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Gatekeepers and proximity in science-driven sectors in Europe and Asia: The Case of Human Embryonic Stem Cell Research

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Abstract:

The production of new knowledge cannot only rely on regional innovation systems but needs also creative inputs and diversity by interactions with actors in other regions. Science-based sectors like stem cell research with its narrow linkage of basic research from different scientific disciplines, a diversified set of applications and potential commercial products for different markets depend particularly on institutions to enhance interactions between actors in different regions to improve efficiency of knowledge production. Gatekeepers serve to provide interface nodes between regional innovation systems by different forms of proximity. The paper analyses political approaches to support gatekeepers in stem cell science in three European and three Asian countries and their impact on the organisation of knowledge production.

German Translation:

Die Produktion neuen Wissens erfordert Interaktionen zwischen Wissensträgern, die über die räumlichen Grenzen regionaler Innovationssysteme hinausgehen. Gerade in wissensbasierten Sektoren wie der Stammzellforschung mit einer engen Verknüpfung von Grundlagenforschung aus unterschiedlichen Disziplinen, Anwendungen und möglicher Kommerzialisierung auf unterschiedlichen Märkten bedarf es ergänzender Institutionen, um Wissensflüsse innerhalb dieser Interaktionen effizient ablaufen zu lassen. Gatekeepers bilden

in diesem Kontext Schnittstellen zwischen einzelnen regionalen Innovationssystemen und verknüpfen regionale Wissensströme mit Hilfe unterschiedlicher Formen der Proximität. Der Beitrag untersucht unterschiedliche Politikansätze zur Unterstützung solcher Gatekeepers in drei europäischen und drei asiatischen Ländern für den Bereich der Stammzellforschung und ihre Auswirkungen auf die Organisation der Wissensproduktion.

1. Introduction

The transition towards the knowledge economy has been accelerated by the emergence of new modes to produce and exploit scientific knowledge. Existing boundaries between disciplines and between basic and applied research seem to vanish in new emerging sectors like bio-photonics, adaptronics, or nano-medicine, where many academic spin-offs act as intermediaries between different epistemic groups and different regions (GIBBONS ET AL., 1994; BENZLER, WINK, 2005). Accordingly, geographical proximity and organisations acting explicitly as gatekeepers between regions to enhance the regional knowledge base seem to be of less relevance than in other – more technology- or culture-based sectors. The amount of codified knowledge should be higher for science-based sectors due to the more theoretical and abstract basis, and the novelty of these new sectors reduce the influence of existing incumbent (cultural) routines. Thus, "out-cluster" strategies seem to be easier for science-based firms (FONTES, 2005). Therefore, literature and policy are concentrating on the enhancement of cognitive proximity within the science-based sectors as prerequisites for successful knowledge generation and exploitation. Typical examples mentioned in the literature are the "Biopolis" in Singapore, where scientific researchers and firms are spatially concentrated in a specific area and leading Western scientists act as cognitive leaders for funding schemes, systems of academic qualification and recruitment, or Taiwan with an explicit innovation platform strategy (FINEGOLD ET AL., 2004; GALLAUD; TORRE, 2004).

Within this paper, we analyse how gatekeepers are implemented in European and Asian regions and which consequences for knowledge management in science-driven sectors can be observed. We restrict our investigation to human embryonic stem cell research as a typical example for a relatively young scientific research field with high public awareness and several public supporting schemes in all industrialised countries (for overviews LIYANAGE ET AL., 2007). It is characteristic for the new “mode-2”-knowledge based sectors (NOVOTNY ET AL., 2001), as the knowledge base is interdisciplinary with incumbent technological paradigms (e.g. transplantation medicine) and new scientific models (e.g. cell nuclear replacement as a new technique to emerge and derive new stem cells), the research has to integrate theoretical basic knowledge as well as concrete applications and the awareness of the general public is relatively high due to the expected options to cure so far incurable diseases and ethical concerns. This controversial assessment of ethical concerns could also create additional incentives for researchers to use international collaboration as a means to be at the leading scientific edge despite restrictions on a national level. The paper is organised in four parts. Firstly, an introduction into the theoretical basis is given leading to some basic hypotheses on the relevance and functions of gatekeepers. Secondly, the challenge for interregional knowledge interaction is described, which is then followed by a brief overview to stem cell research policies in selected European and Asian countries. Finally, experiences from selected regions and countries in Europe and Asia are used to discuss the chances and limits of interregional gatekeepers to enhance the knowledge base in science driven sectors.

2. Knowledge and Proximity in Science-Driven Sectors

As already described in the introduction, science driven sectors are distinguished from other sectors by several characteristics (ASHEIM; ISAKSEN, 2002; BENZLER; WINK, 2005):

- Abstract and theoretical scientific models serve as the main framework for new knowledge.

- There are no clear boundaries between basic and applied science, new scientific insights can be integrated directly into new services and goods.
- Scientists can act as academic entrepreneurs being simultaneously engaged in scientific research and management.

These characteristics play a major role for the emergence of innovations, which is the result of a process of knowledge production. Within this paper, we follow an innovation system approach, which includes the whole process of knowledge production starting from knowledge generation via knowledge examination to knowledge exploitation. With the term innovation system, we refer to systemic linkages between single innovation networks to enhance interaction of knowledge between the networks and their members and to increase the innovative capacity of the whole system (COOKE ET AL., 2003; HARMAAKORPI; MELKAS, 2005 with further hints on regional innovation systems). These networks have relatively loose structures (compared to formal organisations) and are formed by heterogeneous groups (universities, firms, research units, services organisations etc.). Many papers on innovation systems focus on specific elements of knowledge production, for example scientific and firm research or finance. This paper takes a perspective on the whole knowledge production process to identify the different challenges for the use of gatekeepers along the process (COOKE, 2004, on this systematic perspective on the whole process of knowledge production).

