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A CRITICAL ASSESSMENT OF REGIONAL INNOVATION POLICY IN PHARMACEUTICAL BIOTECHNOLOGY

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Abstract

This paper adopts a system-evolutionary perspective to describe the dynamics of the life science sector and reflect on regional innovation policy. It begins with a brief outline of the evolution of life sciences and of the biotechnology industry. A crucial feature of such evolution is the strong tendency towards geographical concentration of research and related economic activities. The formation and growth of bio-clusters have sometimes appeared to be spontaneous, in that governments have not been in the driving seat. However, many regional and national governments have now developed policy frameworks to support the development of bio-clusters.

Regional and evolutionary economics contribute to explain cluster emergence and growth, but little is known about pre-emergence conditions. As a result, although policy measures aimed at supporting emergence and growth are grounded on direct evidence and observable transformations, starting clusters from scratch often involves replicating the pathways followed by successful regions.

We examine the rational behind regional innovation policy in life sciences and the reasons why some policies have either succeeded or failed. Special emphasis is placed on Scotland, where the local development agency has pioneered the implementation of cluster thinking to support the development of the life sciences sector.

1. INTRODUCTION

This paper adopts a system-evolutionary perspective to describe the evolution and dynamics of the life science sector and reflect on regional and innovation policy in the same area. It begins with a brief outline of the evolution of life sciences and of the biotechnology industry. A crucial feature of such evolution is the strong tendency towards geographical concentration of research and related economic activities. Thus, Section 3 discusses the possible reasons accounting for this tendency as suggested by theoretical and empirical research. A crucial insight provided by this literature, however, is that while much has been learned about the ingredients of a successful cluster, little is known concerning the processes that lead to the formation of a cluster (Section 4). Subsequently, the discussion turns to the policy implications of these debates: how has policy-making been influenced by alternative conceptual models (Section 5) and how have they been actually implemented (Section 6)? Finally, against this background, in

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Section 7 the Scottish experience is discussed. The concluding section identifies some important unresolved issues and directions for future research: in particular, as it concerns i) our understanding of the dynamic processes that underlie cluster emergence and evolution and ii) how integration of the basic constitutive ingredients of clusters can be successfully achieved.

2. EVOLUTION AND DYNAMICS OF LIFE SCIENCES

At the beginning of the 70s, two major discoveries relating to molecular and genetic biology gave rise to a new wave of scientific research. In 1973 at the University of Cambridge UK, Millstein and Kohler realised the discovery of monoclonal antibodies. This discovery allowed elaborating efficient procedures to combine and multiply cells. From the beginning, it appeared evident that these discoveries had the potential to help develop new therapies. In 1975, Cohen and Boyer at Stanford University and at the University of California at San Francisco managed to develop the recombinant DNA technique, by which a portion of a different gene can be inserted into another one. In this way, the genetic map of some micro-organisms has been restructured in order to generate, for example, new proteins.

The biotechnology industry has since coalesced into various industrial sectors: primarily in pharmaceuticals, where interesting applications have been made, not only in therapeutics but also in diagnostics – such as in vitro techniques. Biotechnology's influence on the chemical industry has also been very important, allowing the replacement of polluting chemicals with bio-convertible substances. Other innovations involved instrument or processes technologies, such as laboratory basic equipment, high-tech instrumentation used to perform tests and complex procedures, information databases and hardware/software solutions for the elaboration of data, and molecular modelling and design.

More scientific breakthrough have characterised the history of this industry so far. Purification and separation technologies, cell and tissue culture, protein engineering have been followed by subsequent generations of innovations, including the polymerase chain reaction, transgenic and anti-sense technologies. In the 90s, the advent of the so called platform technologies (combinatorial chemistry, high-throughput screening and computational chemistry) led to what has been termed "industrialised R&D" (Pisano, 2006), offering the potential to understand and identify much more precisely the causes of diseases, to create new compounds, to screen them much more efficiently and to rationally design drugs with specific effects. More recently, genomics

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have revolutionised the way that biotechnology is perceived. Genomics is the study of genes and their function and adds to our comprehension of the molecular mechanisms of disease, including the interrelation between genetic and environmental factors. Considerable improvement in the capacity of gathering and making use of genetic information can be accomplished using biochips and IT tools. They consist of a variety of technologies created to miniaturise biological procedures into a low-cost and high-quality format.

The discipline of proteomics has been initiated to complement physical genomic research, and consists of the study of proteins and their characteristics. Synthetic biology is a new and rapidly emerging discipline that aims at the design and construction of biological systems. It has an interdisciplinary nature (science and engineering) and can potentially be applied in various areas, such as healthcare and energy production. Pharmacogenomics is a new branch of pharmacology which considers the influence of genetic variation on drug response in patients by correlating gene expression with a drug's efficacy or toxicity. By doing so, it aims to optimise drug therapy, with respect to the patients' genotype, to guarantee efficacy with minor adverse effects.

The application of molecular biology has led to an observable change in conventional drug development routines which encompass product and process innovation. As a consequence of the fundamental importance of basic research for the discovery of new products and processes public research organisations (PROs) such as universities, medical schools and hospitals are often the key drivers in the discovery of new solutions for patient healthcare. Worldwide, thousands of dedicated biotechnology firms (DBFs) – typically backed by venture capital and exploiting a favourable intellectual property regime - have been created in proximity to PROS and employ genetic information to produce new therapies and diagnostic tools. However, these new methods of knowledge production entail high levels of complexity and transdisciplinarity. Moreover, DBFs typically lack the resources, capabilities and complementary assets needed to drive promising molecules through clinical trials, regulatory procedures and marketing. Thus, large multinational pharma-corporations (MPCs), whose R&D productivity has been significantly decreasing over the past two decades or so, not only monitor advancements in life science as a vital source to feed drug development pipelines, but they also provide resources and capabilities for integrating the required fragments of knowledge. Biotechnology is thus emerging as an industry in which complementarities are mostly important at an organisational level, in that the relevant capabilities - scientific, medical, commercial, legal, financial, regulation-related, and industrial - are not normally developed by a single organisation (Porter et al 2005). The

industry structure is characterised by the development of dense network of market and non –market relationships among MPCs, DBFs, PROs and venture capital.

