (1993) finding that knowledge spillovers from universities to firms were relatively regional or even local was found to be true in the Senker & Van Zwanenberg research on European biopharmaceutical firms. Exacerbating this, Owen-Smith et al. (2001) found that public research organisations (PROs), with which such DBFs are likely to seek to interact, have far more intensive and extensive inter-institutional research networks than European firms. The latter had much smaller, sometimes dyadic, networks and these were often nationally constricted, except for occasional transatlantic contact with a US institute, and consequent potential linkage into wider US knowledge networks. However, so few and restricted were the active international linkages that less knowledge exploitation was feasible, and more slowly, than in the case of the better-networked US institutes. Hence, it can be argued from a

'capabilities' perspective as outlined in Section 1 of this paper, that the better networking for purposes of knowledge *exploration* and support for knowledge *exploitation* displayed by US research institutes is a sign of superior *institutional capability*. Given their role as key intermediaries in the knowledge management process, the institutional capability in the US Biosciences Innovation System, adds significant value to an already doubly advantaged initial research resource base.

It can be further shown, as Owen-Smith et al. (2001) go on to do, that US networks among PROs are hierarchically structured. Over the period from 1988-1998, the Boston cluster has remained at the peak of US interorganisational research linkages, and its connections to other clusters has doubled to over 50% of its total contacts over the period. San Diego has moved to second place in the hierarchy over San Francisco, while Seattle and New York have exchanged positions, Seattle rising above New York in terms of the number and strength of its inter-regional PRO linkages. Thus relationships between PROs and firms in their clusters are augmented by the institutional capabilities of both to benefit from spanning therapeutic areas, engaging in multiple stages of the knowledge exploitation value chain, and involving diverse collaboration. The institutional system takes on certain characteristics that have resulted in the term 'collaboratory' being used to describe such interorganisational networking. As has been suggested, European DBFs and PROs have tended to engage in more attenuated innovation networks, with more specialised than diverse interactions, and a more limited external value chain involvement that is also mostly national in character.

The weaknesses of European international networks of PROs and DBFs can be understood in terms of the relative immaturity of regional science infrastructures. This in turn, echoes the relatively small budgets that have traditionally been available for systemic medical, health and life sciences research integration. This is changing rapidly in some European countries, and has been rather better developed in some smaller EU economies for some time. Thus Germany and France have changed business regulations to encourage innovation and academic entrepreneurship, while a long period of under funding in the UK health service has been reversed both in service delivery budgets and scientific research budgets. In the UK, the world's

largest scientific research charity, the Wellcome Trust, has become highly active in co-funding with the UK government investments in research infrastructure and basic exploration research such as the Human Genome and new post-genomic research at such centres of excellence as the Sanger Research Institute at Cambridge (UK).

Nevertheless, some important parts of the exploration and exploitation infrastructure remain underdeveloped to varying degrees. In the UK, much emphasis has been placed upon funding Centres of Excellence. These are relatively few in number and highly imbalanced between regions and within them. In an earlier paper (Cooke, 2002b) it was shown that implicitly or explicitly policies are set to strengthen specific, often potentially or actually multi-purpose, sites with the strongest possibility for elaborating a medical and life sciences knowledge value chain to the fullest extent. Modelled to some degree on Boston, Cambridge (UK) has been a major recipient of Wellcome Trust and UK research council funding, complemented by special Treasury funding to enhance academic entrepreneurship through linkage with the Massachusetts Institute of Technology, and new investments in hospital infrastructure, including a Clinical Research Centre, to fill out its emergent megacentre character. It is well known that Cambridge was already the UK's leading biotechnology commercialisation location, consequent on long term cultural change efforts to stimulate academic exploitation of world class exploration knowledge. A case in point of the latter is the shift in the Medical Research Council's Molecular Biology Institute from essentially giving away Intellectual Property Rights to discoveries like Monoclonal Antibodies as occurred with Milstein and Kohler's discovery, to stimulus for contemporary scientists to become academic entrepreneurs. Now the MRC lab has some 30 spinout firms, some like Cambridge Antibody Technologies valued in many millions of pounds on the UK's technology stock market.

