Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

Third report after enactment of the Stem Cell Act (Stammzellgesetz, StZG)

Reporting period: 1 December 2004 to 30 November 2005

The Central Ethics Committee for Stem Cell Research

The Central Ethics Committee for Stem Cell Research (ZES) is an interdisciplinary expert body which reviews applications for the import and use of human embryonic stem cells. For each application it submits a written opinion to the competent authority, the Robert Koch Institute. The activities of ZES are governed by the Act ensuring the protection of embryos in conjunction with the import and use of human embryonic stem cells (Stem Cell Act, *Stammzellgesetz – StZG*) of 28 June 2002 (BGBl. I p. 2277) (http://www.gesetze-im-internet.de/stzg/index.html), the Regulations concerning the Central Ethics Committee for Stem Cell Research and the competent authority pursuant to the Stem Cell Act (Verordnung über die Zentrale Ethik-Kommission für Stammzellforschung – ZESV) of 18 July 2002 (BGBl. I p. 2663) (http://www.gesetze-im-internet.de/zesv/index.html).

The members and deputy members of the ZES (Table 1) were appointed by the German Federal Government for the first time with the enactment of the Stem Cell Act in July 2002. In July 2005, 15 members and deputy members were reappointed and 3 members/deputy members were appointed for the first time to the ZES. In accordance with Article 8 StZG, the ZES currently consists of two members from the field of biology, three members from the field of medicine and four members from the fields of philosophical, medical and theological ethics. For each member a deputy has been appointed. In accordance with the ZES Regulations, the deputy members also regularly attend the deliberations on applications. The members and deputy members of the ZES perform their obligations on a gratuitous basis.

The ZES is responsible for determining, on the basis of the documents submitted by the applicant, whether the proposed research project complies with the criteria of Article 5 StZG and is ethically justifiable within the intendment of that Article. In this context, it must be examined whether the proposed use of human ES cells serves research purposes of premium importance for increasing scientific knowledge pursuant to Article 5 (1) StZG, whether the pre-clarification stipulated in Article 5 (2) a StZG has been undertaken and the results justify the use of human ES cells and whether the desired findings can only be obtained with human embryonic stem cells. The ZES summarises the results of the application review in a written opinion which is passed on to the competent authority.

The ZES has to prepare an annual report published by the BMG (Article 14 ZESV). The previous ZES annual reports can be accessed on http://www.bmg.bund.de.

Review of applications pursuant to Article 5 StZG during the reporting period

During the reporting period the ZES held seven meetings at which a total of nine applications for the import and use of human ES cells were reviewed. The ZES issued a positive opinion on eight of these applications while one application is still being reviewed. The report – in line with the stipulations in Article 11 StZG concerning the publication of certain data from approved research projects – contains statements on the contents of positively reviewed applications which have already been approved. This applies to seven applications reviewed during the reporting period. An overview of these applications is given in Table 2. Two of these applications concern an extension to an already approved project.

The majority of the applications reviewed by the ZES during the reporting period involved the establishment of methods for efficient and reproducible differentiation of human ES cells into clinically relevant cell and tissue types. In this context, the conditions are to be examined under which differentiations of this nature, for instance to neural and glia cells (Projects

Academic areas	Members	Deputy Members
Biology	Prof. Dr. med. Dr. rer. nat. Henning M. Beier **(Deputy Chairman)** Institut für Anatomie und Reproduktionsbiologie Rheinisch-Westfälische Technische Hochschule Aachen	Prof. Dr. rer. nat. Hans R. Schöler Max-Planck-Institut für Molekulare Biomedizin Münster
	Prof. Dr. rer. nat. Anna M. Wobus Institut für Pflanzengenetik und Kulturpflanzenforschung (IPK) Abteilung Zytogenetik Gatersleben	Prof. Dr. rer. nat. Ursula Just Biochemisches Institut Universität Kiel
Ethics	Prof. Dr. phil. Ludwig Siep **(Chairman)** Philosophisches Seminar Westfälische Wilhelms-Universität Münster	Prof. Dr. phil. Jan Beckmann Institut für Philosophie FernUniversität Hagen
	Prof. Dr. med. Claudia Wiesemann Institut Ethik und Geschichte der Medizin Georg-August-Universität Göttingen	Prof. Dr. med. Giovanni Maio, Lehrstuhl für Bioethik Albert-Ludwigs-Universität Freiburg
Medicine	Prof. Dr. med. Gustav Steinhoff Klinik und Poliklinik für Herzchirurgie Universität Rostock	Prof. Dr. med. Mathias Bähr Neurologische Klinik Georg-August-Universität Göttingen
	Prof. Dr. med. Marion B. Kiechle **(Deputy Chairwoman)** Frauenklinik und Poliklinik Klinikum rechts der Isar Technische Universität München	Prof. Dr. med. Ricardo E. Felberbaum Frauenklinik Klinikum Kempten Oberallgäu
	Prof. Dr. med. Anthony D. Ho Med. Universitätsklinik und Poliklinik Abt. Innere Medizin V Ruprecht-Karls-Universität Heidelberg	Prof. Dr. med. Ulf Rapp Institut für Medizinische Strahlenkunde und Zellforschung (MSZ) Bayerische Julius-Maximilians-Universität Würzburg
Theology	Prof. Dr. theol. Klaus Tanner Institut für Systematische Theologie Martin-Luther-Universität Halle-Wittenberg	Prof. Dr. theol. Hartmut Kreß Evangelisch-Theologische Fakultät Abteilung für Sozialethik und Systematische Theologie Rheinische Friedrich-Wilhelms-Universität Bonn
	Prof. Dr. theol. Dr. phil. Antonio Autiero Seminar für Moraltheologie Katholisch-Theologische Fakultät Westfälische Wilhelms-Universität Münster	Prof. Dr. theol. Konrad Hilpert Lehrstuhl für Moraltheologie Department für Katholische Theologie Ludwig-Maximilians-Universität München