Knowledge generation as the source of knowledge production is based on learning and/or creativity (STEINER; HARTMANN, 2006). Learning means the conscious or sub-conscious processing of own or foreign experiences, while creativity implies unconventional breaks with previous knowledge (ABERNATHY, CLARK, 1985). Both processes depend on interaction, because stimulation for the human brain would be too weak without experiences from others to continuously form new knowledge. Knowledge examination means the critical assessment of the quality of new knowledge, including the range of possible applications of the new knowledge, its prerequisites and limits, and possible intended or non-intended side effects (LIYANAGE ET AL., 2007). Interaction offers the opportunity of more unbiased assessments and broader diffusion. Finally, knowledge exploitation requires an understanding of suitable applications of the new knowledge and the prerequisites to integrate the new knowledge into different contexts and to process the experiences of the applications within continuous learning processes. Again, interaction is an essential prerequisite to understand possible fields of applications and to communicate the prerequisites for adjusting new knowledge and incumbent application fields to each other.

These needs for interaction cause two specific problems of mutual dependence between the interacting parties: (1) the risk of misperception of the message due to different cognitive patterns by the interacting partners, and (2) the risk of default due to a lack of mutual trust and secure expectations on the credibility of the interacting partner.

The risks of misperceptions are related to the cognitive context of the interaction. The individual cognitive patterns – based on genetically determined preconditions in the human brain and social experiences – determine, how an individual interprets messages from interacting partners, connects these with already stored knowledge and decides on the actual meaning of this message for future contexts. If the interacting partners use different communication codes, they will come to different interpretations and conclusions reducing the relevance of the communication for the individual knowledge bases. Therefore, common communication codes serve as standards to reduce costs of misperceptions and cognitive translations (WINK, 2003). These standards have network good characteristics, as the individual benefit of every user is positively correlated to the number of users of this standard – the more individuals understand the code, the more options for communication are given. In science-driven sectors the risk of misperception is seen as less relevant, as communication is based on formalised media (publications) with common codes stemming from the scientific community. Challenges, however, are caused by the need of more inter-disciplinary collaboration in science driven sectors, e.g. in stem cell science molecular biologists together with experts from regenerative medicine, information science or respective tissue engineering fields and organ transplantation medicine. This might lead to a specification of the knowledge base, which cannot be communicated completely in papers and reports and depends on the actual participation in the development (ZUCKER ET AL., 2002, referring to "natural excludability" of new scientific discoveries in biotechnology).

The risk of default is caused by the asymmetrical distribution of information between the interacting partners typically discussed within the principal-agent-framework (HART; HOLMSTRÖM, 1987). Only the individual knows whether he or she reveals correctly the experiential knowledge. Therefore, every partner fears to be exploited, as long as he or she cannot actually proof whether the communication partners answer to the revelation of new experiences with reciprocal interaction. Two different problems occur: quality uncertainties, which means that the receiver actually does not know whether the data received are worth to be processed and whether the time used to understand, interpret and apply the data is wasted and leads to failure, and moral hazard, which includes the risk of a communication partner to be exploited by the other partners, if she is providing her best information but only receives worthless data (BLUM; MÜLLER, 2004). These fears can be reduced by common norms based on socio-cultural or legal rules to solve two institutional needs: an institution to reduce quality insecurities by credible signalling or screening, and an institution to overcome incentives for default by credible control and sanctions (ZAHEER ET AL., 1998; NOOTEBOOM, 2002). Again, this requires certainty that all partners comply with the norms. In science-driven sectors, knowledge asymmetries should be lower due to the common cognitive basis and the codified way of knowledge interaction. This should help creating prerequisites and incentives for intensive collaboration.

Innovation systems shall offer solutions to the two basic problems of communication codes and institutions to prevent default by providing systemic linkages between actors and organisations with different experiential knowledge on the basis of common communication codes to overcome cognitive misperceptions and common formal or informal institutional norms to increase trust between communication partners. The concrete design of innovation systems differs according to the specific requirements of the knowledge exchanged, the affected organisations and actors and the historical background of the systemic linkages. The functionality of all networks, however, depend on the proximity between the nodes, as increasing proximity makes connections more reliable in contexts with different and changing conditions, which are typical for innovative environments. Gatekeepers are nodes that belong to different (regional) innovation systems and are able to integrate experiential knowledge developed in one system into interactions in the other system influencing the cognitive frames and institutional norms of the partners in the other system. Their integrative performance relies heavily on the proximity to nodes in both systems. But which type of proximity is necessary?

In this paper, we refer to a typology, which is based on the terminology of a paper by Boschma distinguishing between geographical, cognitive, social, organisational and institutional proximity (BOSCHMA, 2005). The risk of misperception can be reduced, if proximity helps to communicate frequently and develop routines in using common communication codes. *Social and geographic* proximity offers the chance to use frequent and repeated face-to-face-(F2F)-communication with continuous interaction to test, whether the intended message has reached the sender (BATHELT ET AL., 2004), and this F2F communication is not only restricted to specific professional events but also existing in private personal contacts (DAHL;

PEDERSEN, 2004). Formal communication codes like written language can be easily used, if there is already given a specific joint cognitive dimension (*cognitive proximity*), for example due to common professional or scientific backgrounds (HARHOFF ET AL., 2003). In these cases, publications and manuals are options for communication, although an additional temporary geographical proximity might be necessary to understand specific context conditions of the data provided (BRESCHI, LISSONI, 2001). Organisational and institutional proximity are means to build up specific and exclusive communication codes on the basis of formal and informal rules. With the term *organisational proximity*, we refer to shared formal relations reaching from relatively weak ties based on inter-organisational contracts (for example joint venture) to strong hierarchical organisations with only a low level of autonomy for the individual (BOSCHMA, 2005). Many concepts of knowledge management on the firm level look for necessary prerequisites for communication, including technological solutions, incentives for documentation and formalisation of non-formal experiential data and opportunities for interaction and creation of codes by routines (ARGYRIS; SCHÖN, 1996; NONAKA ET AL., 2000; CHEN, 2004). *Institutional proximity* refers to a more general set of formal or informal rules for individual behaviour (NORTH, 1990). The stability of these institutions is again closely related to social and cognitive proximity, as they can support the effectiveness of interactions and options to sanctions against non-compliance with institutional rules (COLEMAN, 1986).

