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Contested governance in human embryonic stem cell science: uncertainty and standardisation in research and patenting

Introduction

The development of stem cell science takes place in the context of the globalisation of all aspects of the knowledge economy of biomedicine. Scientific activity and networks are international and collaborative; research materials such as oocytes and embryos form part of a global tissue economy (Andrews and Nelkin 2001; Waldby and Mitchell 2006); clinical trials are increasingly outsourced as part of the pharmaceutical industry's global strategy (Petryana 2005, 2006); financial institutions make their investment decisions in this field on a global basis (Kenney *et al* 2002); and industrial interests are continually bio-prospecting for new forms of information on human and non-human biological material that can be commodified and traded (Parry 2005, 2006).

In parallel to the globalisation of the bioeconomy, a second process is also in train: the globalisation of the governance arrangements that facilitate scientific and commercial exchange. Perhaps unsurprisingly given the cultural ramifications of the new health technologies of biomedicine, the gestation of the new forms of governance are as contentious as they are necessary. States compete for positions of authority in the governance terrain, regional organisations such as the European Union (EU) search for agreement on harmonising principles, international organisations such as the World Trade Organisation (WTO) review the implications for their governance responsibilities and the transnational networks of science and civil society reflect on their potential policy contributions.

In this paper we explore a somewhat neglected aspect of global governance; the negotiation of transnational technical standards. Standardisation processes are essential for any scientific field to develop and are applicable to all stages of the knowledge production process from the basic science through to the market product. They are required for collaboration, for the performance of laboratory tasks, the assessment of research results, for peer review, for the development of intellectual property claims and for clinical applications. Standardisation is necessary in all scientific fields and in the commercialisation of scientific results, but in human embryonic stem cell research, the political volatility of the research and the divergence of national regulations introduce an extra dimension. Attempts to develop global technical standardisation is entwined with global bioethical standardisation. Scientific professional bodies recognise that

international research collaboration will necessitate internationally agreed bioethical standards, if scientists are to comply with the national legislation that governs both their own and their partner's research and gain access to international funding (Nature Editorial 2006).

In what follows, we focus on two nodal points in the knowledge economy of human ESC science where the drive for global technical standards is interwoven with a drive for global bioethical standards: the UK Stem Cell bank (standardisation of the scientific process) and, closely associated with this, the patenting of human embryonic stem cells (standardisation of the market process). How do these two domains of governance interlink and what are the implications of our analysis for the development of global governance.

Standardisation, Science and Global Governance

Standardisation is a central process of all scientific practice, and one of the major demarcators of scientific from non-scientific knowledge. As Parry notes in her history of biobanking, the development of standard forms of testing, classification, handling and storage was crucial to the development of the biological sciences as such.

> If knowledge about the relationships between (biological specimens) was to be accurately transferred and combined, that knowledge could no longer be subjectively determined; it needed to be justified within particular terms of reference supplied by a stable, universal framework to which all contributors subscribed (Parry 2005: 27).

Standardisation is important in science because it creates the conditions for stable comparison and the interoperability of technical elements. Scientific discovery is impossible without agreed measures, protocols, classificatory systems and technical benchmarks shared by laboratories working in the same research field (Timmermans and Berg 2003 book). Scientists require shared and standardised definitions and classificatory systems if they are move out from the particularity of their laboratory language and culture and work with other scientists in other sites. Standards bind communities of practice together across space. Stable classification systems create 'good comparability across sites' (Timmermans, Bowker and Star 1998: 204), ensuring that concepts and definitions are the same in every geographical location and cultural context, and allowing predictable communication and shared understanding and practice.

Standardisation of laboratory protocols is also essential for scientific practice. Laboratory objects like stem cell lines are inherently prone to artifactual distortions and contaminations. Different laboratory practices will produce different outcomes and objects and scientific management of this volatility requires more 'black boxing' in Latour's terms (Latour 1987), more standardisation of technologies, processes and outputs, to ensure the credibility and stability of a discovery. Agreed laboratory protocols produce predictability, stability and easily reproducible results. Standardisation is also essential for collaboration; if a research program is to be carried out in numerous sites,

than the technical conditions in each site must be the same, to eliminate artifactual 'noise' and make results comparable.

> Standards … function as stabilizing and enabling tools, and standardisation is a common and often successfully applied strategy in new and emerging fields of research, and indeed, acts to recruit and co-ordinate participants in the field. Standards also have an inbuilt spatio-temporal function in that they seek to maintain stability over time and place of practices, materials, as well as terminologies. Where these three are configured successfully they become established as design standards, assemblages that help a network establish future research and its lines of inquiry and the resources and skills that are needed to pursue them. To set standards, then, is also to set futures (Eriksson and Webster (2007: 7-8).

Standards are not merely technical artefacts however, and the process of agreeing standards is intertwined with broader issues of scientific governance and the negotiation of relations between international bodies, regional organisations, state regulatory bodies and professional expertise. In many domains, standards touch upon issues of public good (for example safety standards) and ethics. As we will discuss in detail in the following sections, quality standards for stem cell line derivation are a complex example of this ethical aspect of standardisation. Moreover, standards emerge from the political process generated by negotiation, debate and compromise between interested parties, including factions within scientific communities, state agencies, community groups and market interests, and the outcome is not socially neutral (Bowker & Star 1999). As Schepel notes,

> [Standards] bring to the table economic, political, moral and technical arguments and ultimately arrive at a solution that will to some extent hurt some groups and in some degree benefit others … Standardisation is a microcosm of social practices, political preferences, economic calculation, scientific necessity and professional judgement (Schepel 2005: 6).