Yet this process can often be rather unsystematic, as the experience in neighbouring Oxford, also home to world-leading medical and life sciences research, and to numerous start-up and more mature biotechnology firms like Oxford Glycosciences, Oxford Asymmetry and Xenova. A key part of the maturation of exploration into exploitation knowledge occurs in incubators. Oxford Innovation, under the wing of the Oxford Trust, a non-profit commercialisation institution, runs Oxford

BioTechNet, responsible for a number of early and mid-stage start-up biotechnology firms. However, such is the relatively precarious nature of the funding needed for such businesses that, in reality, it is impossible to posses all the skills required of intermediaries such as those found in US megacentres like Boston in one incubator or even one small university city. Thus issues of funding, from seedcorn to business angel to full-blown venture capital, legal questions, ranging from incorporation to patent defence, management issues like in-licensing and out-licensing, development of supply chain linkages or milestone payment agreements with 'big pharma', and more mundane questions of property acquisition as companies grow and leave the incubator, are all dealt with by a single incubator manager.

Interestingly, through a research partnership with such well-found innovation intermediaries as BioM in Munich and GenoPole in Paris, it is clear that comparable difficulties apply in their cases too. That is, finance may not be such a problem as finding appropriate expertise. For even though it is said that Munich had some thirty venture capitalists in the seven years after BioRegio, the German Federal government's regional biotechnology commercialisation initiative, such is the newness of most of the twenty or so new biotechnology firms that special early-stage management expertise and support is a greater weakness than investment finance (Kaiser, forthcoming). As will be seen below, Munich is now assessed as being Europe's leading high technology cluster, at least in ITC if not biotechnology. But while it has a few mature biotechnology firms kike MediGene and MorphoSys, most of its start-ups are in their infancy, heavily dependent on public venture finance, and it is unclear how viable many are were they to be wholly reliant on even the protected regime by which most biotechnology firms survive without showing profitability.

This compares rather unfavourably with the picture of relatively healthy research-led networking painted by Orsenigo et al (2001) where collaborative relationships among firms and research institutions initiated from the US are shown to be diverse, capable of including linkage with some of the above-mentioned European firms, and sophisticated enough in knowledge management of the revolutionised 'rational drug design' methodologies consequent upon the revolution in molecular biology (Henderson et al., 1999) for 'big pharma' to seek entry to the networks rather than

vice-versa. The change from a 'chance discovery' model of scientific research to a 'rational drug design' model based on combinatorial chemistry, molecular biology, high throughput screening, genomics and bioinformatics has meant that those regions and localities with clusters of DBFs of various kinds, linked also to ICT firms and knowledge management intermediaries are absolutely advantaged, even to the extent of making 'big pharma' dependent on them for key knowledge of both the exploration and exploitation kind. Increasingly such DBFs even manage the due diligence and trial management processes, leaving 'big pharma' to exchange contracts with the DBF networks for the license to market and distribute the hoped-for biopharmaceutical drug at the end of the pipeline.

