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The right mix of biology, metaphysics and culture: stem cell research in Europe and China

Abstract

Stem cell research is a field that has attracted considerable scientific and financial investment and attention in China and Europe. It is also a field surrounded by ethical controversies and policy developments concerning cloning, the moral status of human embryos, sourcing of human embryos and gametes for research, human-animal hybrid embryos as well as stem cell therapy tourism. Based on work done by BIONET, this paper examines efforts to develop systems of science governance in the field of stem cell research and how these relate to the cultural and historical contexts of the countries in question. This includes, on the one hand, deliberative efforts to determine what constitutes scientifically sound and ethically appropriate stem cell research, and on the other, regulatory efforts to establish rigorous systems of ethical and peer review of stem cell research.

Key words

Stem cell research, science governance, biological materials, spare embryos, bioethics, China, Europe

1. Introduction

In both Europe and China, stem cell research has emerged as a key strategic field attracting considerable national investment and public attention (European Commission 2001; Hennig 2006; Pei 2007b; Salter, et al. 2006; Sleeboom-Faulkner 2004).¹ At the same time, it has also become a contested area of scientific research, emblematic of both the hopes and fears that are associated with advanced bioscience, most of which have centred around human embryonic stem cells because of beliefs about their unique clinical potential and ethical uncertainties. On the one hand, it is hoped that some of the most debilitating diseases and disorders can some day be treated if not cured using stem cell therapies based on the pluripotency of stem cells. On the other hand, the sourcing and manipulation of such cells appears particularly ethically problematic. Human embryonic stem cells are 1) *sourced* from six-day old *in vitro* fertilised human blastocysts; 2) in order to be *manipulated* and cultivated in laboratories in a quest to understand and harness their pluripotent properties; 3) with the hope that they can then be *transplanted* back into human patients in the treatment of degenerative diseases. Each of these stages of research and treatment embodies ethical challenges, even more so in a context of globalised scientific research, where biological samples and expertise can be speedily exchanged across national borders and continents. Hence, in both Europe and China, the challenge for regulators, and for stem cell researchers, is whether, and how, these stem cell lines can be generated in ways that are scientifically, clinically and ethically acceptable. What is more, a key question for BIONET is how research collaborations between Chinese and European scientists in the field of stem cell research can be practically organised when faced with multiple national regulations and/or science governance systems.

While stem cell research has received considerable investment in China and many European countries, there has been a multiplicity of national responses to the ethical challenges raised by stem cell research. Key scientific, ethical and regulatory debates have focussed on the procurement of human embryonic stem cells, somatic cell nuclear transfer (or ‘therapeutic cloning’), creating human-animal cybrid embryos for research purposes and distinctions between ‘research grade’ and ‘clinical grade’ stem cell lines in

human treatment. Many European countries, including Germany, the United Kingdom, Denmark, Sweden and France have passed legislation specifying what kinds of stem cell research are allowed. Some countries allow for the *in vitro* creation of human embryos for the purpose of procuring hES cell lines, some allow for the procurement of hES cells only from so-called ‘surplus embryos’ (unused by a couple following infertility treatment) while a number of countries have explicit and wide ranging prohibitions on procurement from human embryos. And so within Europe, one finds a plurality of ethical governance systems relating to stem cell research.

In China, a number of papers, guidelines and regulations have been drafted and debated in recent years to address some of the ethical and regulatory challenges surrounding stem cell research. In 1999, a set of “Recommendations on Ethical Principles and Governance of Human Embryonic Stem Cell Research” was submitted to the Ethics Committee of the Ministry of Health by researchers in Beijing. A few years later, in October 2001, the Ethics Committee of the Chinese National Human Genome Center in Shanghai drafted and then revised a set of “Ethical Guidelines for Human Embryonic Stem Cell Research”. Neither of these drafts were officially approved at the national level, although both formed the basis of the “Ethical Guiding Principles for Research on Human Embryonic Stem Cells (2003-460)” jointly approved by the Ministry of Science and Technology and the Ministry of Health on 24 December 2003. As it stands, stem cell research is not governed by law in China, as will be discussed later. More recently, new regulations from the Ministry of Science and Technology on scientific misconduct (2006) as well as from the Ministry of Health on the ethical review of biomedical research involving human subjects (2007) have been passed.

In both China and Europe, some clinics have offered patients ‘experimental’ stem cell therapies, for example in the treatment of multiple sclerosis or neurodegenerative diseases. But this remains controversial. Many of the procedures that are offered have not been tested rigorously through clinical trials and many claims that are made for their efficacy are unproven or misleading. In addition, there are safety, quality and ethical concerns about where and how stem cell lines used in the treatments have been procured

and manipulated. In many cases, such experimental treatments stand in conflict with existing regulations which suggests deficits in monitoring capacities as well as in communication of regulatory standards. Moreover, there have also been concerns about ‘stem cell therapy tourism’, where individual citizens travel within/to Europe or Asia in order to undergo often costly and perhaps risky regenerative medicine treatment (Baker 2005; Sheldon 2006; White 2007).

