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# International stem cell research considerations

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**Abstract –** Legislative bodies in the international arena and in individual countries are actively engaged in developing policies regarding the establishment, distribution and use of human embryonic stem cells. Present and anticipated policies concerning research on human adult and embryonic stem cells of possible medical importance reflect the wide spectrum of popular views that range from complete rejection to enthusiastic support. Since the public debate concerning the use of human gametes or embryos for research purposes is not likely to abate anytime soon, all the more urgent becomes the quest for alternative approaches toward generating stem cells that are not embryonic and yet are pluripotent. ***To cite this article: H. Westphal, C. R. Biologies 325 (2002) 1045–1048.*** © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

**stem cells / human embryos**

**Résumé** – **Les recherches sur les cellules souches : réflexions à l'échelle internationale.** Des décisions législatives sont activement engagées à l'échelle internationale aussi bien que nationale pour réglementer la création, la répartition et l'utilisation de cellules souches provenant d'embryons humains. Les décisions déjà prises ou envisagées au sujet des cellules embryonnaires ou adultes d'origine humaine et d'intérêt médical potentiel reflètent la grande dispersion des points de vue en vogue, qui vont du rejet total au soutien enthousiaste. Puisque le débat public sur l'utilisation de gamètes ou d'embryons humains pour la recherche n'est pas prêt de s'apaiser, le plus urgent est de rechercher une autre voie d'obtention de cellules souches qui ne soient pas d'origine embryonnaire, mais cependant pluripotentes. ***Pour citer cet article : H. Westphal, C. R. Biologies 325 (2002) 1045–1048.*** © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

**cellules souches / embryons humains**

An extensive body of information has been accumulated over the years concerning the differentiation potential of mammalian embryonic stem cells. These cells became a focus of intense public interest when, in 1998, James Thomson and colleagues announced their successful derivation from human embryos [1]. Embryonic stem cells, derived from the inner cell mass at the blastocyst stage of embryo development, are not totipotent, i.e., they cannot give rise to a living organism. However, they are pluripotent, that is, under restrictive conditions, they can be propagated indefinitely in an undifferentiated state, and they can also be induced to differentiate into a wide range of cells and tissues. The lines of such pluripotent cells that are currently available to researchers were derived from embryos unused after infertility treatments that would otherwise be destroyed.

Another potential source of human pluripotent stem cells are embryos generated via somatic cell nuclear transfer into denucleated oocytes [2]. Once successfully

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grown to the blastocyst stage, such cloned embryos would be destroyed in order to derive embryonic stem cells that hold the potential for the development of cell replacement therapies. Any cloning through human somatic cell nuclear transfer, if successful, necessarily involves the creation of a living human embryo and for this reason the technique raises profound ethical and moral questions and is highly controversial. There is at present an overwhelming international consensus directed against human reproductive cloning aimed at creating groups of genetically identical individuals by uterine transfer of embryos generated by somatic cell nuclear transfer.

There is also a vigorous debate over the use of pluripotent stem cell lines from human embryos for research aimed at cell replacement therapy as possible avenues for conquering disease. Animal experiments provide very encouraging results. Parkinson's disease, diabetes, spinal cord lesions, heart infarction, or damage to the skeletal system are only a few examples of disorders for which stem cells might bring lasting help. The potential use of nuclear transfer technology is based on the hope that it might become possible to generate 'individualized' pluripotent stem cells from an oocyte fitted with a patient's own somatic cell nucleus. In theory, differentiated derivatives of these stem cells would be compatible with the host and thus well suited to replace his or her own damaged or non-functional tissue [3]. However, many object on principle to deriving stem cells from human embryos for research purposes. The intersection of science and ethics in the generation of pluripotent human stem cells has captured the attention of researchers, ethicists, lawmakers and the general public in many nations around the world.

Legislative bodies in the international arena and in individual countries have only recently begun to deal with the question of human embryo protection in the context of cloning technology. The right to life in general, though not explicitly defined as beginning at the time of conception, is proclaimed in the Universal Declaration of Human Rights of 1948, the International Covenant on Civil and Political Rights of 1966 and the African Charter on Human and Peoples' Rights of 1948. The text of the American Convention of Human Rights of 1969 is more specific, because it mentions the right to life of the conceived child [4]. The issue of cloning is presently being addressed by several international organizations. The General Assembly of the United Nations has been asked to adopt a legally binding international convention banning human reproductive cloning [5]. The Council of Europe has condemned reproductive cloning and has approved a protocol prohibiting it as well as the creation of human embryos for research purposes. Some of its 43 member states (but not, for example, France, Germany, the United Kingdom, Italy or the Netherlands) have ratified the protocol and are obliged to incorporate this resolution into their national legislation within the next five years [5, 6]. As will become evident from the following examples, these topics are at the center of high-profile debates in individual nations.

