Report

of the

Central Ethics Committee for Stem Cell Research

Second Report after Enactment of the
Stem Cell Act (Stammzellgesetz, StZG)

Reporting Period: October 1st 2003 to November 30th 2004

The Central Ethics Committee for Stem Cell Research (Zentrale Ethik-Kommission für Stammzellenforschung, ZES) was established with the enactment of the Stem Cell Act on July 1st 2002. The basis for the function of the ZES are the Stem Cell Act (Gesetz zur Sicherstellung des Embryonenschutzes im Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen (Stammzellgesetz – StZG) from June 28th 2002, the Regulations on the Central Ethics Committee for Stem Cell Research and on the Competent Authority according to the Stem Cell Act (Verordnung über die Zentrale Ethik-Kommission für Stammzellenforschung und über die zuständige Behörde nach dem Stammzellgesetz (ZES-Verordnung – ZESV)) from July 18th 2002 and the Rules of Procedure for the ZES (Geschäftsordnung der ZES).

The Stem Cell Act seeks to prohibit the import and use of human embryonic stem cells (human ES cells). At the same time, the Act also defines the exceptional conditions under which the import and use of these cells is permissible for research purposes. The compliance with these requirements is assessed by the licensing authority, the Robert Koch Institute (RKI), in an approval procedure. Within the scope of this approval procedure, the RKI must obtain a written opinion of the ZES.

The ZES is charged with the task of reviewing and evaluating applications for research projects that involve experiments with human embryonic stem cells. The legal basis for the review of applications are articles 5 and 9 of the Stem Cell Act. On the basis of the scientifically elucidations of the applicant the ZES has to determine whether the intended use of human ES cells serves research goals of premium importance for the acquisition of scientific knowledge pursuant to article 5 (1) of the Stem Cell Act (criterion of premium importance of the research goals). Furthermore, the ZES assesses whether the appropriate pre-clarification stipulated in article 5(2)(a) of the Stem Cell Act has been undertaken and whether the results justify the use of human ES cells (criterion of adequate pre-clarification). Lastly, in accordance with article 5(2)(b) of the Stem Cell Act, the ZES considers whether the gain of scientific knowledge to be gained in the project requires the use of human stem cells or whether the same research goal can be accomplished with alternative cellular material (e.g. human somatic stem cells) (criterion of need for human ES cells). The ZES summarises the results of the review procedure in a written opinion. This opinion has to be transmitted to the RKI within 6 weeks, at the latest within 10 weeks of submission of the complete application documentation.

The members and deputy members of the ZES (see Table 1) were appointed for a three-year term with effect from July 1st, 2002 by the German Federal Government on the basis of a joint proposal put forward by the Federal Ministry of Education and Research and the Federal Ministry of Health. The inaugural meeting of the ZES was held in Berlin in July 2002. Currently the ZES consists of three members from the field of medicine, two members from the field of biology and four members from the fields of medical, philosophical and theological ethics. For each member a deputy member has been appointed. According to Article 10 of ZESV, the deputy members also regularly attend the ZES meetings. The members and deputy members of the ZES perform their obligations on a gratuitous basis.

The ZES has to compile an annual activity report which is published by the Federal Ministry of Health and Social Security (article 14 ZESV). The First Annual Activity Report (covering the period from 2002/07/01 to 2003/09/30) can be accessed on
http://www.bmg.bund.de/fileadmin/redaktion/pdf_misc/TaetigkeitsberichtZES.pdf.
(for the English version see
http://www.rki.de/EN/Content/Institute/DepartmentsUnits/StemCell/StemCell_node.html)

Academic Fields	Members	Deputy Members
Ethics	Prof. Dr. phil. Ludwig Siep **(Chairman of the ZES)** 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	PD Dr. med. Giovanni Maio, Zentrum für Ethik und Recht in der Medizin Albert-Ludwigs-Universität Freiburg
Medicine	Prof. Dr. med. Axel Haverich Klinik für Thorax,- Herz- und Gefäßchirurgie Medizinische Hochschule Hannover (bis 10.02.2004)	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 Klinikum Kempten Oberallgäu
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Table 1: Members and deputy members of the Central Ethics Committee for Stem Cell Research (November 2004).

During the reporting period the ZES held six meetings and considered five applications for the import and use of human ES cells. Five written opinions were issued. The Information Leaflet for Applicants, elaborated together with the RKI during the previous reporting period, was extended and concretised (http://www.rki.de/DE/Content/Gesund/Stammzellen/Antragsteller/antragsteller-inhalt.html).

Review of Applications in Accordance with the Stem Cell Act

During the reporting period, five applications were intensively discussed, some of them on several occasions. The ZES issued a positive opinion on two of these applications. Both applications came from the Max Delbrück Center of Molecular Medicine (MDC), Berlin. These projects encompass basic research but one project also defines medium-term research goals in the field of therapy. Both projects involve the import of stem cell lines registered at NIH.

