Report

of the

Central Ethics Committee for Stem Cell Research

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

Reporting Period: July 22th 2002 to September 30th 2003

The Central Ethics Committee for Stem Cell Research (*Zentrale Ethik-Kommission für Stammzellenforschung, ZES*) was established on July 1st, 2002 with the enactment of 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 Stem Cell Act seeks to prohibit the general import and use of human embryonic stem cells (human ES cells), however, at the same time, the Act provides an exception for research purposes, defining the specific conditions under which the import and use of these cells is permissible. Accordingly, import and use of human ES cells require a license. The competent licensing authority, the Robert Koch Institute (RKI), reviews and evaluates whether a given application to import and use human ES cells meets the requirements defined in the Stem Cell Act. Additionally, the Stem Cell Act specifies that the licensing authority must obtain a written opinion of the ZES regarding each application.

The basis for the function of the ZES are articles 5, 8 and 9 Stem Cell Act, the Regulations concerning the Central Ethics Committee for Stem Cell Research and the Competent Authority according to the Stem Cell Act from July 18th, 2002 (*Verordnung über die Zentrale Ethik-Kommission für Stammzellenforschung und über die zuständige Behörde nach dem Stammzellgesetz (ZES-Verordnung – ZESV)*) as well as the Rules of Procedure for the ZES (*Geschäftsordnung der ZES*). The ZES is an independent, interdisciplinary expert body, which submits a written opinion to the RKI assessing whether the application it has reviewed merits the granting of a research license in accordance with the requirements of the StZG.

The members and deputy-members of the ZES are appointed by the German Federal Government on the basis of a joint proposal put forth by the Federal Ministry of Education and Research and the Federal Ministry of Health for a three-year period. The inaugural meeting of the ZES took place in July 2002 in Berlin. The ZES presently consists of three members from the field of medicine and two members each from the fields of biology, ethics and theology, and nine deputy-members who have also been participating continuously in the ZES meetings (see Table 1). The members and deputy members of the ZES perform their obligations on a gratuitous basis.

The ZES is charged with the task of reviewing and evaluating applications involving research plans requiring human ES cells on the basis of the documents submitted by the applicant. The ZES has to determine whether the research proposal fulfills the requirements set forth by article 5 Stem Cell Act and is, in the sense of article 5, ethically acceptable. In accordance with the Stem Cell Act, the ZES must submit a written opinion for each application. The written opinion of the ZES summarizes the results of its reviewing process setting forth whether the application's intended use of human ES cells serves goals of a premium value for the acquisition of scientific knowledge pursuant to article 5 (1) Stem Cell Act. The ZES further assesses, whether the appropriate preliminary experiments as required by article 5 (2) (a) Stem Cell Act have been undertaken and whether their results justify the use of human ES cells. Lastly, in accordance with article 5 (2) (b) Stem Cell Act, the ZES considers whether the research project and the intended gain of scientific knowledge 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 or animal embryonic stem cells).

During this reporting period, the ZES held nine regularly scheduled meetings and considered seven applications involving the import and use of human ES cells, issuing five written opinions. In addition, the ZES defined criteria for the documentation to be provided by the applicant which have been set forth in the joint bulletin of the RKI and the ZES defining the requirements for application documents (http://www.rki.de/DE/Content/Gesund/Stammzellen/Antragsteller/antragsteller_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 in 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 Klinikum der Albert-Ludwigs-Universität Freiburg
Medicine	Prof. Dr. med. Axel Haverich Klinik für Thorax-, Herz- und Gefäßchirurgie Medizinische Hochschule Hannover	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 Klinik für Frauenheilkunde und Geburtshilfe Medizinische Universität zu Lübeck
	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
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. Davor Solter Max-Planck-Institut für Immunbiologie Abteilung Entwicklungsbiologie Freiburg
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	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 Departement für Katholische Theologie Ludwig-Maximilians-Universität München

Table 1: Members and deputy members of the Central Ethics Committee for Stem Cell Research (September 2003).

Review of Applications in Accordance with the Stem Cell Act

After intensive and repeated debates, the ZES submitted written opinions pertaining to five applications seeking to import and use human ES cells during this reporting period. All five of these applications, four of which were filed by universities or institutions and one of which came from a company, were favourably assessed. Two additional applications remain under consideration. The purpose of the heretofore assessed research proposals is initially to seek access to cell cultures that are homogenous and comprised of ES-cell derived populations of differentiated cells. The differentiation protocols for certain cell types (e.g. neural progenitors, neuronal and cardio-vascular cells) are to be established and optimized, and the resulting