Hence, there are strong incentives for scientific and professional bodies to take the initiative in creating standards. Their configuration can determine to a certain degree who has the upper hand in a research field or a market, and this configuration, once made, tends to persist. As Bowker and Star (1999) note, once set, standards have significant inertia and are expensive and time consuming to change, so that the interests encoded in a set of standards may provide benefits for a long time.

Finally, questions of standardisation are important for our investigation because technical standards play an increasingly important role in global governance. Standards are usually negotiated between private and public bodies, and states necessarily take a strong interest in technical matters with public good implications (Schepel 2005). At the same time, the growing importance of global standard setting as a form of governance reflects the difficulties for state regulatory power to manage issues that exceed national boundaries. One of the major effects of globalisation is the decentering of state power and its

weakening as a central regulatory coordinator in the face of risk management, industrial developments and scientific innovations that do not observe national boundaries. As one commentator puts it,

> Markets take on a greater prominence at both international and domestic levels of government, but not because of a philosophical decision to cede power to the private sector … Rather, the market and private actors are more prominent because they can approach problems without the limits of arbitrary, territorial boundaries imposed on them (Aman 2001: 391).

Naturally aware of this, states seek to engage proactively with the process of globalisation in order to influence emerging forms of governance to their own national advantage. As part of this political arena, standardisation processes that involve public bodies with non-state agencies and expertise become vehicles for international regulation through professional affiliation, negotiation and consensus building, rather than through top down, state driven law. Standardisation processes and risk management are forms of social steering that align the regulatory interests of states with the research and market needs of science.

> The importance of standards networks in globalised risk regulation is their capacity to internalise and renegotiate the boundaries between science and politics, to tie expert knowledge to local professional judgements, institutional structures, social relationships and economic conditions (Schepel 2005: 28).

Frequently they relate intimately to formal institutions of governance such as the European Union (EU) and the World Intellectual Property Organisation (WIPO) that construct legally binding forms of standardisation.

Research Standardisation and the UK Stem Cell Bank

The human embryonic stem cell field is very poorly standardised compared to more established fields of biomedical research (e.g. genomics). As a very new field, which has attracted large number of scientists and established working laboratories and funding streams very recently, many of the basic aspects of classification, culture protocols and laboratory handling are not yet established. Eriksson and Webster (2007) note that stem cells present certain problems for stable classification precisely because, by definition, they lack a biological identity. All the varieties of stem cell have in common is their potential to differentiate into dedicated cell types, and to date there is no single biomarker that can be used to securely classify all types of human embryonic stem cell. They also present difficulties of handling, storage, transfer between laboratories and laboratory procedure. The quality that makes them epistemologically and therapeutically, valuable, their pluripotency, is fragile, and requires considerable husbandry if it is to be retained across sites.

> The handling of stem cell lines, whether for clinical or research purposes, requires considerable care since, when manipulated and passaged in vitro, they can be

> prone to subtle changes which may not only damage their ability to replicate as stem cells but also cause a loss of their original capacity to differentiate into different cell types. Whilst it is likely to prove an extremely hard or even an impossible task to standardise the cells themselves, the framework of procedures and conditions under which they are cultured, preserved and characterized can be carefully controlled and documented so that these may be reproduced in the recipient's laboratory (Healy *et al.* 2005: 1982).

This material fragility, combined with the ethical volatility of hESC lines, means that many social and technical interests converge around the issues of standardisation. As Eriksson and Webster put it,

> The question asked by regulators as well as scientists is how the socio-technical 'quality' of embryonic stem cells can be stabilized and thereby provide assurance that stem cell lines will function the way they are supposed/hoped to do (Eriksson and Webster (2007: 7-8).

The UK Stem Cell Bank has emerged as a key institution in managing these standardisation issues, at both a national and an international level. While clearly designated as a British organisation, it nevertheless works as an exogenous, global actor (Waldby & Mitchell 2006), effecting international standardisation in a number of ways.

In terms of its national role, the bank is the central institution managing stem cell quality and supply in the UK. It is a condition of an HFEA licence (necessary to carry out human embryonic stem cell research in the UK) that a sample of any hES cell line derived in the UK be deposited in the bank. The bank maintains master banks of cells and makes them available to the UK research community. While UK researchers may access stem cells from elsewhere, they must nevertheless inform the UKSCB's steering committee. In this sense the bank is constituted as an 'obligatory passage point' (Latour 1988) for all stem cell research in the UK, a point through which all researchers must pass in order to carry out their work.

As this central repository, the bank is responsible for the material viability of the UK stem cell stock. Hence it has a strong interest in issues of quality management and standardisation, because these will determine the material basis of the UK research effort.

> Probably the greatest challenge for stem cell banks is the requirement that they conserve various characteristics of the cells for which some of the key biological processes are not yet fully understood. This places a particularly heavy onus on the Bank to establish robust procedures to demonstrate that the stem cell lines remain stable in culture, that key biological indicators remain intact, and that the cell line is safe to use clinically (Healy *et al.* 2005: 1982).