3. THE SECTORAL GEOGRAPHY of INNOVATION

The role of bioscience in the transformation of healthcare is also having a major impact on the sectoral geography of innovation. Most MPCs build networks and knowledge links worldwide in order to expand the scale and geographical scope of their activities. However, the development of the biotechnology industry tends to happen at the interfaces of co-located PROs and industrial firms, which is leading to "a shift in the drivers of the triple helix, from the pharmaceutical industry to capable universities, supported by judicious government plus private foundations" (Cooke 2003, p. 8). Indeed, ever since its inception, the development of the biotechnology industry has been characterised by high and persistent concentration at the geographical level. The industry is strongly clustered in few regions in the USA (the Bay Area, Boston and San Diego) and other regions have struggled to catch-up. Various regional development bodies have tried to exploit the local bio-scientific base to promote the emergence of bio-clusters, with mixed results. While new important clusters have successfully developed, like Cambridge (UK), Stockholm, Grenoble, Heidelberg, Singapore and Israel, still the history of policies for cluster formation remains characterised by failures and even the more successful clusters have not been able to displace the original locations.

These observations raise immediately three main questions. Why do innovative activities in biotechnology (and in many other technologies and industries) tend to develop within specific geographical areas? What is the structure of these clusters? And why has it proven so difficult to catch-up and to create new clusters?

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

bounded**.** This is particularly the case when knowledge is tacit, i.e. it cannot be easily transferred absent of face-to-face communication and direct exposure to practice and experience.

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

According to Maskell and Lorenz (2003), the "cluster is a form of market organisation that is particularly efficient in allowing firms to generate, use, and coordinate knowledge activities where genuine (Knightian) uncertainty prevails" (p.2). Proximity can help the development of localised markets insofar as bio-knowledge generated by local PROs is directly exploited or licensed to private companies where scientists/entrepreneurs own shares, occupy managerial position and sit in advisory boards. New opportunities for specialisation and service provision arise as a result of biotechnology-related activities proliferating within the locality. Flexible labour markets (mainly for scientists) contribute to knowledge transfer, and this is more likely to happen within the region due to overlapping social ties and networks (Rosiello 2007).

Even when knowledge is neither complex nor tacit, "co-location provides firms with an arsenal of instruments to obtain and understand even the most subtle, elusive and complex information of possible relevance" (Maskell 2001, p. 929). As argued previously, in biotechnology, since industrial research focuses on complex, multi-technology, and multi-skill products and processes, it is extremely important that teams and individuals learn how to complement the expertise and new knowledge that they develop (Coombs and Metcalfe 2000). In this view, interaction among DBFs, PROs (Rosiello 2007) and intermediaries such as lawyers and venture capitalists (VCs) (Powell et al 2002) is prevalently local. Indeed, DBFs (and scientific founders) often face a crucial trade-off. On the one hand, diffusion offers two basic advantages. First, idiosyncratic knowledge can be traded or shared to gain access to complementary assets. Second, diffusion may help other practitioners in making new discoveries or realising improved applications, which has positive implications for the scientific and entrepreneurial network as a whole. These advantages are represented by the

possibility of working in a dynamic, open and scientifically advanced environment, which is likely to provide every member with positive feed-back (Zucker et al., 1995).

Localised networks of scientists and *knowledge-creation subsystems* (Cooke 2004) are often characterised by openness and the exploitation of synergies (Owen-Smith and Powell 2004). The use of "boundary-spanning" social network enhances absorptive capacity and flexibility in ways that might not be feasible within a completely hierarchical system or a pure market system (Audretsch and Stephan, 1996; Rosiello 2007). Owning to the observable advantages of operating within the context of knowledge intensive bio-clusters and such "attractive power" (Cooke 2003) of bioscience, MPCs have started and increasing number of collaborations with DBFs, and financed research activities and established research facilities within bioscience-intensive intensive areas (Zeller 2004; Porter et al 2005; Rosiello 2007). As a consequence, agglomeration of innovative activities tends to occur and biotechnology develops within specific geographical clusters.

On the other hand, because of the prevalently *synthetic* nature of knowledge used to generate innovation in biotechnology (Asheim et al 2006) and the role of intellectual property rights (IPRs), biotechnology clusters are characterised by features which differentiate them from classical models. First, biotechnology can hardly be interpreted as a case where knowledge within a cluster simply "spills over". Rather, access to such knowledge seems to require deep involvement in the research process and bench-level scientific collaboration as well as the conscious investment of resources not simply to search for new knowledge, but to build the competencies to absorb the knowledge developed by others. In many cases, knowledge flows occur via (localised) mobility of researchers and of the workforce. These 'flows' are mediated by market transactions and other institutionalised or quasi-institutionalised mechanisms involving not simply mutual trust and face-to-face contacts, but also highly complex economic and social structures. Indeed, knowledge tends to remain sticky within biotech clusters also for reasons related to attempts at privately appropriating knowledge and at restricting its circulation. Thus, in these clusters, knowledge is not simply "in the air" (Breschi and Lissoni, 2001). Similarly, differently from other accounts of clusters, "soft" factors like trust seem to play an important but not necessarily predominant role, given that knowledge flows in the biotechnology industry appear to be channelled significantly through market transactions and inter-organisational rules.

Second, mainly as a consequence of the crucial role played by science, biotechnology clusters are not simply local, but they are strongly open to interaction with other firms and institutions located everywhere in the world. In other words, biotech clusters are not

strongly geographically embedded – functional proximity is probably at least equally important and they are eminently global in nature (Cooke, 2007).