Institutions to prevent default are supported by *social proximity*, which creates trust through personal contacts (NOOTEBOOM, 2002; DUPUY, TORRE, 2006). Credibility is built up by personal reputation. Any non-compliance with the expectation of the communication partner will not be only sanctioned by loss of professional contacts but also by loss of personal contacts and social acceptance. *Geographical proximity* might support this option by providing opportunities of social control via ongoing F2F contacts between different individuals spreading information on misbehaviour. Sanctions not only affect the relationship between sender and receiver but also other possible communication partners within the area (GERTLER ET AL., 2000). *Cognitive proximity* reduces the risks of quality uncertainties and moral hazard by a lower level of asymmetries. The receivers of data are more able to identify sources of low quality, as they can stick to some formalised hints or can use their own experiential knowledge to test. Sanctions are extended to the loss of professional reputation. *Organisational proximity* might include specialists on examining new data before spreading them within the organisation (HARADA, 2003). Sanctions cover the exclusion from the organisation with all its benefits and requests for compensation by the other members of the organisation (FOSS, 1999). *Institutional proximity* contributes to the credibility of signalling and screening by securing these instruments with the help of either informal personal sanctions or external – public regulatory – sanctions. Similarly, institutional proximity helps prevent moral hazard by external incentives in contracts, for example shared risks of using data or obligations to compensate for any failure caused by wrong data (TIROLE, 1999).

A gatekeeper should be able to span the boundaries between regional innovation systems (COOKE, 2004, on boundary-spanning institutions). Gatekeepers act as nodes within regional networks contributing to additional knowledge via interaction and establish linkages to nodes in networks of other regions. A suitable differentiation of gatekeeper functions and shapes is however so far missing. Therefore, we present in the following a differentiation of functions along the knowledge production process and of shapes along the different types of proximity. For *knowledge generation*, a creative and diversified knowledge pool is needed to produce ideas, which can be examined, adjusted and improved via interaction (AKBAR, 2003; IAMMARINO; MCCANN, 2006). The function of the gatekeeper from the perspective of the regional innovation system refers to the establishment of linkages to creative ideas outside the system. This creation of external links serves as a solution particularly to overcome lock-in constellations within the regional system, but is only possible, if the absorptive capacity of the regional network is adjusted to the cognitive needs of the external link (COHEN; LEVINTHAL, 1990). This adjustment is the specific requirement the gatekeeper has to provide. *Knowledge examination* requires the generation of standards and codes to assess the quality and applicability of new knowledge. Gatekeepers help to integrate standards and codes from other regional systems and extend the spatial scope of new ideas. This requires knowledge on actual implementation of examination procedures, not only on formal standards. Gatekeepers shall contribute to the establishment of suitable documentation and assessment procedures. *Knowledge exploitation* includes the final commercialisation of new ideas as well as the integration into new research processes. Therefore, knowledge on sales markets, public opinions on controversial research results and requirements for commercial application is necessary (LIYANAGE ET AL., 2007; POON ET AL., 2006). Gatekeepers help to provide this knowledge. Again, it is not sufficient only to have general information on the conditions for exploitation in other systems available but to know about actual management of this knowledge in other systems. Thus, gatekeepers might also contribute to the change of existing commercialisation strategies and structures and help to build up new skills particularly to cope with hitherto not considered ethical concerns.

Who is actually able to act as a gatekeeper, depends on the kind of proximity needed to span the boundary between the systems. Cognitive proximity is based on professional or scientific standards and codes. Therefore, scientific or professional excellence with a diversified spectrum of knowledge might ideally qualify to act as a gatekeeper in this context (MIOTTI; SACHWALD, 2003; JUNOLD; WINK, 2006). World-class researchers and research or professional associations with a high reputation might be ideal examples for gatekeepers in this context. Social proximity is built on personal linkages, joint experiences not only in professional contexts and mutual sympathy (BRESCHI; LISSONI, 2001; CANTNER; GRAF, 2006). Here, mutual exchange programs for researchers or entrepreneurs or the organisation of social events with participants from different regions could contribute to the establishment of gatekeepers. Organisational proximity refers to common organisational umbrellas from contracts to joint formal organisations. The support for interregional R&D contracts or the attraction of multi-national companies or other organizations could serve as instruments to develop gatekeepers (PISCITELLO; RABBIOSI, 2006; PEDESEN ET AL., 2003). Institutional proximity does not only include close formal linkages but also informal rules and international conventions. The support of an institutional framework on research standards or the internationalisation of professional standards can be seen as a means to help establish gatekeepers, which implement these required standards first and help diffuse the experiences along the region. Finally, at least temporary geographical proximity can support the emergence of the other types of proximity and gatekeeper functions (AMIN; COHENDET, 2003). Fairs and conferences are typical instruments to establish such types of temporary geographical proximity (BATHELT; SCHULDT, 2005).

In the context of science driven sectors, geographical proximity might play a less prominent role, as actors and organisations can refer to existing formalised rules of exchanging codified knowledge via publications, examining knowledge in peer review processes and commercialising knowledge on the basis of patents and classifications of successful proofs of the theoretical concepts (ALECKE ET AL., 2006). Cognitive proximity should be driven by joint scientific and theoretical experiences and codes and less relevant on cultural issues. Consequently, interregional knowledge exchange should be more common and gatekeepers should face fewer difficulties to be integrated into different innovation systems and communicate between them. For our investigation, this motivates three hypotheses to be analysed in the case study of human embryonic stem cell research:

- Knowledge interaction in science driven sectors is more based on cognitive proximity than on geographical proximity.

- Consequently, interregional gatekeepers should be particularly in the process of knowledge generation and examination world-class researchers.
- For knowledge exploitation groups with other knowledge (firms, financial intermediaries, patients, non-governmental organizations) have to be integrated. For this process, organizational and institutional proximity should be more relevant.

Before we turn to the experiences with interregional interaction, a brief overview to human embryonic stem cells shall help to understand the challenges for knowledge management in this segment.

3. Human Embryonic Stem Cell Research as Science Driven Sector

Stem cells are special kinds of cells, which have the unique capacity to renew themselves and to give rise to specialised cell types. Although "normal" cells are committed to specific functions (heart, skin or pancreas), stem cells remain uncommitted until they receive a signal to develop into a specialised cell. Human stem cell therapies are by no means a recent phenomenon. Prior to the 1950s, research on clinical applications of stem cells via bone marrow transplantation had started. Only in the 1970s, bone marrow transplantation became an integral part of therapies, particularly in cases of leukaemia. Other applications of adult stem cells followed, such as corneal transplantation, skin grafting, cell therapy for the repair of cartilage or the transplantation of pancreatic cells from cadavers in cases of diabetes (SCI, 2005).