This paper, which draws on research and discussions that have been undertaken in connection with the work of the BIONET consortium, examines and compares how ethical challenges surrounding the procurement, manipulation and transplantation of stem cell lines have been addressed in recent years both in Europe and China. Over three years (2006-09), BIONET’s work on ethical governance in biological and biomedical research will focus on four major areas: reproductive medicine, regenerative medicine, clinical trials and biobanking. In its first half, BIONET has focused in particular on the links between reproductive medicine, human embryonic stem cell research and regenerative medicine. “Informed consent” has been chosen as a methodological tool for BIONET’s investigations, in order to generate accurate descriptions of differences between informed consent regimes – which indicate the reality of existing standards on the ground (among researchers, clinicians, patients and other stakeholders) – and actual informed consent practices.

By analyzing the ways in which the work of stem cell researchers has come under the purview of regulators, bioethicists, law experts as well as the ‘public’ in both regions, it is suggested here that these processes might be understood, on the one hand, as attempts at finding, a right mix of biology, metaphysics and culture (cf. Johnson 2007; Rehmann-Sutter 2007), and on the other, a system of good science governance. While these attempts usually take place within national jurisdictions, they are also unavoidably enmeshed in international debates concerning what constitutes ethically acceptable stem cell research. This international perspective falls within the remit of BIONET as it addresses ethical governance issues that arise from Sino-European collaborations

involving scientific and ethical standards (often linked to funding requirements) in both regions.

2. Ethical governance of stem cell research

The ‘Hwang scandal’, which became public in November 2005, made it clear that integrity in stem cell research not only concerns rigour but also ethical propriety in the conduct of scientific research. As a result, ‘tainted data’ has increasingly come to be understood as, not just that which has been fraudulently manipulated, but also that which has been obtained without regard for basic ethical requirements such as the autonomy, dignity and legal rights of involved individuals (whether they are donors of biological materials for research or patients undergoing treatment linked to clinical research). Peer review has long been considered a robust system (albeit not without contestation) for ensuring quality in scientific research. In more recent years, ethical review has emerged as a parallel mechanism of quality control. Informed consent procedures, ethical guidelines, codes of conduct, ethical review boards and other related institutions or processes have all emerged as methods for ensuring that scientific research is carried out in an ethically appropriate and approved manner. At the same time, it has also been shown that peer review and ethical review alone cannot prevent misconduct, perhaps especially so in fields (such as stem cell research) where there is national competition and prestige at stake. As argued by Herbert Gottweis, when it comes to research integrity “science culture matters” and “peer-review is no substitute for good science governance” (Gottweis 2007).

But what might ‘governance’ mean outside the Euro-American context in which the idea and language of governance has come to political and theoretical prominence over recent years. While there is a growing debate on governance in China (e.g. Howell 2003; Sigley 2006; Yu 2002), the term does not have a terminologically established counterpart in Chinese. The terms *guǎn zhì* (管治) and *guǎn lǐ* (管理) are often used to describe ‘good governance’ (*liáng hǎo de guǎn zhì/lǐ* 良好的管治/理), in contrast to both *zhèng fǔ* (政府) which means ‘government’ and *zhì lǐ* (治理) which means ‘to govern, administer or control’. Nevertheless, all four terms convey a certain top-down directedness where

decrees, ordinances, orders, laws, statutes and regulations are passed and adherence is ensured through some form of coercion. In the former terms, the common character *guǎn* (管) means ‘to take care (of), control, manage, be in charge of, look after’ while *zhì* (治) means ‘to rule, govern, manage, control’ and *lǐ* (理) means ‘reason, logic, science, inner principle or structure’. The distinction between top-down and bottom-up is important, as argued by Yu Keping:

Power of government operates always from top-down to bottom-up primarily through orders, statutes, bureaucracy and coercion while power of governance operates mutually, interacting both from top-down to bottom-up and from bottom-up to top-down, primarily through collaboration, coordination, negotiation, social networking, neighbourhood, identity or consensus. (Yu cited in Sigley 2006: 503)

But it is not necessarily language that constitutes the greatest difference when it comes to forms of governance,² for even among those who are familiar with the debate, there is no consensus in China or Europe on what a blueprint for ‘good science governance’ would look like in the field of stem cell research. As a minimum, Zhai Xioamei of the Peking Union Medical College has suggested that it requires good regulations (with ethically justifiable norms that are operable), implementation capacity (which requires education and training), mechanisms of oversight (both peer and ethical review and perhaps some form of licensing), incentives and disincentives, a regulatory body and sufficient resources to fund all of these (Zhai 2007). But at the same time, Gottweis has argued that, in addition to this regulatory infrastructure, “research integrity is increasingly a matter of network integrity” where networks can link international collaborators, scientists, fertility clinics, hospitals, reputed international and national journals, government officials, regulators and corporate sponsors (Gottweis 2007). From this perspective, ‘good science governance’ is not just about how guidelines and regulations are implemented and followed (especially since science is often well ahead of regulation), but also involves a complex system where research practice is guided by respect for the rule of law, transparency, scientific and ethical accountability, human rights and freedom from corruption.