5. Which Are Leading Megacentres and What Is Regional Science Policy?

We have seen already that Boston is perhaps the leading biosciences megacentre, not because it has the heaviest medical or even bioscientific research budgets, but because it is presently one of, if not the leading centre for exploration research. So much so that while the Swiss drug company Novartis announced in 2000 a path-breaking agreement to spend $25 million on first access to the results of plant and microbial biology research conducted at the University of California, Berkeley, in the heart of the Northern California biotechnology cluster, in 2002 Novartis announced the establishment of a $250 million Novartis Genomics Research Institute in Cambridge, Massachusetts on the grounds that it was the leading exploration and exploitation centre for genomics and post-genomics knowledge. Boston's current primacy has not been the product of the operations of the market mechanism alone. In 1999, $770 million of mainly public or charitable research funding was earned for medical and bioscientific research. That figure is likely to have exceeded $1 billion shortly afterwards. This was marginally less than the amount of National Institutes of Health funding alone passing through the Northern California cluster in 1999, a statistic that increased to $893 million in 2000 (CHI/PWC, 2002). Most of the exploration research conducted in both Cambridge/Boston and Northern California is conducted in institutions that are dependent on public funding, though private research foundations are also functional in both. In Boston, the Massachusetts Biotechnology Council is an active and successful biotechnology association that lobbies industry and political forums at State and Federal levels, pressing for an FDA presence in Boston to offset

the advantage enjoyed by emergent firms and research institutes located in Maryland near the head offices of both NIH and FDA (see table 4).

Institution	Rank (1994)	Amount ($million)
Program Resources Inc., Reston VA	1	$98.0
Westat Inc., Rockville, MD	2	$50.0
Adv. Biosc. Lab Inc, Kensington, MD	3	$30.6
U. of Alabama, Birmingham, AL	4	$16.2
Research Triangle Institute, RTC Park, NC	5	$15.1
Johns Hopkins U., Baltimore, MD	6	$14.6
ROW Sciences Inc, Rockville, MD	7	$14.5
Harvard U., Cambridge, MA	8	$13.2
Southern Research institute, Birmingham, AL	9	$12.9
U. of Texas Health Science Centre, Houston, TX	10	$11.3

Table 4: Top Ten Institutions for NIH R&D Contracts, 1994
Source NIH

The figures in Table 4 are somewhat out of date but their significance lies in the evidence of a few years ago that geographical proximity explained the largest share in the variance of grant allocations by NIH, something that has been changed somewhat by the more piecemeal evidence that Johns Hopkins and Harvard Universities now vie for top position in consequence of their recognition of various biases in the system revealed by the statistics for 1994's allocations.

Let us look more closely at the manner in which the assets of biosciences megacentres like those in Northern and Southern California are now packaged in documentation that promotes the image that is intended to appeal to investors of all kinds into the regional innovation system. The two following examples, from Northern and Southern California are produced by a non-profit association (The California Healthcare Institute) and a consultancy (Michael Porter's *Monitor*) respectively. The California Healthcare Institute is a public policy institute for California's 200 leading biotechnology firms and research institutes. It is thus comparable to the Massachusetts Biotechnology Council. Its political brief is expressed clearly by CEO Gollaher who despite noting '…funding for basic science is strong..' bemoans the fact that '…many federal and state lawmakers advocate policies that would impede medical innovation. Our greatest threats include a total ban on human cloning ad severe restrictions on stem cell research; a Medicare administration that…. effectively excludes new

products…. and a leaderless FDA facing the greatest wave of new inventions in history' (Gollaher in CHI/PWC, 2002). The demand is for collaboration among members of the biosciences innovation system to change laws that are perceived as threatening the evolution of the industry in the post-genomic era.

Northern California is presented as the birthplace of biotechnology, which, along with biomedical innovatons like cardiac stents, has a strong base of some 819 biomedical/biotechnological firms, employing 86,000 people (28,000 in biotechnology), total R&D of $1.1 billion, NIH grants of $893 million and $4.1 billion in worldwide revenues, including $2.7 billion exports.. New infrastructure projects include University of California San Francisco Medical School's new $1.4 billion Mission Bay bioscience research campus, the new California Institutes for Science and Innovation, and the California State University CSUPERB joint ventures programme where universities and the private sector collaborate in bioscience research, technology transfer, business and even residential development. Much emphasis is placed on survey results showing that significant interaction occurs among firms and the institutional research base in Northern California.

