The Biosciences Knowledge Value Chain and Comparative Incubation Models

Philip Cooke[1]
Dan Kaufmann[2]
Chen Levin[2]
Rob Wilson[1]

ABSTRACT. This research derives from an EU DG Enterprise (IPS Programme) project on bio-incubation, called Bio-Link. The Bio-Link project is innovative in three ways. First, it involves an international comparative analysis of biotechnology incubators of the kind that is rarely if ever done. Second, the incubator representatives are monitored and investigated by an academic partnership team. Third, there is a stated aspiration by the incubator companies to engage in co-incubation across borders. Co-incubation is, as far as we are aware, a new kind of boundary crossing innovation in which advanced start-up businesses are assisted to enter other national markets and/or benefit from specialised services or scientific, technological, or commercial knowledge absent in the home country but present in a partner country. Evidence from research on European, Israeli and North American bioincubators is included to compare, contrast and enable future judgements of incubator appropriateness to biotechnology.

Key words: biotechnology, innovation, incubators, universities, knowledge transfer.

JEL Classification: A14, O33, R11, R58

1. Introduction

This paper is concerned with incubation of start-up businesses in biotechnology, and specifically whether there are prospects for co-incubation of start-ups through international incubator linkages. It asks three key questions about the problems of transforming basic, exploration knowledge into commercialised products and services in biotechnology. First, we inquire as to whether the span of knowledge control required varies according to regional setting (Cooke *et al*., 20031)? We further ask about the knowledge : institutions balance in contextuating commercialisation capabilities. Second, it asks further if incubation is the only or best general method for enhancing exploitation of basic research and assesses alternative means. Third, we ask to what extent the incubation process, located at the higher risk end of the commercialisation continuum, is necessarily a non-profitable, publicly subsidised service and whether regional location influences the subsidy requirement unduly. The data that enables us to answer those questions in our conclusions were generated during the first and second stages of an EU project (Bio-Link) conducted during the first and last 3 months of 2003.

This involved researching five European and Israeli incubators in the first stage and comparing them with three North American ones in the second stage. The resulting analysis provides detailed presentation, monitoring, assessment and evaluation of incubators by type, by service offered, by ownership and by position in what can be called the *knowledge value chain* (KVC) for Life Sciences more generally, and biotechnology more particularly. A pilot conceptual model of such a "KVC" is presented in the following section. It passes from *exploration* through *examination* to *exploitation* knowledge as basic research evolves to the stage of pre-clinical and clinical trials and then to the commercialisation stage where due diligence skills and venture capital skills ultimately determine whether or not a "prospected" start-up may reach the stock market, license its technology or be acquired by another owner.

Following this brief expository section, the paper then moves onto the main stage of comparing and contrasting, monitoring and evaluating the eight incubators in the study, recording the judgements of both academic observers and incubator managers regarding their specific incubator type, strengths and challenges, or preferred market

[1]*Centre for Advanced Studies*
Cardiff University
Cardiff, CF,103 BB UK
E-mail: cookePN@cardiff.ac.uk
[2]*Jerusalem Institute for Israel Studies*
Jerusalem, 92186 Israel

position. An attempt is made to resolve these judgements where variation occurs. There is always an attempt both to situate the bio-incubators in the wider local or regional innovation system (Cooke, 2001) within which they reside, and to recognise that where one may offer a wider range of services to academic entrepreneurs, this may be a sign of system weakness rather than strength, although for other reasons—"the one-stop shop"—it may of course be a sign of efficient focusing of many support functions under one roof (Wolter, 2002; Cooke, 2002a,b).

2. A model of the KVC in Life Sciences and the role of incubation

The point of co-location practices by innovative start-ups and their support organisations, such as incubators, is to enhance the competitiveness of *firms* by increasing *productivity* and *innovation*. Proximity yields *knowledge spillovers* (Audretsch and Feldman, 1996; Feldman and Audretsch, 1999; Audretsch, 2001; Andersson and Ejermo, 2002). Some of these do not travel very far, Jaffe *et al.* (1993) suggest fifty miles for patent citations by entrepreneurs referring to university research.

This has been confirmed for Europe by Senker and van Zwanenberg (2001). However, in addition to strong local spillovers in relations among researchers and entrepreneurs, U.S. researchers enjoy more extensive network relationships among public research organisations than their European counterparts (Owen-Smith *et al.*, 2001). But, either way, at least for biotechnology, the *complementarities* are conditioned very strongly by arm's length exchange when valuable exploration knowledge is being transformed by exploitation knowledge as "star" scientists interact on serious commercial projects, for example, joint patenting or product development with biotechnology entrepreneurs (Zucker *et al.*, 1998). This corrects somewhat for an "over-socialised" view of the importance of "untraded interdependencies" in cluster-type settings. This is not to deny knowledge spillovers that enable "free-riding" happen, rather that they are relatively trivial in nature (Giesecke, 2000; Granovetter *et al.*, 2000; Fritsch, 2001).

Nevertheless, for the acquisition of localised spillovers of a trivial or a non-trivial kind, a number of key knowledge spillover "types" need to be available, and, following Porter (1998) and others, they are better if local because of *time* economies. These refer to:

- swift receipt of value-adding knowledge prior to its general release (anticipatory knowledge);
- timely availability of complementary local assets or capabilities (participatory knowledge);
- early access to local inventions, discoveries or innovations (precipitatory knowledge).

These correlate to three more thoroughgoing kinds of knowledge that is central to knowledge production in research and commercialisation activity that are not spillovers but core knowledge production activities. These are shown on the left side of Figure 1 and explained here:

- *Exploration knowledge*: The aim of fundamental research, as, for example, in post-genomics, proteomics and molecunomics conducted in laboratories of universities, research institutes and DBFs in the main.
- *Examination knowledge*: The kind of "feedback" knowledge that comes from clinical trials of new treatments, therapies and drugs to find out if they work or work better than existing treatments.
- *Exploitation knowledge*: The mix of knowledge skills, including scientific, technological, entrepreneurial, financial and legal that enables discoveries to be transformed into commercial products with market demand.