Moreover, Ole Doering argues that when it comes to the management of diversity within highly heterogeneous contexts, such as ones of international scientific collaboration, subsidiarity should be a key organising principle according to which “matters ought to be handled by the smallest (or, the lowest-level) competent authority. It is the idea that a central authority should have a subsidiary function, performing only those tasks which cannot be performed effectively at a more immediate or local level” (Doering 2008).

3. ‘Permissiveness’ in European and Chinese regulatory mixes

Starting from their historically established legal regimes, European countries have developed diverse laws and regulatory mechanisms related to stem cell research. And, in recent years it has been common to classify countries according to degrees of ‘permissiveness’ when it comes to especially human embryonic stem cell research (Hinxton Group 2008). As a number of scholars have shown, it is possible to class European countries into those that: 1) prohibit research involving destruction of human embryos and the production of ‘spare’ embryos; 2) allow creation and research on ‘spare embryos’ donated by couples in IVF clinics; 3) allow the creation of embryos for research through Somatic Cell Nuclear Transfer (SCNT); and 4) allow research only on imported hESC colonies. More recently, a fifth category has emerged, i.e. those countries allowing, or intending to allow the creation of cybrids for research purposes. Thomas Streitfellner has argued that “European regulation is getting more permissive over time” as, for example, whereas only three countries had a legislative framework authorizing stem cell research in 2001, by 2007 this had increased to 14 and what is more, four countries had explicitly legalized research involving SCNT (Streitfellner 2007). According to Streitfellner, some of the key factors contributing to national systems of stem cell research governance are: political interests, religious belief systems, public support, economic strength, funding structures/ bureaucracy, networking amongst scientists and collaboration with other disciplines (e.g. social scientists), and cultural and historical heritage.

Just as the United Kingdom is considered to have a ‘permissive’ regulatory approach to stem cell research in Europe, so too is China. Stem cell research in China is currently

only the subject of ethical guiding principles which are not enforceable: there are no requirements regarding the qualifications of stem cell researchers, no oversight mechanisms and no agency specifically responsible for overseeing the upholding of the guidelines (Qiu 2007). As Liu Yinliang (2007) of the China University of Political Science and Law has pointed out, there are important differences in scope and enforceability between the several regulatory instruments currently in use in China, such as laws, regulations, measures, ethical guidelines and technical norms. Laws (*fǎ* 法) are passed by the People's Congress or its Standing Committee and are fully enforceable by the responsible institution specified in the law. Regulations (*tiáo lì* 条例) are approved by the State Council and are also enforceable. Technical norms or standards (*jì shù guī fàn* 技术规范) and ethical principles (*lún lǐ yuán zé* 伦理原则) on the other hand are only enforceable if they are specifically authorized in the text of a law or regulation. Finally, there are also measures (*guǎn lǐ bàn fǎ* 管理办法) which are directed at the administration and management of certain research and therapeutic practices and which are binding for those institutions, which are licensed to carry out these practices. And, as already mentioned, stem cell research is only the subject of ethical guiding principles in contrast to Assisted Reproductive Technologies or Organ Transplantation Technologies which are subject to technical norms, ethical principles and administrative measures (Doering 2003; Doering 2006).

Qiu Renzong of the Chinese Academy of Social Sciences has argued that “current policies seem to be maximising scientific freedom and minimising ethical/regulatory constraints”, perhaps as a way for China to achieve “the ambition to be a power in bioscience and biotechnology” (Qiu 2007). Yet, Zhai Xiaomei argues that this idea that the “development of biomedical research and biotechnology without constraint will allow China more rapidly to catch up with efforts in developed nations” is “both wrong and dangerous”. Wrong because it assumes that ethical accountability impedes scientific progress and dangerous “because Chinese science and technology could lose its essential integrity and public support both at home and abroad – the scandals over Hwang Woo-suk in South Korea and Chen Jin³ in China convincingly illustrate this point” (Zhai 2007). And as Margaret Sleeboom-Faulkner has shown, there are ongoing debates in

China over who should be charged with “the important function of governing bioethical morality in the medical sector” (Sleeboom-Faulkner 2008: 33).

4. The moral status of biological materials

The most controversial ethical debate about stem cell research in Europe has concerned the moral status of the human embryo – the source of human embryonic stem cell lines. This debate has involved attempts at agreeing on a precise moment when full moral status (full legal respect of dignity and human rights) is accorded to ‘biological material’. Should it be from the moment of fertilization, nidation, perception of ‘primitive streak’ or birth? Is pinpointing such a biological moment for legal purposes relevant for ethical deliberation?