In one project mechanisms are investigated that play a role in the maintenance of the undifferentiated status of human ES cells. In this context, signalling pathways that transport signals from the cell surface to the inner of the cell, thereby modulating the activity of certain gene products, are to be examined in detail. Furthermore, an intention of the project is also to identify and more closely characterise soluble factors secreted into the cell culture medium by the stem cells or by the murine feeder cells that help to maintain the undifferentiated status of human ES cells. In the second project assessed favourably by the ZES, the aim is to differentiate human ES cells into hepatocytes and to examine these cells with regard to their *in vitro* characteristics and their ability to integrate into regenerating mouse liver. These experiments will be performed in comparison to human umbilical stem cells. particulars of both projects can be obtained from the RKI stem cell registry (http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html).

When reviewing applications the ZES has to evaluate whether the research projects, for which an application has been filed, serves research goals of premium importance within the intendment of Article 5(1) Stem Cell Act. This is done on the basis of the statements made by the applicant. Besides formulating a research goal of premium importance, the plausible, i.e. scientifically comprehensible presentation of the project is an important criterion when assessing premium importance. In the opinion of ZES the applicant must present a scientific hypothesis as well as a comprehensive scientific method to achieve his/her research goal. As a matter of course, the ZES takes the open-ended nature of basic research into account. However, the use of human ES cells is not justified in projects which are not plausible in this way. This applies, for instance, to projects where it was already clear at the time of application that the proposed scientific research methods are not suitable for achieving the intended goal and where the applicant fails to undertake a critical assessment of these facts. If necessary, the ZES also expresses a view if it is of the opinion that existing legal norms, in particular provisions of the Embryo Protection Act, are touched on.

ZES further assesses whether the project, for which an application has been made, has been sufficiently pre-clarified within the intendment of Article 5 (2) (a) Stem Cell Act. This evaluation is also undertaken on the basis of the documents provided by the applicant and might consider both the applicant's own studies as well as outside application-related preliminary results. In the case of the projects that were favourably assessed during the reporting period, sufficient pre-clarification of the project involving murine stem cells was demonstrated by the applicant. Moreover, results obtained abroad in research projects on a similar topic using human ES cells were presented by both applicants in conjunction with their statements on the premium importance of research goals and pre-clarification of the intended research. Since ongoing international research will lead, in the short-term, to a major increase in knowledge about these cells, the results of this research must also be considered to a greater degree when assessing applications. This can also mean that transition to the use of human embryonic stem cells may have already taken place abroad in projects with an identical or similar topic. Thus, in certain justified cases there might be no need for additional preliminary studies involving animal cells since they would not lead to a significant increase in knowledge.

Lastly, the ZES has to evaluate whether the intended acquisition of knowledge can only be acquired using human ES cells or whether it can be also obtained using other cell types, for

example animal ES cells or human adult or foetal stem cells. However, the conclusion that a material other than human ES cells could be considered for a project can only be drawn if there are plausible reasons justifying the assumption that this material is suitable for answering the specific scientific question. There are divergent results in the field of human adult stem cell research. This means that, in many cases, a sufficiently reliable prognosis on the suitability of these cells for a specific project is not possible. In these cases the ZES is of the opinion that if ES cells are in principle suitable, approval for the project may not be refused by referring to other materials, the suitability of which has not been unequivocally proven according to the scientific knowledge currently available. In this context, it must be borne in mind that particularly the assessment of the need for human ES cells must not result in a request for a research project different to the one submitted. The alternative use of foetal cells also poses ethical problems especially if these cells are directly derived from aborted foetuses and a large number is required. This has been taken into account by the ZES when examining the need for human ES cells pursuant to Article 5 (2) (b) of the Stem Cell Act (StZG). In conjunction with the assessment of the need for human ES cells, the ZES continuously researches the latest knowledge available in the various areas of stem cell research, particularly in the field of somatic stem cells.

Given that the applicant's statements were incomplete or not sufficiently documented with regard to the requirements laid out in Article 5 Stem Cell Act, these applicants were asked to submit additional documents that were needed to assess the project. This necessitated a re-discussion of these applications at additional ZES meetings. Once the full documentation was available, the written opinion of ZES was always issued within a period of six weeks as laid down in Article 13 (1) of ZESV.

Concluding Remarks

The fact that ten applications for the import and use of human ES cells have been filed since the enactment of the Stem Cell Act two and a half year ago illustrates that there is an interest in research involving these cells in Germany and use is being made of the possibility of conducting this research within the scope of the Stem Cell Act. Up to now, this has applied to basic research projects although, in some cases, the long-term goal was formulated of obtaining findings in conjunction with the development of novel diagnostic or therapeutic methods. Since the main details of approved research projects involving human ES cells are published in the RKI stem cell registry, there is a high degree of transparency in research with human embryonic stem cells in Germany, even in comparison to other countries. Various sides have expressed the view that the number of applications for the import and use of human ES cells is low. There may be many reasons for this and they need not necessarily be linked to specific provisions of the Stem Cell Act. However, there could be a need for renewed scientific and ethical-legal discussion of certain provisions of the Stem Cell Act, particularly the cut-off date, if it should turn out that relevant research projects or potential applications were no longer possible with cell lines in compliance with the cut-off date.

The second Report was unanimously approved at the 17th meeting of the ZES on December 13th, 2004.