Where clusters have the fullest range of these "knowledge production" and "knowledge spillover" capabilities they exert synergies upon a diverse range of scientific research and commercialisation actors that, on the one hand, causes further and further "swarming" (à la Schumpeter) at the cluster epicentre and, on the other, boundary extension through network-like market relations to specialised support services in demand. These are externalised services such as biomanufacturing, bioimaging or clinical research organisation (CRO) services that function effectively at greater distance from the cluster epicentre. Indeed, these may be points hitherto related to different

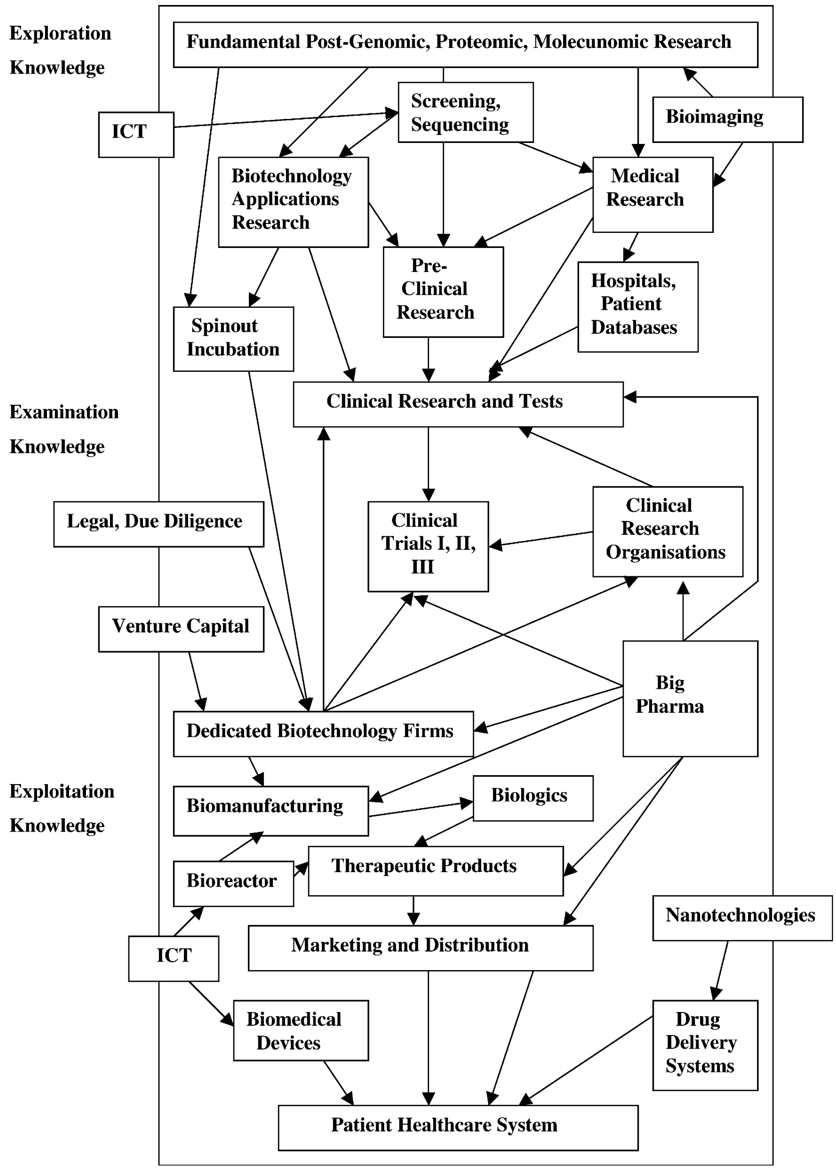

Figure 1. Conceptual model of the bioscientific and biotechnological value chain.

industries and earlier economic histories, as with synchrotrons (particle accelerator/colliders), formerly key to nuclear physics but now more important for bioimaging, or biomanufacturing that has a lineage in bulk chemicals production. In Figure 2, a conceptual model of such links according to knowledge spillover and production typologies is presented. That is, the three "Es" structure the vertical dimension of the KVC, from exploration, through examination, to exploitation process-phases. The three "Is" are embedded in the process linkages among actors in which *intelligence*, *insurance* and *investment* appear as key rationales for proximity relations. These facilitate *anticipatory*, *participatory* and *precipitatory* spillovers, respectively (for fuller exegesis, see Cooke, 2005).

The role of incubation in the Life Sciences KVC on the one hand, and in knitting together exploration, examination and exploitation services to

Processes / *Knowledge*	**Intelligence**	**Insurance**	**Investment**
Exploration	*Anticipation Spillovers* (e.g. 'foresight')	*(Ethics)*	*(R&D, patents)*
Examination	*(Trials/Tests)*	*Participation Spillovers* (e.g. likely approvals)	*(Trial Leadership)*
Exploitation	*(Risk Assessment)*	*(Syndication)*	*Precipitation Spillovers* (e.g. funding rounds/IPO)

Figure 2. Varieties of knowledge spillover in bioscientific value chains.

start-ups and evolving businesses, on the other, is clearly crucial. In both North America and Europe, influential reports have recently been published urging incubation upon policy-makers and markets. In the U.S. case, they were seen as exerting a positive effect on growth in new technology sectors generally though this was less clear for biotechnology incubators benchmarked (NBIA, 16). In a U.K. report, CSES (4) focused on bioincubation, 22 facilities were examined, were found expensive at £4.6 million average running costs per year but likely to grow in demand for space in the near future. From an intellectual viewpoint we may simply list the kind of "boundary-crossing" services of value to spinout biotechnology businesses according to the span across the "three Es" we consider our eight bioincubators to cover in varying degrees:

- In relation to exploration—incubators co-located or otherwise in reasonable proximity to basic research institutes may offer services related to assisting transform the germ of a business idea into a business. Proof of concept, validation and selection of exploration candidates for possible incubation by virtue of "prospecting" and technological "due diligence" may characterise this variant of an examination service. This occurs through network knowledge of scientific or technological and financial expertise, knowledge of sources of seedcorn finance, or personnel and sources of public funding, training or advice.
- In relation to examination—apart from the functions noted above, bioincubation will involve advising and servicing requirements start-up firms that have passed beyond proof of concept to pre-clinical trials may need regarding the administration of such trials. These may involve CROs, large pharmaceuticals firms or other means of mobilising appropriate mammalian testing resources. Other forms of testing of diagnostic kits or biomedical devices will also be provided directly, or indirectly through the bioincubator management's trust-based "social capital."

- In relation to exploitation—equity-based syndication conducted by investors may be mobilised by incubator management, strategic partnering, joint ventures of a technological nature and connections to consultants, specialist lawyers and IPR advisers and management accountants for business "engineering" will be supplied in-house or through the social capital networks that accrue to bioincubators and constitutes their key management resource of value along with the capability to supply appropriate "wet lab" space. Relationships with markets are especially important in assisting firms to find expert commercial partners (Norton, 2000; Zook, 2000; Cooke, 2002a,b); Powell *et al*., 2002). In Section 3 efforts will be made to characterise the eight bioincubators in the Bio-Link study according to the range of services they supply and the direct and indirect nature of those services.

