A MULTI-LEVEL ANALYSIS OF BIOMEDICAL INNOVATION PROCESSES IN THE UK AND US

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INTRODUCTION

Recent models of innovation recognize the interactive and recursive nature of innovation, with market pull and technology push occurring simultaneously such that the causal relations between inputs and outputs are no longer considered to be predictable or straightforward (Rothwell and Zegveld, 1981). It is argued therefore that linear models of innovation are no longer relevant. Instead a 'Triple Helix' non linear model has been proposed which is characterised by close interaction and overlap between university, industry and government (the three helices) (Etzkowitz & Leydesdorff, 1999; 2000, Leydesdorff, 2000). This overlap creates a knowledge infrastructure in which innovation occurs through interactive networking between firms (large and small), government laboratories / agencies and academic research groups. In the Triple Helix III mode of innovation, a complex system co-evolves around 'an emerging overlay of communications, networks, and organizations among the helices' (Etzkowitz & Leydesdorff, 2000, p. 112). Notably, the entrepreneurial university – one that combines basic and applied research - emerges as a key player in the Triple Helix III model of innovation (Owen-Smith, 2002). The inter-relationships between these three actors are seen to be crucial for innovation generating knowledge flows back and forth. A distinctive feature of the Triple Helix III model is an emphasis on the co-evolution between technological developments and their cognitive and institutional environments which over time fundamentally alter the Research & Development (R&D) environment (Leydesdorff, 2000) often encouraged but not controlled by government (Etzkowitz & Leydesdorff, 2000). *More recently it has been noted that the relations that emerge and co-evolve are also significantly shaped by regional as well as national systems of innovation (Cooke, 2005).*

The Triple Helix III model of interactive innovation appears to be particularly relevant in the context of biomedical innovation where academic groups interact with dense networks of large pharmaceutical firms, a myriad of biotechnology firms (Coombes et al, 2002, Powell, Koput, & Smith-Doerr, 1996; Powell, White, Koput & Owen-Smith, 2005) and Government agencies (funding and regulatory). Moreover the biomedical sector typifies the blurring of boundaries between these three institutional actors as government regulation is increasingly influenced by pharmaceutical firms (Ernst & Young, 2005, Morris, 2000) and scientists move back and forth between the public and private sectors (Lam, 2005, Oliver, 2005, Owen-Smith,

Riccaboni, Pammolli, & Powell, 2002). Notably however, the length of time it now takes to launch new therapeutics (@13 years), in combination with rising costs ($50 billion was spent on R&D by the top 20 global pharmaceutical firms) and declining productivity (the numbers of new molecular entities entering the market in 2004 reached an all time low of 20) suggests that the biomedical innovation process is becoming increasingly complex and problematic (CMR International, 2004; Ernst & Young, 2005). Many of the problems of translating scientific breakthroughs into biomedical innovation are considered to arise because of a lack of interaction and also conflict between the helices. For example, it is not uncommon for new therapeutics and treatments to be developed and given FDA approval, only to be rejected by clinicians unconvinced of their efficacy, particularly when they require changes to medical practice (Dopson, 2005, Hilton et al, 2002,). Leydesdorff (2000) has demonstrated that in the case of competing technologies, which typifies many therapeutics and services within the biomedical sector, the interactivity across the three helix can generate highly unpredictable effects, because of the "negative (that is selective) feedback loops involved"(:252). Thus whilst the Triple Helix III model of innovation may characterise research systems in a social context, there is very little detailed empirical work that has focussed on precisely what interactivity promotes innovation and what interactivity might pose constraints to innovation. As Etzkowitz & Leydesdorff emphasise the "sources of innovation in a Triple Helix configuration are no longer synchronised a priori. They do not fit together in a pre-given order, but they generate puzzles for participants, analysts and policy makers to solve" (:112). In this paper we aim to provide empirical examples of interactivity and some of the positive and negative outcomes for biomedical innovation.

The limited empirical support there is for the Triple Helix III model is primarily US *research which has developed broad macro analyses of innovation trajectories (Ledesdorff, 2000) arising from interactivity across the helix and other US research which characterise the effects of the co-evolution of the helix over time (Morris, 2000, Owen-Smith, 2002), but again only at a macro level. The theoretical underpinning of the Triple Helix is that the university plays an increasingly important role in innovation in knowledge based societies and the role of MIT in stimulating interactivity in Massachusetts is often cited as an exemplar of the model in action (Cooke, 2005). However, o*ther attempts to implement the model, in Australia and Sweden have been notable by their failure (Gunasekara, 2005, Jensen & Tragardh, 2004). Detailed empirical

analyses of the micro / meso level dynamics of interaction across the helix and the institutional arrangements that support or inhibit interactivity are currently missing.

An important implication for research that wants to more fully explore this new mode of interactive innovation is that it requires a *shift from broad macro level analyses to* a multi-level analysis, including project, organizational, national and multinational levels as well as a consideration of the nature of the relationships that develop between the helices. The Triple Helix III model exemplifies relations which are expected to be interactive and recursive within and between levels. In order to develop a multi-level analysis we have utilized a variety of different research methods in our comparative study of biomedical innovation in the UK and the US, and in this paper we intend to bring together the findings from these different datasets to identify institutional (macro), meso and micro arrangements that appear to either constrain or promote biomedical innovation. Figure 1 is a schematic representation of the Triple Helix III model in the context of biomedical innovation highlighting the factors at the macro level, in combination with the processes occurring at the meso and micro level, which constitute the innovation process.

Insert Figure 1 about here

Notably, the model as it stands (Etzkowitz, 2000) omits a key actor (clinicians) in biomedical innovation which will be considered further in the discussion. Specifically, we use a combination of secondary data and survey data collected from a variety of different actors (N=98) implicated in the different helices to provide the macro and meso level accounts of interactivity and in-depth case study data from 6 different biomedical innovation projects that were at the stage of entering, or engaged in clinical trials to provide an account of micro-level dynamics. We argue that it is only through triangulating (Denzin, 1988) these different sources of data that a multi-level analysis can be developed that helps us to explore the dynamics involved in Triple Helix III innovation systems.

In the next section we discuss the various literatures which have informed the perspectives we have utilised to characterise the dynamics of interactivity within and across the helix. A detailed section on methods employed[1] follows which highlights the pertinence of a US / UK comparison. Drawing on our empirical data we then present our findings in two sections. The

[1] This jointly funded ESRC/EPSRC funded project is ongoing and will be completed in November 2006.

first section focuses on the findings from our first phase interview survey and recent sources of secondary data in order to develop a more nuanced account of the ways in which the institutional context serves to shape the availability of human resources, access to technology and finance in the UK and US biomedical sectors. Insights derived from this institutional analysis serve as a backdrop to the second section which presents the dynamics and interaction occurring within specific biomedical projects and the positive and negative outcomes with respect to innovation.