The bank works closely with depositors to identify their procedures and practices and transform these into standardized protocols that can be used by recipient laboratories.

Importantly, the bank does not limit its service to UK scientists but also accepts lines from international depositors and makes them available to international researchers. This is one way in which the bank exceeds a national remit. By acting as an international passage point and clearing house for stem cell researchers world wide, it necessarily extends it standardisation practices out beyond national boundaries. Researchers world-wide are required to meet the bank's requirements regarding the quality of the cells and also the bioethical procedures and rationales set out by the bank's Steering Committee. This bioethical component is discussed in greater detail below.

The bank has also extended its remit through its role in the initiation and coordination of the International Stem Cell Initiative (ISCI), a transnational network of stem cell scientists designed to promote the standardisation of the basic science. The aim of the Initiative is to compare and biologically characterise the majority of ES cell lines available worldwide and place the data in the public domain. Participant laboratories in the initiative come from Australia, the UK, the USA, Canada, Sweden, Finland, Japan, Israel, The Netherlands, and the Czech Republic. The ISCI Steering Committee states that the project is,

> critical for progress in the field to understand the similarities and the differences between the various isolates, so that research results from different laboratories can be compared in a meaningful fashion. For example, a recent flurry of papers has described a variety of new culture systems for the maintenance of hES cells *in vitro*. These studies potentially represent important technical advances for the field. But without knowing how much particular cell lines differ under a given set of growth conditions, or how the properties of a given cell line vary when grown in different laboratories, it is difficult to assess the generality of these results (The Steering Committee of the International Stem Cell Initiative 2005: 795).

The UKSCB is providing technical coordination to the project. Each project uses standardised methodologies, cell cultures and reference reagents provided by the bank, and deposits its resulting lines with the bank, which encodes them and forwards them to expert laboratories for investigation and benchmarking. Again, the bank has constituted itself as an obligatory passage point for standardisation, this time on a global scale. This gives it a powerful position as a key institution in the emerging collaborative relations between the participating laboratories made possible by exactly the processes of standardisation that are in train. As the Steering Committee notes, the ISCI paves the way for truly global collaboration.

> The opportunities and challenges in the field are sufficiently complex, and the resources required to address them so substantial, that the field will need to rely not only on individual investigator project grants but also on large, international collaborations along the lines of the Human Genome project (Steering Committee of the International Stem Cell Initiative 2005: 797).

So in this way the UKSCB has positioned itself as a key broker and negotiator across the transnational networks of the international scientific community. As the global leader in

brokering technical standardisation, and as the access point to well characterised and stabilised stem cell stock, it is a key creator and enforcer of the material standards which will mediate relationships between key laboratories in the field.

The UKSCB is also developing forms of standardisation that will mediate between more diverse groups. As Waldby has argued elsewhere (Waldby & Mitchell 2006) human tissue banks are institutions that must manage complex and often competing social values and the often divergent interests of a variety of social actors. Human tissues like hESC lines are the repositories of often incommensurable values – ontological significance, community significance, market value, therapeutic usefulness and research utility. These disparities in value are nowhere more marked than in tissues arising from human embryos, as we have explored throughout the book. Hence, as the leading tissue bank in the stem cell area the UKSCB has a complex bioethical and biopolitical brief – to reconcile successfully the interests of embryo donors, civil society, researchers, industry and clinical users.

This value management takes a number of forms. A major part of the Bank's *raison d'etre* is to minimize the number of hESC lines derived in the UK, a measure understood to maximize both the research utility and bioethical value of each line. The Bank Code of Practice states,

> The UK Stem Cell Bank will reduce the need for individual research teams to generate their own stem cell lines, minimise the use of human tissues, and enable different researchers to work on identical material so that direct comparisons may be made between studies (Code of Practice for the use of Human Stem Cell Lines 2006:9).

In other words, by minimising the number of lines derived, and ensuring that each new line has a serious rationale for its creation, the bank both pre-empts the gratuitous destruction of embryos and ensures that more researchers work on comparable material, neatly dovetailing epistemological and bioethical issues. Value management also takes place through the constitution of the bank's Steering Committee. The UK Medical Research Council convenes the Committee and its members are representatives from medicine, bioethics, theology and the community, whose role is to oversee the ethical conduct of stem cell research. The constitution of the Committee emphasizes the bank's status as a public institution, with an explicit brief to maintain both technical and ethical standards for the pubic good. The Steering Committee decides in each case of stem cell lines for deposit that the procurement process has ensured the proper information and protection of the donor, and that each case for access meets the criteria for serious and necessary biological or biomedical research.

In making such decisions, the Steering Committee necessarily relies on forms of standardisation that attempt such reconciliation. As Bowker and Star (1999) note, institutions that deal with complex, irreducible ethical issues, for example hospitals, whose staff must take frequent life and death decisions on behalf of patients, rely on processes of codification and standardisation to avoid constant recourse to internal and

external debate and conflict. Codification depoliticises the issues involved, making them more procedural and less conflict-ridden.

> Algorithms for codification do not resolve the moral questions involved, although they may obscure them …when a seemingly neutral … mechanism is substituted for ethical conflict about the content of the forms, the moral debate is partly erased (Bowker & Star 1999: 24).