3. Comparing eight bioincubators By KVC services and governance

Rationale for incubator selection

The first question is to inquire about the selection of bioincubators for the study. Given this is a policy research project funded by DG Enterprise of the E.U., policy concerns were naturally foremost. Thus from Europe and Israel (a signatory and financing member of E.U. RTD programmes) the range of funding and governance forms, from public to private was sought. Moreover, those in prosperous and less prosperous regions were of interest, as were any distinctive characteristic specialisation in services provided. Hence, two heavily subsidised public bioincubators, one in the prosperous Paris region of France, the other in the less favoured Sardinia region of Italy were selected. Moreover, the former planned seedcorn funding to a wide range of tenants while the latter offered no seedcorn funding but offered access to the unique Sardinian gene bank for bioscientific and genomics research firms.

A second group of bioincubators were privately funded, albeit by private foundation rather than solely by market transactions. These are located in prosperous Oxford, England and less favoured Jerusalem in Israel. The Oxford bioincubator is surrounded by a rich infrastructure of exploration, examination and exploitation knowledge services ranging from Oxford University's celebrated *Isis* Knowledge Transfer Office (KTO), and CROs to regional public and private venture capital funds. The Israeli bioincubator is the heart of a small, dynamic biotechnology cluster connected to the internationally renowned Hebrew University and related teaching hospitals, the former one of the world's richest patent income earners, at third with 2002 income of over $100 million resulting from the invention in its biosciences faculty of the globally consumed "cherry tomato." However, surrounding such excellence is a relative desert of KVC support services, such that firms are forced to seek cheap and not always appropriate CROs abroad, often in eastern European settings such as the Czech Republic. This incubator provides many services others do not, notably IPR services and early stage funding. However, for it, the idea and prospect of international and even global networking through bioincubator nodes abroad acting as gatekeepers to desired services is highly attractive.

The third European bioincubator "system" is that presided over in Munich, Germany by the public–private partnership funding and exploitation agency BioM, winner of the prize as one of Germany's main biotechnology clusters under the BioRegio programme that ran from 1995 to 2002 and resulted in Munich becoming Germany's main biotechnology cluster location. Hence, such a public–private funding partnership was intellectually interesting in bridging the gap between largely or wholly public support as in France and Germany, and the private, foundation support found in Britain and Israel. Moreover, BioM offers a variety of support services for new biotechnology firms, including assistance in accessing space at the bioincubators in Martinsried, the south-western Munich suburb where a major bioscientific research and commercialisation "megacentre" has evolved, albeit relatively recently with respect to spinout activity.

Next, staying with the governance, funding and regional service profiles as selection criteria, the following North American bioincubators were selected for examination. The first is a mainly public sector supported facility in Quebec, Canada based near Montreal on the University campus at

Laval. The Quebec BioIncubator Centre (QBIC) is part of a large Biosciences innovation complex and comparable in philosophy to Genopole. Montreal and environs has experienced significant industrial restructuring, loss of traditional manufacturing industry, and particularly financial services to Toronto during the 1970–2000 period. However, bioscientific research is deeply embedded in the region and commercialisation has produced world-class firms, notably and also at the Laval campus, BioChem Pharma discoverer of Epivir, the first AIDS treatment marketed through Glaxo. Since acquired by U.K. firm Shire Pharmaceuticals, BioChem was in late 2003, experiencing significant corporate re-positioning towards less costly therapeutic targets while advanced research was being focused more towards home base.

The two bioincubators selected in the U.S.A. were, first, the Broad Hollow Bioscience Park, at Farmingdale, Long Island, NY, part of the State University of New York campus at Farmingdale and on the doorstep of the Cold Spring Harbour Research Institute, headed by James Watson, co-discoverer of DNA and co-initiator of the Human Genome project. The building of this bioincubator was funded by the state of New York, SUNY Farmingdale and the support of Cold Spring Harbour. The incubator's running costs are largely met by Cold Spring Harbour spin-out OSI Pharmaceuticals (acquirer of British Biotech in 2003), a successful business employing 120 and occupying most of the incubator. OSI was gifted one of Pfizer's R&D projects for an oncology drug on monopoly legal grounds consequent upon their acquisition, also in 2003, of Pharmacia, possessor of its own oncology treatment. Hence, while not a public–private partnership, this incubator receives private maintenance and related services from the private sector.

The second American bioincubator in the comparison is Massachusetts Biomedical Initiatives (MBI) and specifically its MBIdeas Centre at Winthrop St., Worcester, MA. MBI established in 1985 is an independent, tax-exempt corporation created to support the growth and expansion of biotechnology and medical device companies throughout the region. The set-up funding for the MBI facility came from a grant of $1 million from U.S. Federal level through the Economic Development Administration (EDA) of the Department of Commerce. This was matched by a $1 million of private sector funding and $1 million from the State of Massachusetts. The healthy financial model at MBI is underlined by the fact that the majority of its operating income (80%) for the Worcester facility comes from rents with the remainder coming from State of Massachusetts in the form of grants, with the latter portion of income falling gradually. The intention is that, if extra space can be bought in the former St. Francis Hospital that houses MBI, the bioincubator will become self-funding. Hence MBI is the nearest to a non-foundation, private bioincubator operating in the market with low public funding. However, in essence, its funds come from rents and will come from a 1% equity investment from incubator tenants. Hence, it is becoming a market-facing institution unlike the other incubators in this research study.

Thus a degree of complexity underpins the precise choices made. Key determining criteria were nature of funding, extent of institutional support from agencies or market services available nearby, nature of scientific research and exploitable knowledge, receptivity of scientists towards academic entrepreneurship, and rigour of spinout screening. Each bioincubator illustrates in distinctive ways strengths and weaknesses in this set of criteria. Hereafter, we will take account of the observed position of each bioincubator in the range of elements for which it takes responsibility from the KVC and illustrate a governance model that characterises each of our eight incubators. This will be attempted in Figure 2 by deploying a two-by-two schema arranging governance on the "*x*" axis and KVC on the "*y*." This follows brief thematic accounts of each bioincubator.