The discussion highlights power effects, in many instances embedded in the network relations existing across the helix, in influencing innovation outcomes which has largely been ignored in the development of the Triple Helix III model. In addition, clinicians are identified as a fourth stakeholder / actor that must be included in the helix of interaction in order to understand the major influences on the development of biomedical innovation. Whilst it may be feasible to suggest that clinicians could be classified as a government actor in the case of the UK and an industrial actor in the US our empirical material suggests that this professional group has unique characteristics that shape innovation outcomes and therefore needs to be acknowledged specifically within the model. This draws attention to the problems of universalism inherent in the Triple Helix III model which breaks down when subject to detailed empirical enquiry.

We conclude by highlighting the way in which the co-evolution between technological developments in the biomedical sector and their cognitive and institutional environments over time, has fundamentally altered the R&D environment in terms of the characteristics of the regulatory environment and the increasingly important role played by biotechnology firms in biomedical innovation compared to large, global pharmaceutical firms.

THEORETICAL BACKGROUND

Macro Perspectives

Three major institutional factors – availability of human resources, access to technology and access to finance - have been identified as influencing the development of business competencies (and thus innovation) in biotechnology firms (Casper,2000,Casper & Kettler, 2000). We have utilised these as a macro level framework that underpins (in terms of facilitating or inhibiting) the dynamic and recursive interaction within and across the helices involved in biomedical innovation.

Availability of human resources

Casper (2000) highlights important similarities and also differences between the UK and US in terms of availability of human resources. In broad terms, both contexts have deregulated labour law and decentralised wage bargaining that help to create more active labour markets and career development based on movement across organizations. This should in principal facilitate what Owen-Smith et al, (2002) refer to as the development of integrative and relational capabilities linking public and private science. The former refer to the ability to move back and forth from basic scientific research to clinical development, whilst the latter refer to the ability to work collaboratively across diverse organizations specializing in different fields.

These capabilities however are themselves shaped by distinctive cultural and institutional conditions which Owen-Smith et al (2002) have demonstrated differ across the US and Europe. For example, in the US, career paths are less specialised and there is more movement of key scientists across organizations in the private and public sector compared to Europe as a whole. Our findings explore these differences in more depth across the US and the UK specifically. In the US, co-authorship between university scientists and firms is also encouraged, whereas UK scientists tend not to be rewarded for this. Moreover, the high failure of UK biotechnology firms since the mid 1990s, and the high visibility of clinical trial setbacks, has increased the emigration of reputed 'stars' to the US, where remuneration of scientists and clinicians is also much higher (Zucker and Darby, 1999).

In terms of career development, young post doctoral researchers have greater access to funding opportunities in the US as citations, operating as an impersonal indicator, rather than personal networks, play a more important role in providing access to both public and private funding. The sponsoring of post doctoral researchers into firms from universities is also far less problematic in the US than in the UK, again encouraging public/private collaboration (Casper & Kettler, 2001, Whitley, 2000) although this strategy is beginning to be adopted more widely in the UK (Lam, 2005). These institutional dynamics indicate that differences in the supply and coordination of personnel, and differences in career and incentive systems, may impede interactivity across academia and the private sector in the UK, as compared to the US.

Access to technology

Access to technology concerns access to a high quality basic science, coupled with appropriate regulatory policies and institutions for technology transfer to effectively exploit and

commercialize the science base. Casper and Kettler (2001) suggest that licensing protocols, supportive IP laws, rules governing the transfer of research between the public and private sectors and technology transfer expertise in universities are all more widely available in the US than in the UK. The Bayh-Dole Act introduced in the US in 1980 was specifically aimed at encouraging strategic research partnerships between public and private organizations allowing US universities, to claim patent rights on discoveries produced by research paid for by federal government grants. Importantly, it also meant that academic researchers could be rewarded directly for the patents they produced (Link et al, 2002). The Bayh-Dohl Act has been widely credited with improving university-industry collaboration in the US and has been emulated to some extent (although never formalised in law) in UK regulatory frameworks governing public science. Whilst this change has spurred UK universities into commercial activity through increased numbers of spinouts (Hague and Oakley, 2000; Nicolaou and Birley, 2003) it does not necessarily have a positive impact in terms of innovation outcomes in that these spin-outs have not generated significant wealth creation in the UK (Lambert, 2003).

Access to high risk finance

Access to high risk finance is influenced by national financial institutions (especially venture capital funding) and general market confidence in the ability of financial analysts. The development of biomedical innovations is directly linked to the ability of biotechnology firms and large pharmaceutical firms to raise finance. Significantly, there are differences between the major sources of finance in the UK and US biotechnology sectors i.e. the venture capital markets, in terms of size, composition (the profile of the venture capitalists) and characteristics of their investment decisions (Henderson et al., 1999; Tylecote, 1999; Manigart et al., 2000; Lockett et al., 2002). Historically the US venture capital market was the first to emerge, and is larger than, the combined markets of the UK, France, Belgium and the Netherlands (Manigart et al, 2000). In 2004 venture capital financing of the biotechnology in the US was $3.55 billion compared to £256 million in the UK (Ernst & Young, 2005, BVCA, 2005). This disparity has existed since the VC markets for biotechnology emerged and the gap is not closing (NVCA, 2004). The profile of many venture capitalists is also quite different in the US compared to the UK. Informal venture capitalists, often referred to as ‘business angels’ – ‘rich individuals using their own personal funds, industrial knowledge and contacts’ (Tylecote, 1999:10) - are far more important in the US than formal venture capital - and the majority of these funds are allocated to the high technology

sector which includes biotechnology (NVCA, 2002). In the UK, informal venture capital exceeded formal venture capital by only a factor of 2, and a far lower proportion of these investments are in the high technology sector as compared to the US (Tylecote, 1999). The reason for these differences, at least in part, is the profile of the informal venture capital markets. In the US, business angels tend to be individuals who combine high levels of expertise and experience within high technology industries with financial and business acumen. They are, therefore, in principal well placed to invest in high risk, early stage opportunities in the high technology sector (Tylecote, 1999; Manigart et al., 2000). In the UK, business angels typically do not have specialist backgrounds and so a far greater proportion of investments are made in high technology management buy-outs rather than start-ups which are considered to be less of a risk (Lockett et al, 2002). The current impact of availability of venture capital and the type of investment decisions made are explored further in the discussion.

In the analysis that follows the interaction between these macro level institutional factors and their influence on the development of meso level relational and integrative capabilities and micro level project dynamics will be explored further in order to identify the ways in which different examples of interactivity serve to facilitate or constrain biomedical innovation.