The primary technology used by the bank to manage these kinds of conflicts is its criteria for donor information and consent. The creation of the bank in late 2002 in fact forced a nation-wide standardisation of IVF clinic procedures for research embryo donation. Prior to the creation of the bank IVF clinics in the UK used in house consent forms to process embryo donation, albeit forms that complied with broader bioethical instruments. The advent of new legislation around hESC research, the introduction of the Human Tissue Act (2004), and the need to regularize procurement and provenance conditions for the administration of the bank itself, created the impetus for standardization of the consent process.

Any researcher wishing to deposit cell lines with the bank must demonstrate that their lines have been derived from embryos donated under a codified set of conditions. The Code of Practice states that:

Each gamete provider must consent in writing to the following:

1. to the use of embryos created using their gametes in the research project for the derivation of stem cell lines
2. that they understand that a sample of any stem cell line will be deposited in the UK Stem Cell Bank and that the derived stem cell lines may be used in other research projects
3. that they are under no obligation to take part in the study and that a decision not to participate will not alter the treatment that they would normally receive
4. that they understand that they have a right to withdraw their consent without giving any reason, at any stage until the gametes and / or embryos have been used for research.
5. that they understand that any cell line derived from their donated gametes/ embryos may eventually be used for treatment purposes (including cell replacement therapies) in the future
6. that they understand that cell lines or discoveries made using them may be patented and used for commercial purposes, but that the donor will not benefit financially from this
7. whether they agree to be contacted in the future in the unlikely event that that the Stem Cell Steering Committee considers that they should be contacted in relation to confirmed test results performed on stem cell lines that are of direct relevance to their own, their family's or public health. (Code of Practice for the use of Human Stem Cell Lines 2006: 16).

The conditions themselves represent possible points of conflict between donors and other interested parties. Some of them are designed to protect donors from undue pressure from a research community closely aligned with the IVF industry. Hence point 1 is intended to ensure that donors fully understand the kind of research their embryos will be used for. Points 3 and 4 are intended to ensure that potential donors don't feel that their fertility treatment hinges of donation. Point 7 concerns the bank's duty of care regarding the donors' genetic health. Points 2 and 5 make clear the destination of the embryos. They inform the donors that, once donated, they become research objects at the disposal of laboratories and the UKSCB, and that they may eventually become therapeutic objects, used by clinicians and patients. Along with point 4, they clarify that the donation is a non-reversible process, and that once given, the embryos cannot be returned. In that sense, they negotiate the relationship between the donors and the scientific community and ensure that the research community has clear rights of disposal. Point 6 is perhaps the most contentious, and mediates relations between donors and commercial interests in stem cell research. Human embryonic stem cell lines are patentable entities in the UK, and this clause in the consent form is designed to deliver unencumbered intellectual property rights to the laboratory recipient of the embryo donation. Donors can only donate on the condition that they transfer all rights in the materiel to the receiving party. In this respect, the consent form acts like a type of property contract, to the benefit of the receiver and the commercial investor (Waldby & Mitchell 2006).

Hence, through the dissemination and enforcement of the donor consent conditions, the bank has standardized complex ethical and social negotiations that might otherwise impede research progress. These relations are not limited to the British nation. For international depositors, the same consent requirements apply, creating impetus for international laboratories to harmonize their consent requirements, and the social values they encode, with the UKSCB. The participants in the International Stem Cell Initiative were also asked to certify that their lines were derived using similar ethical guidelines (Steering Committee of the International Stem Cell Initiative 2005). Hence the UKSCB uses its bioethical guidelines as a gate keeping device. Laboratories wishing to get access to its considerable resources, and to the collaborative networks developing round it, must demonstrate that the ethical provenance of their stem cell lines conforms to those deemed appropriate by the bank's Steering Committee. Cleary this creates pressure for harmonisation of consent procedures among a number of disparate laboratories and the IVF clinics they use to procure embryos. Over time, it seems likely that its consent requirements will create pressure for an international harmonization of consent procedures at a national regulatory level, particularly among nations whose scientists work closely with UK scientists. The bank already has a formal understanding with the US National Institutes of Health, so that hESC research given ethical clearance by the NIH is accepted as cleared by the bank Steering Committee as well. Such memoranda of understanding, another form of standardization process, facilitate research collaboration.

At the same time, it is important to acknowledge the *limits* of bioethical standardization. While in the controlled space of the laboratory, biological standards can be made relatively stable, bioethical standards are much more volatile in their effects. They must

operate in a complex social field where local culture, hierarchies and values may undermine the ideal social relations of autonomy, informed consent and decisional freedom both assumed in and created by the consent procedure. Bharadwaj and Glasner's (2004) ethnographic study of embryo donation in India suggests the extent to which consent procedures can be followed to the letter, but the social context in which they operate nullifies many of the aims of the procedure. Hence, they found that Indian clinics would routinely offer free IVF for couples who were prepared to donate embryos for research. They note that in the context of the Indian social stress on fertility, the expense of IVF treatment and the relative lack of value placed on embryos, the offer of free treatment constitutes overwhelming pressure, particularly on the female partner who must otherwise bear the stigma of childlessness. They describe this as a case of the ineffective importation of ethical practices developed within judaeo-christian traditions, and an instance of 'the use of informed consent by clinicians to mask the provenance of stem cell lines, and hide the wider socioeconomic conditions from which they are derived' (Bharadwaj & Glasner 2004: 18). Glasner notes elsewhere (Glasner 2005) that this local complexity of the social relations of consent, particularly in cases of embryos procured outside Western Europe, will need to be taken into account by the UKSCB in its assessment of the provenance of stem cell lines, an accounting that would necessarily mean moving beyond procedural approaches to assessment. These are the kinds of social complexities that, as Bowker and Star noted above, standardization processes are designed to mute and simplify.