Thus, California's academic research institutions are credited with playing a central role in the growth of nearly one-third of biomedical/biotechnological firms, 42% of firms had at least one research contract with a California research institution, 56% of firms planned to broaden or maintain such agreements and up to 70% of firms having patent license agreements planned to maintain or broaden them in future. The key Northern California life sciences and clinical research institutes cited include Stanford University (Biomedical Technology Information Programme), Lawrence Berkeley and Lawrence Livermore National Laboratories, and the University of California, San Francisco Medical School, Berkeley (BioSTAR industry-academic collaboration), Santa Cruz (with Berkeley, the California Institute for Bioengineering, Biotechnology & Quantitative Biomedical Research, QB3) and Davis (Life Sciences Information programme). More than 19,000 are employed in research in the region, and nowadays two of the top ten NIH R&D grant recipients in the US are UCSF and Stanford. A picture of this cluster that is developing the characteristics of a biosciences megacentre is presented in www.biospace.com. But the judgement as to whether it yet is, is occluded by the lobbying points that although some larger firms such as Abbot

Laboratories and Genentech are present, most are SMEs, 49% without products on the market, 45% with no revenue in 2000. Finally, of the pharmaceutical pipeline products reported, 53% are in preclinical trials. This is by no means unusual, but nevertheless testifies to the apparent fragility of the *exploitation* aspect of the Northern California cluster, once its strength, but never adequately backed up with strong bioscience *exploration* capabilities and now, belatedly perhaps, seeking to embed them.

In Southern California, the San Diego biotechnology cluster has larger claims to be considered a biosciences megacentre than even that in the North. In Porter's (2002) competitiveness study San Diego's biopharmaceuticals cluster is presented as long established and among the most significant outside Boston, especially for R&D. Cluster employment growth was more than 8,000 from 1988-1997 and San Diego had the most rapid growth in patent output compared to the twenty largest US biotechnology clusters. There are some 400 SMEs, focusing mainly on one or two preferred drug targets, the University of California, San Diego, with numerous specialist research centres, and finally, some globally known research institutes, the Salk Institute, the Scripps Research Institute, the Burnham Institute, and the La Jolla Institute for Allergies and Immunology, each focusing upon aspects of life science, medical or clinical research. The Scripps Institute, since establishment in the 1950s required its researchers to raise their own funds encouraging collaborative innovation with larger firms (like Dow). By contrast, the Salk Institute does not conduct corporate research but licenses its discoveries and takes equity stakes in companies. UCSD emphasised medical research and academic entrepreneurship. One early fruit of that approach was Hybritech, a 1978 biotechnology start-up, from which more than fifty other local biotechnology DBFs were spun out. In 1986 it was sold to Eli Lilly for $400 million. A further feature of this cluster is its strong and long-established networking propensity, signified by the establishment since 1985 of the UCSD CONNECT network, a model for cluster integration in many other new economy clusters such as Scotland's and Cambridge's (UK) (ICT) networking associations.

In Fig. 2 an analysis is provided of the origins of the San Diego biotechnology cluster firms in relation to the San Diego CONNECT network. It is notable that

'entrepreneurs' (like the first owners of Hybritech) are far more important sources of direct spin-out firms than either the university or research institutes.

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CONNECT (San Diego) Biotechnology Cluster Linkages

(Adapted from Lee, C. & Walshok, M., 2001, *Making Connections,* Report to UC Office of the President)

Overall, the Lee and Walshok (2001) report concludes that the San Diego biotechnology cluster is characterised by the following features:

- 400+ Companies
- 248 emergent firms
- 28,000 employees
- UCSD CONNECT – ' a network of professional competencies focused on building shared knowledge…. for technological companies'
- UCSD, Salk Institute, Scripps Research Institute, Burnham & La Jolla Institutes
- an innovation support infrastructure of investors, consultants and technology intermediaries