Meso-level perspectives

Biomedical innovation across nations is characterized by an extensive reliance on meso-level networks which rely on the development of integrative and relational capabilities highlighting interactivity and recursivity occurring across the macro and meso levels. Specifically however, at the meso level: given the social embeddedness of knowledge, literature on the development and activities of communities and networks of practice are important in relation to the legitimization of knowledge for innovation (Brown and Duguid, 2001). Communities of practice typically extend beyond the boundaries of a single organization and can involve actors from the three different helix, for example in professional or disciplinary networks. Communities and networks of practice play a critical role in legitimating knowledge by engendering shared identity (e.g. as a ‘clinician’, ‘scientist’, or ‘professional’) which is tied to valued practices and behavioural norms. However, different communities and networks of practice also produce distinctive identities. This means that, whilst communities and networks of practice may promote innovation *within* communities, they may simultaneously constrain innovation *across* communities as different communities with particular vested interests contest what is, and is not,

legitimate knowledge whilst seeking to sustain power and control within their own knowledge domains and over their own work practices (Abbott, 1988; Drazin, 1990; Friedson, 1970). In the context of biomedical innovation power is therefore embedded in these dense networks of interaction (Callon, 1986) and yet power and the effects of power relations inherent within and across communities and networks of relations have not tended to be the subject of empirical research (Contu & Willmott, 2003; Fox, 2001). By incorporating power into our analysis explicitly, we aim to explore the way in which incentives can be used to mobilise powerful communities of practice to promote innovation and also the ways in which powerful firms may serve to disrupt communities and possibly constrain innovation. Our data thus illustrates both the constraining and enabling effect of these meso level networks for biomedical innovation.

Micro- level perspectives

At the micro level we define innovation as a learning process and use a situated learning perspective (Lave and Wenger, 1991) to explore how individuals involved in the case study projects interact and share and create knowledge related to the specific innovation they are focussed on developing. The emphasis from a situated learning perspective is on practice and, in the context of biomedical innovation; a situated learning perspective highlights the way in which universal scientific knowledge is combined with real time, iterative problem solving in the development of innovation. Situated learning, whilst originally conceived of as occurring within organisations, is easily extended to networks of organisations (Araujo, 1998) and even where the site of innovation i.e. the project, is located within a focal organisation, it needs to be recognized that an organization is not simply an aggregation of different communities of practice. Rather organizations are open, fluid systems, of communities of knowing each of which is embedded within a wider epistemic community, or some functional or geographic area (Boland & Tenkasi, 1995). A situated learning perspective also emphasises the embeddedness of learning (and innovation) in power relations. This important characteristic has been ignored more recently (Contu& Willmott, 2003) but is one we wish to emphasise in our discussion of findings. Data from our in-depth cases illustrate that there are significant differences in the ways in which project teams engage in the ‘practice’ of innovation, for example, some adopting a more mechanistic approach to the pooling of knowledge (Knights and Wilmott, 1997) while others achieving a more generative level of knowledge sharing (Newell and Swan, 2000).

METHODOLOGY

The research findings reported here are work-in-progress, drawn from an ongoing study of interactive innovation in the biomedical field in the UK and the US. The primary aims of this research include the development of a taxonomy that captures variation in interactive biomedical innovation and the development of a framework that identifies the factors facilitating and impeding innovation in interactive biomedical projects.

Why a comparative approach across the US and UK?

The US and UK contexts were considered to be useful points of comparison in relation to biomedical innovation because, from a 'Varieties of Capitalism' perspective, they are both 'liberal market economies' that should excel in developing the necessary competencies to innovate in industries dominated by rapidly emerging health technologies (Casper, 2000; Whitley, 2000). In both the UK and US, national systems of innovation are largely supportive of biomedical industry (Casper and Kettler, 2001) – both have world class research facilities and science bases, and internationally recognized pharmaceutical firms (Department of Health, 2004). Indeed, the US and the UK rank as the two most innovative pharmaceutical producers in the world (Department of Health, 2004). The US is the global leader with 1089 biotechnology firms focussing on healthcare technologies in 2003, and the UK is second in Europe with 239 firms (DTI, 2005). Since both nations benefit from comparative institutional advantages governing the organizational competencies needed to innovate within such technological fields (Soskice, 1994), they therefore represent important contexts in which to study interactive biomedical innovation.

The trajectory for development of the UK biotechnology industry has also been closely modelled on regulatory frameworks, strategies and structures for institutional support developed in the US (Casper and Kettler, 2001). Thus, the UK has adopted a so-called 'accommodation' strategy, whereby it has attempted to accommodate its own business system to US entrepreneurial strategies (Casper, 2000). The UK and US are also broadly similar in other respects. For example, the distribution of specialist expertise is similar across contexts and both have strongly established, and powerful, specialist professions. Thus many of the problems influencing the development of interactive biomedical innovation (e.g. inter-professional conflict and asymmetrical power relations between professions) might also be similar across contexts. These broad similarities suggest that meaningful comparisons are possible, as well as opportunities for learning from one context to the other.

Recognizing similarities, there are also critical differences across the UK/US contexts which can inform theory development (Massey et al, 1992) – differences that are not sufficiently addressed in the Varieties of Capitalism perspective. For example, financing and the organization of healthcare is very different across nations and this may have an effect on the development of biomedical innovations. Thus, by comparing the UK and the US – systems that are relatively similar but also distinctive – particular differentiating influences at the institutional level might be explained and understood together with their influence on micro level project dynamics.

1st Phase Research

Given the exploratory nature of the research and the difficulties in establishing a clear picture of the population from which a diverse range of respondents would inevitably need to be drawn (clinicians, scientists, industrialists, etc), the approach taken was to explore biomedical innovation processes in two main phases. The first phase, which comprises the primary data-base for the macro level account of the influence of the institutional context, consisted of a large-scale, interview-based survey conducted with a wide range of relevant and prominent key informants across the UK and the US. The aim of the interviews was to gather as rich and representative a dataset as possible about experiences of innovation in the biomedical field. Obtaining such information enabled an exploration of the social and organizational factors influencing biomedical innovation in general, and also enable a preliminary assessment of the effects of institutional context and of the interplay between meso-level and macro-level influences. This primary data were supplemented with secondary data from a variety of published sources such as specialist reports, recent journal articles etc. that supported the data derived from interviews.