In the United Kingdom, the Warnock Committee, for example, adopted a gradualist view where there is a “gradation in the respect accorded to a foetus as it develops from zygote to early embryo to its birth” (Johnson 2007). In doing so, they “set out the central principle of a gradualist approach to the developing moral status of the embryo that accorded it a special legal status such that human embryo research is permitted *only under licence from a regulator* and is limited to a maximum of 14-days *in vitro*” (Johnson 2007). In contrast to the UK’s 14-day limit, which has since been adopted in many countries, the German Embryo Protection Act from 1990 accords full protection to “*any fertilized human oocyte* after that point in time at which the pronuclei have fused, *any later stage of its development* and to *any totipotent parts* which could, under the proper circumstances, be able to develop into an individual being” (Germany. Parliament 1991). In China, although not binding, the ethical guiding principles on stem cell research do invoke the 14-day limit. As Qiu Renzong (2007) has put it, even though there are many who hold that a ‘traditional Confucian view’ according to which “a person begins with birth and ends with death” still stands, the ethical guiding principles clearly see the “human embryo [as] a human biological life, a precursor of person, not merely ‘stuff’ like placenta... so it deserves due respect: if there is no sufficient reason, it should not be permitted to manipulate or destroy it” (see also Cong 2007).

Christoph Rehmann-Sutter of the University of Basel has argued that what he calls “genomic metaphysics” plays an important role in strategies of legitimisation in stem cell politics. If it is “the potency of E to become a person (future) which confers a right to be protected (present)” then the question of whether one ascribes to ‘program genomics’ (which privileges DNA) or ‘system genomics’ (which looks at DNA-cell-environment interactions) will play an important role in attempts to decide just what should be protected as well as from what moment (Rehmann-Sutter 2007). What empirical studies show is that this act of ‘drawing the line’ is both arbitrary and essential and it cannot be resolved by appeal to nature or to a universal moral philosophy (e.g. potentiality or dignity) as they do not close controversy. Instead, it appears that, as Martin Johnson put it in discussions at BIONET’s workshop on stem cell research in Shanghai “each country must find the right mix of biology, theology and metaphysics to satisfy it – to fit with its cultural narrative” (see also Metzler 2007).

5. Sourcing stem cells

Potentially self-renewing stem cells can be sourced from six-day old *in vitro* fertilised human blastocysts, aborted human foetal tissues, umbilical cord blood, bone marrow, brain as well as other somatic sources. That is to say, stem cell lines are derived from biological samples, which are taken from human embryos, fetuses, newborns or adults. This of course raises questions of informed consent as well as ownership: who should consent and what are they consenting to? It also raises questions of how to distinguish between ‘biological waste’ and ‘biological samples’, especially since new markets have redefined biological materials as commercially and scientifically valuable (Waldby and Mitchell 2006).

One of the most ethically controversial areas of hESC research concerns the donation of eggs and embryos for research by recipients of fertility treatment. This research relies on a steady supply of ‘spare’ eggs and embryos and as a result the links between fertility treatment and stem cell research are intimate (Franklin 2006; Haimes, et al. 2008; Rehmann-Sutter, et al. 2008). This link can also create conflicts of interest, as clinicians may feel ‘obligated’ to stimulate ‘extra’ eggs or to create ‘extra’ or ‘better quality’

embryos for research rather than reproductive purposes (Svendsen and Koch 2008). For example, Fan Minsheng of the Shanghai Medical Ethics Association has reported on his experience in reviewing an application for a licence to establish a fertility clinic. Although the application was of a very high quality and “indicated that the hospital had equipped research rooms, proper facilities, researchers, an organized ethical review committee to support the research as well as the competent medical experience, since the objective of the application was research instead of reproduction, the application was rejected” (BIONET 2007).

Another example comes from Switzerland, where, as explained by Rehmann-Sutter, the law on IVF allows clinicians to fertilize only as many oocytes as can be transferred to the uterus of the women within one cycle (i.e. usually 2 or 3 depending on the age of the woman). Yet this law is in contrast to recent developments in fertility treatment techniques which favour longer *ex vivo* cultivation and transfer of a single viable embryo after 5 days. As had been commented by a director of an IVF clinic: “In my clinic, I would reach two ethically important goals at once: improving the pregnancy success rate of my patients and providing embryos for research in our stem cell group. The 0.5 Mio SFR technical investment for clean air facilities in our fertilization laboratory can be useful for both” (BIONET 2007). And finally, in Germany, all research on human embryos whether ‘spare’ or not to obtain human embryonic stem cell lines, is a prosecutable offence (Woopen 2007).

