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Science, Innovation and Technology Transfer Pathways in Translational Research: A Study of Divergent Trajectories in the Healthcare Sector in Europe

by

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Abstract:

This paper explores place-specific factors that come together to enable firms and other kinds of organisation to produce new products, services and processes. The geography of the biomedical sector, that of clustering in particular regions, presents an opportunity for place-specific understanding of processes involved in translational research in medical sciences, particularly with regard to the role of public policy and its outcomes in four bioscience regions in Europe. This might be in the way that public sector intervention can help actors in regions better to leverage resources to create synergy, or by building physical infrastructure leading to specific local pathways of translational research through which advances in healthcare are made. To explore these themes, the paper draws on data from a recently completed EU FP7 funded study (2010-2013) Healthcare Technology and Innovation for Economic Success (HealthTIES) of the 'Healthcare Technology Innovation cycle' in four bioscience regions: Medical Delta (Leiden, Rotterdam and Delft, Netherlands) Oxford and the Thames Valley, (UK), Biocat (Catalonia Spain) and Life Science Zurich (Switzerland)

Key Words: Healthcare, translational research, clustering, public policy

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1. Introduction

A major area of research across disciplines is innovation geographies, that is place-specific factors that come together to enable firms and other kinds of organisation to produce new products, services and processes. As Feldman (2014) points out, while investments in innovation in certain places yield jobs, growth and prosperity, similar investments in others fail to produce the desired local effects. In this paper the focus is on innovation in the healthcare field at the local level through increased capacity-building in the form of infrastructures of different kinds and knowledge transfer programmes. Healthcare is defined broadly to incorporate life sciences and other sciences resulting in the development of diagnostic, therapeutic and convergent technologies.

New areas of innovation, for example where new combinations of actors are required in order to support the value chain in a sector, often require policy experimentation to increase the effectiveness of the innovation process. Such experimentation is both facilitated by and results in geographic clusters of research and related activities as proximity facilitates different kinds of interaction (Cooke 2013). In the broader healthcare sector, research universities are often the central players in the geography of innovation - their research is funded through various government and non-government institutions, such as the National Institutes of Health in the United States, the Medical Research Council in the UK and under the Horizon2020 Programme¹ in the European Union.

In the case of the UK, medical charities and private sector research laboratories are often co-located with major research universities (Arbo and Benneworth 2007, Bagchi-Sen and Lawton Smith 2010) and hospitals. Medical charities are important funding sources. The link

¹ <https://ec.europa.eu/programmes/horizon2020/en/h2020-section/nanotechnologies-advanced-materials-advanced-manufacturing-and-processing-and> (accessed November 18 2015)

among these various organizations provides the means through which the results of research are translated into commercializable technologies to benefit the end users – patients.

This translational process is commonly known as “bench to bedside” research, that is, a system of taking laboratory discoveries to useful clinical applications and beyond through a translation process. Woolf (2008, 211) refers to translational research as the "effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease." In bioscience for example, the US has been the leader in translation research in the healthcare sector (Kenney 1986a and b, Bagchi-Sen et al. 2004). In Europe such efforts are noticed in the UK, Germany (see for example Cooke 2004), and Switzerland (Gebhardt 2015). Other countries (e.g. Israel, India) with strong science bases are yet to deliver effective support for this process (Breznitz 2013).

While much of this translation occurs at the extra-territorial levels, local relationships and variations in the extent of local networks cannot be ignored (Lawton Smith and Bagchi-Sen 2010, Casper 2013, Feldman 2014). Where they are effective, they facilitate the engagement between local stakeholders (e.g., entrepreneurs, intermediaries) who create the capacity (e.g., start ups, supplier networks) that sustain the development of the platform needed for translational research. The implication is that a university's success in translational or entrepreneurial activities depends on the quality of the regional environment around the university, that is the capacity of regional economies to support science and technology discoveries and their application (Casper 2013). Moreover, it is increasingly common for universities, one of the major stakeholders, to make internal adjustments to external conditions so that there is increased potential for translational research. Structural and procedural changes within universities (Oliver, 2004) have captured two institutional

“revolutions” in which such adjustments have been made. The first “institutional transformation” within universities opened the way to create new knowledge from academic research and collaboration. The second “institutional revolution“ made it possible to translate knowledge into commercial returns (Etzkowitz and Leydesdorff, 1998). Incentives put in place to create synergies between various organizations and individuals, resulted in collaborations for commercial opportunities, but not at the same rate or in the same form in different locations.

The geography of the biomedical sector, that of clustering in particular regions, therefore presents an opportunity for place-specific understanding of processes involved in translational research in medical sciences, particularly with regard to the role of public policy and its outcomes. This might be in the way that public sector intervention can help actors in regions better to leverage resources to create synergy, or by building physical infrastructure leading to specific local pathways of translational research through which advances in healthcare are made.