Interviews in the first phase were conducted with a wide range of individuals, all of whom had recent experiences of working in interactive biomedical innovation projects. We focused in particular on selecting those with experience of working in innovation projects that could be described as involving 'systemic production networks', or "formal inter-organizational units jointly producing a product or service in pursuit of a super-ordinate goal" (Alter and Hage, 1993). This differentiates interactive innovation projects aimed at the joint development of specific predefined outputs from other forms of collaboration (e.g. open ended discussion forums or platforms) aimed broadly at sharing learning or ideas. The sample of respondents was diverse and consisted of research scientists, lead clinicians, academics and academic entrepreneurs, technology transfer managers, venture capitalists, policy makers and executives from

biotechnology and pharmaceutical companies. Individuals were initially identified for interview using contacts within the UK and US scientific advisory boards that had been set up to oversee the research. Board members were selected on the basis of their prominence and active involvement in the biomedical sector and were able to identify individuals who had the experience of interactive innovation that the research team were looking for. From these initial contacts, additional interviewees were identified using a snowballing technique. This kind of non-probability convenience sampling can be extremely useful when the research is exploratory and population parameters are unknown (Saunders et al, 2000).

In total, 98 full interviews were conducted, 45 in the UK and 53 in the US[2]. Table 1 shows the distribution of interviewees by type of respondent – in total and separately for the UK and US.

Insert Table 1 about here

The distribution profile reflects an attempt at an approximate stratification of the sample, according to the prominence of different groups involved in biomedical innovation. So, for example, a reasonably large group of 'entrepreneurial' academics researchers and industrialists (from both small biotech and large pharmaceutical firms) were interviewed, as these were likely to be the principal actors engaged in the types of innovation of interest to the research team (as opposed, for example, to academics involved in 'pure' genetics research or companies marketing incrementally innovative medical devices).

Interviews lasted between 45 to 80 minutes and were predominantly face-to-face, with less than 15% being conducted over the telephone. Interviews were semi-structured and followed a pre-designed interview format, in which respondents were asked about their background, their experiences of innovation projects and of the processes involved, relationships with other organisations and their more general views on barriers and enablers to innovation in the biomedical field. Interviewees were also prompted to relate stories of one or more innovation project (successful or unsuccessful) that they had been involved with. Interviews were tape-recorded and the transcripts were coded and analysed using NVIVO software. The results of each

[2] A further 22 exploratory meetings were held to discuss the research and possible participation (17 in the UK and 5 in the US).

analytical ‘cut’ were described using the ‘memoing’ technique (Glaser, 1978). Each researcher initially tied together different pieces of research information into a recognisable cluster, derived appropriate methodological and theoretical/conceptual lessons (Miles and Huberman, 1994) and sent to the rest of the research team for comment. This process generated the major findings around the three factors – availability of human resources, access to technology and access to finance - that we have used to frame the institutional context for biomedical innovation in the US and UK.

2nd Phase Research

The second phase, which is currently ongoing, comprises 6 longitudinal case studies of interactive innovation projects in the US and UK. The projects were selected on the basis that the innovation project was about to, or had just entered clinical trials. This point in time was chosen on the basis that the innovation process is typically characterised by significant interactivity during this period across academia, a host of private sector firms, public research organisations, clinicians, patients and government regulatory agencies. Interviews with project team members, observational and documentary data (pertaining to project meetings) is being gathered to develop rich, micro level accounts of the interactivity occurring within the projects, the nature of the situated learning taking place and the factors at a macro, meso and micro level that are facilitating or constraining the innovation process. Again all interviews are being transcribed and coded using the ‘memoing’ technique within NVivo and shared across the team. As the project is ongoing it needs to be emphasized here that this paper reports our preliminary findings regarding the factors facilitating and constraining biomedical innovation across these 6 projects. All projects have also been anonymized to maintain confidentiality.

FINDINGS

The US/UK contexts compared

Availability of human resources

Secondary data in combination with our survey data confirmed that, in particular, integrative capabilities skills are not as well developed in the UK compared to the US. Owen-Smith et al’s (2002) work compared the US with Europe as a whole whereas our research focuses specifically on a US/UK comparison. These skills are fundamental to promote the interactivity required across government, academia and industry to promote biomedical innovation. Our data suggests

that in the UK the movement of scientists between public and private science throughout careers is far less common compared to the US. In the US it is not at all uncommon for scientists to spin-out firms (with the support of Technology Transfer offices), spend a period of time working in that firm, whilst continuing to be employed by their university and subsequently return to their academic post. This is not at all common in the UK. A number of interviewees made comments typical to the one below:

> *"I think that the major difference is that academics are less predisposed to be entrepreneurial in this country [UK], and if they do look in that direction, they've got fewer role models to look at. Generally, if an academic in the States is interested in forming a company, he can probably find two or three of his colleagues who have done that already and can talk to them and learn the process."* (Industry representative, UK)

In addition many US academics have active consulting posts that involve them working part time for companies. This strategy is starting to be adopted by large pharmaceutical firms operating in the UK that are beginning to extend their internal labour markets by entering into collaborative, often short term arrangements with academic scientists. Lam (2005) however demonstrated that in the UK context this is problematic for the individuals concerned. Managing the tension between academic norms of free communication with industrial requirements for confidentiality is considered difficult, particular for young academics that are dependent on research output for future employment. Lam's (2005) work highlighted that in the UK academic scientists who simultaneously engage in science and business systems experience a "great deal of role pressure and tension" (:271) and a number of our interviewees commented that scientists who managed to combine an academic career with entrepreneurial activity *'did not really fit'* in the UK system and were *"often treated with suspicion"* within their academic communities. In the US there is a much longer tradition of working simultaneously in both the public and private sector and conflicts of interest are addressed much more explicitly. Our data suggests that in the UK there is far more reliance on informal commitments when operating in both contexts that involve trust between academia and industrial actors which is ultimately not particularly helpful and is supported by Lam's recent findings.

Our survey data highlighted that the education system plays an important role in the development of relational and integrative skills necessary to become an entrepreneurial scientist. In the US for example, it is common to find universities that offer those pursuing a scientific or

medical career the opportunity to combine this with the study of business subjects at postgraduate level which better equip individuals to engage in entrepreneurial activity. Of the 27 universities that Owen-Smith (2002) identified as Research 1 universities 24 offer dual degree programs. However in the UK only University College London offers a dual MBA, PhD and a further 2 universities offer an undergraduate business degree in combination with a medical degree. In the US comments were made such as

> *"The students on these courses become aware very early in their scientific careers of thinking ahead to what the results of their research can be, beginning to understand what it takes to get from a interesting experiment that you might be able to publish a paper on and how do you get to a product or a company or whatever. That changes the culture. If you think about the fact that yes, some of the good students are going to grow up to be professor clones, but a lot of them are going to go on to work in industry, this kind of knowledge is a critical part of their competence." (US academic)*

Interview data also suggested that when Cambridge University in the UK attempted to introduce a dual Masters program combining science and business, there was considerable resistance from faculty who were unwilling initially to engage in the development of such a program.