In recent years, anthropologists and sociologists in Europe have carried out in depth, qualitative research into the embryo donation process, taking into account patients’, clinicians’ and scientists’ views. What they have shown is that defining ‘spareness’ in the context of IVF-stem cell research is far from clear cut. For example, while some couples explain that they would like to “give something back” by donating any leftover embryos, they might prefer donating to fertility rather than stem cell research (Parry 2006). Some might consider allowing spare embryos to perish as ‘wasteful’, while others might see the inevitable destruction of spare embryos through hESC research as ‘wasteful’ (Haimes 2007). Also, some couples are considered “young and rich in beautiful embryos” and

have a superior therapeutic outlook in which case 'spareness' might not only refer to 'poor quality' embryos (Svendsen and Koch 2008). And finally, if some embryos which are graded as 'poor quality' on day three (thereby becoming 'spare' and potentially available for stem cell research) can turn out viable *in vitro* on day six, were they spare to begin with (Wainwright, et al. 2006)?

One important difference in the kind of social scientific research being carried out on the patient perspective in stem cell research is that while in Europe there is often focus on qualitative research methods where patients are interviewed, in the first studies in this field in China there is a focus on quantifiable survey research. For example, Tu Ling of the Hunan Institute of Reproduction and Stem Cell Engineering in Changsha, carried out a random analysis of 414 signed informed consent forms which showed that in 62% of the cases patients had indicated that they would donate frozen 'spare embryos' for research as an indicator of patient attitudes to stem cell research. Fertility patients in Changsha must decide whether they want to "voluntarily contribute poor quality embryos" as well as "surplus frozen embryos" after the successful delivery of a healthy baby following treatment for scientific research (Tu 2007). Guo Hui, a fertility counsellor in Changsha, has however noted that while she has experienced widespread support for donating non-viable embryos, there appears to be less support for donating 'good quality', frozen embryos as some patients are afraid that these embryos might be used for non-scientific purposes, or implanted in another person (Guo 2008). Thus while there seems to be unanimous agreement in Europe and China that "it is the patients who must decide the fate of their embryos" (Tu 2007) and that the informed consent process is key to this, 'spareness' is understood and negotiated in many different ways. Nonetheless, in China as in Europe, as fertility clinics and stem cell laboratories have entered into alliances, the stem cell-IVF interface has become a key transactional site, therapeutically, technically and ethically.

6. Manipulation and cultivation – the quest to understand and harness pluripotency

Stem cells are considered a promising avenue in the search for cures and treatments for degenerative disease because of their particular biological properties. Especially human

embryonic stem cells are often described as possessing the innate capacity to become any cell in the human body. Ideally, if understood, this self-renewing and pluripotential generative capacity of stem cells could be harnessed to repair damaged cells (e.g. in cases of degenerative disease or brain trauma injuries) and/or to produce certain tissues (e.g. heart valves, livers). Pluripotentiality is the ‘holy grail’ of stem cell research – i.e. how to cultivate, harness and control it for therapeutic purposes. Yet, if one thing is clear from hitherto stem cell research, it is that understanding mechanisms of action is very complicated; it is time consuming, expensive and requires a large and steady supply of biological materials from consenting human subjects. What is more, with human embryonic stem cells still considered one of the most promising sources of viable therapeutic stem cell lines, scientists face numerous ethical challenges in securing access to research material. As a result, a number of scientific research projects have in recent years sought to circumvent the need for access to human eggs or embryos.

The stem cell research community in China is certainly discussing these issues. Pei Duanqing, stem cell scientist at the Guangzhou Institute of Biomedicine and Health has recently argued that the key challenges in stem cell research are, first, understanding how stem cells amplify self-renewal and, second, understanding how they differentiate into, for example, liver, brain or heart cells. Because “once you understand you can manipulate” (Pei 2007a). And partly as a response to difficulties in obtaining eggs and embryos in China, his lab has begun focussing on discovering how differentiated cells can be coaxed ‘back’ into becoming pluripotent cells – induced pluripotential cells (iPCs). In this way pluripotentiality can be engineered out of differentiated cells using transcription factors and knowledge of epigenetics, allowing scientists to bypass the ethically sensitive task of procuring embryonic stem cells.

Another strategy to circumvent ethical controversies surrounding the procuring of human eggs and embryos for research has been that of using SCNT to create human-animal cytoplasmic hybrids or cybrids where the nuclear material of an animal egg is removed, and replaced with the nucleus from a human somatic cell. One of the issues emerging from the work of Hwang and his team was the sheer number of human eggs (over 2,000)

that had been used in efforts to carry out human SCNT. That is to say, even if it is possible to use human SCNT to make ‘patient specific’ therapeutic stem cell lines, at this stage the efficiency of the procedure is so low that huge quantities of human eggs are required for research. Cybrids have therefore emerged as another option that might alleviate the need for human eggs, at least at the research stage.

In China, the creation of hybrid embryos has been very controversial following the publication of work by Sheng Huizhen formerly of the Second Medical (now Jiaotong) University in Shanghai in 2003. Sheng reported that she and her team had successfully transferred a human skin cell nucleus into a denucleated rabbit egg, created about 400 human/animal cybrid embryos and then derived stem cells from them. The research was published in *Cell Research* in August 2003 (Chen, et al. 2003) sparking an international ethical debate in which some condemned such work on cybrids as unethical. Others have discredited the results suggesting that there may have been fraudulent use of data, though without any evidence to back up such claims in public to date.