Third, for the very same reasons, biotech clusters have a distinct hierarchical nature. Scientific excellence is strongly concentrated in few regions and this generates and attracts new opportunities, funding (both from venture capital and large corporations), and new firms. Thus, dominant bioregions strengthen their leadership. As scientific capabilities diffuse and grow in other locations, new smaller and more specialised clusters appear but they cannot displace the old ones. Rather, they link – scientifically and commercially –with the existing "megacentres" (Cooke, 2007). The same hierarchical structure observed at the geographical level is visible also at the industrial level: the network of alliances among firms and other research centres exhibits the same properties (Orsenigo, Pammolli and Riccaboni, 2001). Indeed, this is likely to be the outcome of the very nature of the processes of scientific advance and of the processes of construction and integration of innovative and industrial capabilities. They both involve first mover advantages and self-reinforcing tendencies which give rise to hierarchical structures, with some firms and clusters performing as *integrators* of spatially dispersed and specific knowledge, research tools, and capabilities. In this respect, geographical agglomeration results not only as an outcome of traditional externalities but also (and perhaps mainly) as a result of increasing returns, whereby clustering results from processes of spin-off – as distinct from spillovers – from knowledge-rich organisations (Klepper, 2002; Orsenigo 2006).

4. THE EMERGENCE OF BIO-CUSTERS

Most of the literature on bio-cluster suggest the existence of a series of commonalities as regard the importance of some key drivers for bio-cluster emergence: the strength and width of the scientific base, entrepreneurship and serial entrepreneurs, venture capital and a favourable IPR regime, linkages with large firms and other industries, institutions, policies and other infrastructures that support and promote entrepreneurship, effective networks, are all important ingredients to transform science into a viable commercial asset. However, these observations refer to existing successful clusters, but they tell little about how these ingredients have come into existence, i.e. how do cluster emerge and develop (Braunerhjelm and Feldman, 2006).

A significant fraction of the theoretical literature on clusters explains spatial agglomeration patterns as the solution of static trade-offs between agglomeration and dispersion forces, particularly combinations of static externalities, transport costs and economies of scale (see for instance, Krugman (1991), or on various forms of

increasing returns to scale (or indivisibilities) at the level of individual agents (Fujita and Thisse (1996)).

Other contributions emphasise much more forcefully the relevance of the dynamic processes leading to agglomeration. In many instances, the process of emergence is considered to be self-reinforcing as a consequence of the progressive materialisation of positive external economies. This stream of analysis emphasises that a meso-level of analysis which focuses on the structural and institutional features of the local system is probably best suited to describe its evolution and dynamics and provide hints to policy-makers to develop effective supportive frameworks.

Other interpretations still, for example Klepper (2002), do not rely on the standard notions of externalities, but introduces the idea that other forms of dynamic increasing returns might lead to clusterisation, in particular as it concerns the cumulativeness of innovative processes and related spin-off processes from incumbent firms (or other organisations like universities). Several accounts of the rise of Detroit as main location of the US automobile industry (Klepper 2002) or the development of the Silicon Valley (Kenney and Von Burg, 2001 among others) emphasise, in a strikingly similar way, the role played one or few companies - like Fairchild and the Fairchildren – in spurring processes of agglomeration. Irrespective of their intrinsic merits (which can only be assessed through careful empirical analysis), these approaches somehow raise the question about the direction of causation between innovation and clusters. Whereas most of the literature focuses on the conditions that make a particular area conducive to innovation, - i.e. on the idea that clusters promote innovation – the opposite nexus of causation might turn out to be at least equally important: it is an original innovation that creates clusters. Equally, these arguments suggest that perhaps more emphasis should be attributed to specific characteristics of the firms and other key agents active within a cluster.

As Giuliani, (2004) argues, both cluster and network studies tend to consider the meso-level (i.e. a cluster or a network of firms) as the unit of analysis. And hence most of research has been undertaken to analyze the effects of meso-level characteristics (e.g. degree of inter-firm co-operation, presence of localized knowledge spillovers, structural features of the networks, etc.) on the innovativeness and performance of the cluster or network. Less research has instead been directed to the understanding of how the meso-level characteristics come into being or evolve as a results of micro-level, non-structural characteristics.

In any case, as argued by Bresnahan and Gambardella (2004) in the context of the ICT sector, a meso-level of analysis remains problematic when attempting to unveil the

origin of clusters before they have emerged. As a consequence of the different patterns of growth followed by bio-clusters and variety in the factors and events which led to their emergence, designing bio-clusters from scratch and/or predicting how they will grow very remains a very difficult task. According to Bresnahan and Gambardella (2004), once the cluster has emerged, it is likely to develop intrinsic incremental dynamics.

Empirical research has indeed shown that bio-clusters grow through cumulative processes which lead to the concentration of a critical mass of private companies, skilled individuals, experienced intermediaries and the development of an adequate infrastructure to support R&D activities in a specific location. But the structural features of emerged bio-clusters and intrinsic dynamics of the process that led to their emergence can be quite different. For instance, Owen-Smith and Powell (2004) argue that the Boston bio-cluster is characterised by geographically bounded and open networks which guaranteed a proliferation of discoveries and ideas to be turned into business opportunities. According to Porter et al (2005), this is the result of the "strong presence of public research organisations" and the initial absence of VCs, a situation which led many Boston-based DBFs to focus more on "orphan drugs and medicines for well-defined patient groups than have Bay Area biotechs, which have aimed their R&D efforts at larger markets with first-to-the-world medicines" (p. 263).

In Europe we find the same variety of structures and growth paths. For instance, Rosiello (2005) comparison of the Scottish, Swedish and Danish biotech industry highlights that Denmark and Sweden are characterised by a higher proportion of industrial spin-offs and R&D investment by MPCs, Denmark and Scotland by a relatively higher inflow of VC, Sweden and Scotland by the central role played by public agencies. Cambridge UK has managed to develop, attract and exploit science, skills and VC like no other European bio-clusters. However, unlike US clusters Cambridge does not produce many large and global companies (Pacec 2003) or vertically integrated pharmaceutical companies. The majority of local successful firms are sold to foreign MPCs or biotechnology companies; recent examples include companies such as *Cambridge Antibody Technology (CAT)* and *Arakis*.

There is still a long way to go before a satisfactory degree of understanding and consensus can be achieved among practitioners coming from different disciplines, backgrounds, and countries as to the emergence and growth of innovative clusters. But these issues remain crucial not only in terms of academic understanding but also for policy reasons.