The recent hype on stem cell research was driven by new scientific possibilities in regenerative medicine. The basic idea in this context is to grow stem cells to very large numbers in culture and let them differentiate in a wide set of various therapeutic cell types. Adult stem cells, from the bone marrow for instance, have a restricted potential to differentiate into more specialised cell types. On the contrary, embryonic stem cells are pluripotent, i.e. they can become almost any specialised type of cell in the human body. The differentiated cells can then be transplanted into patients to restore the functions lost due to accidents or diseases. In combination with tissue engineering, it is anticipated that cells in the laboratory can be transformed into highly organised tissues, which can then be transplanted. Researchers analysed the conditions for these differentiation processes, primarily with mice in vitro and in vivo, while simultaneously looking for prerequisites to derive human embryonic stem cells. In 1998, the first human embryonic stem cell lines were derived in Wisconsin, USA (THOMSON ET AL, 1998). Sources for these stem cells were either embryos from In-Vitro-Fertilisation (IVF), surplus to actual requirements, or embryos created by IVF specifically for research purposes. These embryonic stem cells could be differentiated into specialised cells, which could then be transplanted into patients. Such therapies, however, might cause risks of rejection by the patient's tissues and the emergence of tumours by stem cells. A revolutionary change of medicine could be achieved, if therapeutic cloning (cell nuclear replacement) could be used. Here, cells would be generated that directly match the tissue of the patient. Hence, the stem cell transplant would not be rejected by the patient's immune system. This can be the source for personalised medicine (SCI, 2005), which would cause huge changes to the existing pharmaceutical business model based on scale economies. So far, however, only one research team in Newcastle successfully used therapeutic cloning, and the "efficiency rate" (the ratio of embryos compared to the total number of used oocytes), is relatively low (STOJKOVIC, STOJKOVIC ET AL. 2005). Other options for the use of stem cells are drug screening (toxicological tests, which can also be used for testing chemical substances instead of animal tests), disease simulation for drug developments, combinations with drugs to modulate the activity of stem cells, for example, neural stem cells to support anti-psychotics, or a better understanding of the biology of cancer cells.

Public controversies refer almost exclusively to the use of human embryonic stem cells (heSC) as the embryo inevitably dies, after the stem cells have been isolated from the blastocyst (a four to six day old embryo consisting of a ball of about 100 cells) and ethical debates refer to the status of the blastocyst and prerequisites for these research methods (POMPE, BADER ET AL. 2005). The legal handling of these cases differs between countries, as will be expressed in the next section. Researchers argue that only heSC have pluripotency and can therefore hardly be substituted by other forms of stem cells, for at least as long as basic research to understand the mechanisms of stem cells is needed.

What explains the character of human embryonic stem cell research as a science driven sector? So far, practical applications are only rarely given and most of the impact on future therapies is based on hopes. For the understanding of knowledge required, however, the abstract relationship between research in human embryonic stem cell segments and the potential target markets is more relevant and at least partly visible. The technological paradigm based on stem cell research, regenerative medicine, transplantation medicine and tissue engineering implies a radical change from incumbent paradigms in pharmaceutical markets, if personalised therapies are available, which are based on cells that are originally derived from the patients. This requires an accepted theoretical concept on the functioning, emergence and differentiation of stem cells, which has to be proved in labs as well as clinical research, thus basic research has to be related to experimental applications to achieve new products (therapies). Without any understanding of the theoretical concepts, new products in tissue engineering or drug screening cannot be developed, while without practical experiences in the derivation of new stem cells progress in theoretical concepts is limited. Consequently, scientific excellence decides on the capabilities to develop innovations and new markets, and any exploitation and commercialisation crucially depends on the integration of scientific researchers.

For the knowledge production process, these science-driven characteristics have important implications. Knowledge generation mainly depends on interaction between researchers from different segments in stem cell research to understand the complexity of existing challenges and the requirements for successful applications. Most of the scientists in these fields are specialised in single segments, like the derivation of stem cells based on cell nuclear replacements or other sources, the differentiation of cells into specific functions, the understanding of cell functions and their activation in specific contexts, or the development of tissues. Gatekeepers face two cognitive and institutional challenges: the enhancement of interaction within the specific fields, but in different regions, and the enhancement of interaction between different fields of research. Due to the ethical controversies, any new insight on the emergence, derivation and differentiation of human embryonic stem cells has implications for possible conflicts with normative assessments and legal definitions. Therefore, any knowledge generation automatically causes the need for new knowledge in ethical and legal decision-making. Knowledge examination in stem cell research means the proof that scientific and ethical quality standards have been met in the knowledge generation process. These standards are formulated on the level of scientific communities and formal legal frameworks and have to be communicated to all researchers involved and asserted in accepted procedures. Finally, knowledge exploitation requires additional and intensive interaction first in clinical research processes and then within possible fields of application. These challenges might include the need for changing production and marketing models, for example if new screening processes substitute existing animal or other testing methods, or if personalised medicine would replace or reduce the market for those pharmaceutical business models, which are based on the exploitation of economies of scale and the dominant role of multinational pharmaceutical firms as gatekeepers between cooperation networks (ROIJAKERS, HAGEDOORN, 2006).

In the next section, we take a look at policy initiatives and instruments on the national level to overcome these challenges for knowledge production in human embryonic stem cell research and enhance the interregional knowledge interaction.

4. Stem Cell Policies in Selected European and Asian Countries

Stem cell policies refer in most countries to three categories:

- financial incentives for knowledge production,
- general regulatory framework for knowledge production, affecting inter alia intellectual property rights, access to capital markets, organisation of research associations and qualification schemes, and
- specific regulatory framework aimed to affect directly stem cell research methods.