Patenting standardisation

Domains of scientific governance are rarely separate from, or impervious to, their governance neighbours. So although the UK Stem Cell Bank is an influential player in the standardization of basic hESC research, it acts within an overall governance context that may facilitate or constrain the global significance of its standardization procedures. In this section we explore how the governance domain of patenting, an arena of standardization apparently quite distinct from that of research, can nonetheless impact on how the standardization of research progresses.

In their 2005 report *Intellectual property as an economic asset: key areas in valuation and exploitation*, the EPO and the Organisation for Economic Cooperation and Development (OECD) argue that in the global knowledge economy an increasing share of the market value of firms derives from their intellectual assets. They continue,

> As firms shift to more open models of innovation based on collaboration and external sourcing of knowledge, they are exploiting patents not only by incorporating protected inventions into new products, process and services, but also by licensing them to other firms or public research organisations (PROs). Moreover, they are using patents as bargaining chips in negotiations and as a means of attracting external financing from banks, venture capitalists and other sources. (EPO and OECD, 2005: 3)

Pursuing this economic logic, intellectual property rights (IPR) are regarded as an essential component of this kind of economy because they commodify the intangible capital of knowledge, generate value and facilitate trading. Without IPR, and in particular patent protection, emerging markets such as stem cell science would find it difficult (or more difficult) to develop since the tangible product has yet to appear and economic value is embedded in the potential application of the knowledge. This problem is particularly acute in high-tech and research based Small to Medium Enterprises (SMEs) for whom their IPR is their main asset.

The economic significance of patents is further enhanced by the need for new forms of knowledge to compete for attention in an increasingly global venture capital market with its own clear demands: investors, often institutional investors, make their decisions in the light of the patents held by companies (Florida and Smith, 1990; Florida and Samber, 1999; Haemmig, 2003). For capitalisation of a new knowledge market to occur, then, investors need to be reassured that the value of the knowledge, as opposed to the value of the eventual product, is in the hands of the company concerned. (Evidence of the relationship between patents and financial markets is shown in the responsiveness of stock prices to both the issuing of new patents and the number of patents owned by a company (Coriat and Orsi, 2002: 1501; Zeller, 2005: 17).) Investors are likely to be particularly sensitive to the patenting issue in high risk areas such as the early stage development of health biotechnologies where the science is very new and the potential therapies very distant.

In a perfectly rational world where economic arguments dominate, the political implication of this logic is that states will seek to adjust their governance of patenting to enable more knowledge to be patented more efficiently with the intention of maximising their capacity to compete effectively in the global knowledge economy. Patenting policy will be harnessed to the national interest. Further, that having made the domestic policy adjustment themselves they will then apply international pressure for the harmonisation of inter-state patenting standards along lines consonant with their national approach. Whilst perhaps not perfectly rational, we can see that in the important case of the United States (US), for example, an early adjustment was made to accommodate this logic in the field of health biotechnology. In its 1980 decision on *Diamond v Chakrabarty*, the US Supreme Court ruled that a living organism (in this case a bacterium of the genus pseudomonas modified using molecular techniques) could be patented. In general, it commented, patents could be granted for 'anything under the sun that is made by man' and in this respect living organisms are not exceptional (Jasanoff, 2005: 49) – a generous view of intellectual ownership. Other states have been less persuaded that the knowledge property generated by the life sciences should be so broadly interpreted. In 2002, Canada's Supreme Court rejected Harvard University's application for a patent on its oncomouse (a mouse with a cancer promoting gene) on the grounds that higher life forms are distinctive and transcend the patenting definition of 'composition of matter' (Nador and Loucaides, 2003: 7).

Although individual states may resist the economic logic of patenting so comprehensively embraced by the United States, the national level is not the only, nor

necessarily the most critical, political site where the conflict over the appropriate definitions of ownership of the products of the life sciences takes place. Three international bodies have provided a continuing target for political pressure through their attempts to promote the international standardisation of patenting rules: the United Nations' (UN's) World Intellectual Property Organisation (WIPO – established in 1967), the World Trade Organisation's (WTO's) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) and the European Patent Office (EPO). The creation of TRIPS in 1994 by the Final Act of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) was in large part a response by developed countries, and in particular the United States, to the manoeuvrings of developing countries within the WIPO during the 1970s and 1980s seeking to resist international encroachments on their sovereign intellectual property rights. TRIPS drastically limited their political space in two ways. First, it tied membership of the WTO (which most developing countries wanted and needed) to agreement on TRIPS. (Currently 144 states are members of the WTO and therefore signed up to TRIPS). Second, it set detailed and mandatory harmonising standards of intellectual property law on the ownership of two major technologies: digital technology and, importantly, biotechnology (Drahos with Braithwaite, 2002:10-17).