Table 1: Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES), November 2005

4 and 6 in Table 2), cardiac muscle cells (Projects 3 and 5) or liver parenchyma cells (Project 1) are possible. Factors and signal trandsuction pathways involved are to be clarified thereby contributing to a greater insight into processes that play a role in the genesis of these cell and tissue types during human embryonic development. Compared to projects reviewed in previous reporting periods, the focus of these projects is increasingly on the use or establishment of systems and methods leading to the formation of three-dimensional tissue-like structures from human ES cells. The aim is to simulate the natural, three-dimensional

conditions under which cellular differentiation occurs and bring about improved differentiation successes. In addition these projects aim at the creation of three-dimensional cellular structures – also using supporting materials along the lines of tissue engineering – which could be used for instance for transplantation purposes at a later stage. Two of the applications formulate research goals linked to basic biological or biotechnological research (Projects 2 and 7). In one of these projects molecular processes are to be clarified by inhibiting the expression of specific genes in human ES cells which play a role in maintaining the pluripotency of human ES cells. The other project focuses on examining the immunological properties of human ES cells and cardiac cells derived from them.

Two of the positively assessed projects draw on an already approved research project that has been up and running for two years (Projects 4 and 6) and considerably expand on it. Since some of the goals formulated in these projects require new applications or applications for human ES cells for which no request had been filed up to now, deliberations and a renewed written opinion of the ZES were necessary.

Some of the work, for which approval has been sought up to now, envisages transplantation experiments in which there are plans to transfer materials derived from human ES cells to animals. In each case the ZES examines the ethical acceptability of transplantation experiments of this kind. Special ethical attention is necessary when the plans involve higher mammals or the transfer of human neural cells to the animal brain. During the reporting period the ZES again dealt with this problem in conjunction with one application (Project 4). In this context, the Committee – also in full knowledge of the ethical opinion-shaping process currently taking place for example in the USA – was of the opinion that the transfer of already differentiated or specified cells, that only have limited development potential, to the brain of later foetuses or adult animals cannot lead to the transfer of higher cerebral functions involving consciousness from man to animals. Furthermore, it is ruled out that these animals will ever reproduce.

Information on the contents of projects already approved by the RKI, which had all previously been positively assessed by the ZES, can be accessed in the RKI stem cell register http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html). The main arguments advanced by the ZES concerning the premium importance of the research projects, their adequate pre-clarification and the need to use human ES cells have been included in the register texts because of the concurring assessment of the applications in all cases up to now by the ZES and the RKI.

Research into human ES cells is a rapidly developing area; the number of experimental works involving human ES cells published in international journals increased almost fourfold to about 100 per year between 2001 and 2002. In the course of its activities now spanning three years, the ZES has reviewed 19 applications for the import of and research on/use of human ES cells. It issued favourable opinions on a total of 15 applications: one application is currently being reviewed. The majority of applications contain goals oriented towards clarifying specific basic research questions like the mechanisms of differentiation or the maintenance of pluripotency. However, these research goals are increasingly being formulated in connection with specific use options. They refer on the one hand to cell replacement therapies for humans which can probably be only achieved in the medium-term and most likely cannot be conducted with the cell lines in compliance with the cut-off date.