Within this paper, it is not possible to go into detail on every category for several countries (SCI, 2006; HALLIDAY, 2004, for further information). We will concentrate on strategic priorities within the three fields distinguishing three European and three Asian countries particularly considering the impact on different forms of proximity and the role of gatekeepers. In the following fifth section we will take a look at the actual interregional outreach from these countries and the role gatekeepers actually play.

Within Europe, the three countries under consideration are United Kingdom (UK), Germany and Sweden, as there are remarkable differences in strategic objectives and instruments between the three countries. UK integrated its stem cell policy within an already existing regulatory framework based on the Human Fertility and Embryo Act and the central role of the Human Fertility and Embryo Authority (HFEA). There are two main strands within these specific regulatory frameworks:

- adjustments and amendments to existing regulations for research with human embryos, defining specific preconditions for the allowance of therapeutic cloning and access to the UK stem cell bank and leading to a clear and transparent procedure of standard setting, applications and decision-making processes,
- support for the exchange of experiential knowledge between researchers and between researchers and representatives from regulatory authorities and other affected groups creating a joint identity as a British stem cell network.

In the context of general regulatory frameworks, stem cell research was integrated into existing initiatives to bridge the gap between research at universities and research institutes and commercialisation and to improve the public understanding of science to enhance public awareness and acceptance for the new technology. Financial support was provided from different single programs summing up to 25 million GBP in the years 2004/05. Compared to other countries and regions (like China, Singapore, Spain, California or Massachusetts) financial support is not at the centre of stem cell policy but the strengthening of linkages between researchers and the emergence of an actual innovation system including the whole knowledge value chain from generation to commercialisation. Consequently, they lost researchers to other countries offering higher research budgets and better access to resources but gained researchers from other countries who are particularly interested in networking and access to a supportive legal framework. The philosophy of proximity within this strategy is driven by a connection between (at least temporal) geographical and social proximity with institutional and cognitive proximity. Geographical and social proximity is enhanced by the organisation of social events and conferences also trying to develop a common identity of the epistemic group within the country. This common sense of belonging shall help to improve institutional proximity (HINXTON GROUP, 2006), which means in this context the participation in processes to discuss adjustments of legal rules to new experiential knowledge and to ensure compliance with these rules. Researchers act as gatekeepers between innovation systems not only based on cognitive proximity but also include temporary geographical, social and institutional proximity. This wide range shall help include other groups (non-governmental ethical groups, patient representatives, firms) from other countries, which will be particularly important for knowledge examination and commercialisation, into domestic innovation systems.

Germany created a specific regulatory framework for human embryonic stem cell research, allowing imports of stem cell lines under specific circumstances (e.g. stem cells have to be derived before Jan, 1, 2002) and prohibiting any creation of human embryonic stem cell lines in Germany by criminal law. In the contrary, generation and exploitation of new knowledge in other stem cell research segments is strongly supported by public funding and network infrastructures. Several regions developed specific stem cell network programs to enhance knowledge flows within the scientific community and between research and clinical applications. Changes within IPR law and provision of public venture capital shall also contribute to faster commercialisation of new knowledge in stem cell research. The focus of proximity here lies on improvements in cognitive proximity, looking for better inter-disciplinary interaction between researchers from different stem cell research directions. Researchers shall act as gatekeepers via temporary research stays and participation in international programs. The specific situation of human embryonic stem cell research makes it more difficult to come to common institutional approaches for the stem cell community and many scientists find it difficult to communicate with groups representing ethical and political concerns, as the codes are too different to adjust the semantic meaning of terminologies and arguments. Accordingly, gatekeeping functions mainly focus on knowledge generation, while exploitation is restricted to the specific German rules.

Compared to United Kingdom and Germany, Sweden represents a relatively small country. Thus, researchers are more dependent on international collaboration to have a necessary basis for interaction. The regulatory framework for human embryonic stem cell research is relatively liberal to help researchers to be embedded into international networks and to prevent relocations of research groups to other countries. Easy access to venture capital and transparent rules for clinical applications shall also contribute to knowledge exploitation within the domestic context, although the Swedish market is too small to offer sufficient sales potential without additional international sales. Accordingly, there is a strong focus on geographical and cognitive proximity in the domestic focus to develop a necessary "critical mass" for knowledge interactions. On the basis of these domestic linkages, gatekeepers between regional and international innovation systems not only focus on cognitive linkages based on research collaboration. Access to international capital markets and cooperation with multinational firms shall also lead to organisational and institutional proximity, although these options are so far restricted to niche applications and adult stem cell research options due to the early stages of human embryonic stem cell knowledge production. However, these gatekeeping activities already aim at knowledge examination and commercialisation needs.

In Asia, Singapore, China and Korea follow different strategic pathways in stem cell policies due to different starting conditions and potentials. China as the biggest country with several research centres focuses particularly on the emergence of a national innovation system based on experiential knowledge from Chinese researchers with experiences in other countries. By providing a world-class infrastructure and a regulatory framework with only few barriers to human embryonic stem cell research, fast development of concrete applications is the main strategic objective. Proximity on a domestic level is strengthened by geographical proximity at several regional centres and cognitive proximity within these centres. International gatekeepers are mainly oriented to cognitive and organisational (contractual) proximity supported by temporary geographical proximity of Chinese researchers in Western research centres and the possibility for earlier clinical applications of new knowledge than in Western countries. The main focus so far is on knowledge generation with a clear focus on those elements of knowledge commercialisation, which allow fast access to emerging international market shares (POON ET AL., 2006, on similar experiences in telecommunication).

On the contrary, Singapore as one urban agglomeration focused on international collaboration with Western researchers from the beginning. With the creation of a "Biopolis", geographical proximity of researchers and firms from different fields in biotechnology and medicine shall contribute to intensive knowledge interaction. Cognitive and social proximity shall be connected by offering all necessary infrastructures for daily life within the Biopolis. International gatekeepers are Western researchers consulting the management of research groups in Singapore and being integrated into research as well as representatives from Singapore visiting foreign labs and participating in international stem cell networks. This shall not only include the cognitive proximity dimension but also institutional and social proximity to understand the actual content of standards for knowledge examination and commercialisation. Korea stands between the other two countries, when looking at size and domestic research potential. The main driver for stem cell policy in Korea was the high awareness a domestic researcher achieved with his results on derivations of human embryonic stem cells via cell nuclear replacement. Consequently, the Korean government particularly supported this research segment and research centre with a main focus on achieving cognitive proximity for world-class research results. International researchers were invited to the Korean labs mainly to discuss research experiences and results. Only as international collaboration required common legal standards, they were implemented. The main focus, however, was still laid on the access to international scientific networks to achieve cognitive proximity on research experiences.