No	Applicant	Research Objectives	Date of the ZES' opinion
1	Prof. O. Brüstle, Institut für Rekonstruktive Neurobiologie, Universität Bonn	Derivation of neural progenitor cells form human ES cells and investigation in an animal model of their developmental and regenerative potentials.	October 10th 2002
2	Prof. J. Hescheler, Institut für Neurophysiologie, Universität Köln	Differentiation of human ES cells into cardiomyocytes and their characterisation.	October 15th 2002
3	PD Dr. W.-M. Franz, Klinikum der Universität München	Derivation and enrichment of cardiomyocytes from human ES cells and their characterisation and functional analysis in an animal model.	February 24th 2003
4	ProteoSys AG, Mainz	Differentiation of human ES cells into neuronal cells and characterisation of their proteom. Analysis of effects of embryo-neurotoxic substances.	July 03rd 2003
5	Max-Planck-Institut für Biophysikalische Chemie, Göttingen	Differentiation of human ES cells into dopaminergic neurons and their characterisation in animal models of Parkinson's disease.	September 8th 2003

Table 2: Applications on import and use of human ES cells evaluated by the ZES during the reporting period

(differentiated) cell populations are to be analyzed with regard to their characteristics *in vitro* and - in four of the applications after transplantation into an appropriate animal model - also *in vivo*. It is expected that the projects will provide essential insight regarding the factors and conditions which are necessary for the differentiation of human ES cells, thereby contributing to our fundamental understanding of human stem cell differentiation. Transplantation experiments are expected to reveal information regarding the ability of differentiated human ES cells to migrate and to integrate into tissue(s) as well as on their functionality *in vivo*. Ultimately, these transplantation experiments should also help to clarify whether cells differentiated from human ES cells could find use in cell replacement therapies at a future point in time. One project proposes to investigate the time-dependent cellular protein patterns ("proteoms") as the human ES cells differentiate into neuronal cells. Changes in protein patterns, which will be triggered by exposure of differentiating cells to neurotoxic and/or embryo-neurotoxic substances, are to be analyzed and compared to untreated cells.

In all projects assessed thus far, the import and use of human embryonic stem cells have been foremost deemed to advance research purposes of premium importance for the acquisition of scientific knowledge in basic research. A common aim shared by the already evaluated projects is the future development of novel diagnostic, preventive or therapeutic practices, e.g. cell replacement therapies for the treatment of neuro-degenerative disorders or myocardic infarction. The ZES notes the long timeframe of these aims: Despite the numerous animal experiments demonstrating that murine ES cells can improve the clinical situation in certain disease models, many questions concerning the biology of human ES cells and stem cell derived differentiated cells remain to be answered before respective replacement therapies can be developed. This also includes the analysis in animal models of the potential of human stem cells to cause malignant tumours. Given that the results obtained with non-human stem cells are only limitedly applicable to human stem cells, the projects assessed by the ZES thus far are expected to contribute primarily to the clarification of a number of fundamental questions.

Perspectives on the Stem Cell Act Relative to the Applications Already Reviewed

In their meetings the ZES has discussed the criteria and measures that should be included in the basic assessment of applications according to the Stem Cell Act. In addition to the specific requirements of the Stem Cell Act, the intent of the German Embryo Protection Act (Embryonenschutzgesetz) was taken into consideration when making decisions on applications.

Certain terms used in article 5 Stem Cell Act such as “research goals of premium importance” or “clarified as far as possible” require further definition in the course of the ZES’ activity. On one hand, the lawmakers’ choice to use these open-ended legal terms provides the ZES with the scope appropriate for the assessment of these applications. On the other hand it assigns to the ZES the task of fleshing out these terms through its decisions in specific cases. These clarifications which are devised in the course of evaluating specific application were a substantial part of the ZES’ activity during this period. As an outgrowth of the ZES’ accumulated experience, the development of general standards for decision-making in individual cases cannot be simply the creation of a catalogue of fixed general criteria for the scientific and ethical assessment of applications. In fact, considering that human ES research remains a sophisticated and in no way fixed field of research, the ZES’ evaluation must weigh the particulars of each application; in doing so the ZES furthers development of the aspects considered significant in the process of application assessment. The careful scientific and ethical appraisal of each application with regard to its compliance with the criteria of article 5 Stem Cell Act, which calls for a basic and comprehensive examination of each application, necessitates repeated discussion of each application by the ZES, which is, at the request of the ZES, commonly also supplemented with further essential information provided by the applicant.