The judgement of Porter's (2002) team is that the close proximity of research centres and firms on the Torrey Pines Mesa was a key advantage in encouraging collaboration and growth. Regarding patenting San Diego registered 360 patents in biopharmaceuticals in 1997, a rate of 13.17 per 1,000 workers and the growth rate was the US's fastest, though the intensity was less than nine other bioclusters. Venture capital was invested at a much higher rate than nationally with $421 million having been placed 1995-99, nearly 10% of the national total. But research organisations are the greatest strength, with Novartis and Dow having joined the public institutes, making a total of some 16,000 employees in biopharmaceuticals research alone, larger than that specific category in Northern California. However, both Californian clusters have strongly emergent megacentre properties, based especially on their strength in exploration knowledge and an abundance of SME DBFs that are capable of rapidly forming molecular discovery networks due to geographical proximity and critical mass. In the Orsenigo et al. (2001) study of rational drug design research networks18% of interacting firms and institutes were in Boston, 16% in Northern California and 12% in San Diego. The few partners outside the USA were located in Munich (2), Cambridge (2) and Oxford (2).

This brings us neatly to brief consideration of the status of bioscience megacentres in Europe. In terms of possession of the key exploration and exploitation institutes and firms, it is clear from maps produced regularly by Ernst & Young, e.g. (1999) that the greater London area has the greatest number of DBFs concentrated in an agglomeration with few *exploration* institutions south and west of London and two clusters at Cambridge and, slightly smaller, Oxford where exploration and exploitation

go hand in hand in geographical proximity. Cambridge has the strongest case for being considered a potential megacentre at present. Cambridge has a rather diverse biotechnology processing and development as well as services support structure, even though the industry is relatively young and small. Some of the service infrastructure and perhaps the equipment sector benefits from the earlier development of Information Technology businesses, many also spinning out from university research in Cambridge. 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 region are also located important research institutes in the 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. Its core biotechnology industry consists of approximately 90 firms and the broader cluster (venture capitalists, patent lawyers etc.) consists of approximately 200 firms, with the core biotechnology firms employing 2,500-3,000 people. Of relevance to the biotechnology community are the activities of the Eastern Region Biotechnology Initiative. This biotechnology association is the main regional network with formal responsibilities for: newsletters, organising network meetings; running an international conference; web-site; sourcebook and database on the bioscience industry; providing aftercare services for bio-businesses; making intra- and inter-national links (e.g. Oxford, Boston, San Diego); organising common purchasing; business planning seminars; and government and grant-related interactions for firms.

Munich seems to have become a more significant biotechnology player in recent times, particularly since the onset of BioRegio in 1995. It was well established in *exploration* knowledge institutions but like the rest of Germany, weak in *exploitation* mechanisms. This seems to have been re-balanced but it is too soon to say how significantly as key second-round funding demands are only in 2002 coming on-stream. The science base in Munich is broad, but with special expertise in health-

related and agricultural and food biotechnology. There are three Max Planck Institutes of relevance, in Biochemistry, Psychiatry and the MPI Patent Agency. GSF is the Helmholtz Research Centre for Environment and Health, and the German Research Institute for Food Chemistry is a Leibniz Institute. There are three Fraunhofer Institutes, one of Germany's four Gene Centres, two universities and two polytechnics. The main research-oriented 'big pharma' companies are Roche Diagnostics (formerly Boerhinger Mannheim) and Hoechst Marion Roussel (since 2000, Aventis). The work areas of this science community include; 3D structural analysis, biosensors, genomics, proteomics, combinatorial chemistry, gene transfer technologies, vaccines, bioinformatics, genetic engineering, DNA methods, primary and cell cultures, microrganisms, proteins, enzymes and gene mapping. The Bavarian commitment to biotechnology (and other new technologies) was realised through its state government decision to privatise its share in power-generation and distribution companies in the 1990s, thereby creating a funding pool to subsidise applied technology developments. Nevertheless, the numbers of start-ups are not overwhelming, perhaps because of the quest for 'quality' start-ups in whom substantial sums may be individually invested.