Table 1 presents a brief summary to this overview. The information refers to stem cell policies in general. As human embryonic stem cell research is the research segment within stem cell research with the strongest international differences, the described differences are even more visible for this research segment. We see gate-keeping functions as a product of already existing concepts of proximity and priorities in the knowledge production on the domestic level. Germany in Europe and China in Asia are the countries with the strongest focus on cognitive proximity and the use of domestic researchers as gate-keepers, but for different reasons: for Germany the reason lies in legal restrictions due to ethical concerns, in China the strategy is based on the need to catch-up for knowledge generation capacities and is seen as an interim step to follow commercialisation strategies in a second phase. United Kingdom, Sweden, and Singapore follow broader concepts of proximity including also institutional, organisational and social proximity. Their view is already directed towards knowledge examination and commercialisation. Korea follows a niche strategy with researchers as gatekeepers and formal institutional proximity via common formal rules. In the next section, we take a look at the actual interaction between researchers in the different countries and try to relate these results to the strategic differences observed in policies.

Insert Table 1 here

5. International knowledge flows in human embryonic stem cell research

In the second section, we introduced the concept of the knowledge production process including knowledge generation, examination and exploitation. We will use this differentiation in this section to analyse the existing international interaction in human embryonic stem cell research and the role gatekeepers play in this context. The results are mainly based on three empirical sources derived from a joint research project on transnationalisation of knowledge flows in stem cell science (JUNOLD; WINK, 2006): (1) a bibliometric investigation of international collaboration in stem cell and human embryonic stem cell research based on analysis of co-authorship in international journals in the years 2001-2003 (WINTERHAGER, CAMARGO, 2005), (2) an investigation of existing international research and market collaboration in stem cell research, and (3) a set of 40 expert interviews with representatives from research institutes and associations, firms and pubic administration in the investigated countries. The bibliometric study serves as a starting point to understand cognitive proximities between the research systems in the investigated countries. Formal collaborations are used as an indicator for organisational proximities between researchers and firms from different countries. The series of interviews help to control for the actual relevance of organisational and cognitive proximity in single cases, but particularly to understand the relationship between social and institutional proximity to actors from innovation systems in other countries and the possibilities to act as gatekeepers. We stick to these qualitative statements for social and institutional proximity to integrate the subjective and personal character of opinions on sympathy and trust. We structure our results on the relevance of different kinds of proximities and gatekeeping functions along the knowledge production process.

Knowledge generation includes learning and creative processes. Both processes are dependent on interaction between researchers with different knowledge bases. The bibliometric study offers a picture on some results of such interactive processes (for a discussion on the methodology and the limitations WINTERHAGER; CAMARGO, 2005), as the analysis of addresses of co-authorships show, if there has been collaboration across the borders and whether they are systemic priorities of such linkages between countries or between single organisations. The total number of publications in human embryonic stem cell research increased sharply after 1999.

The share of international co-publications decreased however in the period from 2001-2003. Furthermore, international co-publications do not cause a decrease in national co-authorships. The relevance of national linkages is still more important in big countries like UK or Germany, where co-publications within the same organisation (50.8% of total co-publications in UK, 44.1% in Germany) as well as national co-publications between different organisations (UK 20.5%, Germany 25.2%) play a dominant role. In smaller countries like Sweden, however, the share of international co-publications is nearly 40% of all co-publications. Countries with the highest output in international publications on human embryonic stem cell research were the US (46.5% of total international publication output), Japan (15.3%), Germany (11.2%), UK (10.2%), and France (5.6%). China and Korea, however, increased their share remarkably between 1991-93 and 2001-2003 from 0.3% to 2.8% (China) and 1.1 % (Korea).

The relations between the national innovation systems are illustrated in Figure 1 with the help of network structures. The structures in 1991-93 are compared with the structures in 2001-2003. The distance between the countries illustrates the intensity of collaboration: the closer the countries are, the more co-authorships have been counted. The size of the nodes represents the national share of international co-publications. It becomes obvious that between 1991-93 and 2001-2003 several new countries appeared into the international networks and more linkages have been established. The major core countries remained the North American and European countries as well as Japan. Singapore is relatively well integrated into the network, while China and Korea are more at the periphery of the collaboration. Similarly, Sweden as the smallest European country investigated grew stronger between 1991/3 and 2001/3 than the bigger countries UK and Germany, which nevertheless still have higher absolute numbers of international co-publications. Thus, a part of these differences might also be related to the higher dependence of small countries (Sweden, Singapore) on external linkages than bigger countries. The linkages between the EU countries are weaker than between the single European countries and the USA underlining that geographical proximity is not a dominant factor to explain international collaboration. Additionally, the bibliometric material was analysed to identify specifically intensive international inter-organisational linkages, i.e. whether co-authorships are mainly realised between authors from the same organisations. This investigation, however, reveals no concentration on specific organisations, i.e. organisational proximity cannot be proved. The linkages are driven by personal relationships not by organisational linkages. This means that cognitive and social proximity seem to be more important for international linkages than organisational proximity.

Insert Figure 1 here

These observations were confirmed by the investigation of formal and informal cooperation and the interviews. The cooperation patterns were analysed on the basis of official documentation (on websites or publications) and a questionnaire sent to representatives of 600 firms, universities and research institutes. A great diversity of international partners was mentioned, even those researchers with a high number of international partners reached only small numbers on the question to name the most important international or national partner in stem cell research. This underlines the observation that personal contacts play a major role for knowledge interaction, and that organisational proximity across the borders is not so important for knowledge generation. Within the interviews, we asked for major driving forces for international research cooperation. Most of the interviewed researchers mentioned research excellence as the most important factor – stressing the relevance of cognitive proximity as motivation for interaction –, followed by existing personal and social contacts. Here, temporary research stays, e.g. for postgraduate research, play an important role for continuous linkages. Permanent migration of researchers still is an exception, primarily caused by better access to crucial resources (e.g. oocytes for the derivation of embryonic stem cells), as most researchers try to maintain their social embeddedness. Summing up, cognitive and social proximity seem to be important factors defining the importance of gatekeepers for international interaction in knowledge generation processes.