Clinicians are also naturally implicated and involved in the development of biomedical innovation (a point to which we will return in the discussion) and here again we find significant differences across the UK and US in their educational backgrounds. In the US anyone wishing to specialize in medicine must already possess a first degree in a basic science whereas this is not a requirement in the UK. This educational foundation in basic science means that clinicians in the US do have an appreciation of the value of scientific discovery and our survey data suggested that this is potentially beneficial when it comes to their enrolment in innovation projects.

Our data suggests that relational capabilities are roughly equivalent across the UK and US. This is not particularly surprising given the survey sample – individuals active in biomedical innovation projects – and the fact that the biomedical sector is characterized by intense collaboration across a host of organizations (Powell et al, 2005), which is still gaining momentum as illustrated by the fact that the number of pharmaceutical firm/ biotechnology firm alliances increased significantly by 27% to 831 in 2003/4 (Ernst & Young, 2005).

Access to Technology

A high quality science base naturally requires government investment in academia in order to develop. When we compare the UK and US, we find that total spending on health (R&D), science and technology in the UK was £4.2 billion in 2004, compared to $33.6 billion of funding provided by the National Science Foundation and the National Institute of Health. It is evident therefore that overall investment in the science base for biomedical innovation by the UK Government is much lower than in the US (HEFCE Report, 2005). However, the UK ranks second in the world only to the US in terms of world citations in the sciences, providing good evidence of the quality of the science base. In addition, citations per researcher are approximately twice that of the US indicating that the UK government is achieving very good value from its investment (Office of Science and Technology, 2005).

If we consider the regulatory policies that exist and the institutions for the transfer of technology, we have however found from our own data, supported by secondary sources that there are significant differences between the US and the UK which appear to put the UK at a disadvantage in terms of mechanisms for technology transfer (BVCA, 2005). Whilst the UK has to some extent emulated the Bayh-Doyle Act, the UK lags behind the US in its expertise in technology transfer and one of the reasons cited for this is the lack of clarity of ownership of IP in research collaborations, particular those involving joint university industry funding (Lambert, 2003). If we consider the number of patents and licensing agreements produced we find that UK universities produce roughly equivalent numbers of both per £1million of research, but significantly lower income from intellectual property licensing agreements. In addition UK universities produce a far higher number of spin-outs per £1m of research than the US however again these spinouts are often unsustainable (Lambert, 2003, Office of Science & Technology, 2005). The reasons given from both secondary sources and from our own survey data regarding the lack of economic viability and profitability from licensing deals and spin-outs in the UK is the lack of expertise of technology transfer staff in the UK (Lambert Review, 2003, Lockett & Wright, 2005). The following comment was typical:

" Most of the technology transfer people in the UK are useless ……they try to negotiate the best deal for the university by screwing everyone down to the last penny – academics, industrial partners". (Academic UK)

With very few exceptions UK academics perceptions of Technology Transfer offices in the UK were that they were a *'blocking step', 'greedy', 'alienating', 'short term focussed'* and lacking in

professionalism. In contrast, the MIT technology transfer office was often mentioned by interviewees in the US as a model of excellence and was considered to be highly professional. It was suggested that MIT technology transfer office was populated by individuals with both academic and industrial experience who had developed well-defined procedures for managing licensing and spin-out activity and took a hands-off long term approach to the relationship. The importance of the region however was also emphasised highlighting the point made by Cooke (2005) about the development of regional innovation systems and the Massachusetts area in particular:

"MIT benefits from our geography. We are in highly entrepreneurial communities with experienced entrepreneurs, with venture capital willing to do early stage stuff, with people who know how to work in small companies, so we are very different very much because of the climate which we have created over 50 years". (TTO US)

Access to Finance

Many interviewees commented that the halcyon days of very high investment in biotechnology had long since passed (following the lack of short term returns following the hype around the sequencing of the human genome) and it was becoming increasingly difficult to attract early stage financing that would support the movement from proof of concept into clinical trials. This situation exists in both the US and the UK (Ernst & Young, 2005). Whilst venture capital investment in biotechnology has increased in the UK in 2004 over 2003 to around £375 million (Ernst &Young, 2005) the amount invested in early stage actually decreased by 30% in 2004 over 2003. The number of firms financed in early stage actually increased but the figures indicate that the funding they received was significantly less. Partnering arrangements between large pharmaceutical firms and biotechnology firms also appear to be in the same situation insofar as large pharmaceutical firms are looking increasingly to partner innovations that have already entered clinical trials, in order to reduce the amount of risk they take on. This point was made by a number of interviewees in the US and UK and confirmed by the all the venture capitalists we interviewed.

In summary we find therefore that in broad terms the US context is more supportive of biomedical innovation than the UK in terms of availability of human resources with superior integrative capabilities, the expertise of technology transfer staff in securing revenue generating arrangements for IP and availability of high risk finance, the scale of which does not compare.

However, there a number of other institutional factors which are similar across contexts. Our survey data suggests that relational capabilities are probably equivalent across contexts. Biomedical innovation is inherently collaborative, as individual firms typically do not possess all of the necessary resources (expertise and financial) for innovation. This finding from our survey data seems to be supported by the US and UK's dominance of the sector. The science base is also clearly exceptional in both countries and whilst there is a much larger VC fund available in the US for biotechnology, access to venture capital is difficult in both the US and UK for early stage innovation.

Moreover, the data derived from our 6 biomedical projects which are presented below illustrates that while macro-level differences do exist and influence biomedical innovation processes, the extent of their influence often depends upon the power effects operating across the helices.This is explored further in the discussion.

The micro-dynamics of interactivity in biomedical innovation projects

Table 2 presents a summary of the important characteristics of the innovation process across all 6 projects paying particular attention to the interaction occurring across the helices, including the interactivity occurring between clinicians and other actors, specific macro/meso level influences on project working and importantly, specific power effects that were shaping the innovation process and potentially innovation outcomes.

Insert Table 2 here

DISCUSSION

The case data demonstrates that there was significant interactivity occurring across the helix in all of the cases providing empirical support for the model. The vast majority of science on which all of the innovations are based originated from public sector funding demonstrating government /academia interaction and the important role government plays in the UK and US in promoting innovation. Industry/academia interaction was also often referred to in projects but typically occurring at an earlier stage in the innovation process. Case 1 however demonstrates the way in which doctoral students are able to spend time in industry working on leading edge research in the US without necessarily compromising their academic positions,

facilitating the development of integrative skills. In case 6 in the UK there is also evidence of the application of integrative skills in the innovation process with two of the executives of the firm also working simultaneously in academia. This is not typical however and might be explained by the fact that these individuals are 'star scientists' recognised globally in their field. Hence they are sufficiently secure and professionally powerful to engage in what are considered to be atypical activities in the UK. This assertion is also supported from UK 1st phase data insofar as a number of individuals were identified as simultaneously moving between academia, the UK National Health Service and the private sector but all were acknowledged as leading in their particular fields, possessing the expert power to operate in this way without compromising their academic positions.