5. ALTERNATIVE APPROACHES TO REGIONAL INNOVATION POLICY IN LIFE SCIENCES

The emphasis on the role of clusters and more generally on the regional dimension of innovation has not surprisingly important implications for policy-making. In particular, whether biotechnology clusters can be built through policies and public support remains an open question. Attempts at stimulating the development of biotechnology as an industry have been undertaken almost everywhere in the world, often with an explicit emphasis on clusters. Results are mixed, of course, but probably closer to failure than to success. Yet, success stories exist and in some of these cases public intervention has been crucial in determining a positive outcome: Singapore is an obvious example, but – in rather different ways – also in Israel, Germany, Sweden, France and Washington D.C. the role of the public sector and public investment has been crucial for the stimulation of research activities and their commercialisation. Thus, the original question could be reframed as "what kind of policies and what kind of preconditions is necessary to support the development of biotechnology, especially at the local level?

To begin with, and on the basis of our previous discussion about the characteristics of bio-clusters and of the processes leading to their emergence, it is possible to contrast two main types of approaches. The first one considers policy action – in a rather orthodox way – as a response to the market failures associated to innovative activities, i.e. mainly the public good aspect inherent in R&D. Here, the scope of public action is identified in the reduction of the risk associated with R&D investment and in granting protection over intellectual property.

This approach is often related to the so called "linear model" of technological change, which essentially maintains that investments in basic research "inevitably" lead to new products and processes. The Linear-Model of knowledge and technology transfer had constituted an instrument of cognitive, organisational and normative interpretation. First, science was considered to have a more speculative and open-ended character and to be conducted by PROs, whereas applied research was problem-oriented and conducted by private firms. Science can therefore be easily codified and treated as information. It is published in academic journals and freely accessible. Private firms will combine it with personal/organisational know-how to innovate. Thus, policies should be mainly concerned with funding basic research and providing appropriate incentives – e.g. IPRs - for the further economic exploitation of the opportunities for innovation created by scientific research.

However, new socio-economic explanations of the process of technological change and innovation are increasingly understood as a "non-linear" and nested system of feedback loops between actors engaged in the activities of research, development and commercialisation. "Non-linear" and "systemic" perspectives assert that innovation and technological change happen in a

more complex fashion and the outcome of much R&D investments is dependent on the organisation of research and production systems, particularly the way in which agents cooperate and learn.

Pavitt (1998), for example, argues that the linear hypothesis does not reflect reality primarily because applied change and learning frequently precede scientific advancements: for instance, a comparison of the experiences of Germany and Britain in the twentieth century shows that scientific catching-up followed the industrial and technological ones. Similar observations are frequently advanced also for other more recent cases like Japan, Korea, India, China, etc. In addition, authors such as Von Hippel (1988) demonstrate that new opportunities to innovate are often recognized and exploited by users and innovation seems to originate from a "demand-pull" exercised by users rather than a "science push" operated by inventors.

According to these views, technological change cannot be described as originating from the mere application of science. On the contrary, it largely hinges on an independent practical body of knowledge, whose "legitimate outputs are artefacts and the means by which they are designed, constructed and operated and intrinsic worth is to be judged not only by the truthfulness of the knowledge but its practical utility" (Metcalfe 1997, pp 727). Moreover, this body of knowledge often intersects with questions of economic viability and social acceptability. As highlighted by recent debates about the use of genetically modified food and human embryonic stem cells, even ethical concerns can play an important role in selecting winning technological trajectories. Markets, societies, public policies and technologies co-evolve in complex and sometimes unpredictable manners. Policy-making has then become explicitly concerned with issues concerning knowledge transfer, economic foresight and social acceptability.

Thus, this second, systemic, approach stresses that the performances of individual agents do not uniquely depend on the way markets operate. Rather, innovation is the outcome of the ways in which agents cooperate and learn. Thus, innovation policy should be increasingly aimed to improve connectivity between actors holding complementary fragments of knowledge, resources and capabilities.

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

"market failures policies" tend more frequently to act on the "ingredients" and the "incentives", while "systemic policies" are likely to target the "processes" and "capabilities".

Finally, as discussed above, perhaps fundamental distinctions have to be considered between policies aiming at the creation of new clusters as opposed to policies for already existing clusters. As stressed by Bresnahan and Gambardella (2004), the requirements are likely to be very different. The autonomous dynamics of a successful cluster might reduce the need and/or scope of public policy. Martin and Sunley (2005) even argue that targeted policies normally result in old-fashioned inclinations to pick winners and that the notion of cluster is "either unnecessary or even constraining" when policy-makers decide to go ahead with targeted policies.

Against this background, policies for the promotion of regional growth have undergone profound changes of perspective. First, it is increasingly recognised that the competitiveness of regions seems increasingly related to the capability to generate new ideas and use them to innovate. Second, in turn, these capabilities are dependent upon regional resource endowments. Third, in a globalised and "non-linear" world, resource endowments have to be continuously renewed, raising demands for *regional dynamic capabilities*, such as interactive learning, networking, fore sighting, and mobilising complementary competences to respond to new challenges and opportunities. Fourth, the emergence, deployment and transformation over time of dynamic capabilities are frequently the result of cumulative and context-dependent processes. Accordingly, the concept of Regional Innovation Systems (RIS) has been developed, conceived as a network of individuals, organisations and institutions with regular and strong internal interaction that promotes innovative thinking and it is characterised by embededness.

This vision calls for regional innovation policies (RIPs) and strategies able to support the creation and renewal of dynamic capabilities. Second generation RIP (not inspired by "linear" thinking) have been generally directed not only to remedy private disincentives in investing in basic research and the problems associated with the exchange of codified knowledge, but also to improve systemic interaction.