A further explanation for conservatism is that BioM AG, the 'midwife' agency to the cluster, funded partly by BioRegio and set up as a corporation, makes investments with its shareholders' (state, industry and banks) money. Banks seeking to earn high returns hold most of the shares. They also use this method to learn about biotechnology, its risks and prospects. Thus, an already well-subsidised system is further protected from risk by the influence of banking culture, itself highly conservative in Germany, to ensure, as far as possible, risk avoidance. Hence, while BioM is the network face of the biotechnology cluster in Munich, its activities are ultimately orchestrated indirectly and directly by the banks, abetted by a fairly risk-averse, mostly publicly-funded, venture capital industry and the local pharmaceutical and chemical companies (Giesecke, 2000).

So, for the moment Europe's best candidates (to which may possibly be added Stockholm-Uppsala in Sweden, VINNOVA, 2001) are either somewhat lacking in the maturity or critical mass of their DBFs, as is the case to varying degrees of both Cambridge and Munich. This is an *exploitation* rather than *exploration* knowledge

deficiency. It is arguable, judged by Nobel Prizes awarded that Cambridge with eleven is superior in biosciences to any of the stronger candidates in the USA. But it is unquestionable that the latter have been more entrepreneurial, even though large numbers of DBFs everywhere have neither products nor profits.

What does this signify? In an earlier paper, an extensive analysis of the response by the large number of non-megacentre, even non-bioscience regions in the USA, Canada and the UK was undertaken (Cooke, 2002b). This showed that fifteen US States had undertaken science base analyses and developed science strategies with targets and mechanisms for augmenting their capture of basic science funding in biosciences. Some piecemeal evidence of the outcomes of these are the statistics that show universities like Harvard, Johns Hopkins, UCSF, Stanford and Duke as occupying highest places in the NIH R&D allocations compared to hitherto. But the US has also an interesting mechanism for supporting ambitious if underdeveloped universities in lagging States to access national competitive funding. The EPSCOR scheme under the NSF competitive bidding procedure for accessing, first programme, now project funding allows designated States, e.g. Oklahoma and Mississippi to bid competitively for such bioscience research funding by lowering the grant aid qualifying bar below that expected of the rest of the USA. This, in EU terms, is a 'structural funds' mechanism within the Framework Funds and it has produced generally positive rather than futile results in the USA.

In Europe, some regional bodies have begun to develop regional science strategies, most notably Scotland that identifies its £800 million R&D spend annually and seeks to augment it through intra-regional collaboration and the furtherance of existing science-funding mechanisms. Medical and Biosciences are two if the three funding areas to be targeted. In Finland a central government policy of seeding regional Centres of Expertise, and later, Centres of Excellence has produced up to six regional bioscientific Centres of Excellence that follow the US system of linking *exploration* to *exploitation* but through largely public rather than private knowledge exploitation mechanisms. Regional governance institutions are now somewhat more aware now than they were until only very recently, that health is a large part of their economy, that it links directly to some of the most exciting science being done in the world today, and that as well as making a direct economic contribution through purchasing

and employment, it can make an important indirect contribution to economic welfare through possible academic and corporate spin-out activities. It is likely that regional analysis and policy will be more rather than less influenced by issues such as those discussed in this paper in future.

6. Conclusions

These are brief and orientated towards future implications for regional science and policy rather than being a simple reprise of what has been said. First, of significance to the never-ending debate about the viability of SMEs in a globalising world dominated by multinational firms, events during the past decade or so show just how misplaced arguments prophesying the demise of SME significance can be. It is 'big pharma' that is in crisis as its traditional expertise in fine chemistry is subverted by the molecular biology revolution and the demand for transdisciplinary teams of DBFs to form project-based networks to seek 'rational drug design' solutions based on reagents and their inhibitor compounds at the molecular and even sub-molecular levels. Meanwhile 'big pharma's' drug innovation pipeline dries up as R&D costs escalate, giving a further imperative to externalise projects to the 'knowledge value chain'. DBFs in turn rely effectively upon the deep pockets of 'big pharma' for licensing cash, marketing and distribution. Some DBFs are now quite large and one (Celltech) recently bought a mid-size 'pharma' (Medeva) in the UK. Other global 'pharma' has been merging at pace recently as they seek to reap one-off shareholder value from reducing the competition as Glaxo, Pfizer, Wyeth, Aventis and Novartis to name a few, testify. The regional science implications of these shifts towards public R&D exploration and exploitation and away from 'big pharma's' traditional metropolitan redoubts require swift and serious analysis.

