Stem-cell research: the state of the art

Future regulations of embryonic-stem-cell research will be influenced more by economic interests and cultural history than by ethical concerns

Sven Pompe, Michael Bader & Christof Tannert

Research using stem cells that are derived from human embryos has been hotly debated ever since scientists first established human embryonic-stem-cell lines in 1998 (Shamblott *et al*, 1998; Thomson *et al*, 1998). The ability of these cells to differentiate potentially into any human cell type has spawned great hopes for a revolution in regenerative medicine. But research using stem cells has been accompanied from the very beginning by an intense debate about the ethical issues of using human embryos for biomedical research. This has led to moratoria, regulations and limitations on this research in various countries. As international regulations are influenced by research, public debate and economic interests—all of which are in constant flux—these regulations could change as science and medicine advance.

As international regulations are influenced by research, public debate and economic interests—all of which are in constant flux—these regulations could change as science and medicine advance

Increasing public and media interest, as well as growing economic expectations of therapies, are becoming important factors in the political and ethical debate. Indeed, economic interests and media coverage during the past few years have put pressure on lawmakers and have sometimes produced misleading statements and advertisements intended to advance stem-cell research. Various private enterprises, for example,

now offer the storage of umbilical cord blood as part of an 'individual health plan', although the therapeutic use of stem cells derived from this blood is not yet clear and is likely to be fraught with risks. While the public is led to believe that human stem cells could soon provide cures for a wide variety of diseases—including diabetes, Parkinson's, Alzheimer's and others—scientists remain much more cautious about the medical prospects. What has been shown so far is that both embryonic and adult stem cells—the latter produced by adult tissues—can be differentiated into various cell types and tissues *in vitro*. This could lead to renewal or even growth of tissues and organs and treatment of degenerative diseases, but it is also extremely valuable to researchers who are interested in human developmental biology (President's Council on Bioethics, 2004).

Despite this potential, the ethical issues surrounding embryonic-stem-cell research have created intense controversy. The main concern is not the therapeutic possibilities or scientific research *per se*, rather the source of the cells. Embryonic stem cells, which have the greatest potential to differentiate into all cell types, are harvested from 5–7-day-old embryos in the blastocyst state; these embryos are then discarded. Whereas John Gearhart from Johns Hopkins University (Baltimore, MD, USA) originally used aborted human foetuses to establish stem-cell lines, scientists in countries where the use of human embryos for research is legal now use surplus embryos from *in vitro* fertilization (IVF). An alternative is to use adult or somatic stem cells that are taken from the patient, grown in culture and differentiated into various tissue-specific cells, but many experts believe that

Although religious beliefs were very influential in the early stages of the embryonic-stem-cell controversy, scientific arguments are slowly becoming more important...

these cells do not have the full potential to differentiate into every cell type, which limits their therapeutic usefulness.

Although adult stem cells have already shown positive results in treating heart-attack patients in clinical trials (Wollert *et al*, 2004), research with human embryonic stem cells has become entangled in an ethical, political and legal quagmire. The arguments against using these cells centre around the fact that their production involves destroying human embryos and, therefore, human life. As a consequence, the ethical debate now focuses on defining the stage at which life is considered to begin, and therefore from what point the embryo should be protected. Differing beliefs have led to a variety of national legislations. The Human Fertilisation and Embryology Authority in the UK, for example, licenses such research on embryos up to 14 days after conception. Laws in the USA prohibit federal funding for any research that uses human embryonic-stem-cell lines created after August 2001. The German law for the protection of the embryo makes it illegal to use human embryos for research, although stem-cell lines created before 1 January 2002 can be imported provided the corresponding research proposal has been reviewed by the ethical committee of the Robert-Koch-Institute (Berlin, Germany).

Whereas conservative Christian groups, particularly in the USA, regard a fertilized oocyte as human life that must not be destroyed for any purpose, more pragmatic Christians allow research with human embryos up to 14 days old. By contrast, Judaism, Islam and Buddhism do not regard an embryo as human life. Most Jewish scholars, for example, do not regard a human embryo as sacrosanct until the fourth month of pregnancy (Reichhardt *et al*, 2004; Schickltanz *et al*, 2003). Similarly, many Islamic theologians would permit research on embryos until the 40th day after conception. These religious and moral views are also reflected in national laws: at present, Israel allows research using surplus embryos from IVF provided that both parents have given their consent. This has allowed Israeli researchers to establish several human stem-cell lines (Revel, 2003), which are registered in an international database established by the US National Institutes of Health (Bethesda, MD, USA).