However, by its-own nature, the application of system-evolutionary thinking – with its emphasis on the various dynamic, non linear processes leading to agglomeration and innovation, - to different contexts presents distinct challenges and lead to diverse interpretations; our concern with context-dependency, cumulativeness and "industry cycles" implies that the analysis of emergence processes is likely to reveal significant variations among regions. So, a major challenge facing research in this field is the identification of possible profiles or typologies of emergence, including sets of conditions that precede emergence, sets of policies and possible outcomes - in terms of structure and entities that emerge or that develop without having

emerged. For example, Cooke (2005) proposes a general theory for the evolution of bio-clusters: phase1 - a number of ideas are initially patented and start-ups are created to exploit them; phase 2 - some of these firms develop into sustainable businesses while maintaining strong relationships with local PROs; Phase 3 – money and skilled people flow in, the lines of research are multiplied and cross-fertilisation happens within as well as outwith the cluster; and phase 4 – big budgets for R&D are now available, MPCs invest in the region, a consistent number of DBFs develop large and sustainable businesses, VC is available in big numbers, serial entrepreneurs and experienced executives get involved in an increasing number of new ventures

An obvious conclusion that stemmed from this model is that different policy strategies are needed to promote and/or support bio-cluster emergence in different phases. For instance, while one of the central features of RIP in this area is represented by the relation between firms and the set of institutions that shape discovery (especially PROs), technology development and commercialisation, such relationship and the typology of firms involved in the process varies over time. In an embryonic phase the majority of the firms composing the local system are either start-ups or small spin-outs. These firms normally focus on fairly specific projects and do not have enough resources and capabilities to operate at large scale and target global markets. In this phase a priority for RIP is to increase their number and promote experimentation and variety of strategic approaches. In later stages policy makers can focus on achieving critical mass by facilitating access to vital resources for growing ventures and enhancing connectivity and knowledge flows. Once critical mass has been achieved, the main goal may become avoiding remaining locked into obsolete trajectories and exploiting forms of complementarities and technological convergence.

6. NEW DEVELOPMENTS IN REGIONAL INNOVATION POLICY

Many American states, European regions and Asian countries have developed policy frameworks to support bio-science/technology transfer and the development of bio-clusters. The type of approaches and strategy adopted across regions/countries is extremely variegated.

To begin with, the emergence of Silicon Valley outlined an “American Model” to organise knowledge and technology transfer within the context of RIS, characterised by formal and informal interaction between industry and academia, start-ups, VC, a dynamic market for IPRs, R&D investment by large private firms and public procurement. Moreover, in the US, the Bay-Dole Act in 1980 gave Universities the right to exploit commercially publicly financed academic research via the outsourcing of research results to third parties and/or the setting up of privately owned start-ups. The Bay-Dole Act and further sentences of the *American Supreme Court* strengthened IPRs over research and assigned them to PROs in an attempt to i) stabilise and reduce transaction costs in relation to knowledge transfer from PROs to industry, (ii) prevent the

private sector (especially foreign firms) from free-riding on research financed by American tax payers, and (iii) create an institutional framework for the emergence of a market for IPRs that was intended to bring financial benefits to American PROs. This legislation led to an intensification of the investment made by PROs in technology transfer offices (TTOs) and patent applications, and revenues earned from IP licence agreements, royalties and disposal of private equity share. As noted by Mowery and Nelson (2004), bioscience - as a discipline - has benefited most from this legislative framework, although this may be the result of significant public investment in basic research over the past 30 years.

In Europe, as the innovation gaps vis-à-vis the US became evident, the debate hinged around the "British" and/or "European (or Swedish) Paradox doctrine". In synthesis, this doctrine maintained that Europe (or particular European countries) produced an excellent research output which was not turned into commercially viable innovation. The blame for this failure was essentially attributed to weaknesses in the mechanisms that should facilitate technology transfer, because of (i) market failure relating to the transfer of intangible assets and (ii) the absence of effective university-industry links.

This observation led to the formation of various European versions of the "Linear-Plus Model" (Tait and Williams 1999). Changes in IP legislation took place in many countries and mimicked the US Bayh-Dole Act; important investments were also made in support of knowledge transfer from PROs to industry.

In parallel to these attempts to import the "American model", in many European countries – and especially at the regional and local level – other policies were devised and implemented broadly inspired by the "systemic" approach. Thus, we assist to the proliferation of national and regional initiatives to sustain not only formal technology transfer, but also to stimulate a stronger and more proactive interaction between the various components of national and regional innovation systems. Especially in Northern Europe, various policies have been implemented to reform the allocation of public research funds and achieve a better coordination of innovative efforts: turning science policies into innovation policies and explicitly attributing to universities the "Third Mission" to contribute to the commercial development of research. For example, in Sweden since 2000 the national system for research-based innovation is headed by the Swedish Agency for Innovation Systems (Vinnova), with a budget of €110M per year to co-finance research programmes and regional economic development in cooperation with industry. Stimulating innovation and growth is to be achieved by investing in problem-oriented research, focusing on the supply of good personal skills, easing and stimulating knowledge sharing and transfer, and promoting interaction and cooperation among industry, governmental bodies and PROs.

Vinnova's vision hinges on the consideration that the technological, organisational and market-related characteristics of each sector ought to be understood and exploited to achieve success. Despite this sectoral focus, most initiatives apply horizontally, to all industrial sectors included into 18 growth areas in which Swedish regions are believed to have a competitive advantage because of their skill and resource endowments. In particular, biotechnology is seen as a field in which Sweden can play a leading role thanks to its strong research base, health system and industrial tradition in pharmaceuticals, diagnostics, biomedical engineering and bio-food. Interestingly, Swedish professors continue to enjoy full ownership over IP generated by academic research. There have been recent discussions about abolishing this "privilege" and Vinnova has disagreed (Nordfors et al, 2003) because such a move may lessen scientists' incentive to become involved in entrepreneurial activities and give all responsibilities to universities' TTOs, which would not make knowledge transfer necessarily easier (Rosiello 2005).