With regard to the premium importance of research goals the ZES contends its task is not to give a priority to basic research projects or projects aiming at the development of diagnostic, therapeutic or preventive procedures applicable to humans. According to article 5 Stem Cell Act basic research has its own value and must not necessarily be directed solely at therapeutic goals, although basic research in medicine and developmental biology will normally be of relevance for future medical appliance. Decisive in the evaluation of a basic research proposal is a positive assessment of its scientific quality and plausibility. At the same time the answers to the questions posed by the project through the use of human ES cells must be of high scientific significance. To provide convincing substantiation is incumbent upon the applicant. When possible in its deliberations regarding the scientific quality of a project, the ZES takes into consideration the reviews of the project by scientific institutions at home and abroad.

In addition to goals in basic research, the majority of the projects assessed thus far also points to goals in the area of therapy, though qualified by a rather long-term perspective. When included by the applicant such aims were also considered during the discussions of the ZES. However, the explicit goals regarding the advancement of basic research knowledge satisfied the necessary requirement of premium importance. It is expected that the successful execution of this research will yield important insights in the fields of human embryonic development and cell differentiation. With respect to the long-term therapeutic goals of the previously considered applications the ZES is aware that the currently available human ES cell lines that are in agreement with the lawful cut off date (January 1st 2002) are presumably not suitable for therapeutic application to human beings. This is predominately due to a potential contamination of these cell lines with xenogenic viruses due to co-cultivation with murine fibroblasts. However, the use of these cell lines for the investigation of specific questions of human stem cell biology as well as for the establishment of the suitability of human ES cell lines for therapeutic approaches in animal models is still possible.

The Stem Cell Act obligates applicants to demonstrate in a scientifically rigorous manner that the explicit objectives of the research project have been explored and clarified as far as possible in *in-vitro* models with animal cells or in animal experiments (article 5 (2) (a) Stem Cell

Act). From the perspective of the ZES these preceding clarifications have to answer the fundamental question of whether additional knowledge can plausibly be acquired through the use of human ES cells. The ZES can require further clarifications if such information indicates that essential knowledge can be acquired within the scope of the asserted research objectives without using human ES cells. In this context, the ZES saw no need to require the applicant to perform experiments with stem cells of an additional mammalian species beyond mouse stem cells before being permitted to start experiments involving human ES cells. The opinion of the ZES is not to require prior clarification of every imaginable detailed question in the context of the use of human ES cells. Consequently, in the discussion of applications assessed so far, the ZES was interested in the prior clarifications of significant points advanced either by the applicant personally or in the published results of other research groups before approving work with human ES cells. All applicants were able to refer to their own application-related *in vitro* studies with animal stem cells in addition to their own and/or outside preliminary investigations in animal models, which were sufficient, in the expert consideration of the ZES, to justify a transition to the use of human ES cells. Additionally, all applicants and/or principal investigators demonstrated that they were skilled in the cultivation and differentiation of animal ES cells and, where required, that they had experimental expertise in dealing with these cells in animal models.

According to the Stem Cell Act, the import and use of human ES cells is only permissible if the intended acquisition of knowledge of the research project cannot be achieved without human ES cells (article 5 (2) (b) Stem Cell Act). In its analysis of this question the ZES scrutinizes the requirement of using human ES cells in the proposed project with respect to the present state of the art in view of the availability of alternative systems. The evaluation of possible alternatives to human ES cells can only proceed with reference to the actual scientific objective. In this sense – and given the constitutionally guaranteed freedom of research – the ZES cannot make its approval of a research application contingent upon the applicant undertaking work with an alternative system. To be able to assess the necessity of the use of human ES cells in the particular projects, the ZES during its various meetings has been intensively engaged in the assessment of the currently possible alternatives to human ES cells. In this context, background information was gathered regarding the most current state of knowledge in the fields of “somatic (adult) stem cells”, “foetal stem cells” and “embryonic germ cells”. In its assessment of applications the ZES took into account the present state of the art in these fields.

The RKI was asked to encourage the holder of the license – while protecting his/her legitimate interest - to make the results of his/her research with human ES cells accessible to the scientific community and to the public. In the view of the ZES, this is in agreement with the intent of the Stem Cell Act only to permit human ES cell research for research goals of premium importance aiming at scientific acquisition of knowledge in the fields of basic and medical research. With the publication of the scientific results of these projects other researchers could also be enabled to build upon them.

The applications assessed by the ZES during the reporting period illustrate that the possibilities to work on scientific objectives through the use of human ES cells that serve research goals of premium importance are in fact used in Germany. The concerns voiced in the public when the Stem Cell Act was enacted that there would be either a flood of applications or that ES cell research would be impossible in Germany have not come to pass. The scientific objectives put forth by the proposals submitted thus far demonstrate that research on human ES cells possesses its own independent value and – in addition to the investigation of miscellaneous systems for the development of new diagnostic and therapeutic strategies – can make contributions to the clarification of important cellular and developmental biology questions.

The first Report was unanimously approved during the 10th Meeting of the ZES on October 15th, 2003.