An obvious caveat is that of geographical scale. This paper discusses activity at the level of the region in four countries. ‘Regions’ are complex entities differing in scale; they are not only administrative entities but can be functional regions built for a particular purpose. To illustrate this we make two points. First, the EU’s own concept of ‘region’ is flexible. “Regions” are defined in the broader sense such as Länder, communities, autonomous communities, departments, provinces, counties, metropolitan regions and any other political entity with relevant competences to accomplish their engagements². Second, our case study draws on data from a recently completed EU FP7 funded study (2010-2013) Healthcare

² http://cor.europa.eu/en/takepart/eer/Documents/EER_Leaflet_2013_EN.pdf

Technology and Innovation for Economic Success (HealthTIES) of the ‘Healthcare Technology Innovation cycle’ in four bioscience regions: Medical Delta (MD; Leiden, Rotterdam and Delft, Netherlands) Oxford and the Thames Valley, (OTV; UK), Biocat (Catalonia Spain) and Life Science Zurich (LSZ; Switzerland) along with an emerging region, Debrecen (Hungary)³. Conceptually, the Healthcare Technology Innovation Cycle connects engineers and medical professionals, scientists and entrepreneurs, developers and end-users (medical doctors and patients). It specifies inputs into an innovation cycle (the science in the research base, research funding human capital), characteristics of innovation systems (technology transfer capacity building e.g. infrastructure and support for technology transfer) and outcomes such as the development of the biotech sector (new jobs, products and so on).

The project investigated, in a benchmark comparison, a set of indicators which comprise innovation system parameters and best practices by region, an analysis of the scientific strengths at the universities and companies by region, together with a Strengths, Weaknesses/limitations, Opportunities and Threats (SWOT) analysis. The HealthTIES analysis is one of the first to undertake cross-national comparison by collecting data in a standardized way. The regions were chosen because all of them are leading national centres in the healthcare innovation value chain. However, these ‘regions’ vary in size, in the composition of their research and industrial bases, as well as in their administrative and functional status.

We follow the HealthTIES framework to answer the following research question: What explains how translational research in the healthcare sector has developed in the four regions? Included in translational research is drug development, diagnostic businesses and other

³ HealthTIES: Healthcare Technology and Innovation for Economic Success

therapies. It is argued that it is necessary to look beyond just universities and the biomedical sector to map the elements of different innovation systems (national, regional, sectoral and entrepreneurial ecosystem) within individual regions in order to account for their differing strengths, weaknesses and the prospects for their own healthcare technology innovation cycle.

In order to contextualize the research question, we next review conceptualisations of different forms of innovation systems in order to highlight the impact of differences in structures and agency of individuals, organisations and policy-making (see Lundvall 2007, Autio et al., 2014). These are then used as a basis for explaining the resulting patterns of activity. This is followed by the profile of each of the four major European bioregions: the methodology used to assess performance and then the data are examined. Finally, some conclusions are drawn on what has been learned about regional differences and the implications for prospects for future developments.

2. Policy in systems approaches: implications for analysing translational research in healthcare at the local level

Embedded in the analysis of what happens within individual regions with respect to translational research in healthcare are geo-historical innovation infrastructures and elements of different kinds of innovation systems. As Carlsson et al. (1999) point out, systems can be viewed in several dimensions including national (Lundvall 1992), regional (Cooke 1992, Cooke 1998) and sectoral (Malerba 2002, 2005). More recently the term ‘ecosystem’ (entrepreneurial, business and innovation) (Isenberg 2011, Feld 2013, see Spigel 2015 for a review) has been used to describe the interconnections of local actors for a common purpose, that is, supporting private sector-led economic development. In this paper, we are interested

both in technology transfer and in nested layers of policy, that is, the co-existence and interaction between policy intervention at national and regional/local scales. We consider how the science base and the agency of policy-making appear in each conceptualisation.

We begin with the literature on national innovation systems (NIS) (Freeman 1995, Lundvall 1988 & 1992, Nelson 1988 and 1993). This is because the scale of resources allocated by national governments in many countries to supporting the research base which includes universities from which translation science develops varies. A key criticism of the NSI literature is that this ‘structuralist mode of explanation’ (Lundvall, 2007) means that individual-level agency and the micro-processes of entrepreneurial innovation have been largely overlooked (Autio et al, 2014). Indeed, ‘enterprise has become the forgotten element in the innovation systems story’ (Metcalf and Ramlogan, 2008, Holden 2015).

This criticism can equally be applied to how universities are treated in the NIS approach. Indeed, more recent developments have introduced agency by discussing how universities have broadened their scope to become entrepreneurial universities. These are noted for their societal role in creating wealth through making the applications commercializable and profitable (Etkowitz 1983, Shane 2004, Wright et al., 2011).

Closely tied to the concept of NIS are regional innovation systems (RIS) and sectoral innovation systems - both of which include knowledge infrastructures as the basic component for translational research (see Malerba 2002). Unlike NIS, however, these concepts are evolutionary having a focus on process/agency/change.

The RIS concept (Cooke et al. 1992, 1998) focuses neither on technology nor on sectors but on the growth trajectories of regions taking into account broader industrial/sectoral,

institutional and research contexts. A RIS consists of “interacting knowledge generation and exploitation subsystems linked to global, national and other regional systems” that may stretch across several sectors in the regional economy (Asheim and Coenen 2005, 1174). Knowledge transfer mechanisms which account for clustering include contract research, formal R&D co-operations and forms of knowledge transmission that do not involve financial compensations for universities such as knowledge spillovers (through the provision of graduates to the local labour market) and informal contacts with firms.

Universities in the RIS approach are important knowledge producers that may play bridging roles between themselves and the industrial world in the innovation-production spectrum at the regional level (Trippel et al. 2015). Perkmann et al. (2013) calls this ‘academic engagement’, bringing the agency of individual academics into play. Academic engagement represents an important way by which academic knowledge is transferred – or translated – into the industrial domain. Perkmann et al. show that the forms that it takes are related to the characteristics of individuals as well as the organisational and institutional contexts in which they work (see also Ankrah et al. 2013). Academic engagement is also related to innovation policy agenda (national, regional, local) on the translation or commercialisation of research. Therefore, the availability of knowledge and other resources in a region is associated with a concentration of firms, universities, research centres, and related innovation facilitating institutions and policy mechanisms.