Other European regions have engaged in the definition of regional policies that go beyond the need to grant the necessary pre-conditions – such as investments in basic sciences, education and physical infrastructure - for the emergence of RISs in biotechnology (bio-clusters), by providing direct and indirect financial support to new ventures and to the formation of angels groups and VC firms, setting up local and international networks, creating centres of scientific and industrial excellence, promoting public-private partnerships, etc. The Bio-Region initiative in Germany can be considered as a prominent example of this approach, aiming at facilitating the development of bio-clusters by sustaining the growth of the structural preconditions, but also the agents and the interactions among them needed for cluster emergence. In countries (such as Finland), RIP is now moving towards the idea of exploiting forms of convergence, complementarity, and related variety (Boschma et al 2004) among knowledge bases and sectoral innovation opportunities. In this respect, Harmaakorpi (2004) discuss the "regional development platform method" for innovation policy (related variety) and Harmaakorpi and Tura (2006) develop the innovative concept of "network-facilitating innovation policy".

The outcome of these investments is uneven and controversial. In other cases, it is simply too early to derive any robust conclusion. But, for example, Senker (et al 2003)'s European survey of Universities' TTOs shows that they are generally failing to promote an effective commercialisation of IP in biotechnology. More generally, despite some successful cases where bio-clusters have emerged, the innovation gap between Europe and the US has not disappeared: if anything it has remained constant or even increasing (Dosi et al., 2005).

In part, these failures might be attributed to a disproportionate attention given to technology transfer (in its various forms and interpretations). Indeed, overwhelming evidence, including scientometric and industrial data, suggests that Europe is significantly lagging behind the USA in

its ability to produce high level scientific research, as well as in the industrial commitment to R&D (Dosi et al, 2005). A further indication of this phenomenon is that almost all of the European MPCs have been able in recent years to regain levels of competitiveness comparable to their American competitors, also by strengthening their research efforts and largely relocating them in the USA. Especially in the case of biotechnology, availability of world class basic research on a large scale is recognised to be the essential pre-requisite for any attempt to develop further innovative activities: if there is little to transfer, technology transfer becomes irrelevant (Orsenigo, 2001).

More generally, while fully recognising the crucial importance of interactions among agents in the innovative process, perhaps too little attention has been devoted to the characteristics of the nodes which populate a network (or a system), which in turn are crucial to determine the structure of the relationships and of the network itself. And in some cases, the emphasis on systemic interactions runs the risks of leading to interpretations where "everything depends on everything else", with clear methodological and epistemological limitations.

It might be argued that in practice innovation policies, especially at the regional level, have in many cases tried to blend together aspects of the American model (e.g. IPRs and venture capital); "linear model – oriented" conceptions of the innovative process; different interpretations of systemic- evolutionary approaches. It should come as no surprise that this cocktail can yield a striking variety of outcomes depending on the dosage of ingredients and the specific practices of the stirring / shaking process used to mix them.

Thus, one should begin to ask again and to rigorously study what kind of different policy mixes in biotechnology have been conceived and used, whether they have hitherto led to any tangible results (where it has been implemented), and why they has either succeeded or failed. Further, while it is possible to assume that "third-generation" policies should be concerned with achieving "coherence by developing a good match between individual instruments and objectives as well as compatible instruments and objectives in different policy areas" (OECD 2006, p. 181), how can effective coordination be achieved in practice? This applies, for instance, to the relationship between national regulation (IPRs or ethical issues in areas such as GMOs or stem cells) and RIP.

7. THE CASE OF SCOTLAND

7.1 The Scottish Life Sciences and Scottish Enterprise Framework for Action

For a number of years the performances of the Scottish economy have been influenced by the presence of some multinational corporations (MPCs) concentrated in the financial services, gas, oil, transport and utility sectors. Moreover, during the 90s Scotland attracted inward investments in microelectronics by MPCs seeking to exploit its skilled and relatively inexpensive labour

force. During the mid-90s the Scottish *Silicon Glen* was home to some of the world's top semiconductor equipment manufacturers, including eight of the world's top ten semiconductor equipment suppliers, seven information technology (IT) fabrication plants, sixty supplier and support companies and sixteen companies with semiconductor design capacity. By the early 00s, however, the downturn of the global economy and the difficulties faced by some of the abovementioned MPCs led to the shutting-down of some plants and the considerable downsizing of others, with negative implications for the whole Scottish economy. Although oil, gas, transport and financial services continued to flourish and to improve the competitiveness of the Scottish economy, market analysts began to lay emphasis on the need to develop a competitive and dynamic economy, in order to counterbalance the volatility deriving from an excessive reliance on investments made by foreign MPCs.

As a result, the focus of policy interest shifted towards possible ways of stimulating entrepreneurship and the creation of locally anchored businesses with high growth potential. In the UK, Scotland has then pioneered the implementation of cluster thinking. The new strategy was launched by Scottish Enterprise (SE) in 1999 and five industrial sectors were identified as those where Scotland could achieve a competitive advantage based on the characteristics of local skills and resources, demand conditions, sectoral structure and the dynamics of national and international competition: biotechnology, microelectronics, tourism, food and energy. Later, the scope of the strategy was expanded to include other sectors.

A comprehensive framework for action (see table 1) was developed by the Executive and SE to grow a sustainable biotechnology cluster in Scotland. The framework started with a £40m investment and includes investments in basic research, education and in the commercialisation of intellectual property, measures to improve connectivity and promote networking among local actors, programmes designed to support the process of internationalisation of the local industrial and research-base, and the provision of a solid and efficient infrastructure. This strategy builds on Scotland tradition in education and research in life sciences and it has so far led to the proliferation of about five hundred organisations working in biotech-related activities, an important proportion of which are private firms with core competences in the use and implementation of life sciences (about one-hundred) in various sectors, including therapeutics, med-care, environmental remediation, agriculture, marine biotech, etc. Most of these programmes operate horizontally across various industrial sectors. However, some of them pertain exclusively to the life science industry. For example, SE’s support to the creation of industrial and scientific networks, creation of medical hospitals or the Intermediate Technology Institute (ITI) for life sciences in Dundee, collaboration among public and private organisations (NHS, PROs, private companies, etc), and to the development of technical and managerial skills.