In regional policy terms, the new model is more foresight-driven, more collaborative, based on shared vision and leadership than old redistributive policy used to be. This is necessarily policy for securing 'generative growth' (Cooke, 2002c). It must take seriously the long-established presence of hospitals and universities and seek to forge links along the biosciences value chain. It must do this in a sometimes hostile environment in which national or federal governments prefer to see a few Centres of Excellence, possibly not too far away from their seats of government, rather than in

obscure and peripheral regions. Yet policy-makers in precisely such regions will surely seize upon the obvious notion that for once in history public sector investments are new sources of innovative development and generative growth, seeking ways of mobilising enterprising coalitions to bid for infrastructure and 'star' scientist recruitment from a variety of funding sources. Or, if this is insufficient, pressing their multi-level governance structures for affirmative research allocation action such as that already pioneered in the USA through EPSCOR.

References

Audretsch, D. & Feldman, M. (1996) Knowledge spillovers and the geography of innovation and production, **American Economic Review**, 86,630-640

Becattini, G. (1989) Sectors or districts: some remarks on the conceptual foundations of industrial economics, in E. Goodman & J. Bamford (eds.) **Small Firms & Industrial Districts in Italy**, London, Routledge

Best, M. (2001) **The New Competitive Advantage**, Oxford UP

Brusco, S. (1989) A policy for industrial districts, in E. Goodman & J. Bamford (eds.) **Small Firms & Industrial Districts in Italy**, London, Routledge

California Healthcare Institute & PriceWaterhouseCoopers (2002) **Biomedicine: the New Pillar in Northern California's Economy**, La Jolla & San José, CHI/PWC

Chandler, A. (1990) **Scale & Scope**, Cambridge, Harvard/Belknap

Coase, R. (1937) The nature of the firm, **Economica**, 4, 386-405

Cooke, P. (2002a) **Knowledge Economies**, London, Routledge

Cooke, P. (2002b) Towards regional science policy? The rationale from biosciences, paper to Conference on *'Rethinking Science Policy: Analytical Frameworks for Evidence-Based Policy'*, Science Policy Research Unit, University of Sussex, March 21-23

Cooke, P. (2002c) Future challenges for regional development posed by economic globalisation, **International Journal of Technology Management** (forthcoming)

Curzio, A. & Fortis, M. (eds.) (2002) **Complexity & Industrial Clusters**, Heidelberg, Springer

Dosi, G. (1988) Sources, procedures and microeconomic effects of innovation, **Journal of Economic Literature**, 26, 1120-1171

Ernst & Young plc (1999) **European Life Sciences: Sixth Annual Report**, Reading, Ernst & Young

Feldman, M. & Audretsch, D. (1999) Innovation in cities: science-based diversity, specialisation and localised competition, **European Economic Review,** 43, 409-429

Galison, P. (1997) **Image and Logic: A Material Culture of Microphysics**, Chicago UP

Gibbons, M. et al. (1994) **The New Production of Knowledge**, London, Sage

Giesecke, S. (2000) The contrasting roles of government in the development of biotechnology industry in the US and Germany, **Research Policy**, 29, 205-223

Glaeser, E., Kallall, H., Scheinkman, J, & Shleifer, A. (1992) Growth in cities, **Journal of Political Economy**, 100, 1126-1152

Griliches, Z. (1992) The search for R&D spillovers, **Scandinavian Journal of Economics**, 94, 29-47