No.	Applicant	Research objectives	Date of ZES opinion
1(8)	Professor Dr. Jörg Gerlach AG Experimentelle Chirugie Klinik für Allgemein-, Viszeral- und Transplantationschirurgie Charité Campus Virchow-Klinikum, Berlin	Development of a 3D culture system for the expansion of human embryonic stem cells and their differentiation into hepatic cells	15 December 2004
2 (9)	Max-Planck-Institut für Molekulare Genetik Berlin	Functional characterisation of pluripotency control genes and their role in the shaping of fundamental transcription networks and of signal transmission mechanisms in stem cells	25 January 2005
3 (11)	Professor Dr. Heinrich Sauer Physiologisches Institut der Universität Gießen	Redox-mediated signal paths of vascular differentiation of human embryonic stem cells for cardiovascular *tissue engineering*	4 April 2005
4 (10)	Professor Dr. Oliver Brüstle Institut für Rekonstruktive Neurobiologie, Universitätsklinikum Bonn	Harvesting and transplantation of neural precursor cells from human embryonic stem cells	13 May 2005
5 (12)	Professor Dr. Wolfram-H. Zimmermann Institut für Experimentelle und Klinische Pharmakologie der Universität Hamburg-Eppendorf	Construction of artificial cardiac tissue from human embryonic stem cells	23 August 2005
6 (13)	Professor Dr. Oliver Brüstle LIFE & BRAIN GmbH	Laser-backed clean-up and trans-fection of human embryonic stem cells and neural precursors derived from them	13 September 2005
7 (14)	Professor Dr. J. Hescheler Institut für Neurophysiologie Universität Köln	Characterisation and immunological properties of human embryonic stem cells and derived cardiac cells	14 November 2005

Table 2: Projects which were given a definitive positive assessment by ZES. The numbers in brackets correspond to the approval numbers in the RKI stem cell register.

Medium-term objectives of this kind are designed to serve, for instance, technology developments to optimise the cultivation and targeted differentiation of human ES cells, as formulated in several of the applications reviewed during the reporting period. In addition, the development of three-dimensional ES cell-derived structures, partially involving the use of supporting materials, has a medium-term goal in the field of therapy. However, the Committee assumes that specific fundamental issues, which would be the precondition for any use of material derived from human ES cells to replace tissue in human beings, have not yet been clarified so that specific therapeutic applications of human ES cells and their derivatives in tissue replacement therapy are not yet on the agenda. To an increasing degree, the applications do, however, on the other hand also formulate options involving the *ex vivo* use of material derived from human ES cells. For instance, in one of the proposed projects a three-dimensional cell culture system is to be developed which, on the basis of hepatic cells derived from human ES cells, is to be used for extracorporal liver replacement therapy. ES cells derived from cardiac tissue-like structures, whose development is planned in another proposed project, could be used to test the cardiac side-effects of known and new pharmaceuticals. Applications of this kind have a shorter time horizon than the use of material from human ES stem cells in tissue transplantation. However, according to Article 4 (2), the Stem Cell Act permits the import and use of embryonic stem cells for “research

purposes" only. The consequence is that German research on human ES cells that is now being conducted on a by no means insignificant scale, is limited to creating the foundations for the later use of cells for therapeutic, preventive and diagnostic purposes outside Germany.

The cut-off date provision in the Stem Cell Act is seen as problematic by researchers and in the public debate. In this context, they point out various scientifically comprehensible reasons as an obstacle to the broad development of research on human ES cells in Germany. So far, this problem has not cropped up in the applications examined up to now which mainly involved basic scientific research. This does not, however, permit the conclusion that basic research on human ES cells is not impeded by the cut-off date provision in the Stem Cell Act. The cut-of date provision would certainly be problematic for projects with a stronger therapeutic orientation in the field of regenerative medicine. The question is also open as to whether and, if so, on what scale certain approved research work would have to be repeated at a later date or elsewhere with other stem cell lines because the characteristics of the cell lines in compliance with the cut-off date may differ from those of cell lines possibly used for clinical applications at a later stage.

The applications submitted for review to the ZES during the reporting period confirm the growing institutional anchoring of international cooperation in research on human ES cells. Work in three of the applications assessed during the reporting period is conducted in internationally backed projects involving partners from countries with very different legal provisions for research on human ES cells. The structure of the research processes documented in the applications highlights the fact that German researchers can only be involved to a limited degree in international cooperation because of the cut-off date provision in the Stem Cell Act. For instance, it became clear that technologies developed or under development involving cut-off date compliant cell lines are to be applied to novel ES cell lines in countries with a different legal position. These cell lines can then not be re-imported into Germany and used here. This has a major impact on the extent to which German research on human ES cells can engage in cooperation.

In international research on human ES cells and the accompanying scientific debate, further reasons are emerging which will probably lead in other countries to increased use of ES cell lines which were established after the cut-off date in the StZG. The debate on possible obstacles to research into and the use of human ES cells in Germany should be pursued with respect to the international developments but also with regard to the ethical and legal arguments on which the German legislation is founded.

The third report was unanimously approved at the 24th regular meeting of ZES on 14 December 2005.