Knowledge examination includes proofs of quality of new knowledge, intended or non-intended side-effects and possible applications. Here, joint understanding of standards for knowledge generation and dissemination play an important role to trust in the data provided. Within human embryonic stem cell research, researchers stress the specific challenges of knowledge examination, as most of the research results still consist of tacit elements of experimentations due to the novelty of research methods and experiences, and several additional proofs are needed to verify them. The interviews revealed that there is a relatively high amount of uncertainty on the international compliance with research standards, particularly after the proof that research results by a Korean team in two “Science” publications were faked and the research was carried out with oocytes donated by dependent research assistants. Researchers mentioned that the delayed revelation of the fakes and the lack of knowledge on these fakes of the US co-author of one of the papers, were caused by cultural differences in the research teams: While in North America and Europe discursive processes within the research teams and specific protection of research assistance against exploitation are routines, the former is relatively unknown to research cultures in Korea and the later was only later implemented into legal rules. Accordingly, trust in research results is concentrated on research teams with similar institutional research standards and personal contacts: institutional and social proximity are assessed as main prerequisites for knowledge interaction. These prerequisites will gain importance, if the first human embryonic stem cell therapies will reach the stage of clinical tests in the next years. Many researchers fear that without strengthening institutional proximity on standards for research first clinical applications for human patients will be introduced too early and cause risks of bad experiences discrediting the whole research field. This determines their willingness to act as gatekeepers to innovation systems in other countries. Consequently, personal and cognitive proximity seemed to be decisive prerequisites for institutional proximity in this context.

Knowledge exploitation refers to the derivation of new therapies and products. So far, only few products based on human embryonic stem cells have been marketed in drug screening and toxicological testing. Most firms, however, already mentioned that they are looking for international markets with high sales potentials for future applications. Connections between stem cell research and pharmaceutical applications and between stem cell research and tissue engineering require ongoing interaction between research and therapy teams, which have been realised so far by few research organisations and firms. As human embryonic stem cell research is still diversified along many different research segments, the cognitive linkages between more theoretical research fields and more application-based fields are relatively weak with researchers still talking on “different disciplines”. According to the interviews, however, international interaction on knowledge exploitation not only requires more efforts to bridge cognitive gaps but to improve organisational proximity to develop long-term frameworks of cooperation with transparency on objectives and organisational routines. Again, gatekeepers do not only have to focus on cognitive proximity, but here also on organisational proximity to build up suitable collaboration or firm structures. Within the statements of the experts interviewed, the British approach to link different types of proximities together and to support gatekeepers, which are not only focused on cognitive proximity, was seen as the most suitable way to deal with the uncertainties of international collaboration. This and the relatively positive attitude of the international experts towards the approaches in Sweden and Singapore might also be motivated by the relatively strong focus of policies in these countries on integration into international knowledge flows, while for other countries other objectives (ethics) or possibilities (high amount of national researchers) might be more important. Any assessment of policies has to be seen against the background of national contexts.

What do these observations mean for the hypotheses on international gatekeepers in science-based sectors formulated in the second section and stem cell policies described in the fourth section? Our first hypothesis in the second section referred to the dominant role of cognitive proximity for interregional knowledge interaction. Within the survey on politics, this expectation has been confirmed by attempts in all countries to improve particularly cognitive proximity. The results, however, show that for most researchers cognitive proximity is not sufficient for the selection of partners and the organisation of cooperation. Social proximity plays an important role, even for knowledge generation, where most of the communication is based on knowledge from related disciplines. For international knowledge flows, this means that the Asian countries with fewer direct contacts based on personal experiences and different research cultures face specific challenges to enhance cooperation. Researchers from Singapore, where policies do not only focus on cognitive proximity, but also on institutional and social proximity is closest to the core, according to the interviews particularly through the influence of Western European and North American researchers, who are at least temporary in Singapore. Even China and Korea, however, improved their position in international co-publications. Therefore, linkages based on cognitive proximity seem to help for international knowledge integration, but not as much as cognitive plus institutional or social proximity.

The second hypothesis referred to the focus of interregional gatekeepers in science-driven sectors. Their main function should be the improvement of cognitive and institutional proximity by organising joint conferences and publications and executing reviews. In practice, however, the social contacts seem to play a role as vital as these organisational and cognitive attempts. In particular for knowledge examination, the experiences show that institutional proximity might still be too weak even in the case of scientific norms to guarantee common actual understanding of standards and compliance with them. Trust is dependent on social belonging, and the strong focus on national research communities as well as the attempts particularly initiated from the UK researchers to strengthen joint cultural and social understanding of standards (HINXTON GROUP, 2006) show the necessities of amendments to cognitive proximity.

The third hypothesis stressed the dominant role of interregional knowledge flows for knowledge generation, while geographical proximity should be more important for knowledge examination and exploitation. So far, only few experiences are given for knowledge examination and exploitation. But the statements of researchers and firm representatives as well as location decisions seem to support the expectation that at least temporary geographical proximity is crucial for knowledge examination and exploitation, because the uncertainties on research results, their quality and application are higher between different research cultures and researchers are increasingly aware on the need for acceptance by the general public and possible patients. Even in knowledge generation, however, geographical proximity is still more important than expected, which stress similar observations from biotechnology (ZUCKER ET AL., 2002). The bibliometric results show that the majority of co-publications in all countries of consideration are still executed by partners from the same organisation or at least with addresses from the same country. The fiction of "footloose science" with global virtual knowledge flows cannot be confirmed by these empirical observations. Table 2 once more summarises the observations on different types of gate-keeping functions along the production process.