The trust-funded incubators

These are Oxford BioTechNet and Hadasit in Jerusalem. The former is a "virtual" incubator networking some 70 "mentors" available to sell at or below cost (if subsidy is available) market services to start-up tenants in hard accommodation owned by the bioincubator as an affiliate of the Oxford Trust, a charitable foundation, itself arising from the profitable activity of Oxford Innovation a successful scientific instrumentation business. To help set up the bioincubator a

€600,000 grant was won under a U.K. government (DTI) "Bio-challenge" scheme in 1997 which assisted investment in incubator buildings. Although initial plans were for 1000 m^2 at Churchill Hospital, land was found at the site of Yamanuchi research the Oxford home of Japan's third largest pharmaceuticals business. Other shareholders invested nearly double the "Challenge" funding and space was opened at the end of 2000. Oxford is one of the U.K.'s leading biotechnology "clusters" with some 50 core biotechnology businesses (in the early 1990s only 3 or 4) and a further 70 support firms, located at various sites, including along the A34 "corridor" to Abingdon.

Most are spin-outs from Oxford University Life Sciences and Medical School centres and departments. The Oxford incubator has 12 tenants, mostly single person companies moving towards second or third phase development. All are in biopharmaceuticals, ranging from reagents, to therapeutic sugars, gene therapy, cancer therapy, antibodies and bio-instrumentation. Most have U.K. innovation awards, following exhaustion of which if proof of concept is validated business angel funding is intended to lead to product sales after some 5 years. One successful firm associated with the bioincubator is Oxford Glycosciences recently acquired by Celltech as the U.K.'s biotechnology sector begins to consolidate. Thus BioTechNet is a private, not state-funded facility, though it has clearly benefited from state set-up funding. It lacks either the power or responsibility to seek a return for incubator services beyond rent. It provides market network access to private equity linking to, among others, Oxfordshire's University Enterprise Network. Firms coming to the bioincubator are thoroughly vetted and validated by Oxford University's *Isis* commercial office. Its strengths are its reputation, it's image as a model to other incubators, its uniqueness in Oxfordshire and its strong university and mentoring links. Its weaknesses are small size, with only three staff, dependence on trust funding, and absence of a seed fund of its own. Future plans are to grow and offer "accelerator" and "follow-on" space. It is anticipated that the Yamanuchi site will soon host a Science Park which may meet such aspirations.

Hadasit is fundamentally a for-profit, incorporated company founded by the Hadasah Medical Organisation (HMO), a women's health foundation that owns 100% of Hadasit's shares. It is unlike the Oxford bioincubator as it incorporates the KTO function, generating a royalty stream from its investment in spin-offs (see also the MBI account below). In this way it offers a more comprehensive, one-stop-shop service. Hadasit's aim is to increase the revenue base of the incubator. Its procedure involves screening firm candidates, agreement for pre-proof of concept funds followed by an IPR assessment. If it passes muster a patent filing occurs conducted by Hadasit, leading to a final prototype, preparation of a business plan and auditioning for venture capital. Hadasit has U.S. partners and also links to incubation facilities in Singapore and Australia. It offers firms the widest range of services and benefits from growth in its equity stake in incubated start-ups. The incubator has firms specialising in thrombosis, cancer care, rheumatoid arthritis and hormone research.

The key differences between these similarly originating incubators is that Oxford has a strong knowledge and institutional base, hence the incubator is a waystation for well-screened candidates from the *Isis* spin-out system. Despite that, it breaks even financially because of trust support for its not-for-profit business model. Hadasit is a one-stop shop in a rich knowledge but poor institutional environment for whom co-incubation opportunities are desirable. It generates an equity-based income stream to augment rental income, but payback times are such that new business models that speed up investment engagement are actively being assessed.

The public subsidy bioincubators

Genopole is member of a French network of such incubators with Evry (Paris) as the leader. BioM is a public–private partnership, mainly public, promoting biotechnology entrepreneurship in Munich. Consorzio Ventuni is a genomics technopole funded by the Sardinian regional government. Genopole's "family" are in Lille, Rennes-Nantes and Strasbourg. Genopole was established in 1998 as a *public* agency with a mission "to create a new BioPark association between public sector and industrial research." Organisations like CNS (gene sequencing), CNG (genetics) and Genplante occupy space amongst public research bodies like CNRS, INSERM, CEA, INRA, and Evry University—employing 1520 people in all. Research focii are gene analysis, gene function, gene therapy, nanobiotechnology and Life Sciences research.

Its strengths are its capabilities to foster "boundary-crossing" interactions between public, private and university research and exploitation. Weaknesses are the difficulty of "prospecting" as few start-ups volunteer to be so and lack of seed stage funding, even for proof of concept support. The Genopole procedure is to prospect, then following detection, sign a protocol for a prevalidation strategy for a spin-out firm. Thereafter progress is repeatedly validated by an audit board leading, if positive, to shareholder agreements, pre-seed funding (mostly grants), and a task force assisting project management towards a business plan presented to venture capitalists. This will include ANVAR the French state venture fund. The aim is to access €1 of grant matched with €1 of equity. The E.U. Fund of Funds (venture capital) brings 25% of such funding. In 1998 there were 10 biotechnology businesses employing 331 persons, in 2000, 34 employed 561 persons and in 2002, 41 employed 602 persons. There are knowledge spillovers in Genopole, partly orchestrated by open seminars for academics and entrepreneurs. Club Genopole meets every 4/5 weeks and *Les Doctorials* are free days when all future doctoral students learn entrepreneurship.

In Munich, Martinsreid in the south-western suburbs marks the centre of biotechnology research and incubation in Bavaria. Aventis opened its Centre for Applied Genomic Research there and the Biotechnology Innovation Centre (IZB) funded €80 million by the Bavarian government is located nearby with 9000 m^2 of laboratory and office space. The organization responsible for managing development of biotechnology, BioM, is also located at Martinsried. The area has become a biomedical research campus with 8000 researchers working in biology, medicine, chemistry and pharmacy located there. BioM AG is a one-stop shop with seed financing, administration of BioRegio awards and enterprise support under one roof. Seed financing is a partnership fund from the Bavarian State government, industry and banks up to €600 K per company. BioM's investments are tripled by finance from tbg (public investment fund) and Bayern Kapital, a special Bavarian financing initiative. The latter supplies equity capital as co-investments. The fund has €200 million for supporting biotechnology activities. Bay BG, and BV Bank-Corange-ING Barings Bank have special public/private co-funding pools, and a further eight (from 16) Munich venture capitalists in the private-market sector invest in biotechnology. By 2003, numerous start-ups had been funded to the tune of €120 million with a third of this coming from BioRegio sources. DBFs increased from 36 to 120 between 1996 and 2001 (Kaiser, 15). BioM is a network organization, reliant on science, finance and industry expertise for its support committees. It also runs young entrepreneur initiatives, including development of business ideas into business plans and financial engineering plans. Business plan competitions are also run in biotechnology.