More generally industry/academia interaction was fairly limited across our cases. This can perhaps be explained by the fact that all of the projects were entering or engaged in clinical trials where it might be expected that interactivity across these two helices diminishes. The stage of development across all 6 projects could also explain why whilst 1st phase data suggested that the mechanisms for technology transfer were not as well developed in the UK, this problem has not emerged from case data, as in all cases IP had successfully transferred into the private sector from academia (where relevant) at an earlier point in time in the project life cycle.

Conversely, in the majority of cases interactivity between government and industry was high. This interactivity was occurring as a result of joint development of regulation, where none existed for particular tissue engineered products and also for orphan products. Interactivity was also high in projects where firms lacked expertise with regard to regulation and guidance was sought from the FDA. Again this interactivity reflects the fact that projects were entering clinical trials but it needs to be highlighted that the interactivity was recursive with the regulatory environment not only influencing industry but also industry influencing the regulatory environment. A point we will return to in the conclusion.

Significantly, clinician interaction with industry was perceived as vital at this phase in innovation projects. If clinicians could not be enrolled at this stage, or decisions were taken by firms not to fully involve this actor then innovation outcomes appeared unlikely to succeed (see Case 3). In the case of radical new therapeutics (Case 1) where the innovation will significantly disrupt existing medical practice then firms also need to have significant power in terms of network centrality and financial resources to be able to promote clinician engagement. In Case 4,

a firm inexperienced in clinical trials, initial design of trials had been conducted in-house and subsequently failed (in terms of recruiting adequate patient numbers). New trials had subsequently been designed in close conjunction with clinical experts in the field from the UK, other parts of Europe and the US in order to be more confident of success. In Case 3, again the trials were designed in-house with limited clinician involvement and again this was perceived as having a detrimental effect on the innovation process.

Evidently, clinicians represent powerful meso level networks / communities of practice that significantly shape activity at the micro project level. They also have the ability to shape macro level diffusion of innovations. Arguably if Case 1 biotech had not been able to enrol such significant numbers of clinicians in the Boston area there would have been little hope of promoting this new therapy for joint repair. Clinicians as a professional group therefore represent a powerful actor that can both support or disrupt the innovation process and firms that do not occupy a similarly powerful position (in terms of position and resources) may find it difficult to generate clinician enrolment. Case 5 illustrates this point. The pharmacogenetic project has very limited resources and intangible incentives have largely been relied upon to promote clinician engagement in the project which ultimately has been deemed to be successful by those involved in one region of the UK. However, there are insufficient resources available to promote broader clinician engagement and other regions in the UK are not considering adopting this innovation despite what appear to be obvious benefits to patients This finding, regarding the need for clinician engagement in order to promote the diffusion of innovations is supported by a number of other UK studies (see Swan, Robertson & Scarbrough, 2003; Dopson, 2005).

Clinicians are also heavily implicated in the situated learning process occurring within project teams, shaping decision making around clinical trails. Where clinician input is limited or business priorities take precedent (Case 3), successful innovation outcomes appear to be jeopardised, particularly in smaller biotechnology firms. Hence whilst this group represent a powerful community with the potential to disrupt innovation, their expertise is invaluable in terms of the situated learning occurring within the firm. More generally project team working was characterised by a very formal approach to project management, using rigid protocols in the majority of cases, many of which were deemed necessary in order to comply with FDA regulation. In case 3 where a more emergent approach to project working had developed innovation outcomes seemed likely to be negative. In all cases there was significantly high

pooled inter-dependency within and across organizational boundaries which demanded high levels of trust. Where trust relationships broke down (as occurred in Case 3) or were strained (as in case 2) project working was sub-optimal demonstrating that high-interdependency relationships naturally demand the development of high trust relationships.

The lack of funding (both VC and equity made available from alliances with pharmaceutical firms) for early stage innovations at the macro level appears to have had a significant influence on the activities of small biotech firms with both positive and negative affects with respect to innovation. Case 3 demonstrates the way in which the firm diversified away from its area of expertise (autoimmune diseases) into the more lucrative and commercially attractive obesity field in the hope that this would attract VC to support the firm. This was a risky strategy and one that appears not to have paid dividends given the lack of in-house expertise and small size of the firm. Conversely, in Case 6 new therapeutic targets are being sought for an already patented wound therapeutic in order to attract more investment that can then be re-invested in other tissue engineering projects. This focus on exploitation in the short term, if successful, could lead to positive outcomes in terms of generating funds to invest in new innovation projects. In case 6 then a lack of VC funding has driven the firm to adopt an exploitation strategy with potentially positive outcomes for innovation as opposed to the exploration strategy adopted by case firm 3 which seems to have been unsuccessful (Levinthal & March, 1993). In case 4, the firm was effectively forced to engage in clinical trials, a route it had not taken before, because of large pharmaceutical firms' reluctance to partner in relatively early stage development projects, mirroring the current investment decisions of VC firms. This has had a positive innovation outcome in terms of generating new learning and expertise in the firm which can be exploited in future projects.

This case, in particular, may provide some insight as to the reasons why the biotechnology industry has recently emerged as more innovative and productive than the pharmaceutical industry. A number of reasons have been proposed for this including the academic culture that exists in many biotechnology firms rooted in academic beginnings (illustrative of the Triple Helix model), their tolerance of risk and the IP rules governing biotechnology products which provide more protection (Ernst & Young, 2005). Case 4 illustrates however, that macro level restrictions on availability of finance appears to promote innovation and productivity in the biotechnology industry as small and medium sized firms begin to engage

in later stage development activities such as clinical trails, which, if successful results in new learning and the development of expertise that was once only possessed by the pharmaceutical industry.

As has already been highlighted it is evident from the case study data that power significantly shapes innovation outcomes. By developing a multi-level analysis, both resource power and power embedded in networks of interaction stand out as mediating variables in terms of innovation outcomes. In case 1 the firm has been able to work with the FDA developing regulation because of its network centrality in the Boston biomedical sector, and in so doing has potentially created barriers to entry for other firms with similar products with potentially negative outcomes for innovation. In case 2, where vast amounts of scientific effort continue to generate new knowledge about the potential therapy, the firm has used its significant financial resources in order to buy patents emerging in the area around the therapy in order to defend its intellectual property and prevent new firms entering the field. This activity is also potentially disruptive to the scientific community engaged in research in this area. In cases 3, 4 and 6, the lack of funding available for early stage development has driven small firms to attempt to engage in clinical trails with both positive and negative affects in terms of innovation outcomes illustrating again the power effects of selective resource allocation by VC firms and powerful pharmaceutical firms.