This international attention to the developments in China happened to coincide with the final drafting of the Ministry of Health and Ministry of Science and Technology’s joint ethical guiding principles on human embryonic stem cell research. These banned hybrid research in stating that “it is prohibited to hybridize human germ cells with the germ cells of any other species” (P.R. China. MoH and MoST 2003). However, of course, the creation of cybrids does not involve human germ cells – it involves animal germ cells and human somatic cells – and thus is not covered by the guidelines. The Ethical Guidelines for Human Embryonic Stem Cell Research which had been issued by the Ethics Committee of the Chinese National Human Genome Center at Shanghai two years before in 2001 had explicitly stated that “use of the ‘human-animal’ cell fusion technique is permissible in basic research with non-clinical application” although it had also stated that “joining a human gamete with an animal gamete is not permitted” (Ethics Committee of the Chinese National Human Genome Center 2002). And so, currently, while creating human-animal hybrid chimeras by fusing human and animal germ cells is prohibited, the creation of cybrids is not. Qiu Renzong has argued in favour of human/animal cybrid

research “because the use of human eggs in cell nuclear transfer research is inefficient, and there is no substantial difference in moral status between cybrid embryos and normal embryos” (Qiu 2007).

In Europe, the United Kingdom has recently debated this strategy, amid considerable public controversy. The Draft Act on Human Tissues and Embryos from May 2007 makes a clear legal distinction between “Research Embryos” and “Embryos for use in treatment” and introduces the legal concept of the “permitted embryo”. In particular, the Bill proposes that a distinct legal category of embryos called “Interspecies embryos” (animal-human embryo chimaeras, animal-human embryo hybrids and cybrids) is created. Interspecies embryos can only be used for research purposes (not for reproduction or for creation of clinical grade stem cell lines) and are subject to the 14 day rule, i.e. they must be destroyed no later than 14 days after fertilisation. One of the driving factors behind these developments has been an argument by some leading stem cell scientists that the creation of cybrids would minimise the need to collect large numbers of donated human eggs and embryos for research purposes, which itself entails both some risk to women whose ovaries are hyperstimulated, and the ethically controversial use of embryos, by allowing vital mechanism of action research to be carried out on these cybrids.

According to stem cell scientist Stephen Minger from King’s College London: “What we do when we take an animal egg, is we remove the nucleus from the egg. We remove not only the genetic identity but we remove the species identity. What makes a cow egg a cow is its nuclear DNA. And we take that out – it’s no longer a cow” (cited in Gifford 2007). Yet, this view has been derided by some church leaders as “a monstrous attack on human rights, human dignity and human life” (O’Brien 2008). From a scientific perspective, Prof. Ian Wilmut, who pioneered the SCNT procedure, has suggested “given the low efficiency, you wonder just how long nuclear transfer will have a useful life” (cited in Highfield 2007). In 2007, the Human Fertilisation and Embryology Authority launched a public consultation on hybrids and chimeras which involved public events and deliberations on the arguments for and against this kind of research. One of their

conclusions was that “whilst some members of the public initially reacted with disgust, after hearing more information and discussing the issues with others, their opinion often shifted significantly” (Human Fertilisation and Embryology Authority 2007: 6.6).

Whatever the research route employed (hESC, somatic stem cells, cybrid or iPC), it is clear that research is crucial at this point since there is neither proof of principle, nor of mechanism, in relation to some key issues. As stem cell scientist Jack Price has argued, what we currently know about pluripotentiality is that it “somehow resides in the enucleated cell [which] gives a mechanism to generate pluripotential cells (stem cells, if you will) with any genetic makeup” via SCNT. Yet, “the attempt to generate patient-specific lines and disease specific lines has [as yet] not proven possible” (Price 2007). As a result, cybrid research has been proposed as a strategy to help improve efficiency of the SCNT technique. Many have suggested that research into induced pluripotential cells has great potential, since there is “no nuclear transfer; no chimerism; no complicated reprogramming – just easy technology using simple laboratory vectors” (Price 2007). Hence some suggest that these scientific developments will make current ethical concerns redundant and that we may well be entering “a new era of human biology in which any type of cell can be prepared from somatic cells of a particular genetic background” which raises an entire host of new ethical challenges (Nishikawa 2007). Yet these hopes may be premature and unfounded as currently the research is confined to model animals, and many issues, including key questions of safety, remain to be resolved.

7. “Tomorrow’s medicine today!” – the dangers of desperation and ‘experimental therapy’

As noted by Qiu Renzong, “since 1999, China’s spending on research and development (R&D) has increased by more than 20 per cent each year. In December 2006 China had moved ahead of Japan for the first time, to become the world’s second highest R&D investor after the US” (Qiu 2007). Although precise numbers are hard to come by, the portion of this used for funding into stem cell research is growing via the national 973 and 863 programmes (Pei 2007b). In China, there is a clear national emphasis on developing clinical applications out of basic research into stem cells (Salter, et al. 2006).