A sectoral system is a set of products and agents carrying out non-market and market interactions designed to bring products to market. Conceptually it is evolutionary with ‘its emphasis on dynamics, process and transformation’ (Malerba 2002, 249). It has a dominant knowledge base (although different mixes of them are found, for example in biotech, Todtling and Trippel, 2015), technologies, inputs and demand. It includes the science base as a source of

knowledge and inputs. In the sectoral innovations concept, policy makers (central government and local authorities) appear as agents of change in the system alongside firms and non-firm organizations (such as universities or financial institutions), as well as organizations at lower (R&D department) or higher level of aggregation (e.g. firms' consortia) and individuals (Malerba 2002) who are missing in the RIS concept.

In both the sectoral and RIS approaches (Todtling and Trippl 2015) policy actors are agents whose interests lie in supporting capacity building for economic development in a locality (city, region) (Uyarra and Flanagan 2012). As, Uyarra and Flanagan (2012) suggest, policies are also part of the system that they are trying to influence. As a consequence, past political decisions become part of the facilitating or constraining environment in which future decisions and action are made. However, as we show below, actors other than public policy makers have agency in de facto policy-making (Uyarra and Flangan 2012), that is, being involved a set of actions designed to target particular outcomes. Thus policy practice rather than being a coherent set of policy actions united by a vision is messy due to the co-existence of multiple stakeholders and interests.

A recent version of an innovation systems approach with a focus on the local level is that of 'ecosystem'. Of the various versions, the entrepreneurial ecosystem approach is the most relevant to this discussion. An entrepreneurial ecosystem is 'a set entrepreneurial actors, entrepreneurial organisations, and entrepreneurial processes ...' All of these, "connect, mediate and govern performance within the local entrepreneurial environment" (Mason and Brown 2013, 5). Here innovation is implicit but this concept is included because of the link Schumpeter (1911/1934) made between the entrepreneur and innovation.

The emphasis in the ecosystems approach is on cooperation, for example by public policy. Indeed, Feld (2012) while arguing that start-up communities, such as Boulder in the US, can be built up in any city is dismissive of the role of the state in stimulating entrepreneurial ecosystems. This allows other actors and organisations to be dominant in a local/regional environment, and also ties in with the notion of functional regions designed for a specific purpose. Spigel (2015) is clear that policy (economic policies and regulatory frameworks) and universities are both important pillars of an entrepreneurial ecosystem which combine social, political, economic and cultural elements within a region.

However, it is most unlikely that all relevant actors will be engaged with others in an entrepreneurial ecosystem. For example, anchor firms (Feldman 2003, Agrawal and Cockburn 2003), that is established firms who use a new technology, may create knowledge externalities that benefit smaller firms and increase overall innovative output in the region. They may not necessarily be engaged in an entrepreneurial ecosystem or in a sectoral or a RIS. Hence their direct articulated inputs may be missing. Again this last point highlights the role of individuals, particularly entrepreneurs, which Feldman (2014) describes as a missing element in the discussion of innovative places. As per the criticism of NIS approaches, Feldman argues that entrepreneurs are agents and are key to the creation of institutions and building of capacity that will sustain economic development. Hence, the role of policy-making, if it appears at all is secondary to the agency of entrepreneurs.

While we have defined each form of system, the analysis needs to take into account elements in each in order to provide a comprehensive understanding of the input, system and outputs. We have also suggested that there are limitations in the literature on innovation systems. For example, national institutions may facilitate or hinder supply and demand in the broader healthcare sector where innovation not just tied to the university laboratory but where a

sectoral innovation system needs hospitals for clinical tests and then needs firms for commercialization. This process is not linear but is constantly reinforcing with learning embedded in each and every feedback loop involving interactions between the different players (Kline and Rosenberg 1988, Rothwell 1994), particularly in this case entrepreneurs who are agents of change (Feldman 2014).

At the regional level a number of factors (individual actions, organisational and institutional contexts and policy agenda) are significant in the extent and form that translational research occurs. Finally, the entrepreneurial ecosystem approach places the emphasis on the entrepreneur and the types of resources that they gain from being in an ecosystem (Spigel 2015). Universities appear in all but one of these approaches as knowledge and human producers although as we suggest, there are limitations to the extent to which they do in practice engage in translational research.

As we go through the analysis of inputs, systems and outputs, we identify where there are the gaps in policy and how policy might be able to help in the future to ensure that there is a better flow of inputs through a system to give outputs. Moreover, as we demonstrate, there has been policy experimentation in each country, with forms of intervention changing over time.

3. Study context: the four bioregions and policy

3.1 National Contexts

The four key bioscience regions of the ‘Healthcare Technology Innovation cycle’: Biocat, Medical Delta (MD) Oxfordshire and the Thames Valley (OTV) and Life Science Zurich (LSZ) are what Cooke (2004) has described as bioscience megacentres, albeit on a smaller scale than ones in the US such as Boston or San Francisco. Where they differ from each other is in the role of national governments in driving developments at the regional level, and the extent to which capacity building is locally based. For example two are regions, MD and LSZ, both created to promote translational medicine, with universities together with private sector engagement as a main driving force in economic development. In both, regional outcomes are related to NIS policies, while universities in Switzerland’s cantons also function within a RIS. In the Netherlands there are elements of sectoral innovation and entrepreneurial ecosystems.