CONCLUSION

The aims of this paper were two-fold; to provide a multi-level empirical account of the dynamics of interaction in the Triple Helix III model of innovation and to empirically demonstrate the co-evolution between biomedical innovation and the cognitive and institutional environment in which it occurs which has altered the R&D environment. The data has amply demonstrated the interactivity occurring across the three helices proposed in the model and has also identified clinicians as a professional group that should perhaps be mapped onto the model of interaction as a fourth interactive helix. This finding highlights the problems of universalism inherent in this type of model of innovation which cannot be overlooked. The empirical data also highlighted the recursivity that was suggested by Etzkowitz & Leydesdorff (1999) to occur across the macro, meso and micro levels such that networks of clinicians at the meso level were seen to influence both macro and micro level innovation activity; individual firms at the micro level were also shown to shape relationships with these meso level networks in terms of enrolment and; importantly, now also appear to have some influence on the macro regulatory environment.

This latter example thus provides evidence of the way in which the R&D environment for biomedical innovation is fundamentally changing. Morris (2000) has suggested that industry involvement in the development of regulation will inevitable lead to conflicts of interest and our case data has highlighted that this interaction does possibly have detrimental effects in terms of innovation outcomes. The biotechnology industry is now emerging as more innovative and productive in terms of R&D compared to the pharmaceutical industry also reflecting change in the R&D environment for biomedical innovation. Our data has highlighted the way in which one previously unidentified factor – the availability of high risk finance - may, in conjunction with other factors previously identified, have promoted this change. Power also emerged as a mediating variable shaping innovation outcomes which has not previously been directly identified in research on the Triple Helix III model.

Temporality, in terms of the stage in the innovation process, was also identified as fore-grounding or back-grounding particular types of interactivity occurring across the helices such that the projects we focussed upon fore-grounded industry/government interaction and back-grounded industry/academia interaction. This illustrates the limitations of our study and highlights the need for researchers to engage in further multi-level analyses of the Triple Helix III model of innovation, across other sectors in order to develop the model further.

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FIGURE 1 TRIPLE HELIX MODEL FOR BIOMEDICAL INNOVATION

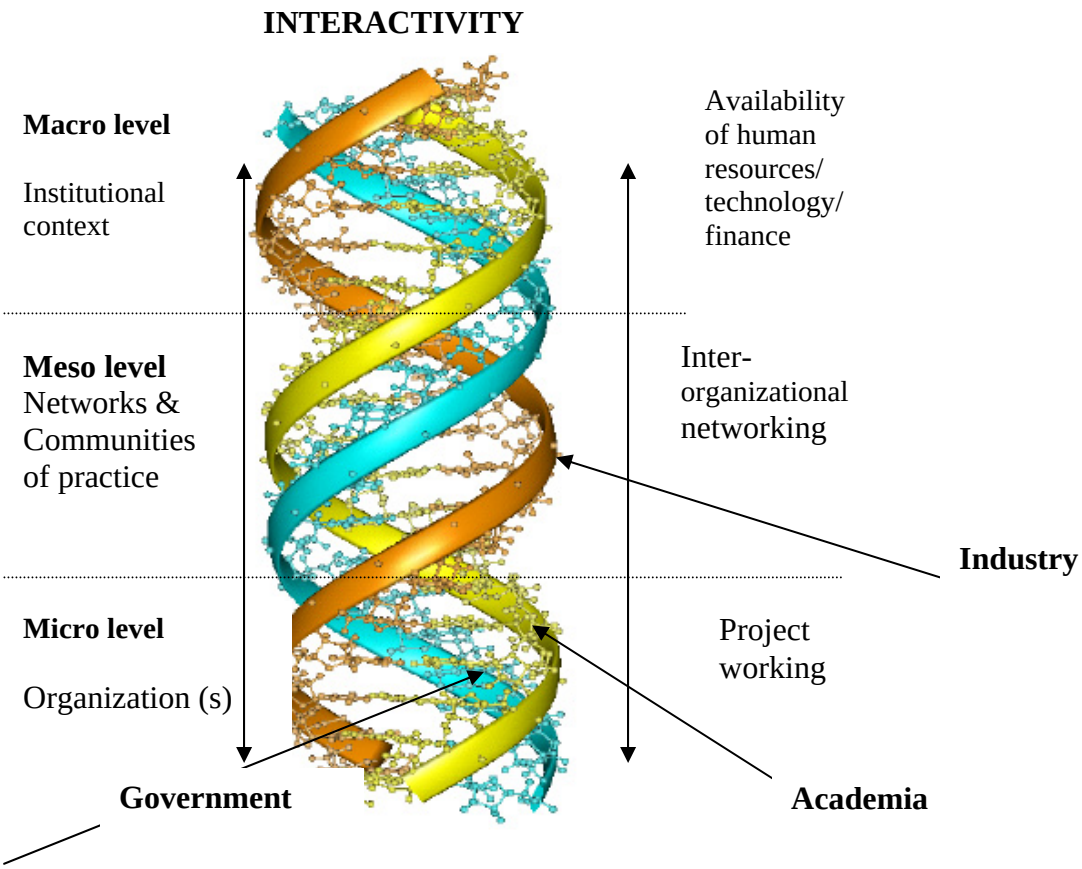

TABLE 1: BREAKDOWN OF SAMPLE OF INTERVIEWEES IN US AND UK

	US	**UK**	**Overall**
Academia	14	16	30
Industry	24	14	38
Support Organizations (VC, consultants)	7	6	12
Tech Transfer	5	4	9
Government	1	2	3
Charities	2	3	5
Total	**53**	**45**	**N = 98**