Yet, despite the worries that are often expressed about the rush to the clinic in the “Wild East”, leading Chinese researchers share the caution of their European counterparts. Thus, although he has carried out pioneer experimental research using autologous adult neural stem cells to treat open brain trauma in Shanghai, Zhu Jianhong of the Department of Neurosurgery, Huashan Hospital is of the view that “stem cell therapy is still a long way off” and that great caution is required: the safety of human patients must come first, especially since “we don’t understand the biology enough” (Zhu 2007). Nevertheless, as is evident from a simple internet search, stem cell therapy is being offered throughout the world to patients who suffer from very serious diseases, often at high costs. In fact, when it comes to regenerative medicine or stem cell therapies today, we can observe two very different worlds.

In the first, therapies are subject to strict clinical trial protocols, ethical review and informed consent procedures and the safety of the patient is the priority. The key principle in this kind of clinical research is that of caution. One of the key ethical challenges for current clinical testing of stem cell therapies is deciding how to proceed when not much is known about the biological mode of action of stem cells as they are used to treat degenerative diseases or brain trauma. It has been common to suggest that one of the principle modes of action of stem cells in treating disease will be through tissue regeneration – hence the term ‘regenerative medicine’ and the focus on pluripotentiality. However, Jack Price has pointed out that “ironically we are discovering that pluripotentiality is less significant than we had previously conceived in the clinical application of stem cells” as there may well be alternative modes of action that are more important, for example, induced plasticity mechanisms, anti-inflammatory mechanisms and immunomodulatory mechanisms (Price 2007). Not enough is known at this stage about modes of action in disease treatment, which raises a number of questions for research priorities, clinical trials and stem cell treatments. For example, should clinical trials proceed at this point?

The general point concerning mechanism is this. You may not at the outset have a defined clinical mechanism for the therapy, by the end of the study you will certainly know more but you still might not have a very refined mechanistic understanding. Why don’t regulatory authorities demand this? Why don’t they demand you understand the mechanism before you

go to the clinic? Because it is too high a hurdle and too imprecise a hurdle, and we would end up denying safe, efficacious medicines to sufferers who need them... Experience tells us that if a medicine is demonstrably safe and efficacious then we have a basis on which to proceed with care (Price 2007).

In China, Pei Xuetao of the Beijing Institute of Transfusion Medicine has suggested that clinical research into regenerative medicine is becoming all the more crucial as China's population continues to age with a growing proportion being over 65 years of age (Pei 2007b). This demographic change means that the prevalence of degenerative and cardiovascular diseases is also on the rise affecting millions of people. And in China, as in Europe, in this first world of regenerative medicine, what is most important is ensuring that any stem cells destined to be transplanted into humans are of 'clinical grade' which means that there must be a quality controlled process for generating a final therapeutic from defined starting materials and that each batch of cells used must be the same. Any move into human testing, it is argued, must start with a small group of patients to demonstrate safety.

The second, much more shadowy world is one of 'experimental' or 'innovative' regenerative medicine. Stem cell tourism has emerged as a new field of health tourism as patients with debilitating and untreatable diseases are willing to travel far and to pay much for unproven or experimental stem cell therapies. The provision of such stem cell therapy across national borders is largely unregulated and it is happening throughout the world from Europe and America to China and India, taking advantage of different levels and policies of regulation, especially across borders. In recent years, the "Preventief Medisch Centrum" (PMC) clinic in the Netherlands had offered unproven therapy using cord blood stem cells to sufferers of Multiple Sclerosis, which attracted many patients from the United Kingdom until national authorities eventually closed down the clinic because they were unable to account for the 'grade' of stem cells that were being used. Developments in China have also attracted considerable attention. A number of clinics based in China offer stem cell therapy (most often autologous, foetal or cord blood stem cells) to unknowing patients, advertising on the internet and in other ways, often making unfounded claims about its effectiveness and charging as much as US\$ 20,000 for treatment (Baker 2005). Some have suggested that in China there is a direct link to the

commercialisation of healthcare and the provision of expensive and unproven stem cell therapies. Zhai Xiaomei provides an example:

A biotechnology company 'invented' neural stem cell therapy to treat neural diseases such as Parkinsonism, spinal injury etc. They work with several hospitals which recruit patients and they provide neural stem cell treatment. After they advertised, a great number of patients went to these hospitals to seek the treatment of their desperate diseases from China and abroad. Each course consists of 4-6 injections and costs 12,000 RMB (€ 1,200). The company has never sought the approval from the Ministry of Health and has not been reviewed by an IRB. (Zhai 2007)

Such developments raise a number of ethical challenges regarding how to safeguard patients who are often in desperate situations and where many of those who can afford it are willing to travel almost anywhere, and pay almost any amount for treatment that appears to offer them hope. In China, 'experimental' stem cell therapies using autologous stem cells do not require approval from the SFDA but do require institutional ethical review board approval. But since the standards of ethical review boards varied from hospital to hospital, Zhai argues that situations can arise where some hospitals are "exaggerating benefits with little mention of risks and actually cheated desperate patients" (Zhai 2007). Informed consent procedures in such cases are at best poor and at worst manipulative and misleading.