The struggle over the TRIPS agenda illustrates that even the economic logic of patenting regulation is less than neutral when political interest is included in the equation: a country's approach to the global harmonisation of patenting will be influenced by the strength or weakness of its competitive position in the international economy. For example, at the insistence of India, Argentina, Brazil, and Turkey, all of whom sought to protect their own industries, TRIPS contains a 10 year delay for the institution of pharmaceutical and agricultural chemical patent protection in developing countries. At the same time, international science was becoming less than enamoured with an economic justification of a form of patenting standardisation that in its view has the effect of either restricting the free flow of scientific information or restricting that information to those prepared to purchase the appropriate license from the patent holder. It should be remembered that the TRIPS agreement was signed at a time in the mid-1990s when the Human Genome Programme (HGP) was strongly promoting the open science model (HUGO, 1995; see also Royal Society, 2003). In this context, the issuing of patents on research tools such the oncomouse granted to Harvard University (subsequently handed over to Dupont Corporation as part of an exclusive licensing arrangement) and the breast and ovarian cancer gene to the University of Utah, the National Institute of Health (NIH) and Myriad Genetics (which enjoys exclusive rights to the exploitation of all of the benefits that can be derived from diagnosing the gene) created the strong suspicion among scientists that 'disproportionate and overlapping patent grants [were] gluing up the research world' (Cornish *et al*, 2003: 19). In their report *Intellectual property rights and genetics* to the United Kingdom's (UK's) Department of Health, the authors expressed the fear that as a result of the US-style of approach to patenting in the knowledge market of new health technologies:

> the cost of care will increase; that patients will be deprived of access to new techniques and drugs; that research and testing tools will be withheld; that

> researchers and carers will not share information; that research will become too complicated to enter upon (perhaps because of the so-called "anti-commons effect" if there being too many right holders); and equally there could be premature commercialisation in the race to get ahead (Cornish *et* a*l*, 2003: 19).

Here we can see that the debate about the relationship between patents and economic advance is emphasising as important factors other than those that contribute to the efficiency of the patents-innovation linkage. Perhaps unsurprisingly, the political agenda of patenting standardisation is broadening as the pure economic arguments (contested though they may be) are supplemented by cross-cutting discourses about rights (eg who should have access to the new health technologies) and, as we shall see, ethics (what is the moral basis of patenting?). The future global politics of this field were to be greatly influenced by the extent to which these broader, cultural factors were able to penetrate the key decision and policy making arenas.

But to take a step back and reflect on the socio-cultural significance of patenting, Jasanoff suggests that patents order the process of invention in ways that are 'intrinsically political' because their extension 'to new domains alters basic notions of what is a commodity and who can assert ownership over it.' In biotechnology, patents 'have the effect of removing the thing being patented from the category of nature to the category of artifice – a profound metaphysical shift' (Jasanoff, 2005: 204). We have already seen in the Canadian case that the act of commodification of biotechnological knowledge for private purposes may indeed be perceived as culturally significant, particularly where human and animal life is the subject. As the international debate over patenting has progressed, so the reservations regarding the universal applicability of the economic logic of patenting have increased, matched by a growing awareness of the range of alternative perspectives that may have a legitimate place in the formation of patenting standards.

Within the TRIPS Agreement, the recognition that non-economic factors may have a proper role to play in patenting policy finds expression in its Article 27 where the Agreement states:

> Members may exclude from patentability, inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by law.(paragraph 2) (Nuffield Council on Bioethics, 2002: 79)

Other permitted exclusions include 'diagnostic, therapeutic and surgical methods for the treatment of humans or animals and plants and animals other than micro-organisms' (paragraph 3). But for these exclusions to have international political impact there would need to be sustained pressure for their activation.

That pressure has emerged in large part through a challenge to the assumption behind the economic approach to patenting that knowledge is a private rather than a public good. In

this context the function of patenting is to facilitate the ability of the individual to maximise the economic benefits of knowledge ownership. Against this has developed the alternative view that knowledge is a public or communal good and that the use of patenting as a market mechanism is less important than its contribution to the achievement of certain human and cultural rights (for example, health, human dignity, cultural identity) (Drahos, 1999; 2002). For the supporters of TRIPS and the US style of patenting (bearing in mind that US patent law has no morality clause), it has been important to limit the strength of this challenge by trying to keep human rights and its associated ethical arguments contained in a separate policy silo. To bring the two policy streams together at the international level, it was believed, would undermine the principles of the global knowledge economy that TRIPS was set up to protect by rendering the application of those principles relative to other, ethical priorities. However, the HIV/AIDS epidemic and the imperative for developing countries to ensure their population's right of access to medicines by resisting the rise in drug prices that accompanied the implementation of TRIPS forced a reappraisal of this separatist approach (Cullet, 2003). Nor is it simply a developing country issue. Citizens in developed countries are likely to be equally energised if they see patenting laws as depriving them of what they consider to be their health care rights. O'Connor predicts that in the United States the promise of stem cell research of cures for cancer, diabetes and Alzheimer's disease means that the pitch of the ownership battle will rise proportionally to the success rate of the research. He continues: 'the public's claim to reasonable access to any crucial life-saving medical breakthroughs that do arise from stem cell research may well force federal, state or local officials to circumvent the existing political opposition to compulsory licenses in the United States' (O'Connor, 2005: 666).