TABLE 2 INTERACTIVITY OCCURRING ACROSS 6 BIOMEDICAL PROJECTS

Project	**Government/ academia interaction**	**Industry / academia interaction**	**Government /industry interaction**	**Clinician interaction**	**Macro/ meso level influences**	**Nature of project team working**	**Power effects**	**Innovation outcomes**
1. US biotech firm. **Tissue eng'nd therapy for joint repair**	Has been significant public funding in both UK and US in tissue engineering research that provides foundation on which this type of innovation is based	Early research conducted by Swedish academic on 1st generation product. Subsequent work done by PhD student in bio-tech on technology acquired from German company which also worked closely with academics in the EU to develop 2nd generation product.	Industry / government interaction to jointly create FDA regulation around 2nd generation product	Had to convince surgeons to use new therapy product; put on fully-paid training sessions in Boston which 10,000 surgeons were paid to attend; enrolled clinicians on firm's advisory boards	Lack of regulation could have constrained innovation but by working with FDA these problems have been overcome	Multi-functional team work using fairly structured project management methodology that includes schedules for meetings, reviews, milestones etc. Most people work in same geographical area making communication easier. High interdependency	Network centrality of US firm conferred power to the firm which facilitated the joint development of regulation with the FDA that has created barriers to entry for similar tissue engineered products	Positive with respect to this one product but negative with respect to these particular tissue engineered products more generally
2. US biotech firm. **Anti-body therapy**	There are more than 23,000 papers published on this particular molecule, much of this by academics whose research is	Core team members see themselves as very much part of the broad community of scholars in this area; they	Have worked with FDA previously to set up fast-track FDA filing for orphan	Have panel meetings with clinical experts who guide them in making decisions about what	Sheer amount of research activity across scientific community interested in	Project is a joint project with UK bio tech. Follow standard US biotech project management protocol and	US bio is in a position to buy up range of patents in this area to prevent other firms	Unknown – despite vast amount of research are only now about to enter clinical trials phase.

	supported by government research funds.	attend conferences and write papers themselves: Some of the initial IP for the project also came originally from academia (the Whitehead Institute).	drugs (to treat diseases where there is currently no cure) and plan to do the same with this antibody.	disease to target, how to design clinical trials etc. Often also use patient advocacy groups to identify patients for trials – use physicians to work with these advocacy groups	this field means that the science base is highly accessible so only companies with considerable power can protect their space and continue to work to find therapeutic targets.	UK biotech has to mirror this. Relationships strained because project has been going on for 5 years, and have not actually managed to get into clinical trials	entering into this specific medical field. Not only acquired IP but also have power to defend that IP	
3. US small biotech firm. **Obesity drug**	Some research in universities sponsored by government but not really a main source of interaction	Do maintain networks with academics but not a main source of interaction	Follow well defined FDA protocol but firm has limited expertise in this area. Regulations clear so limited interactivity	Clinical studies designed in-house and undertaken where could find cheapest and quickest sites to conduct them. Lack of clinician interaction has been a factor in poor design of	Small company with no marketable products. Chose to develop this drug to attract more venture capital but not main area of expertise	Because of its small size the firm relies heavily on close interaction with larger biotechfrom which it was spun out from to help understand the problems. More emergent approach to project working. Insufficient input from	Lack of power given small size and hunger for a quick hit has led them to take a lot of risk; this has back-fired with the failed clinical trial.	Probably Negative. Now considerable scepticism that the polymer will be useful. Now have to go back to animal testing and bring in experts in the field to move

				trials and lack of success		scientists and business criteria has dominated.		forward.
4. UK bio-tech **Anti-Body therapy**	Original science developed in Public Research Organization. No longer any direct interaction	Very limited. The expertise pre-dominantly in-house	Working with FDA to ensure that the product and the clinical trials meet US regulations	Close industry/ clinician interaction in a biotech inexperienced in conducting clinical trials	Equity funding increasingly focussed on later stage innovations has led to firm engaging in clinical trials in order to attract a licensing partner (large pharma)	High trust intra-organisationally and high interdependency across organisations involved in manufacturing for scale up to clinical trials and clinical support service organisations. Generative learning around the clinical trial process	Large pharma who could be potential partners shaping firm strategy to start to engage in clinical trials	Positive innovation outcomes driving the project forward. Relational capabilities enhanced with closer involvement with a host of organisations involved in clinical trials
5. UK Govt. funded project **Geno-Typing** (to identify adverse reactions to an	Government involved through funding of (a) the infrastructure associated with the project as well as the project itself. However, no direct ongoing involvement in the project itself.	Minimal; limited to very specific outsourced activities	Not applicable	High dependence upon clinicians (within the team and across wider constituency) to provide access to patients for clinical trials. Reliance too	Project is part of a wider Govt. initiative and so is a 'showcase' for local relational capabilities centred around meeting	Highly interactive amongst multi-disciplinary team of academics and clinicians, albeit based on clear division of labour that avoids individuals/ groups over-	Lack of commercial drivers and absence of IP issues means intangible forms of leverage (e.g. stressing the originality and practical	Positive outcome - academic and clinician interaction at meso- and micro-level are both crucial and generally positive. Relational capabilities

immuno-suppress-ant drug).				placed upon networks of contacts with clinicians in other parts of UK to provide recruitment bases for patient trials.	wider scientific / clinical needs. It is also the first attempt by the NHS to evaluate the intro of pharmaco-genetics testing in hospitals	stepping their areas of expertise. Structured project management methodology used is seen as unusual in this context and a reason behind the success of the project. Co-location and purpose built facilities seen to facilitate interaction.	value of the research to hospitals; appealing to key gatekeepers' career interests; intensive use of existing social networks) to drive project.. Still problems getting wider NHS buy-in.	here substitute for lack of commercial incentives that promote goal alignment amongst participants.
6. UK small biotech firm **Wound thera-peutic**	Firm spun out to commercialise innovations of a research centre based at top university hospital that specialises in tissue engineering. Government funding has been	Company has preferential rights to exploit current / future technologies emanating from the centre. There are close links with scientists there, including both founders who	Product patented and approved, so less salience attached to regulatory issues.	Direct interaction with clinicians is limited, though links with the research centre and a consultant based at another	Very small company needs a big, quick commercial success to attract more investment. Hence focusing on late stage innovation	Firm operates as a virtual company with three executives. Project team working is highly distributed and focused on new business development.	IP rights over existing product, combined with access to scientific knowledge from research centre run by renowned 'star	Positive for innovation where commercial success involves eschewing discovery and focussing instead on exploitation

	significant in supporting the centre and in providing grants to develop its work. Seed corn funding also provided (through the university) to support work related to the firm.	continue to be involved. However, business managers (with scientific backgrounds) now run the company and less direct interaction between those on the commercial side and those on the academic side		hospital provide direct contacts.	(using already well established product). Firm contributes to basic research by acting as collaborator on research grant applications	However, a decision to move into manufacturing in 2006 means a move to new premises and the recruitment of a project manager and 2 scientific consultants.	scientist' gives the company bargaining power to establish a network of contacts and strategic alliances. Major licensing deal with biotech firm compensates for the firm's lack of resources	of an existing product. Relational capabilities enhanced using this strategy which aims to generate increased revenue for future innovation in tissue engineering