In the United States of America, on August 9, 2001, President Bush announced his decision to allow Federal funds to be used for research on existing human embryonic stem cell lines as long as prior to his announcement (*i*) the derivation process (which commences with the removal of the inner cell mass from the blastocyst) had already been initiated and (*ii*) the embryo from which the stem cell line was derived no longer had the possibility of development as a human being. In addition, the President established the following criteria that must be met: (1) the stem cells must have been derived from an embryo that was created for reproductive purposes; (2) the embryo was no longer needed for these purposes; (3) informed consent must have been obtained for the donation of the embryo; (4) no financial inducements were provided for donation of the embryo. The US National Institutes of Health has compiled a registry of embryonic stem cells that lists the human embryonic stem cell lines – at varying stages of development – that meet the President's eligibility criteria and are eligible for use in federally-supported research. The process to support research on these cells is in operation [7]. The US National Academy of Sciences, chartered by Congress to advise the federal government, recently prepared a report that endorses medical research involving non-reproductive cloning with the caveat that the human reproductive cloning should be prohibited [8]. On July 31, 2001 the US House of Representatives passed a bill (HR 2505), the 'Human Cloning Prohibition Act' that would ban efforts directed at both therapeutic and reproductive cloning. Various bills are pending in the US Senate on cloning and stem cell research. The Senate has held a series of hearings on these topics over the last eight months and more are anticipated. President Bush supports a global and comprehensive ban on human cloning through somatic cell nuclear transfer, regardless of the purpose for which the human clone is produced.

In Canada, a number of guidelines have just become effective: following a March 2002, recommendation by CIHR (Canadian Institutes of Health Research), cloning and the creation of embryos strictly for research purposes are prohibited. However, the guidelines permit funding for research on embryos no longer needed

for reproductive purposes as long as there is informed consent and as long as no financial incentives for embryo donation have been received. The importation for research purposes of stem cells generated elsewhere is permitted only if approved by a CIHR Oversight Committee that will monitor adherence of all research proposals to the guidelines [9].

Here in France, a 1994 law that prohibits embryo research is currently under review. A new law on human embryo and stem cell research was drafted in June of 2001 [5]. This legislation would ban all embryo cloning, but would permit research with embryonic stem cells derived from in vitro fertilized embryos under tightly controlled conditions. In January of 2002, the bill passed its first reading in the National Assembly, with little opposition [10].

In Germany, a law that was enacted in 1990 regards the fertilization of an ovum for purposes other than its reimplantation in the donor as an offense [4]. However, that old law does not specifically address the issue of importing stem cells produced from human embryos. The German Parliament voted in January of 2002 to allow the use of embryonic stem cells, derived prior to this vote, for research conducted within Germany. A new law will allow researchers to import these cells under strict controls, but cloning will be prohibited [11].

The House of Commons and the House of Lords of the United Kingdom passed a law that prohibits reproductive cloning. The 1990 Human Fertilization and Embryology Act permits, for research purposes, the derivation of stem cells from human embryos up to 14 days old [6]. These stem cells can now be used for research on cell and tissue therapy for serious diseases. A UK Court of Appeals bas ruled that embryos created by nuclear replacement are covered by this policy [12]. Similarly, Israel recently approved research on embryonic stem cells derived from embryos generated by in vitro fertilization or by non-reproductive cloning, following a September 2001 recommendation of the Israel Academy of Sciences and Humanities [4].

Elsewhere, the Duma of Russia voted in December of 2001 to ban cloning and the import or export of cloned embryos for five years [5]. In Norway, the law prohibits research on human embryos and bans their use for any purpose other than reproduction. Similar legal provisions are in effect in Brazil (law 8974/95) and Peru (law 26.842). In Spain, law 35/1988 permits research on human embryos unused after infertility treatments, but makes it illegal to extract stem cells. A National Commission on Human Assisted Reproduction has recommended that the law be updated to allow for extraction [4]. In Finland, the use of embryos (up to 14 days after conception) for research purposes is permitted, but strictly regulated. Finland follows the Council of Europe guidelines and does not allow cloning [4]. Sweden allows the use of embryos for research purposes under strict regulations [4].