Although religious beliefs were very influential in the early stages of the embryonic-stem-cell controversy, scientific arguments are slowly becoming more important when creating or revising national laws to regulate the use of human embryos for research. In addition, the potential economic aspects of developing new stem-cell-based therapies have become important arguments in countries that want to take leading roles as knowledge-based economies (Marcus Evans Life Sciences, 2005). However, most scientists think that it will take at least another decade before the first therapeutic approaches using embryonic stem cells become available (Wiedemann *et al*, 2004).

It is therefore necessary to critically assess the current state of stem-cell research. Even if the ethical and moral dilemmas are set aside, serious questions remain about safety. The main technical problems are the control of cell differentiation *in vitro* and *in vivo*, the correct targeting of the desired tissue and the control of proliferation (Blyszczuk & Wobus, 2004). A Delphi study found that German stem-cell researchers believe that it may be decades before stem-cell-based therapies will be sufficiently safe and efficient for clinical use (Wiedemann *et al*, 2004). Some experts even doubt that it will be possible to cure complex diseases, such as Alzheimer's, Parkinson's and cancer, with stem-cell

therapies. For instance, autoimmune diseases such as multiple sclerosis or type I diabetes will not be curable by cell-replacement therapies as long as the precise cause of each disease remains unknown. Similarly, many neuronal degenerative diseases cannot be easily cured by replacing damaged nerve or myelin cells as long as clinicians are not able to tightly control their differentiation. It is obvious that curing diseases by simply replacing cells is not possible in many cases. Only when the processes of proliferation and differentiation are fully understood can stem-cell therapy become a viable option for treatment. Much more research on the fundamental molecular and cellular processes of cell differentiation and proliferation is therefore required, which can only be achieved by using both somatic and embryonic stem cells.

It is obvious that curing diseases by simply replacing cells is not possible in many cases

Biomedical research using stem cells is still in the early stages (Zech, 2004). Taking into account the time it took to establish the safe and efficient transfer of blood stem cells from bone marrow—about 40 years—it could take many more years for current knowledge from stem-cell research to be translated into clinical applications (Wiedemann *et al*, 2004). The integration of stem cells into the target tissue is not yet fully understood—often these cells fuse with host cells, for example after stem cells are injected into heart muscle (Secko, 2003). Research must also find efficient methods for controlling differentiation into tissue cells of the liver, nervous system, bones or heart and prevent uncontrolled proliferation after insertion. It is exactly these experiments that contribute to our understanding of the differentiation processes and therefore to the pathology of disease itself. More knowledge will surely enable new therapeutic approaches for a wide range of diseases (Dayley *et al*, 2003; Fraidenraich *et al*, 2004). These new approaches would use either single cell types or a combination of different cell types, for example for treating neurodegenerative diseases. Several stem-cell types are theoretically available and the next decade will reveal whether they can be used for such therapies. If basic research is not able to provide this knowledge, the

current, often exaggerated, interest in stem-cell therapy will decrease, in both biomedical research and the public arena.

An important requirement for a rational debate is valid information about both the scientific state of knowledge and the ethical arguments. There is a broad consensus that emerging human life needs to be protected. But the current definitions of what constitutes human life, or at what point life must be protected, are not adequate. The debates and definitions should not be left to ethicists, but also require input from natural scientists, in particular when it comes to finding a biological definition of when human life begins. In Germany, for instance, the debate has calmed down since the Law for the Protection of the Human Embryo prohibited any research that destroys human embryos for German research. But scientific activities abroad have put increasing pressure on research institutions, public opinion and the legislature in Germany and elsewhere (Check, 2004), which may lead to a resurgence of the debate. In general, broader public debates take place primarily in countries that severely limit research on human embryos (Knowles, 2004).