Sardinia's regional innovation policy promotes clusters and knowledge economy development through science-based industry, R&D and incubator activity. Pharmacogenomics is one of five clusters in development. In pharmacogenomics, Sardinia's uniqueness in reduced genetic diversity from its long-settled population, especially in the interior, facilitates research and commercialisation in endogamy and consanguinity. There is a strong knowledge base and genetic skills in firms like SharDNA, Neuroscienze, CRS4 and Parco Genos. The incubator has R&D facilities for research into genes with multigenetic disease as targets. The Gene Park has 13 biotechnology firms and research institutes.

Although firms and research institutes specialise, in many instances, in work related to Sardinia's distinctive, genetically undisturbed population, a problem regarding spin-out concerns the reluctance of the local university to work with the research organisations (such as STP). Accordingly no spin-off occurs from university incubator interactions, despite the fact that the University of Cagliari, for example, specialises in genetics, biology, neuroscience and toxicology. Hence, firms may come into being by non-academic routes. SharDNA, for instance arose from research conducted at the CNR Molecular Genetics Institute and funds from Renate Soru, founder of Internet giant, Tiscali based in Cagliari. State involvement is crucial to the existence of the Consorzio Ventuno bio-incubator, as in France. Recently the Sardinian regional government built an animal house for Neuroscienze and there is a regional R&D investment fund for research projects.

Of these, Munich is belatedly, following the success of BioRegio, the most successful generator of new biotechnology firms although many are close to bankruptcy now public subsidy has declined with the ending of the programme. Strength in the knowledge base was augmented by network partnership among funding channels and enterprise support agencies. Consorzio Ventuni is weak because of thin capabilities in knowledge exploration and exploitation. Genopole has a full range of mainly public support services with a moderately good knowledge base but weak commercialisation capabilities due to a weak "deal flow."

Subsidised bioincubators in North America

Each of the three bioincubator comparators from North America is publicly subsidised but this varies as a proportion of total costs to as little as 20% and potentially declining in MBI Massachusetts. The most "European" is the Quebec Biotechnology Innovation Centre (QBIC), inaugurated in May 1996. It was created to promote the launch and development of biotech companies specialising in health, environment, agro-food and forestry industries in the greater Montreal region. The region has a large biomedical cluster with leading companies and a strong research base with four universities in Montreal, an established biopharmaceuticals industry with 145 companies and 14,500 jobs and 50 biological research institutes including the Canadian National Research Council Biotechnology Research Institute, an important federal biotechnology research centre. QBIC is located in the Laval Science and High Technology Park, Montreal. The Park was created in 1989 as the result of a strategic alliance between the INRS–Institut Armand-Frappier (a research centre of Quebec University), the City of Laval and Laval Technopole. The Laval Science and High Technology Park is the focus of "Biotech City," a $100 million initiative launched in June 2001 to develop a business and science centre supported by the Quebec government, Investissement Québec, the Institut National de la Recherche Scientifique (INRS), the Laval Technopole and the City of Laval. Some 30 businesses, biotechnology and biopharmaceutical companies, research centres and IT firms exist in Biotech City.

QBIC had, in late 2003, six firms in its bioincubator. Like Oxford BioTechNet, it is a not-for-profit organisation with two funding partners: first, the INRS–Armand–Frappier Institute of Immunology and Virology at the University of Quebec, and second, Laval Technopole, which is the Economic Development Agency of Laval City. QBIC relies on the support of the Canadian and Quebec governments for around 45% of operating finance with the remainder self-financed through mainly rent (c. 80%) and other services such as the hire of scientific equipment to outside companies. Private sector sponsors such as the Royal Bank of Canada—the main commercial bank in Canada—have also invested.

As with Genopole, the Montreal industry required attention to the pre-incubation as well as incubation stage. Pre-incubation is usually a 6–9 months period which includes help in writing a business plan, negotiations over the intellectual property rights and looking for the first round of investment. Selection of start-ups at the pre-incubation stage is based on the technology alone but the process of incubation puts QBIC in a strong position to evaluate potential incubator clients. This is followed by an incubation stage of 2–3 years during which the company builds its value and brings its technology to a point where it can be successfully commercialised and the company can become independent. QBIC has a wide range of incubation periods, from 3–6 months to 3–4 years with many companies staying the full 4 years. The Centre considers between 15 and 20 proposals for start-ups per year with around 3 accepted.

To ensure that it admits only scientifically and commercially viable companies, the Centre (like Genopole) carefully screens all applicants. A selection committee evaluates candidates according to the following criteria and general guidelines: the company must operate in the biotechnology sector or health industry; demonstrate that its activities result in technological advances; and demonstrate that it has the necessary technologies and financial resources to execute its business plan. The selection procedure takes 2 weeks and is evaluated by two scientists, two financial experts and the QBIC manager before being referred to QBIC's Executive Committee for a decision. To screen companies, QBIC may use external consultants such as other biotechnology incubators in Montreal. The incubator entrepreneur has the opportunity to choose one of the consultants. If a company is accepted the technical director will ascertain their operational needs in discussion with the clients by using a customised database capable of determining the clients' needs in terms of laboratory equipment and layout.

Start-ups at the pre-incubation stage can apply to QBIC's seed-corn fund which is a rotating interest-free unsecured loan up to a maximum of 75% of projected costs repayable in full when companies secure second round funding. The remaining 25% of finance must be raised by entrepreneurs, with regional funds or institutional venture funds the main sources. A business mentoring service is available to help reduce start-up costs and equip companies with appropriate human and financial resources. The mentoring structure relies on the bioincubator manager who acts as a first-line advisor to the heads of resident companies. Further mentoring expertise is provided by a network comprising consultants covering the seven major fields of bioincubation competence and acting as an advisory committee.

QBIC occupies 27,000 sq.ft. of space including 20 wet laboratories and 19 offices, its 2003 enrolment was 6 resident companies, with 13 graduate companies having moved on to other premises. Start-up companies have access to facilities such as laboratories, offices, specialised storage areas and basic furniture. Tenant companies also have access to a host of sophisticated scientific instruments on a time-sharing basis for no extra cost. A key attraction of QBIC to clients is the wide array of equipment available so clients have to buy less equipment themselves, leaving funds to pay for research staff. The broad flexibility in equipment usage is also a key asset of QBIC. Clients are able to use equipment in their own laboratories as well as in the common areas, alleviating security concerns for some clients. The graduation policy at QBIC entails writing a business plan 12 months prior to graduation, raising a final round of financing, and setting a time limit on occupation at QBIC. Part of the graduation policy stipulates that companies are not allowed to grow to more than 25% of the total incubator space. A large majority of companies (90%) graduating from QBIC have been successful in raising capital after incubation with the average amount raised around $120 million. Two companies graduating from QBIC are now listed on the CDNX—the Canadian small-capitalised stock exchange. Hence, the French approach to nurturing spin-out firms from pre-incubation to graduation is pronounced at QBIC as at Genopole, although the need for "prospecting" is less acute in Montreal. This is because there is a stronger knowledge, institutional and market base for biotechnology there than in Paris, although subsidy is vital for bioincubation in both.