Henderson, R, Orsenigo, L. & Pisano, G. (1999) The pharmaceutical industry and the revolution in molecular biology: interactions among scientific, institutional and organisational change, in D. Mowery & R. Nelson (eds.) **Sources of Industrial Leadership**, Cambridge UP

Jacobs, J. (1969) **The Economy of Cities**, New York, Random House

Jaffe, A, Trajtenberg, M. & Henderson, R. (1993) Geographic localization of knowledge spillovers as evidenced by patent citations, **Quarterly Journal of Economics**, 108, 577-598

Kaiser, R. (forthcoming) Innovation policy in a multi-level governance system: the changing institutional environment for the establishment of science-based industries, **European Planning Studies**, 11

Lee, C. & Walshok, M., **(**2001) **Making Connections**, Report to University of California Office of the President

Marshall, A. (1918) **Industry & Trade**, London, Macmillan

Milbank Memorial Fund (2000) **State Healthcare Expenditures**, New York, Milbank Memorial Fund

Niosi, J. (2002) Canadian industry clusters: aerospace, biotechnology and software, Paper to *Innovation Systems Research Network Conference*, Quebec City, May 7-9

Nonaka, I. & Takeuchi, H. (1995) **The Knowledge-Creating Company**, Oxford UP

Orsenigo, L, Pammolli, F. & Riccaboni, M. (2001) Technological change and network dynamics: lessons from the pharmaceutical industry, **Research Policy**, 30, 485-508

Owen-Smith, J, Riccaboni, M, Pammolli, F. & Powell, W. (2001) A comparison of US and European university-industry relations in life sciences, (mimeo)

Penrose, E. (1959) **The Theory of the Growth of the Firm**, Oxford UP

Polanyi, M. (1966) **The Tacit Dimension**, London, Routledge

Porter, M. (1990) **The Competitive Advantage of Nations**, New York, The Free Press

Porter, M. (1998) **On Competition**, Boston, Harvard Business School Press

Porter, M. Sachs, J. & Warner, J. (2000)

Porter, M. (2002) **Clusters of Innovation**: regional Foundations of US Competitiveness, Washington, Council on Competitiveness

Piore, M. & Sabel, C. (1984) **The Second Industrial Divide**, New York, Basic Books

Richardson, G. (1972) The organisation of industry, **Economic Journal**, 82, 883-896

Sabel, C. (2002) Diversity, not specialisation: the ties that bind the (new) industrial districts, in Curzio, A. & Fortis, M. (eds.) **Complexity & Industrial Clusters**, Heidelberg, Springer

Seely Brown, J. & Duguid, P. (2000) **The Social Life of Information**, Boston, Harvard Business School Books

Senker, J. & Van Zwanenberg, P. (2001) **European Biotechnology Innovation Systems**, Final Report to EU-TSER Programme, University of Sussex, SPRU

Stankiewicz, R. (2002) The evolving design space of technology and the public R&D system, paper to Conference on *'Rethinking Science Policy: Analytical Frameworks for Evidence-Based Policy'*, Science Policy Research Unit, University of Sussex, March 21-23

Stewart, T. (2001) **The Wealth of Knowledge**, London, Nicholas Brealey

Suchman, M. (2000) Dealmakers and counsellors: law firms as intermediaries in the development of Silicon Valley, in M. Kenney (ed.) **Understanding Silicon Valley**, Stanford UP

Teece, D. & Pisano, G. (1998) The dynamic capabilities of firms: an introduction, in G. Dosi, D. Teece & J. Chytry (eds**.) Technology, Organisation and Competitiveness,** Oxford UP

VINNOVA (2001) **The Swedish Biotechnology Innovation System**, Stockholm, VINNOVA

Williamson, O. (1985) **The Economic Institutions of Capitalism**, New York, The Free Press.

Zucker, L, Darby, M. & Armstrong, J. (19980 Geographically localised knowledge: spillovers or markets? **Economic Inquiry**, 36, 65-86