In this regard, the media have considerable influence on public opinion (Critchley & Turney, 2004). According to Graumann (2003), the intense media interest in stem-cell research is the result of a public relations campaign by economic and other interest groups (Pincok, 2004) who have put basic research under increasing pressure to establish clinical applications. It is also interesting to note that media interest in stem-cell research is often triggered by related events. The deaths of former US President Ronald Reagan, who suffered from Alzheimer's disease, and quadriplegic actor Christopher Reeve led to a deluge of media coverage of stem-cell research (Rufty, 2004; Tippit, 2004). Private initiatives, but also interest groups from within the scientific community, put further pressure on the US government to ease current restrictions. The engagement of prominent people, including Nancy Reagan, actor Michael J. Fox (who suffers from Parkinson's disease) and eBay founder Pierre Omidyar, has also influenced public opinion in the USA and internationally (Brecher, 2004; Elias, 2004a,b).

Public surveys have shown that knowledge of the scientific, ethical and legislative

aspects of stem-cell research varies with media coverage (Nisbet, 2004). In August 2001, amid coverage of President George W. Bush's restrictions on federally funded stem-cell research, about 60% of US citizens felt that they were well informed on this topic. This number dropped to 28% within a few weeks and to 17% just one year later (Nisbet, 2004). Public opinion also varied in response to the wording of questions in different surveys. If the questionnaire mentioned 'human life' and 'embryo' people tended to be more negative. In 2001, two polls showed that only about 38% of respondents would feel comfortable if research used surplus embryos from IVF, whereas 61% would support the establishment of stem-cell lines from embryos that were artificially produced through therapeutic cloning (Nisbet, 2004). In general, acceptance increased if the research was linked to potential therapeutic applications. These results demonstrate both the insufficient state of knowledge about the science and the suggestive power of expectations of potential cures and therapies.

According to the Delphi study by Wiedemann and colleagues (2004), specialists in the field expect that future research and potential medical applications will further influence the ethical debate. The moral conflict between using human embryos for research and the possibility of curing diseases will come up again as soon as the first medical applications are available. Current import and research restrictions will have to be discussed again (Wiedemann *et al.*, 2004). But there are other questions as well. The knowledge transfer of research results between countries or between the private and the public sector is another point of debate. For instance, it is illegal at present for German scientists to cooperate with colleagues in countries that have more liberal laws in stem-cell research (Vogel, 2003; Stafford, 2004a).

In addition, economic aspects increasingly influence the public debate, particularly in the USA. Competition with countries that have more permissive laws, such as South Korea or the UK, is often used as an argument in favour of liberalizing regulations. Proponents of stem-cell research in the USA criticize particularly the regulations that do not allow federally funded research with cell lines established before August 2001, although few, if any, of the

human embryonic stem cells established before this deadline are suitable for therapeutic purposes, as they are contaminated by viral pathogens or factors that make them immunologically incompatible (Martin *et al.*, 2005), or have general problems of cell ageing (Hayflick, 1985).

To circumvent federal restrictions and reap economic benefits, several states in the USA—among them California, New Jersey and Connecticut—have passed or are passing laws that would allow them to fund stem-cell research (Reinberg, 2005; Oransky, 2004). In January 2005, Democrats in New York proposed legislation that would commit US\$1 billion to stem-cell research (McIntire, 2005). Behind this move are fears that the state might lose out to California, which approved a US\$3 billion stem-cell fund in 2004, and to New Jersey, where governor Richard J. Cody recently proposed supporting stem-cell research and establishing a new research institute (McCook, 2004; Mansnerus, 2005). In addition, several universities, including Stanford (CA, USA), the University of California and the University of Wisconsin (Madison, WI, USA), have also established privately funded centres to support stem-cell research. Despite limitations on federal funding, the USA has a dominant role in the biotechnology sector, which will surely enable it to also have a leading role in stem-cell research in the future.

France and Italy both have restrictive laws on embryonic-stem-cell research, but these laws include provisions that allow lawmakers to revise and modify them periodically so as to respond to scientific progress. However, administrative hurdles can still block research—it took several years for French lawmakers to revise the law to allow the creation of stem-cell lines from surplus IVF embryos for the next five years (Brahic, 2004). Chinese scientists announced in 1998 that they were able to isolate and cultivate human embryonic stem cells. Due to investments from abroad and federal funds amounting to US\$272 million, China plans to become competitive in biotechnology within the next few years (Jia, 2004). Similarly to other countries, the bioethical debates in China are driven by both ethical concerns and potential applications (Sleeboom, 2002). Liberal laws and generous government support have also allowed South Korea and Singapore to advance their stem-cell research. Compared with these countries,

Japan and Australia are less developed due to their more restrictive laws (De Trizio & Brennan, 2004), but both countries are also moving ahead. The Australian Stem Cell Centre (Clayton, VIC, Australia) will provide nearly AU\$110 million until 2011, most of it for the Monash Institute for Medical Research in Victoria. Since February 2004, Japan has allowed the import of stem-cell lines for research and plans to invest US\$45 million to establish a stem-cell research centre in Kobe (Frost & Sullivan, 2004).