Broad Hollow Bioscience Park (BHBP) is a not-for-profit biotechnology research park joint venture between SUNY Farmingdale and Cold Spring Harbour Laboratory (CSHL). The aim of the Park is to establish a bioincubator facility to sustain economic development in the region by attracting public and private funds to further exploration, examination and exploitation knowledge capabilities. A cluster and associated jobs are envisaged in the regional economic development strategy centred upon CSHL, an internationally renowned research and educational institution specialising in research on cancer, neurobiology, plant genetics, genomics and bioinformatics.

BHBP has a $15 million incubator facility, opened in September 2000 with the first building of 63,500 sq. ft. located on a 20-acre section of the Farmingdale campus. In September 2002, New York State support of $20 million was announced to construct a second building of 50,000 sq. ft. for start-up biotech companies. The incubator houses the research headquarters of OSI Pharmaceuticals Inc., the anchor tenant, employing 120 people and occupying 85% of the incubator, and two start-up companies, Helicon Therapeutics Inc., a spin-out from CSHL and Immuno-Rx, Inc., which together employ around 35 people.

BHBP supports the development of biotechnology start-up companies by providing shared facility resources, the resources of the Farmingdale State campus, partnering with surrounding businesses and research institutions. This supports a strategy for growing biotechnology cluster companies along Route 110 Bioscience Corridor. The latter is a regeneration partnership between the public, private, and civic sectors, and two Long Island Towns, Huntington and Babylon. It was established in 2001 to enhance the future development of the Route 110 corridor as Long Island's economic hub by attracting high-tech firms. Efforts are focused on improving the business environment and infrastructure. A group called the Long Island Bioscience Association promotes the region as a bioscience corridor.

MBI was established in 1985 is an independent, tax-exempt corporation created to support the growth and expansion of biotechnology and medical device companies throughout the State. One of MBI's main initiatives is the MBIdeas Innovation Centres, incubation facilities designed to nurture start-up biomedical companies. Since then, MBI and its former venture capital creation, Commonwealth BioVentures Inc. (CBI), have invested over $8 million of public funding and over $50 million of private money in new technology driven companies and have developed two major new Innovation Centres. These have helped to create some 20 companies. Over time firms historically receiving support from the MBI/CBI alliance have employed over 2000 people, 1500 located near Worcester. These companies now have over $50 million a year in payroll and they have raised $600 million of additional financing which has fuelled the economic growth of the region. MBI has served as a national model for leveraging public sector funds with private sector investments to promote economic development. Most of this funding came in the past from federal sources. The operating budget of MBI has grown from less than $500,000 in 1985 to over $2 million in 2003.

The healthy financial model at MBI is underlined by the fact that the majority of operating income (80%) for the facility comes from rents with the remainder coming from State of Massachusetts in the form of grants, with the latter portion of income falling gradually. It is a strong aim of the CEO at MBI for the facility to become self-funded. A further source of income is from MBI's policy to take a 1% non-dilutable equity stake in their start-ups, a policy that should soon reap benefits with two of its graduate companies currently going public.

In late 2003, MBI had 12 start-up product and service companies and the performance of its graduate companies was notable with only two out of 20 graduate companies failing to raise any capital after incubation. On average start-ups at MBI raise $250,000 from "Friends, Family and Fools" (FFF) referring to the social capital finance sources that start-ups use in the absence of seed-corn funding, which is unavailable at MBI. Upon graduating from MBI companies have raised on average $50 million of further funding with one company, ViaCell Inc. a stem cell company, soon to become a quoted company with $120 million of finance. The majority of companies at MBI originate from the two local institutions, the University of Massachusetts Medical School and Worcester Polytechnic Institute, although some come from MIT and from large organizations such as Genzyme, Pfizer and Waters, a local pharmaceuticals firm.

To conclude this profiling section, it is instructive that all bioincubators are subsidised by public infrastructure and running cost budgets, MBI being the nearest to self-sufficiency. It is clear that the harder the spin-out process is the more the incubator is expected to supply services that are available elsewhere on the market. Exploration knowledge capabilities vary and within a narrowed frame of potential spin-out activity, "prospecting" is necessary and often unrewarding or impossible. The attractions of coincubation are clearly greater for those bioincubators lacking surrounding capabilities in key elements of the KVC. For those like Oxford BioTechNet and MBI the abundance of exploitable knowledge and available examination and exploitation services means they are only modestly engaged in other than activities to do with running the incubator and collecting rents.

4. The biosciences KVC and incubator governance

Thus it can be seen that each incubator is distinctive but that they may be analysed usefully in two ways, first by characterising their governance models and, second by considering the extent incubator services cover the range of KVC activities. The latter can be divided into 10 stages and

Table I
Bioincubator assessments through academic research team monitoring

	Public governance		Mixed governance		Private governance			
Value chain	Consorzio	Genopole	QBIC	BioM	BHBP	Hadasit	MBI	BioTechNet
Genetic assets	Yes	No	No	No	No	No	No	No
Research infrastructure	Yes	Yes	Yes	No	Yes	Yes	No	No
Project selection	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Funding	No	Yes	Yes	Yes	No	Yes	No	No
Validation	No	Yes	Yes	Yes	No	Yes	No	Yes
Incubator	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Patenting and licensing	No	No	No	No	No	Yes	No	No
Patenting advice	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
General business advice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Exit advice	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

the former into three types—public, mixed and private—relating to governance, funding and degree of reliance on state subsidy. Table I attempts to classify each incubator accordingly.

Clearly, there are differences, particularly between Consorzio Ventuno and the rest. It could be said (in the monitoring assessors judgement) that it is not really an incubator, but rather a Science Park with incubator aspirations. Hadasit, closely followed by Genopole have the fullest range of services on offer through the KVC. While BioTechNet and BioM offer the least. However, both are surrounded by many such services ranging from a strong external research infrastructure (but not in their premises). And networks for providing patenting and finance. In BioTechNet's case this extends to initial project (firm) selection which is conducted by Isis at Oxford University.