INSERT TABLE 1 HERE

The strategy for life sciences is part of the wider Executive's commitment to create a *Smart and Successful Scotland*. This is a long-term plan that aims to raise the sustainable growth prospects of the economy by stimulating entrepreneurship, commercialisation of research and innovation. While the Executive, along with the British Government and the EU, is largely responsible for defining the policy framework, SE has been invested with the challenge of implementing and realigning it with the evolving needs of the business sector. As far as life sciences are concerned, some ambitious targets were set to be met by 2003. The key targets were: to reach the number of 100 DBFs located in Scotland, increase the number of support and supply organisations to 280, double employment from 12,000 to 24,000 jobs, improve DBFs' performance and build strategic linkages and value added networks within and beyond the boundaries of the local communities.

By the end of that period, the Scottish biotechnology sector employed roughly 26,000 people. However, the majority of Scottish DBFs were small in size. A considerable proportion of those involved in drug discovery struggle in the early phases of discovery and pre-clinical trials. They suffered from the paucity of private venture funds in Europe, the absence of Scottish VC firms dedicated to biotechnology, the lack of managerial talent required to develop sustainable businesses, and the distance from the head quarters of MPCs, which complicated the search for strategic partners (Hood and Peters 2003).

Scotland had not reached yet that critical mass that triggers incremental dynamics in the form of inward investments, inflow of skilled people, presence of local anchors and stable streams of revenues to be re-invested in Scotland. In 2005 the Executive produced a new document – *Scottish Life Science Strategy: Creating Critical Mass* - describing its vision until 2020. This focuses on growth and sustainability and it originated from an "industry-led series of consultations and discussions with almost 200 members of the wider community of industry, academia, other research providers, NHSScotland and policy-makers" (p. 3). The newly shaped strategy incorporated further investments in basic research and applied projects. It also included (i) additional financial support to businesses through the Scottish Venture Fund (SVF) to participate in £2 to £10M investments; (ii) clear foresight on key market trends with the investment made in the creation of the ITI life science centre; and (iii) promotion of more collaboration via the creation of a new network called the *Life Science Alliance*, which aimed to work simultaneously with academia, industry, NHS and the financial community.

More recently, companies such as *Ardana*, *Cyclacel*, *ProStrkan* and *StemCellSciences* have raised significant amounts of VC, managed to float (with different fortune) in the stock exchange, and brought products to the market. These developments along with the visibility of SE's strategy and the reputation of Scottish Universities are some of the factors behind MPCs such as Wyeth recent decision to invest in Scotland. The aim is to develop a network of clinical

and scientific excellence throughout Scotland called the Translational Medicine Research Collaboration (TMRC).

The TMRC involves the Scottish science base and *Wyeth* that will be responsible for all the costs of such studies sponsored by them. The Scottish parties in the TMRC have formed a new company with SE, through which the relationship with Wyeth is managed. Wyeth has invested £50million in the TMRC and the programme involves four major clinical academic centres at the Universities of Aberdeen, Dundee, Edinburgh and Glasgow and the NHS in Scotland. Activities include: (i) setting up of a centre for the development of biomarkers; (ii) developing and coordinating clinical trials on defined disease populations; (iii) linking with the Scottish Clinical Research Network to deal with ethical approvals, data collation and statistical analysis of results; and (iv) coordinating research activities on the samples collected (www.wyeth.co.uk – translational research).

7.2 Discussion

Over the past few years the UK system of governance has been characterised by a process of progressive decentralisation and regionalisation of both political institutions and responsibilities in the area of technology and innovation policy. This is particularly evident in the case of Scotland, where the Scottish Executive is now responsible for fulfilling an overarching strategy to promote innovation; this relies on the strategic direction of SE and significant investments made in infrastructure, skills and community development, business support (such as various financial programs and assistance in developing global commercial links), and public-private-partnership. The strategy is characterised by cluster and systemic thinking with a considerable emphasis on life sciences. For instance, roughly 50% of the money invested by the *Proof of Concept* program and 27% of that co-invested by the *Scottish Co-Investment Fund* (see table 3) has been absorbed by DBFs. The Scottish life science sector also benefits from a number of targeted programs, such as *PreBio* or *Scottish Health Innovation* (see table 3).

The Executive and SE's focus on life sciences is also consistent with a UK-NIS which is particularly supportive of the growth of the industry (Smith et al 2006) and has developed a regulatory system which guarantees a strong regime of appropriability and a pragmatic (in some circumstances permissive) attitude as regards ethical concerns. Ethical and societal issues, however, are not disregarded as insignificant, as demonstrated by the £12 M investment in the ESRC Genomics Network (EGN), dedicated to examining the social and economic consequences surrounding the development and use of genomics. The EGN includes 3 ESRC funded research centres - *Cesagen*, *Egenis* and *Innogen* - and the *Genomics Forum*. These investments range across 5 universities, and currently involve over a hundred researchers; both *Innogen* and the *Genomics Forum* are based in Edinburgh.

Thus, while the focus on life sciences is motivated by excellence in bio-scientific research, medical care and industrial experience in diagnostics, the Scottish sector is now characterized by a growing number of new companies, pervasive professional and industrial networks, public-private-partnerships and incoming investments by MPCs. SE has played a coordinating and critical role, being responsible for the design and implementation of a comprehensive and targeted set of activities. In this sense, the Scottish system is considerably different from other successful bio-clusters, such as Cambridge, where the process of emergence has appeared to be more spontaneous and the East of England Development Agency (EEDA) is only marginally involved in supporting the high-tech cluster. In this sense, one may wonder whether sector-specific policy action is a necessary requirement for emergence.

SE's for action is characterised by a blend of policy approaches as well as a great proliferation of measures - for which SE is not entirely responsible. On the one hand, the framework contains various initiatives directed to counteract disincentives to invest in high-risk start-ups, promote internal and external connectivity, and ease access to key complementary assets - such as technical and managerial competences.