The deaths of former US President Ronald Reagan, who suffered from Alzheimer's disease, and quadriplegic actor Christopher Reeve led to a deluge of media coverage of stem-cell research

The European Union (EU) has yet to make consistent regulations with respect to stem-cell research in member states. Although the European Parliament decided in November 2003 that the EU will not finance the creation of stem-cell lines from human embryos, the new Commissioner for Science and Research, Janez Potocnik, stated in December 2004 that European scientists should be allowed to use surplus embryos for research (Stafford, 2004b). However, there is no consistent policy even after an 18-month moratorium on stem-cell research ended in December 2003. Whereas Germany, Austria, Italy, Finland, Greece, Ireland, Portugal and the Netherlands prohibit or severely restrict the use of embryonic stem cells, Sweden and the UK have created the legal base to support this research and both countries now have established cell-line banks (Pilcher, 2004). Sweden has also created administrative rules that allow them to quickly adapt their regulations in response to scientific progress. Swedish scientists are predominantly interested in commercial applications, the first of which they expect in 2008 (De Trizio & Brennan, 2004). International private and public investment of several million dollars is one of the reasons why Sweden has taken a leading role in stem-cell research.

Frost & Sullivan (2004) expect that Israel, in the long term, will also become a leading nation in stem-cell research due to its liberal laws. In this context, Revel (2003) points out the broad consensus among

Bioethical debates about the therapeutic potential and ethical concerns [...] take place predominantly in countries with very restrictive laws...

Jewish bioethicists, philosophers, rabbis and legal scholars with regard to stem-cell research and therapeutic cloning. Similarly, Knowles (2004) has highlighted other countries in the Middle East, such as Iran; the Royan Institute for reproductive biomedicine research in Tehran created a human embryonic-stem-cell line in 2003 and now focuses its efforts on differentiating these cells into heart-muscle and insulin-producing cells.

Bioethical debates about the therapeutic potential and ethical concerns surrounding stem-cell research take place predominantly in countries with very restrictive laws, notably the USA and Germany. Although there are efforts underway to harmonize laws internationally (Resnik, 2004), each country still weighs the medical and economic opportunities differently based on their social and ethical norms. National laws and regulations will therefore be influenced mainly by national economic interests and cultural history. Public opinion would not necessarily be a good guide for such debates as it is strongly influenced by media reports and claims of potential therapies, so accordingly, it fluctuates strongly.