BioM is largely a key node in a biotechnology services network, and through its committees funds spin-out businesses. BioM links to external infrastructure, such as the Martinsried bioincubator facilities. The KVC gap that BioM plugs is principally seed-corn and other funding for start-up bio-businesses. Generally, there is little variation according to whether incubators are funded publicly or by foundation, Hadasit being notable for the many active and direct services it provides.

In North America, as we have seen, QBIC is comparable to France's Genopole but with aspirations to be independent of public funding, with an income stream from hiring out campus-wide equipment, but relatively few tenant companies. This is something noteworthy from the transatlantic comparison, namely that the range of firms per bioincubator is comparable at between 12 and 3. Broad Hollow is dependent on rental income on the basis of up-front public sector investment aimed at "cluster-building" in biotechnology. The presence of CSHL is a guarantee of interesting spin-out firms and with New York city on the doorstep spin-out funding is not difficult if firms are outstanding candidates. MBI is relaxed about accepting incubator firms. They need only a business plan, IPR and a valid product on which to work and if there is no queue, they gain access. While QBIC has a seed-corn fund, the Americans rely on the "Golden Rolodex" of business network contacts to link firms to venture capital and other services while firms themselves typically arrive with more seed-corn funding from FFF sources than is the case in Europe or Israel.

We now come to the rankings made by incubator managers of their perceptions of what is most important about the services they offer. The main areas of difference between their self-assessment and the academic monitoring assessment refer to research infrastructure, which BioTechNet rates highest in its assets. This must refer to Oxford's surrounding research infrastructure rather than the Oxford bio-incubator premises. "Prospecting" was introduced as a category of incubator knowledge activity. Interestingly, none feel they do it well, particularly Genopole with which it is charged. On selection, Genopole is quite rigorous and considers that its premium service.

Table II
Incubator manger self-assessments of service priority

Factors enabling value creation	Consorzio 21	Genopole	Hadasit	QBIC	BHBP	MBI	OBTN	BioM
Bio-environment assets	1	6	12	12	12	12	12	12
Basic research infrastructure	3	2	1	1	1	7	1	3
Entrepreneurship	9	7	2	11	4	4	2	2
Prospecting	8	12	6	10	11	12	9	11
Selection	10	1	3	6	9	11	11	4
Technology validation	11	10	11	9		8	6	6
Access to physical infrastructure	2	5	7	2	7	3	3	8
Mentoring	6	4	8	8	6	6	4	7
Internal IP services	5	11	9	7	8	9	8	9
Access to funding	4	3	4	3	3	5	7	1
Networking	7	8	5	4	2	1	5	5
Assistance with "exit" strategy	12	9	10	5	5	2	10	10

Consorzio 21 confirms it does modestly or worse for many core incubator services. Interestingly all four incubators ranked their "exit-strategy" services very low, this being classically a risk-facing activity for which venture capitalists have the appropriate skills. Mentoring was also added to Table II and managers felt they were either moderately good or moderately poor at supplying that service with no governance emphasis explaining it. On balance and with a few exceptions, the self-assessments did not diverge massively from the monitoring assessments.

In the North American cases they offer principally a property venture in which good candidate firms can find a home. They each offer equipment and even wider access to campus equipment in two cases. None offers important in-house services, although QBIC has a seed-corn fund. Rather, each relies on network contacts, like Oxford's BioTechNet to link firms to specialist market services of consequence to commercialisation. There is remarkably little selection effort compared to the French and German cases, in particular. Rather, it is known good spin-outs exist, also that resources may be found in the regional community. Hence bioincubators, clearly in the MBI case, rely on self-selection whereby a firm arrives armed with acceptable business plan, IPR and a product or service in view, and if space is available they enter the bioincubator on the assumption that within 18 months they will have graduated to larger premises elsewhere. In North America, too, bioincubator managers are all businessmen not scientists, whereas in Europe and Israel the reverse tends to be the case.

An issue arises from this comparison, based on the small numbers of firms hosted in bioincubators everywhere and the great length of the process whereby knowledge moves from exploration to exploitation phases. This is that incubation may not be the most efficient way to bring products and services to market since the discovering firm is itself less than optimally efficient. An alternative model where knowledgeable venture capitalists spot excellent candidate products at Phase 1 stage (in the laboratory or incubator) then take them forward through Phase 2 with modest patient trialling by outsourcing to CROs, then sell on the strongest candidates to pharmaceuticals firms to do Phase 3 trialling and, if successful, marketing and distribution might be a more efficient model. However, for the moment, incubation is the hegemonic exploitation knowledge-transfer model on both sides of the Atlantic.

Thus we have seen how the KVC in Life Sciences is extremely lengthy, complex and interactive. There are many "boundary-crossing" moments within it and between it and related or contributory fields. From exploration knowledge through examination knowledge to exploitation knowledge there is, as a science-based industry, an enormous range of diverse knowledge categories and specialities to be encompassed in Life Sciences and biotechnology. That it is a clustered industry almost goes without saying as wherever it exists as a sector it congregates around the leading knowledge centres, namely major universities, hospitals and special research institutes. It is an unusual industry in that there is great faith in its capability to deliver miraculous treatments for hitherto incurable diseases like cancer, especially now the Human Genome has been decoded.

Yet few firms make profits, but they prosper on vast public research budgets and the largesse of big pharmaceuticals firms whose own internal capacities for drug development are under siege. Pharmaceuticals firms are chemistry not biology companies and it is now clear that chemical solvents of multiple diseases that began with penicillin and cortisone are now not likely to reappear in new guises. So the new "molecular biology revolution" has yet to fulfil its promise while the old paradigm led by synthetic or fine chemistry has had to become biology's supplicant (Cooke, 2002a,b)). A symbol of this new, "world turned upside down" is the DBF, dedicated biotechnology firm, that has supplanted the large pharmaceuticals firm as the knowledge leader in commercialisation of Life Sciences exploration knowledge. Here are combined many knowledges that hitherto either did not exist or were not so necessary to buy in the market. Building DBFs is a new task of the knowledge economy. Our research shows a wide range of knowledge and its application employed in and around incubators. Bioincubators may, like Hadasit, almost substitute for the market where it does not have the capacity enjoyed in "megacentres" like Boston where MBI has no such demands or problems.

5. Conclusions

What did we learn in consequence of our in-depth interrogation of eight incubators and their self-perceptions (Weick, 1995)? Three key things. First, in terms of the span of knowledge control, it does not matter whether an incubator is publicly or privately governed. Rather it depends on the regional setting. Thus Hadasit is trust-funded in a thin institutional, but thick exploration knowledge environment. Oxford BioTechNet is different, also trust-funded, but in a thick institutional and research environment. It thus has less gaps to plug. It is closer to BioM although much more sparingly funded. The two public incubators are very different. In Paris, there is knowledge but "prospecting" is hard. In Sardinia, there is a genetic gold mine but few takers. In North America, the market assists "boundary-crossing" much more than in Europe and Israel but throughput of firms is not markedly higher. Yet, it must be assumed, financing being easier and incubator candidates more numerous, that those passing through bio-incubation have a more secure future.