The parliament of Japan passed a law that bans the creation of embryos by combining human eggs and non-reproductive cells, as well as mixing animal and human cells to generate chimeric embryos [5]. However, Japanese guidelines allow researchers to use cells left over from in vitro fertilization. Embryos must be donated with proper consent. These guidelines apply to the public and the private sector.

In Australia, the status of stem cell research is currently undergoing review at the national level. Existing laws vary from state to state. Thus, for example, in Victoria and in western Australia, any destructive manipulation of a human embryo is prohibited, whereas stem cell derivation would be allowed in Queensland. The federal government has indicated its intention to make legislation more uniform across the country [13]. In China, the Ministry of Health announced that the government opposes any experiments for the purpose of human cloning, but will allow closely monitored embryo stem cell research for the treatment and prevention of disease [14].

This brief survey summary shows that international and national efforts are well underway to regulate human embryonic stem cell research. Human reproductive cloning is opposed by all nations cited in this review. By contrast, present and anticipated policies concerning research on human embryonic stem cells of possible medical importance continue to be hotly debated, and this debate is not likely to abate anytime soon. In fact, even if performed under tightly controlled conditions, research involving the human embryo is likely to remain controversial. All the more urgent becomes the quest for alternative sources of pluripotent stem cells that are not derived from a viable human embryo. Two sets of data are encouraging in this regard. First, stem cells have recently been derived from parthenotes of nonhuman primates [15]. Parthenotes are chemically activated oocytes giving rise to cells with diploid sets of maternally derived chromosomes. Second, much hope is currently focused on adult human stem cells derived from bone marrow. Recent work performed in the laboratory of Dr Catherine Verfaillie at the University of Minnesota, USA, has already entered the current international stem cell debate [16, 17]. The bone marrow stem cells she was able to isolate are said to reflect two important aspects of embryonic stem cells. They can be propagated

seemingly indefinitely in the undifferentiated state, and they are pluripotent, giving rise of a wide range of differentiated cells of the body. Cells from the patient's own bone marrow could potentially be expanded and differentiated in vitro for cell replacement therapy, without the danger of rejection by the immune system. If corroborated, this would amount to a very important breakthrough in stem cell research.

## References

[1] J.A. Thomson, J. Itskovitz-Eldor, S.S. Shapiro, M.A. Waknitz, J.J. Swiergiel, V.S. Marshall, J.M. Jones, Embryonic stem cell lines derived from human blastocysts, Science 282 (1998) 1145–1147.

[2] I. Wilmut, A.E. Schnieke, J. McWhir, A.J. Kind, K.H. Campbell, Viable offspring derived from fetal and adult mammalian cells, Nature 385 (1997) 810–813.

[3] W.M. Rideout III, K. Hochedlinger, M. Kyba, G.Q. Daley, R. Jaenisch, Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy, Cell 109 (2002) 17–27.

[4] http://www.academy.ac.il/bioethics.html.

[5] http://www.stanford.edu/~eclipse9/sts129/cloning/international.html.

[6] http://www.medinfo.cam.ac.uk/phgu/info_database/ELSI/stem_cells.asp.

[7] http://escr.nih.gov/.

[8] National Academy of Sciences, Committee on Science, Engineering and Public Policy, Scientific and Medical Aspects of Human Reproduction Cloning, 2002.

[9] http://www.cihr.ca/about_cihr/ethics/stem_cell/stem_cell_intro_e.shtml.

[10] http://www.newsday.com/news/health/wire/sns-ap-france-stem-cells0123jan22.story?coll=sns-ap-health-headlines.

[11] G. Vogel, Stem cells. German researchers get green light just, Science 295 (2002) 943.

[12] http://news.bbc.co.uk/hi/english/sci/tech/newsid_1767000/1767503.stm.

[13] http://www.aph.gov.au/house/committee/laca/humancloning/contents.htm.

[14] http://english.peopledaily.com.cn/11/30/eng20011130_85687.shtml.

[15] J.B. Cibelli, K.A. Grant, K.B. Chapman, K. Cunniff, T. Worst, H.L. Green, S.J. Walker, P.H. Gutin, L. Vilner, V. Tabar, T. Dominko, J. Kane, P.J. Wettstein, R.P. Lanza, L. Studer, K.E. Vrana, M.D. West, Parthenogenetic Stem Cells in Nonhuman Primates, Science 295 (2002) 819.

[16] L.R. Zhao, W.M. Duan, M. Reyes, C.D. Keene, C.M. Verfaillie, W.C. Low, Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats, Exp. Neurol. 174 (2002) 11–20.

[17] S. Pagán Westphal, Is this the one? The New Scientist 173 (2002) 4–5.