Spain has one of the ‘world’s leading centres of biotechnology research’ but lags behind in its technology transfer system and creation of new firms (Wharton 2014).⁴ While it has had a robust science base, it lacks strong entrepreneurial ecosystems, a bioscience sectoral innovation system and RIS. Its NIS is weakening when other countries are strengthening theirs. The Wharton Report finds that since the onset of the economic crisis, Spain has been losing its position in the world rankings of research and development activity. The sector has been especially hurt by cuts in public subsidies and the shortage of tax incentives for research, which translates for example into fewer patent registrations. Hence, the potential benefits

⁴ <http://knowledge.wharton.upenn.edu/article/spain-adopts-israel-model-engineer-biotech-resurgence/> (accessed November 26 2014)

from university-industry relationships in this and other sectors have not been realised (Garcia-Aracil et al. 2015). This is because of comparatively weak policy efforts to incentivise knowledge and technology transfer compared to incentives to foster research. Spending on R&D (over half by firms) is concentrated in three main centres – Madrid, Catalonia and the Basque country, with Catalonia being one of the country’s national biotechnology hubs, with 20% of all companies in the sector⁵.

In the Netherlands, the government also ‘actively supported and co-funded a research and development infrastructure based on the concept of open innovation and long-term public–private partnerships’ while investing in the strong research base^{6 7}. These partnerships cover the entire life sciences value chain: they range from basic research to actual product and business creation. In cases where they address human health, they reach all the way from bench to bedside. They include all Dutch university medical centres, together with their associated universities.

The UK has adopted a similar strategic approach to life sciences to that of the Netherlands but with the emphasis being on NIS as the driver rather than an RIS. According to the UK BioIndustry Association, the UK’s strength in life sciences lies in it having “4 of the top 10 universities in the world, 19 of the top 100 universities, a stable of quality service providers, world class charitable supporters of the industry and a rich heritage of globally recognized medical research”⁸. In the UK, a major policy driver of the healthcare innovation cycle has

⁵ <http://www.biocat.cat/en/bioregion-facts-figures> (accessed September 30 2015)

⁶ <http://www.ibnetherlands.org/> (accessed November 26 2014)

⁷ <http://www.hollandtrade.com/sector-information/life-sciences/netherlands.pdf> (accessed September 30 2015)

⁸ <http://www.bioindustry.org/home/> (accessed November 26 2014)

been the government's strategy for UK Life Sciences, introduced in 2011. It was designed to support companies through every stage of the product life cycle. This is of interest because it highlighted weaknesses in the UK healthcare innovation cycle for R&D funding for translational activities or the "translational funding gap"⁹. In spite of these weaknesses, the UK has one of the strongest biotech industries in Europe.

In an attempt to improve translational medicine, the National Institute for Health Research (NIHR) has funded Biomedical Research Centers (BRCs). These are partnerships between universities and hospital trusts/foundations specifically for physician scientists to increase translational medicine – i.e. the NIHR is buying out their time to do more research with the intention of improving bench to bedside times. There are currently 11 BRCs (including Oxford) and major BRCs received around £100 million for 5 years in the second round which ends in 2016. However, funding is still dependent on academic output, possibly to a greater extent than 'business' potential.

In Switzerland, the Federal Swiss government has not made direct investments in regional innovation and cluster policies. Instead the Federal budget for university-based education, research and innovation is very high. In addition Swiss cantons also fund universities and especially universities of applied sciences (Gebhardt 2015). Gebhardt argues that it is not necessary to use innovation policies as developmental measures in Switzerland as private investment is a key driving force. In the pharmaceutical sector, Switzerland, more renowned than the UK, is now leveraging that strength for broader biomedical sciences and the creation of its national biotech chain¹⁰.

⁹ <https://www.gov.uk/government/organisations/office-for-life-sciences> (accessed June 7 2014)

¹⁰ http://www.swissbiotech.org/Php5/aa2/UserFiles/File/pdf/swissbiotechreport/SBR_2014.pdf accessed November 26 2014)

3.2 Regional Contexts

Against this background on each of the four countries, the data in Tables 1, 2 and 3 in section 4 are designed to show the particular inputs, system elements and outputs. These indicate what each possesses in the way of capacity for translation medicine. The regions, as we show below, differ in the sheer scale of activity, both geographically and in component elements. Key organizational differences lie in whether they exist as virtual, functional or administratively defined regions. The lead organizations and major players differ in each case and the relative balance of systemic elements (regional, sectoral, ecosystem) also varies.

In the UK all areas have activity in the sector but the South East (Thames Valley, Oxfordshire), the East of England (Cambridgeshire) and London together contain 60% of all employment¹¹. Entrepreneurs and small firms are key drivers of technological advancement in the biomedical sector, particularly in medical biotechnology. Many are young companies and are often spin-offs from universities (Cooke 2001, BIS 2013). In OTV, although the Thames Valley is included in some metrics, Oxford dominates. Reading University has only recently developed a science park and it does not have the excellence in biomedical sciences of Oxford University.

There is a very strong focus on research: Oxford University's translational trajectory is predicated on its very strong science base (a function of the NIS), much of it being funded by national and international research funding bodies (research councils, national charities, EU).

¹¹ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/298819/bis-14-p90-strength-opportunity-2013.pdf (accessed May 23 2014).

Where it differs from the other three regions is in its local entrepreneurial ecosystem. This is indicated by the much smaller number of biotech companies than in the other three regions and by a lack of large firms. This is particularly distinctive, indicating weaknesses in a biomedical sectoral system of innovation (Malerba 2002).