Second, even so, public determination to create "*constructed advantage*" bears some fruit and serendipitous investment (e.g., Tiscali) from a separate sector may create a means of exploitation of unique knowledge assets. Where such assets are absent but research infrastructure is strong, incubators are advantageous to extract commercial businesses from the laboratory bench, as in the other cases. However, there may be, as yet untried, better models of commercialisation to explore, even where markets may not be deep and support services abundant. Either this is less difficult, as with Oxford, MBI and Broad Hollow, where selection is done elsewhere in the KVC, or it is more difficult , as in Genopole or Hadasit where incubators feel they must also perform a rigorous *selection* function that normal market-facing business start-up business practice looks after in North America. Here, co-incubation is an attractive option.

Finally, "boundary-crossing" institutions with networks based on social capital such as bioincubators are extremely important "hybrid" knowledge management intermediaries without which clusters would probably not exist in less accomplished regional settings and have had to be invented even in richer business service environments for biotechnology innovation. Even so, it is noticeable that pure profit incubators are by no means a predominant form taken by incubation in general, notably not in the U.S.A. although independence from subsidy is in sight in MBI and an aspiration in QBIC, yet none of our sample falls into that category. This kind of knowledge transfer has yet to find its market although it remains essential to the proper functioning of markets.

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References

Andersson, M. and O. Ejermo, 2002, 'Knowledge Production in Swedish Functional Regions 1993–1999,' in paper to International Workshop on *Knowledge Spillovers and Knowledge Management in Industrial Clusters and Networks*, Ljungby, Sweden, 19–21 September, in C. Karlsson *et al.* (eds.), 2004, *Knowledge Spillovers & Knowledge Management*, Cheltenham: Edward Elgar.

Audretsch, D. and M. Feldman, 1996, 'Knowledge Spillovers and the Geography of Innovation and Production,' *American Economic Review* **86**, 630–640.

Audretsch, D., 2001, R&D Spillovers and the Geography of Innovation and Production, paper to International Workshop '*Innovation Clusters and Interregional Competition*' Kiel Institute of World Economics, 12–13 November, in J. Bröcker, D. Dohse, and R. Soltwedel (eds.), 2003, *Innovation Clusters & Interregional Competition*, Berlin: Springer.

Centre for Strategy & Evaluation Services, 2003, *Provision of Bioscience Incubators and Grow-on Facilities in the UK*, London: CSES.

Cooke, P., 2001, 'Regional Innovation Systems, Clusters, and the Knowledge Economy,' *Industrial & Corporate Change* **10**, 945–973.

Cooke, P., 2002a, *Knowledge Economies*, London: Routledge.

Cooke, P., 2002b, Regional Science Policy and the Growth of Knowledge Megacentres in Bioscience Clusters. Presented at the *Regional Science Association 42nd European Congress*, Dortmund, Germany, August 27–31, 2002, in Special Issue – Embeddedness & Regional Development: Guest Editors, Frans Boekema and Roel Rutten, *European Planning Studies*, **12**(4), 2004.

Cooke, P., 2005, Rational Drug Design, the Knowledge Value Chain and Bioscience Megacentres, *Cambridge Journal of Economics*, **28**, (forthcoming).

Cooke, P., S. Roper, and P. Wylie, 2003, "The 'Golden Thread of Innovation' and Northern Ireland's Evolving Regional Innovation System," *Regional Studies*, **37**.

Feldman, D. and M. Audretsch, 1999, 'Innovation in Cities: Science-based Diversity, Specialisation and Localised Competition,' *European Economic Review* **43**, 409–429.

Fritsch, M., 2001, How and Why Does Efficiency of Regional Innovation Systems matter? Paper to International Workshop on '*Innovation Clusters & Interregional Competition,*' Kiel Institute of World Economics, Kiel, Germany, 12–13 November, in J. Bröcker, D. Dohse and R. Soltwedel (eds.), 2003, *Innovation Clusters & Interregional Competition*, Berlin: Springer.

Giesecke, S., 2000, 'The Contrasting Roles of Government in the Development of Biotechnology Industry in the US and Germany,' *Research Policy* **29**, 205–223.

Granovetter, M. et al., 2000, Social Networks in Silicon Valley, in C. Lee et al. (eds.), *The Silicon Valley Edge*, Stanford: Stanford University Press.

Jaffe, A., M. Trajtenberg and R. Henderson, 1993, 'Geographic Localization of Knowledge Spillovers as Evidenced by Patent Citations,' *Quarterly Journal of Economics* **108**, 577–598.

Kaiser, R., 2003, 'Multi-level Science Policy and Regional Innovation: The Case of the Munich Cluster for Pharmaceutical Biotechnology,' *European Planning Studies* **11**, 841–858.

National Business Incubation Association, 2002, *A National Benchmarking Analysis of Technology Business Incubator Performance & Practices*, Washington, D.C.: NBIA.

Norton, R., 2000, *Creating the New Economy: The Entrepreneur and the US Resurgence*, Cheltenham: Edward Elgar.

Owen-Smith, J., M. Riccaboni, F. Pammolli, and W. Powell, 2001, A Comparison of US and European University–Industry Relations in Life Sciences, (mimeo).

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

Powell, W., K. Koput, J. Bowie and L. Smith-Doerr, 2002, 'The Spatial Clustering of Science and Capital: Accounting for Biotech firm-venture Capital Relationships,' *Regional Studies* **36**, 291–305.

Senker, J. and P. Zwanenberg, 2001, *European Biotechnology Innovation Systems*, SPRU: University of SussexFinal Report to EU-TSER Programme.

Weick, K., 1995, *Sensemaking in Organizations*, London: Sage.

Wolter, K., 2002, *Can the US Experience Be Repeated? The Evolution of Biotechnology in Three European Regions, (mimeo)*, Germany: Duisburg University.

Zook, M., 2000, Grounded Capital: Venture Capital's Role in the Clustering of Internet Firms in the US, paper to American Collegiate Schools of Planning Conference, Atlanta, November.

Zucker, L., M. Darby and J. Armstrong, 1998, 'Geographically Localised Knowledge: Spillovers or Markets?,' *Economic Inquiry* **36**, 65–86.