Insert Table 2 here

6. Conclusions

The starting point of this paper was the observation, that regional policies treat science-driven sectors in a different way, because mobility and knowledge interaction are expected to be realised easier due to the high level of codification and geographical proximity should not be important as in other sectors. In most countries, gatekeepers are therefore focused on cognitive proximity. In the case of human embryonic stem cell research, however, these expectations cannot be confirmed. For the researchers, geographical and social proximity still plays a vital role and with increasing relevance of applications for therapies these dependencies might even increase to assure compliance with joint quality standards. For research and regional policies, this should lead to a higher awareness of other forms of proximity than cognitive proximity: the organisation of interregional conferences to strengthen temporary geographical and social proximity as well as joint research project schemes with other countries to build up organizational proximity seem to be important elements within such strategies. In particular to strengthen the linkages between Asia and Europe (and North America), these elements have to be stressed to reduce uncertainties on scientific knowledge exchanged. Stem cell research seems to be a specific case, particularly when considering the ethical debates. The experiences in the interviews, where the high amount of uncertainty was raised as the decisive challenge for collaboration, which is typical for many basic research disciplines, and similar results in other studies on biotechnology, however, lead to the conclusion that science policy in general should more include elements of social, institutional and organizational proximity to improve linkages to innovation systems in other countries.

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Table 1: International Differences in Stem Cell Policies

Country	Political strategy	Domestic proximity	Supported gatekeeper functions
United Kingdom	Integration into existing regulation; public financial support 25 m. GBP in 2004/05	Cognitive, social and institutional proximity, search for common identity	Combination of cognitive, social, organisational and institutional proximity
Germany	Specific regulatory framework; federal public support 48 m. GBP 2000-7	Cognitive proximity, geographical proximity in single regions	Cognitive proximity mainly referring to researchers and associations
Sweden	General research support; public support 19 m GBP 2003-8	Geographical proximity in two centres	Institutional and cognitive proximity referring to researchers, firms, associations as well as institutes
China	Explicit financial support for stem cell research, concentration on clinical applications	Cognitive proximity, organisational proximity due to political influence	Cognitive proximity based on temporary proximity of Chinese researchers in foreign labs
Singapore	Integration into general Biopolis framework, total annual support for biotech-	Cognitive and social proximity by integrating daily life into research centres	Cognitive, social and institutional proximity by supporting temporary geographical prox-

	nology 13-15 m. GBP		imity of international researchers
Korea	Concentration on world-class research niches, annual support 1.03 m. GBP in 2004	Cognitive proximity, institutional proximity as reaction to observed needs	Cognitive proximity via temporary geographical proximity (researcher stays), formal institutional proximity as reaction to observed needs

Figure 1: Network Structures in human embryonic stem cell research (based on co-publications; left 1991-93; right 2001-2003; Winterhager, Camargo, 2005)

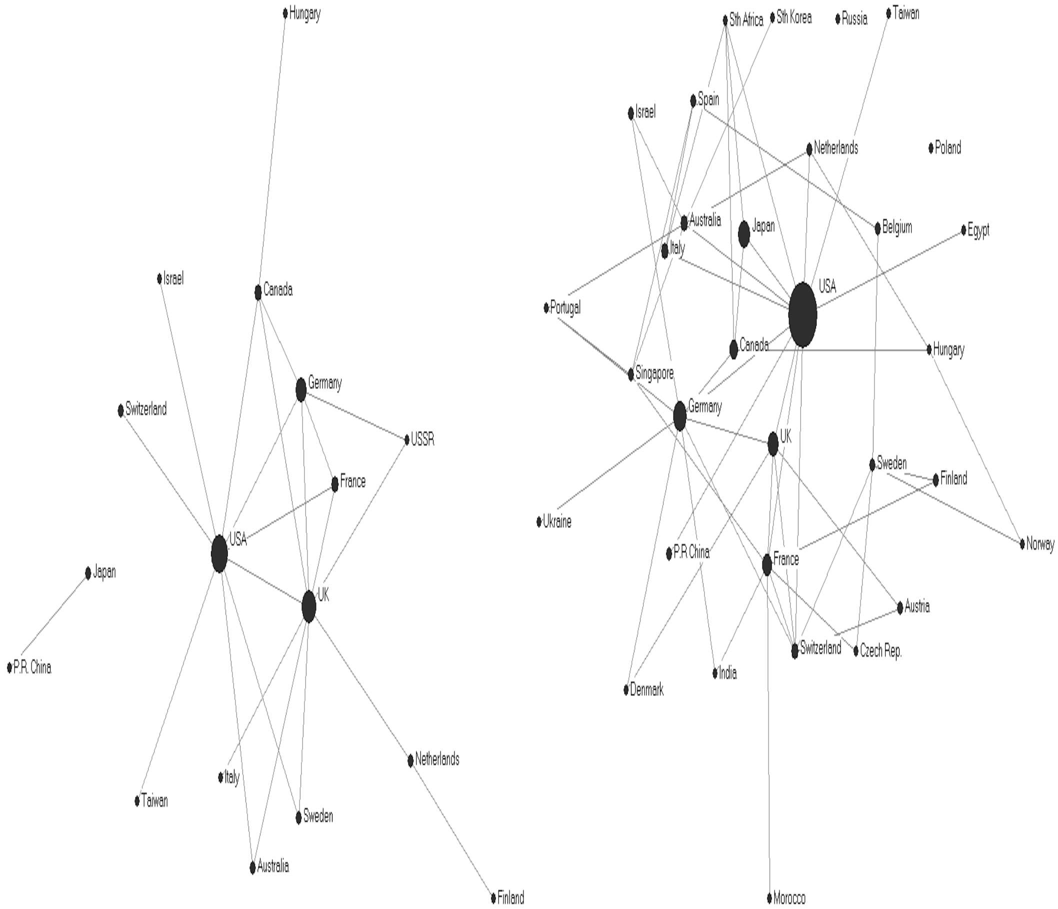

Table 2: Types of proximities and gatekeepers required in different stages of the knowledge production process

	Main proximities needed	Gatekeepers
Knowledge generation	Cognitive proximity connected with social proximity	Researchers with personal linkages organising journals, conferences and joint research
Knowledge examination	Cognitive proximity connected with institutional and social proximity	Researchers integrated into international teams with personal linkages and experiences on standards
Knowledge exploitation	Cognitive proximity connected with organisational and social proximities	Research based firms and institutes connected via R&D and sales contracts