Medical Delta was established in 2006 by the Delft University of Technology (TU Delft), Erasmus Medical Centre, Erasmus University, Leiden University and Leiden University Medical Center, and the City councils of Delft, Leiden and Rotterdam. MD is coordinated through its website¹². Its aim was to realize breakthroughs in medical sciences and healthcare, to develop novel technologies and to fuel related economic opportunities through university-industry linkages. MD is a medical technology cluster, home to a large number of biotech firms, with elements of both RIS (Cooke 1992, 1998) and an entrepreneurial ecosystem (Mason and Brown 2013, Spigel 2015) with stakeholders such as companies, business parks and local government.

The Zurich life science cluster was established in 2001 by the University of Zurich and the Federal Institute of Technology Zurich (ETHZ), both in the Canton of Zurich. It aims to establish co-operation networks bringing together academia, industry and the public sector, and to support science education. Approximately 80% of the cluster activities are related to human health. In addition to the original tasks of promoting networking and communication within the universities and with the general public, two new networking platforms, the LSZ Young Scientist Network and the LSZ Business Network, have been initiated.

¹² <http://www.medicaldelta.nl/> (accessed December 9 2014)

Biocat was established in 2006 by the Government of Catalonia and the Barcelona City Council. Its aim was to facilitate networking among biotech and pharma companies, research institutions/universities and an administration that fosters the biotechnological and biomedical sector in Catalonia (hence both features of a RIS and a sectoral innovation system are in place)¹³. Biocat is led by a biomedical network, the equivalent to Oxfordshire's OBN (see below). Like OBN, it monitors what is happening in the sector in the region, but has more resources and plays a bigger role than OBN since it works closely with universities and hospitals.

4. Data, Methodology, and Findings

In this study we are using input, innovation system and output indicators to compare four leading bioscience regions. These indicators are also used as reflecting long term policy outcomes and/or organizational goals. However, this kind of analysis is fraught with methodological complexities owing to the difficulties in defining what is to be measured as indicators of performance, hence differences between places. For example, the EU's (2011) Economic Performance Indicators (EPIs) for regional biotechnology are categorised under three dimensions: cluster dynamics, enablers, and outputs¹⁴. Differing assumptions about are used what is an input, what is an output and what are system elements. First, cluster dynamics includes the number of jobs created and the number of companies established (including growth and survival rates within the last three years). Second, cluster enablers here are designated as the external environment includes public funds raised, private funds raised; framework conditions; and the number of cluster organisations (cluster

¹³ <http://www.biocat.cat/en> (accessed December 9 2014)

¹⁴ <http://ec.europa.eu/research/bioeconomy/pdf/regional-biotech-report.pdf> (accessed May 23 2014)

management/facilitator). Cluster outputs include revenue from marketed biotech products/technologies; revenue from licensing activities on biotechnology products/technologies, and numbers of newly developed and marketed biotechnology products/technologies.

Other measures of outputs from universities include numbers of university products such as patents, licenses, and collaboration (Lendel 2010) which offer a range of possibilities to be absorbed by the local economy. They also include intangible as well as tangible and measurable outputs. Rossi and Rosli (2013) highlight the importance given to the measurement of the impact of knowledge transfer from universities via intellectual property rights and spin-offs. Measurement by geography and the impact of proximity are also important. Goldstein (2009) for example measures universities' technology transfer by distance, types of research and kinds of universities. He finds spillovers from basic research to be less localised than those from applied research with spillovers from highly ranked research universities more geographically widespread – indicating the complexity of path development processes.

Identifying outputs is problematic as studies do not necessarily agree as to what is an input or an output. For the biotech sector, standard output indicators include founding rates of firms, size (employment, turnover etc), specialization as indicated by new products, patents and drugs in development. Collectively these shape the specialization of a region from the private sector and universities (BIS 2013).

In keeping with the suggested metrics above, the HealthTIES project developed a set of innovation indicators which were grouped into the three innovation phases: Input, Innovation

System and Output¹⁵ (Figure 1). Data were collected by teams by each of the partners. In three, Oxford, (Leiden, Rotterdam, Delft) and Zurich, the teams were academics working with local organizations, for example, in Biocat, data was collected by the Biocat team¹⁶. The criteria adopted for the study across the regions for innovation indicator datasets were that the data should be relevant for the HealthTIES disciplines - biotech, medtech, life sciences, engineering and medical sciences, and that it should discriminate between regional performances. This illustrates that within the healthcare sector, rather than there being just one dominant technology, a number of disciplines are involved (Todtling and Trippel 2015). The datasets needed to be quantitative in order to identify the impact of local expertise and conduct regional SWOT analyses. In this study the focus is on capacity building and exploitation of existing capacity, that is, the system and its inputs. In line with the caveats noted above, we accept that there are limitations to the chosen proxy variables. However, at the current time, these are believed to be the best available.

¹⁵ The innovation indicators, their weighting and scaling were derived as part of the HealthTIES project.