In addition, the *Universal declaration on the human genome and human rights* in 1997 by the International Bioethics Committee (IBC) of the United Nations Educational and Cultural Organisation (UNESCO) initiated a global debate about the moral status of the human body and human life and their relationship to the market that is still gathering political speed in both bioethical and policy making circles worldwide (Salter and Salter , 2005). At the conclusion of its 8th Session on 14th September 2001 the IBC adopted by consensus an *Advice on the patentability of the human genome* which states that 'there are strong ethical grounds for excluding the human genome from patentability' and further recommends 'that the WTO, in its review of the TRIPS Agreement, clarify that, in accordance with the provision of Article 27(2)1 (the morality clause), the human genome is not patentable on the basis of the public interest considerations set out therein, in particular, *ordre public*, morality and the protection of human life and health' (European Group on Ethics, 2002: 56). Ethical discussions about the status of DNA, the human embryo, human dignity and the commercialisation of the human body - often subsequently enshrined in national legislation and, in the case of the Council of Europe's *Convention on human rights and biomedicine*, in a protective international agreement - now form an internationally salient discourse with which patenting policy and practice is obliged to engage. At the same time other international developments, and in particular the *Convention on biological diversity*, have emphasised the importance of the communal ownership of knowledge as a counterbalance to what some have termed the 'biopiracy' of

the developing world's knowledge by Western countries and companies sailing under the TRIPS flag that champions the individual ownership of knowledge (Sell, 2005: 6).

In Europe, the transnational governance challenge created by the clash between, on the one hand, the private ownership requirements of an unrestricted global knowledge economy of human ESC science and, on the other, the communal values of local cultures has been manifest through the continuing political negotiations surrounding the two international agreements for the regulation of patenting in this field: the Council of Europe's 1973 European Patent Convention (EPC) and the EU's 1998 Directive on the legal protection of biotechnological inventions (Directive 98/44/EC). Neither the EPC nor its administrative arm, the European Patent Office (EPO) are EU institutions but have a quite separate legal identity. However, all EU Member States have ratified the EPC (as have several non-EU states, notably Switzerland). In addition, in 1999 the EPO stated that it would use the Directive as a supplement to interpretation of the EPC and included it in its Implementing Regulations (Baldock and Kingsbury, 2000). This is significant because Article 6 of the Directive excludes:

> (a) processes for cloning human beings;
> (b) processes for modifying the germ line genetic identify of human beings;
> (c) uses of human embryos for industrial or commercial purposes;
> (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from this process;

and these exclusions have to be incorporated into the patenting legislation of Member States.

The agreement on the biotechnology Directive and its incorporation into the Implementing Regulations of the EPO not only consolidated the general position of ethics as a factor in European patenting decisions but also provided specific guidance on the treatment of patent applications involving the human body, gene sequences, cloning, human embryos and genetic modification. It is therefore no coincidence that five months later the University of Edinburgh ran into a considerable political storm when Patent No. EP 0695351 entitled 'Isolation, selection and propagation of animal transgenic stem cells' was granted to it by the EPO. The patent was challenged on the basis that its claims extended to a method of somatic cell nuclear transfer in 'animals' and that this included 'humans'. Unusually, fourteen different opponents registered their objection to the patent on the grounds of ordre public (Article 53a of the EPC) including the governments of the Netherlands and Italy. Demonstrations by Greenpeace coupled with national and international press coverage rapidly politicised this part of the stem cell field. When the EPO Opposition Division ruled on the University of Edinburgh patent application in July 2002, it asserted that any claims involving human ES cells violated the European Patent Convention's Rule 23d(c) that excludes uses of human embryos for industrial and commercial purposes from patentability (EPO, 2002). The knock-on effect was immediate with patent examiners using the decision as a precedent to reject an application concerning James Thomson's technique for driving primate ES cells from the

Wisconsin Alumni Research Foundation (WARF) (Vogel, 2004). Other applications from the California Institute of Technology on a method to isolate neural stem cells from embryonic tissue and from the University of Bonn on a method to differentiate neural cells from mammalian ES cells also remain unresolved. As a result of appeals from the University of Edinburgh, the decision on the principle of human ESC patenting now rests with the EPO's final authority, the Enlarged Board of Appeal, a process which may take several years. As a consequence, the future value of hESC science remains an unknown and thus the potential market in which biotechs and venture capitalists might invest a present unreality.

It can be argued, therefore, that the standardisation of technical and bioethical elements by the UK Stem Cell Bank in the governance domain of hESC research has been matched by the failure of international standardisation in the governance domain of hESC patenting. Governance development in different parts of stem cell knowledge production has progressed at different rates with different responses to the cultural context. In the case of patenting governance, the effect of this situation is marked. The United States patent and Trademark Office (USPTO) has, to date, granted 41 patents that claim human embryonic stem cells in their title and front pages. These include patents on culture methods, differentiated cells derived from hES cells and even hES cells *per se*. By contrast, the EPO has not granted a single patent that makes direct hES cell claims (Porter *et al* 2006).