On the other hand, different layers of policy making (EU, UK Government and the Scottish Executive) are in charge of developing and implementing a number of measures that sometimes overlap and/or respond to different strategic approaches. For instance, the *Scottish Life Sciences Funding and Support Guide 2007-2008* cites 40 different types of public funding available to Scottish biotechnology firms from 16 different governmental and non- governmental sources. It simultaneously includes a UK capital investment grant scheme (*Regional Selected Assistance*), UK guaranteed loans (*Small Firm Loan Guarantee Scheme*), and Scottish loans and equity co-investment schemes (see table 1); other schemes are also available (although not contained in the aforementioned document) such as NESTA's (National Endowment of Science, Technology and Arts) direct investment program in start-ups (including biotechnology firms) or the European Investment Fund's (EIF) multi-country venture capital fund, a £72 million fund investing in SMEs in drug discovery, biopharmaceuticals, diagnostics, medical technology and devices, and applications of IT in the above fields). Similarly, Scottish DBFs can benefit from 6 different programs that stimulate networking and collaboration with a variety of different actors.

Emergence is generally perceived as a synonym of achieving critical mass (the real objective of policy action), which remains a difficult concept to grasp and describe. As a result, the emphasis of policy action is on the provision of the necessary ingredients to sustain the process. In this sense, Rosiello (2005) examination of SE's strategy highlighted that very specific challenges remained to be faced as regards meeting demand for both technical and managerial skills, easy and flexible access to finance, infrastructure and information. The capacity to combine

experiences, skills and resources with other local and international partners and to grow a number of local firms into integrated businesses with an international reach seemed crucial steps to achieve that goal.

Accordingly, considering the factors that influence location, Rosiello (2005) indicated that the presence of prominent scientists, the availability of finance and of opportunities to change job and collaborate with a variety of other agents played a key role. Direct and indirect links to practitioners (e.g. clinicians) and end-users (e.g. patients) can be critical sources of information about how to develop and shape successful innovations. Co-location in research partnerships and product development helped communication and monitoring but search routines were generally shaped by technological and functional needs and partners were sometimes located elsewhere (Europe, East-Asia and North-America). Finally, a factor often ignored by economic analyses is regulation, for instance, IPRs, safety measures as regards clinical trials, restrictions on the therapeutic use of embryonic stem cells, etc. Regulation seemed to have clear implications for the decision to undertake basic and applied research and for the ability of the outcome to create new products and services.

8. CONCLUSIONS

The discussion of the experience of Scotland contributes to illustrate in a more concrete fashion some of the crucial conceptual issues discussed in the previous section of this paper.

First, the Scottish case would seem to suggest that, given some basic preconditions –primarily as it regards basic scientific research and education – a thriving biotechnology innovative region can be supported through the interaction of public policies and local actors. In the case of Scotland, these policies were a mix of interventions aiming at correcting static inefficiencies and classical market failures but also -as predicated by cluster and innovation system theories - at promoting networking and incremental dynamics, by organizing localised networks and knowledge links, socio-institutional infrastructure and access to global markets.

Second, it is also worthwhile emphasizing that the Scottish approach is often said to be characterized by “vertical or targeted” initiatives, as contrasted to “horizontal” policies, and reflects a policy agenda expressly aimed at “constructing regional advantage” (Asheim et al 2006). In practice, the strategy adopted by SE is better understood as a flexible and pragmatic mix of “horizontal” and “vertical” measures, and particularly such strategy has reacted and changed in order to meet arising challenges. A typical example of such dynamism is the recognition of the importance of angel groups and small VCs within the Scottish financial community (Harrison and Mason 2003) and the definition of a series of co-investment schemes (which contradicted the central government approach that was based on the establishment of

regional VC funds. More recently, in order to respond to the financial requirement of growing companies (especially DBFs), SE has devised the SFV, which will co-invest in £2-10M deals.

Third, in a somewhat different language, it could be argued that SE has played a crucial role of "champion" and "integrator" of scattered capabilities, agents and institutions, working simultaneously on the provision of infrastructures, promoting the development of capabilities, providing incentives for innovation, fostering awareness and interactions. This function could be contrasted with other case where public strategies supporting the biotechnology industry take the role of "brokers", i.e. they focus mainly on connecting agents, without taking the responsibility of providing a common framework and an active role in devising specific strategies, but letting them emerge spontaneously in a bottom-up fashion.

There is no obvious reason to believe on the basis of first principles that one approach should be better than the other. It is a platitude to observe that this will depend on specific histories, conditions and traditions. Yet, the Scottish case illustrate how emergence can be helped by judicious intervention and how – especially in an industry like biotechnology – emphasis on integration can contribute to improve on the mere focus on brokering and connecting, particularly in the early stages of development of a cluster. As argued earlier, there are some visible risks associated to this approach, such as (i) the proliferation of too many - and sometimes overlapping - initiatives that promoted by various organisations and layers of government, and (ii) the tendency to overemphasize the importance of "connectivity" and "bridging" organisation (whose efficiency has been frequently questioned).

Fourth, it has also to be recognized that Scotland has so far failed to achieve a sufficient critical mass enabling the take-off of spontaneous growth. As argued previously, the maturation of an industry and of a cluster is likely to entail critical thresholds and different sets of policies (maybe even none at all) as specific self-reinforcing processes are set in motion. To a significant extent, our understanding of the ingredients of successful clusters is now satisfactory. It is also increasingly recognized that such ingredients involve appropriate resources, incentives, capabilities and interactions. What remains to be understood much better concerns the procedures through which such ingredients have to be mixed and integrated, the identification and exploitation of their complementarities, the dynamic processes which are implied by alternative mixes of ingredients: knowing also that such processes are inherently hard to study and can lead to strikingly different outcomes given only minor differences in initial conditions and shocks occurring over the unfolding of their dynamics. But some progresses have already been made in this direction which should encourage us to go ahead this route.

A final comment is however worthwhile adding. Most of the policies – both at the national and at the regional level – in support of biotechnology have basically attempted at replicating the American model of development of this industry, based on academic

spin-offs, venture capital and strong IPRs. Yet, it might be legitimately asked whether this model is the only possible one and if it is really efficient as it is usually considered. Indeed, influential scholars like Gary Pisano have recently claimed that the biotechnology industry has substantially failed to deliver its promises and that its business and industry model is deeply flawed (Pisano, 2006). Thus, perhaps new different models should be devised and experimented.

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