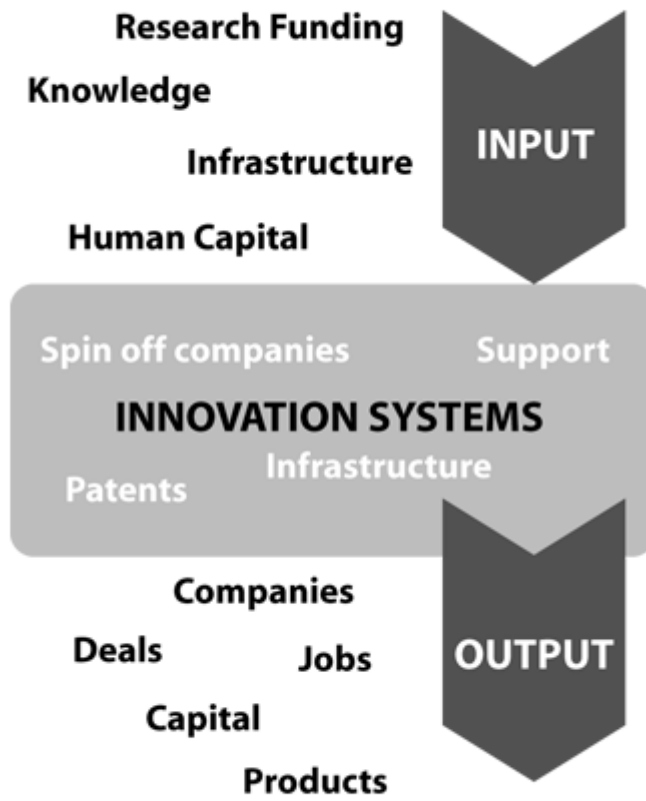


Figure 1. Inputs, Innovation Systems and Output in the Life Sciences

(Source: <http://vrr.healthties.eu/>)

Regional information was collected on universities, research institutes, universities of applied sciences, intermediate vocational education, publications, care and cure providers, government, industry, technology transfer, science parks and incubators. Regional analyses, of trajectories were then performed and compared internally to the consortium and with clusters in other countries using a variety of statistical and graphical techniques¹⁷. Next we show how the focus on life science based R&D, translational research, technology transfer and network development in each location has created place specific trajectories.

4.1 Inputs

Table 1 shows that the four regions are specialized in different areas of research and commercialization activities. For example, OTV is a leading region regarding its research activities and capabilities in the health related sectors rather than commercialization. An indicator of the region's strength in knowledge is the number of professors with an H-index of 30 and above¹⁸. MD, OTV and LSZ have at least a hundred more than Biocat. However, Oxford's professors' publication rates far exceed those in MD and LSZ. It is worth noting that other European countries do not have an equivalent of the Research Excellence Framework (REF), a system for assessing the quality of research in UK higher education institutions that drives academics to publish and obtain research funding¹⁹. This means that Oxford University's academics are primarily focused on publications in order to maintain its global

¹⁷ Data are available at [http://vrr.healthties.eu/\(accessed\)](http://vrr.healthties.eu/(accessed)) June 3 2013)

¹⁸ The H-index is a measure which combines publication output and impact through the number of citations of an academic paper.

¹⁹ <http://www.ref.ac.uk/> (accessed October 9 2015)

reputation. Therefore government policy (NIS) is a key driver of both institutional and the individual academic's behavior.

LSZ is ahead of OTV in the levels of external research funding. However, OTV does match that region in the number of ERC junior research grants but lags behind in the number of senior ERC grants. This might indicate on the one hand that the innovation cycle in OTV is in a comparatively early stage and is focused more on science than translational medicine than that of LSZ. The strength of the research base overall on the other hand illustrates that Oxford University and its teaching and medical research functions in local National Health Service hospitals, notably the John Radcliffe Hospital)²⁰ primary position within the NIS (Freeman 1988, Lundvall 1992).

Moreover, MD, LSZ and Biocat outperform OTV in human capital particularly in the ability to attract more overseas as well as national MSc/PhD students. This suggests that a lack of skilled professionals might create bottlenecks for a growing industry, and is an indicator that OTV is different from the other regions. It is not converging or diverging as it is falling behind in translational medicine given that it is less successful than the other regions in its research being commercialized i.e. that research and patents are not being translated into sufficient startups and spin-offs. Hence the agency of entrepreneurs in creating institutions and building capacity (Feldman 2014) within an entrepreneurial ecosystem (Spigel 2015) is stronger in MD, LSZ and Biocat than in OTV.

Unlike in MD and LSZ, in OTV there is no local focus. Agency for change and underpinning of the translational process lies with national institutions. It should also be emphasized that

²⁰ <http://www.ouh.nhs.uk/default.aspx> (accessed 30 September 2015)

first rate academic basic research and publishing should not always be expected per se to found and develop new firms or applied projects. As Perkman et al. (2013) point out this is related to the characteristics of the individuals as well as their organizational and institutional contexts.

Biocat is the strongest region for translational medicine overall with respect to the number of both research and general hospital beds and in the number of clinical trials. It also has more international PhD students and graduated MSc students, both national and international, suggesting that it has a younger profile than the other regions. This with its smaller number of professors with high H-indexes, lower levels of publications, research income and much smaller research infrastructure indicates that it is more of a teaching and applied research than a basis research region. In this respect there are potentially greater opportunities for agency at the local level to develop translational research activities given the high level of regional funding, building both RIS and entrepreneurial ecosystems.