REFERENCES

- Blyszczuk P, Wobus AM (2004) Stem cells and pancreatic differentiation *in vitro*. *J Biotechnol* **113**: 3–13
- Brahic C (2004) France allows stem cell work. *The Scientist* 15 Jul www.the-scientist.com
- Brecher EJ (2004) Actor decries limitations on stem-cell research. *The Miami Herald* 29 Sep www.herald.com
- Check E (2004) Stem-cell library boosts the case for change. *Nature* **429**: 691
- Critchley C, Turney L (2004) Understanding Australians' perceptions of controversial scientific research. *Aust J Emerg Technol Soc* **2**: 1–26
- Dayley GQ, Goodell MA, Snyder EY (2003) Realistic prospects for stem cell therapeutics. *Hematology* **2003**: 398–418
- De Tizio E, Brennan CS (2004) The business of human embryonic stem cell research and an international analysis of relevant laws. *J Biolaw Bus* **7**: 14–22
- Elias P (2004a) Ebay founder donates \$1 million backing stem cell measure. *Mercury News* 15 Jul www.mercurynews.com
- Elias P (2004b) Big names, bucks back stem cell bid on California ballot. *Houston Chronicle* 5 Jul www.chron.com
- Fraidenraich D, Stillwell E, Romero E, Wilkes D, Manova K, Basson CT, Benezra R (2004) Rescue of cardiac defects in id knockout embryos by injection of embryonic stem cells. *Science* **306**: 247–252
- Frost & Sullivan (2004) *Stem Cells—Emerging Markets and Growth Opportunities*. New York, NY, USA: Frost & Sullivan
- Graumann S (2003) Situation der Medienberichterstattung zu den aktuellen Entwicklungen in der Biomedizin und ihren ethischen Fragen. In: Schickanz S, Tannert C, Wiedemann PM (eds) *Kulturelle Aspekte der Biomedizin: Bioethik, Religionen und Alltagsperspektiven*. Frankfurt, Germany: Campus
- Hayflick L (1985) The cell biology of aging. *Clin Geriatr Med* **1**: 15–27
- Jia H (2004) China moves to reform biotech policies. *Nat Biotech* **22**: 1197
- Knowles LP (2004) A regulatory patchwork—human ES cell research oversight. *Nat Biotech* **22**: 157–163
- Mansnerus L (2005) New Jersey faces tough competition for stem cell scientists. *New York Times* 17 Jan, pB1
- Marcus Evans Life Sciences (2005) *Commercialisation of Stem Cells*. Congress Proceedings. London, UK: Marcus Evans Life Sciences
- Martin MJ, Moutri A, Gage F, Varki A (2005) Human embryonic stem cells express an immunogenic nonhuman sialic acid. *Nat Med* **11**: 228–232
- McCook A (2004) Stem cells in New Jersey. *The Scientist* 19 Aug www.the-scientist.com
- McIntire M (2005) With eye on rivals, Senator proposes New York Institute. *The New York Times* 17 Jan, pB3
- Nisbet MC (2004) Public opinion about stem cell research and human cloning. *Public Opin Quart* **68**: 131–154
- Oransky I (2004) California OKs stem cell measure. *The Scientist* 3 Nov www.the-scientist.com
- Pilcher HR (2004) Britain's stem-cell store opens. *news@Nature* 17 May
- Pincock S (2004) Zavos cloning article pulled. *The Scientist* 20 Sep www.the-scientist.com
- President's Council on Bioethics (2004) Monitoring stem cell research. www.bioethics.gov/reports/stemcell/
- Reichhardt T, Cyranoski D, Schiermeier Q (2004) Religion and science: studies of faith. *Nature* **432**: 666–669
- Reinberg S (2005) Connecticut eyes stem cell law. *The Scientist* 6 Jan www.the-scientist.com
- Resnik DB (2004) The need for international stem cell agreements. *Nat Biotech* **22**: 1207
- Revel M (2003) Human reproductive cloning, embryo stem cells and germline gene intervention: an Israeli perspective. *Med Law* **22**: 701–732
- Ruffy B (2004) Cell research emerges as political 'wedge'. *The Ledger* 24 Jul www.theledger.com
- Schickanz S, Tannert C, Wiedemann PM (2003) *Kulturelle Aspekte der Biomedizin: Bioethik, Religionen und Alltagsperspektiven*. Frankfurt, Germany: Campus
- Secko D (2003) Spontaneous cellular fusion. *The Scientist* 13 Oct www.the-scientist.com
- Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR, Gearhart JD (1998) Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proc Natl Acad Sci USA* **95**: 13726–13731
- Sleeboom M (2002) Stem cell research in China: an intertwining of international finances, ambition, and bioethics. *IIAS Newsletter* **29**: 49
- Stafford N (2004a) Stem cell collaboration illegal. *The Scientist* 31 Aug www.the-scientist.com
- Stafford N (2004b) Potocnik backs ES cell research. *The Scientist* 22 Dec www.the-scientist.com
- Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic stem cell lines derived from human blastocysts. *Science* **282**: 1145–1147
- Tippit S (2004) Reagan focused attention on Alzheimer's research. *Reuters Health* 7 Jun www.reutershealth.com
- Vogel G (2003) Visiting German profs could face jail. *Science* **301**: 577
- Wiedemann P, Simon J, Schickanz S, Tannert C (2004) The future of stem cell research in Germany. *EMBO Rep* **5**: 927–931
- Wollert KC *et al* (2004) Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* **364**: 141–148
- Zech N (2004) Adult stem cell manipulation and possible clinical perspectives. *J Reproduktionsmedizin Endokrinol* **1**: 91–99

Sven Pompe (top left) is at the Research Centre Jülich, Germany. Michael Bader (top right) and Christof Tannert are at the Max Delbrück Center for Molecular Medicine in Berlin, Germany.

E-mail: pompe@mdc-berlin.de

doi:10.1038/sj.embor.7400383