The implications of contested stem cell governance for the work of the UK Stem Cell Bank are considerable. The Bank's advancement of stem cell science through the facilitation of standardised knowledge exchange, regardless of the sophistication of this standardisation, will nonetheless be restricted to the extent that the governance of the patenting domain inhibits the translation from basic science to therapeutic product. The Bank is clear that its sphere of governance does not include intellectual property. When stem cell lines are deposited with the Bank ownership remains with the depositor but the Bank stipulates that:

> A pre-requisite for depositing in the UK Stem Cell Bank is that the owner of the stem cell line signs a Materials Deposition Agreement (MDA) with the Bank agreeing to make the stem cell line available to requestors for research purposes, on terms of access to be negotiated between the depositor and any future requestor in the Materials User Licence (MUL) (UK Stem Cell Bank 2007).

The depositor, meanwhile, acts within the UK's Patents Act 1977, as amended to implement Directive 98/44/EC on the legal protection of biotechnological inventions. Since the latter stipulates that uses of human embryos for industrial or commercial purposes are not patentable inventions, the UK's Intellectual Property Office (IPO) will not grant patents for processes of obtaining stem cells from human embryos. Nor will it grant patents on totipotent cells with the potential to develop into an entire human body because the human body at the various stages of its formation and development is excluded from patentability by Paragraph 39a) of Schedule A2 to the Patents Act 1977. However, human embryonic pluripotent stem cells, with which the UK Stem Cell Bank is

at present primarily concerned, are patentable because they do not have the potential to develop into an entire human body (UK Intellectual Property Office, 2003). Depositors in the UK Stem Cell Bank can therefore benefit financially from their ownership of the stem cell lines through the licensing of the use of the lines to interested researchers and companies.

Because the process of hESC line creation is not patentable under UK law, UK researchers in this field have a fair degree of freedom in their basic research. There is a compromise in this governance domain between the market values of ownership, the cultural worth of the human embryo and the scientific values regarding free flows of information. Not so in the US, the home of permissive patenting law. Here the balance is quite different with the market values in the ascendancy.

The patents granted to the Wisconsin Alumni Research Foundation (WARF) for work done at the University of Wisconsin by James Thompson on embryonic stem cells are said to 'embody one of the strongest possible property claims in the field of stem cells, establishing control at the very root of all possible lineages of cellular differentiation.' (Bergman and Graff 2007). They claim all primate and human embryonic stem cell lines and in 2005 were licensing their commercial use with a $100,000 up-front fee and $25,000 annual maintenance – a prohibitive cost for start-up companies. Geron, meanwhile, has a broad portfolio of human ESC IP rights, is closely associated with the WARF patents, and has secured exclusive US commercial rights to three types of cells derived from ES cells; cardiomyocytes, neural cells and pancreatic β-cells (Geron 2007a and 2007b). Opposition to this open-ended approach to patenting governance in the US has come from scientists claiming that their research is being slowed down as a result of the 'anti-commons' effect of the 'patent thicket' generated by WARF and Geron (Nature News 2005; Stem Cell Business News 2007). The existence of such overlapping patents, it is argued, can cause uncertainty about freedom to operate, impose multiple layers of transaction costs and block pathways to market by dampening investor interest in commercialisation (Bergman and Graff 2007: 419).

Conclusions

The global knowledge economy of human embryonic stem cell science is emerging within a changing governance context that both helps and hinders its development. Bioeconomy and governance are evolving interdependently, but not necessarily efficiently. Furthermore, the various domains that govern the knowledge production process are developing their modes of standardisation at different speeds, influenced by national and international cultural values and political interests.

In this paper we have examined standardisation in the hESC governance domains of basic research and patenting. In the former, the transnational networks of science are collaborating under the aegis of the UK Stem Cell Bank and the International Stem Cell Initiative to develop forms of standardisation that incorporate and satisfy technical and ethical criteria. The institutional leadership of the UK in this domain is thus far accepted and the process of governance development regarded as a neutral international activity

pursued for the good of science. In patenting, however, the situation is much more complex. Here hESC science is situated within an existing structure of global, regional and national governance characterised by a plethora of technical and cultural conflicts manifest in continuing legal debates about standarisation. In this domain, science is one player among many and its governance interests frequently collide with those of the market.

As different governance domains in a common process of knowledge production, research and patenting are politically interlinked: developments in one will have implications for the other. For example, a key part of the strategies of companies such as WARF and Geron is to acquire the benefits of their patenting rights in the global as well as the US marketplace of stem cell science: profit maximisation would naturally ensure that this was so. As we have seen, their ability to do so will vary according to the culture of the state or region they are seeking to access and the configuration of political interests therein. If they are successful, there will be governance implications for the standardisation of human embryonic research led by bodies such as the UK Stem Cell Bank. Research standardisation is necessary not only to enable scientific advance but also as a condition of commercialisation. If the basic research is subsequently seen to be flawed then the clinical and therapeutic products that flow from that research will be seen as suspect. At the same time, if the IP regime either discourages scientists through the dense patenting of the knowledge production process or fails to reward potential investors through a very cautious definition of what may be patented, then commercialisation will be impeded that way. It is therefore sensible to be cautious when assessing the significance of standardisation in any particular domain of hESC governance.

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