Table 1: Inputs Indicators from HealthTIES

Category	Parameter	Biocat	Medical Delta	Oxford & Thames Valley	Life Science Zürich
Knowledge	Professors with an H-index >30	125	245	238	231
	Publications 2001-10	798	1171	2264	1190
Research funding	Research Funding (Euro)	450.69	463.23	632.99	1042.09
Human Capital	International. graduated MSc students	949	331	148	348
	International current PhD students	1384	843	345	2762
	National graduated MSc students	5381	1266	193	1212
	National current PhD students	3742	1367	805	2167
	Junior European Research Council grants 2007-10	5	4	16	17
	Senior European Research Council grants 2008-10	6	9	19	33
Infrastructure	University area for research (m ²)	1147	77545	193353	315000
	Beds in research hospitals	5908	2096	1043	3366
	Clinical trials phase I & II	120	45	40	36

Source: <http://vrr.healthties.eu>

4.2 Innovation System

The main features of the differences in the innovation systems relate to the size of the physical infrastructure (Table 2). For example, Biocat outperforms the other regions in the space on its science parks. Consistent with the evidence above, it has very much stronger institutional capacities in the form of technology transfer officers both on the science parks and in the universities. Not surprisingly it has the most spin-offs, but not that many more than MD. It does not have the same level of big public-private projects that are found in MD and OTV, countries where national policy is much stronger than in Spain. In Switzerland, private sector dominance may help to explain the lower number.

However, while the OTV region has the next largest provision of space, its infrastructure for incubation of new and growing biotech firms is weak. SQW (2013) also identified a lack of

available premises inhibiting the location of Big Pharma in the county as well as and a lack of linkages between Oxford University and local firms. To address the lack of a biotech incubator, Oxford University has now started building a Bioescalator amongst other research institutes and next to the Churchill Hospital. Three other bioincubators are planned in Oxfordshire (part funded by national government, the private sector and in the case of the Bioescalator by Oxford University)²¹. This will improve the institutional environment for translational research (entrepreneurial ecosystem) but as yet, in policy terms, OTV does not yet have a RIS. By contrast, in MD, LSZ and Biocat there are elements of both RIS and entrepreneurial ecosystems.

Table 2: Innovation System Indicators from HealthTIES

Category	Parameter	Biocat	Medical Delta	Oxford & Thames Valley	Life Science Zürich
Innovation	University Spin-Offs 2007-10	63	50	36	33
	Granted US patents 2007-10	50	54	50	40
	Big public-private projects	29	69	59	41
Support	TTO Full-time equivalents	245	62.9	89	37.6
	National governmental innovation (World Economic Forum Index 2010-11)	3.4	4.3	3.8	4.4
Infrastructure	National attractiveness (World Economic Forum Index 2010-11)	4.49	5.33	5.25	5.63
	Science parks area (m ²)	438920	1007500	312528	88700
	Science parks support Full-time equivalents	181	22	49	17.75

Source: <http://vrr.healthties.eu>

²¹

http://www.oxfordmail.co.uk/news/10969638_67m_investment_into_four_science_hubs_in_Oxfordshire_firms_main_part_of_three_part_Oxford_City_Deal_Audio/?ref=var_0 (accessed December 9 2014)

4.3 Outputs

One of the major differences is in the commercial (translational) activity or outputs in the regions (Table 3). LSZ dominates the number of larger biotech companies, which has over twice those of MD. Surprising Biocat which has invested heavily in infrastructure, teaching and hospital beds is second only to LSZ on jobs in the biotech companies has the fewest larger firms, but its smaller firms employ nearly as many people.

In spite of the strong research base in OTV, the number of biotech companies and subsequently the number of their FTEs is very low in comparison to the other regions. OTV's employment in the biotech sector is half that of Biocat and somewhat over a third that of LSZ. It has a smaller number of biotech companies with less than 20 FTEs than other regions, particularly LSZ. OTV's poor performance might indicate that despite the very strong scientific labour market, which is associated with high levels of entrepreneurship (Fritsch and Schindele 2011), the area lacks the people and the capabilities for supporting commercialization or fostering entrepreneurship, which seem to be present in all the more successful regions.

OTV was able to attract throughout Europe the largest amount of investments between 2007 and 2010 with 420.75 million Euro (followed by MD with 215.38). This indicates a perceived (scientific/economic) potential for further growth by investors and this has the potential to increase the output of the region over time. The small number of research hospital beds in the OTV region (Table 1) might hamper the benefits achieved through the interaction between research and patients and thus limit the experimental capacities. This is in spite of institutional capacity in the form of the clinical trials consortium.

Another prime indicator of translational research, from bench-to-bedside, is in the number of products on the market. Here LSZ scores most highly, followed by Biocat. This suggests that in Switzerland it is the private sector that is driving developments, a characteristic of the national innovation system, while in Biocat a government policy of collaboration is having an impact. However, OTV has the highest number of products in clinical trials, but is third highest in products at the discovery stage. This shows that there are no clear cut patterns to translational research across the board, rather there are indicators of where different kinds of agency are being felt in producing outcomes.

Table 3: Output Indicators from HealthTIES

Category	Parameter	Biocat	Medical Delta	Oxford & Thames Valley	Life Science Zürich
Jobs	Biotech companies Full-time equivalents	29981	18636	13563	34440
Companies	Biotech companies with <20 Full-time equivalents	338	195	154	1449
	Biotech Companies with >20 Full-time equivalents	16	108	46	262
Deals	Big Trade Sales 2001-10 (>100 mio Euro)	4	5	4	2
Products	Products on market	207	138	122	282
	Products clinical trials	35	30	66	43
	Products discovery phase	72	55	49	37
	Medicines available in countries EFPIA Patients' W.A.I.T. Indicator Report 2010	36	54	n/a	37
Capital	Total investment 2007-10 (>100 mio Euro)	57.33	215.38	420.75	130.30
	Number investments 2007-10 (>100 mio Euro)	13	11	20	16
	Av. Series A investment 2007-10 (>100 mio Euro)	3.96	9.17	9.10	3.97

Source: <http://vrr.healthties.eu>

While the data in the three tables indicate process outcomes, what they cannot show are direct outcomes in innovative bedside healthcare. Other indicators such as new therapy and health care structures, efficacy and effectiveness indexes could be more appropriately constructed as outcome indicators. These indicators should be seen as first step in indentifying national, regional and local conditions that underpin potential advances in healthcare and hence can be used to identify appropriate policy responses.