Another key ethical challenge is how to ensure safety since it is very clear that in the vast majority of cases stem cell therapies do not consist of 'clinical grade' stem cells but more likely are of 'research grade' or even worse. The main reason for this is that quality control is very expensive. Halme and Kessler has argued that "unlike pharmaceutical products, many stem-cell-based products originate in academic laboratories where researchers are unfamiliar with the applicable regulations" (Halme and Kessler 2006). Controlling quality means ensuring the purity (safety), type and potency (efficacy) of stem-cell-based products which in turn requires that good practice standards must be observed in the selection of donors, retrieval of tissues, testing, processing, storage and delivery of finished tissues, as suggested in a UK Code of Practice for the use of Human Stem Cell Lines (Dobkin, et al. 2007; UK Stem Cell Bank 2006).

In sum, the availability of stem cell treatment – of “tomorrow’s medicine today” – raises numerous challenges including: how to protect consumers/patients, especially across borders; how to ensure validity of claims; how to regulate in conditions of hype, hope and expectation; how to enforce quality control (from risky research to routinized treatment protocols) especially transnationally; and how to minimise conflicts of interests between researchers, patients, families, clinicians and biotech companies. Another important point to be made about the ethics of regenerative medicine concerns health priorities. It is clear that the degenerative diseases which could potentially be treated through stem cell therapy are growing in prevalence throughout the world. Nevertheless, when resources are limited there will always be a debate about whether and how much state investment and private capital should be directed at certain medical fields. Decisions as to where to target investment are not always lead by health concerns, even those of public bodies. They are also influenced by commercial interests concerning the place of the nation in the international bioeconomy, by pressures from prestigious scientists who want to be at the ‘frontier’, and by beliefs that it is in the national interest to be a leading force in bioscience and biomedicine. In both Europe and in China, social and ethical questions concerning public health priorities need to be examined, as well as those that relate to the relevance of the research and its potential benefits to the studied population.

8. Conclusion

This paper has summarised some of the ways in which contemporary ethical challenges in stem cell research are being addressed in the context of Sino-European ethical governance debates and explored some similarities and differences with the situation in various European countries and in China. Both regions have expressed the objective of advancing stem cell research and have tried to ensure this by committing state investment to research and development. In both regions there has been attention to the ethical challenges raised by this work, and a variety of responses to these challenges. In both China and Europe, there is growing consensus that quality control of scientific research requires systems of both peer and ethical review, as well as mechanisms to monitor collaborative projects in particular.

Yet, there are also significant differences. One of the most apparent differences concerns the role of non-State actors, such as religious groups and other non-governmental organisations, in shaping governance frameworks and resulting practices. In Europe, churches, patients advocacy groups, professional associations and other lobbying organizations have each played a vociferous role in the debates over the shape of legislative proposals and the forms of ethical oversight. This has not been the case in China. However, it would be overly simplistic to suggest that it is only State institutions and officials who have a say in policy making and the formulation of guidelines. Bioethicists, lawyers, clinicians, scientists, as well as international controversies play a productive role in the proposal and formulation of guidelines, technical norms, laws as well as in the implementation and monitoring of practice. And in China, bioethicists, researchers and clinical practitioners have drawn attention to the multiple gaps between the formal regulatory regime and the actual situation on the ground, as well as to problems of implementation, oversight and compliance that are even more acute in a region with such variations in the organization and provision of health care.

We should not be surprised by heterogeneity within China and Europe and between these two regions. As is well known, recent international efforts to achieve consensus on ethical issues specifically related to stem cell research ended with consensus on only one single issue: that ‘reproductive cloning’ should be prohibited. Consensus could not be achieved on any other issue. Yet while it has proved difficult and often impossible to agree common international policies, the attempt to do so and the related processes of debate are themselves significant. While many point out numerous shortcomings in these efforts – for example insufficient inclusiveness in deliberation processes or insufficient enforceability of ethical guidelines – it is nevertheless evident that these efforts are under way. Both in China and in Europe there are ongoing national efforts to put together some kind of system of good science governance, and one that respects the right mix of biology, metaphysics and culture.

Endnotes

¹ This paper is based on information gathered as part of the activities of the BIONET Consortium, a twenty partner network of European and Chinese ethicists, social scientists and life scientists focused on the regulation of biomedical research in the context of international collaborations. The activities of the BIONET are discussed in its workshop and conference reports which are available at www.bionet-china.org. This paper summarises some of the key issues covered in these reports. The views presented in this paper are not those of the BIONET Expert Group.

² It should be noted that some European countries have not been able to translate 'governance' into their own languages either, e.g. German.

³ The 'Motorola-chip scandal' at Jiaotong University which became public in 2006 (Barboza 2006).

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