5. Conclusions

The paper considered inputs, the environment (innovation systems) and outputs in shaping clusters in the Healthcare sector in four leading locations in Europe. We are looking at data at one point in time to reflect upon the outcome of regional evolution to create a healthcare/life science sector that is at the forefront of translational research. The inputs tell us what they are working with, the innovation system also tell us what they are working with and how they are working, and the outputs provide indicators of the effectiveness of the translational research process in each. We note how public policy and private sector involvement has produced distinctive characteristics either through enabling or not enabling processes needed for translational research. We have also used the concepts of NIS, RIS, sectoral innovation systems and entrepreneurial ecosystems to identify characteristics of developments in each location, highlighting that no one approach is sufficient to explain observed patterns of translational research.

We show that with respect to ‘inputs’, the four regions are specialised in different areas of research and commercialization. OTV is clearly the odd one out. While the three other regions are converging in the inputs to support commercialization, OTV lags behind the others, especially Biocat, in the number of hospital beds and clinical trials, the later stages of the translational research process. All three other regions have far higher student numbers, both

at Masters and PhD levels, i.e. the next generation of professionals and academics engaged in the translational research process. Biocat, however, is well behind the others in the availability of university infrastructure for research. MD and LSZ are similar to OTV in the number of highly published research professors but this does not translate into the same level of publications. LSZ is well ahead of the others with respect to research funding and associated university research areas for research, thus appears to be maintaining its high quality science base.

In 'innovation Systems' Biocat is the leader of the four regions particularly for physical infrastructure, especially in full time TTO employees. It has more university spin-offs than the others but there is an imbalance between the resources devoted to commercialisation and extent (spin-offs and patents). Similarly the evidence suggests that OTV's TTO resources are relatively inefficient as they have not resulted in as many university spin-offs as might be expected. On other indicators, Biocat is behind the others on national attractiveness, and LSZ in science park capacity. A strength of MD's sectoral innovation system is the number of big public-private projects that have a translational research element.

It is 'outputs' where there is most obvious evidence of divergence across a range of indicators, indicating that the trajectory of each region in translational medicine is different. This is particularly the case with respect to the roles of entrepreneurs in driving innovation systems rather than being merely outputs. OTV in particular diverges from the other three regions in translational activity in the number of biotech companies, both smaller and larger. MD is the leading region in the number of companies, indicating an effective local entrepreneurial ecosystem (Mason and Brown 2013, Spigel 2015) but less so in the number of larger companies with more than 20 employees. Hence there are limitations to its overall sectoral innovation system (Malerba 2002, 2005) Here, LSZ is the most efficient in

generating the largest number of successful firms, as is also indicated by the number of products on the market. However, OTV has the highest number of products in clinical trials and total investments, suggesting that on this indicator, it has the potential to develop an effective translational research portfolio.

The evidence suggests that it is systemic or innovation cycles where MD, LSZ and Biocat (but not OTV) are converging, but not necessarily through the same kinds of public policy intervention. Each shows elements of RIS and entrepreneurial ecosystems through their respective systems of governance through the interactions of organisations at the region level. What is striking is that OTV's excellent science and technology base has not resulted in translational research that has resulted in high levels of entrepreneurship and growing biotech companies – it is massively behind LSZ and Biocat. Overall it lags comparator regions in terms of a wide range of input, innovation system and output indicators, except in publications. As has been suggested above, the strength of the science base should not necessarily result in new firms and applied projects, even though a normative policy agenda suggest that it should. However, as OTV lacks the range of infrastructural support that is present in other regions such as incubators and technology transfer support, there is scope for public policy to identify how the local entrepreneurial ecosystem might be improved.

The OTV HealthTIES innovation cycle appears to be limited by a lack of academic engagement (Perkmann et al. 2013) in translational research which is probably hampering its development. Instead, academics, as is the UK NIS, focus on publication. The comparatively low number of young academics graduating in OTV might result in bottlenecks for the growing biotech cluster but its current capacity to import is high as it is a very attractive region. A serious weakness is its apparent low capability to create spin-offs and to profit from its strong research as well as patent base. This might indicate insufficient capabilities

regarding the commercialization process or translation process as well as insufficient entrepreneurial education. An implication for policy is that, as nations move toward knowledge-based economic development, universities are a necessary but not sufficient condition for translational research to create profitable and societally valuable innovations.

Research from the past two to three decades on the biotech sector (e.g. Cooke 2001, 2013, Stuart & Sorenson 2003, Kim et al. 2009) shows divergent trajectories or uneven development, that is certain universities have provided the pre-conditions to take off. Others which started late or have followed imitative strategies are going to take a longer time to adjust their internal strategies. This said, these universities are recognising that not all will follow the same path although the products are more or less the same (e.g., patents, licensing, spin offs). Thus a limitation to all of the approaches we have identified is how to build in evolutionary change, so that the different actors and organisations and combinations of both over time and influence translational research (see Spigel 2015 on entrepreneurial ecosystems).

In a larger region, coordination among governance bodies may leverage these divergent paths, uneven knowledge base, and complex institutional capabilities to attain some bigger output at the end or realise synergies. In the UK various historical factors on one hand may add to the limitations, but on the other they provide the international reputation for science excellence that could potentially draw in international investment.

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