# Report

**of the**

# Central Ethics Committee for Stem Cell Research (ZES)

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

**Reporting period: 1 December 2005 to 30 November 2006**

## The Central Ethics Committee for Stem Cell Research

The Central Ethics Committee for Stem Cell Research (ZES) is an interdisciplinary expert body which is responsible for reviewing applications for the import and use of human embryonic stem (ES) cells. The results of this review are compiled in an opinion and then submitted 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 *(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 ZES currently has nine members in total (two from the field of biology, three from the field of medicine and four from the fields of philosophical, medical and theological ethics) as well as nine deputies from the corresponding disciplines (Table 1). In accordance with the ZES Regulations the deputy members also regularly attend the deliberations on the applications. The members and deputy members of the ZES perform their obligations on a voluntary basis and were appointed the last time in July 2005 for a period of three years.

The ZES is responsible for determining, on the basis of the documents submitted by the applicant, whether the proposed project complies with the criteria of Article 5 StZG and is ethically acceptable 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 value for increasing scientific knowledge pursuant to Article 5 (1) StZG, whether the preliminary clarifications stipulated in Article 5 (2) a StZG have been submitted and the results justify the use of human ES cells and whether the desired knowledge 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 activities of the ZES call for an ongoing preoccupation with the latest scientific developments in the field of stem cell research. In this and its monitoring of the public debate about stem cell research, the Committee is supported by its secretariat within the RKI. The ZES has taken interested note of the new, alternative approaches to obtaining pluripotent stem cells.

The ZES has to prepare an annual report that is published by the Federal Ministry of Health (Article 14 ZESV). The previous reports of the ZES can be accessed on the BMG website http://www.bmg.bund.de and in English on the RKI website http://www.rki.de/EN/Content/Institute/DepartmentsUnits/StemCell/StemCell_node.html.

## Deliberation and review of applications pursuant to Article 5 StZG during the reporting period

During this reporting period the ZES held four meetings at which a total of five applications for the import and use of human ES cells were extensively discussed, some on numerous occasions. All the applications were viewed positively by the ZES. Individual applications were comprehensively revised and supplemented because of the complaints and further questions from the ZES. Only then the Committee could approve them. One application, which had already been viewed positively by the ZES in the previous reporting period, was approved during the current reporting period by the RKI. In accordance with the stipulations in Article 11 StZG on the publication of data from approved applications, information on this

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

Table 1: Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES), November 2006

application is included in this report for the first time. Table 2 gives an overview of the applications approved by the RKI during the reporting period. All the projects assessed definitively by the ZES during the reporting period met the preconditions of Article 5 StZG and were, therefore, ethically acceptable pursuant to Article 9 StZG.

Two of the approved research projects (Projects 4 and 6 in Table 2) focus on the development of improved methods for the cultivation and cryopreservation of human ES

| Number | Applicant | Research objectives | Date of positive ZES opinion |
|---|---|---|---|
| 1(17) | Professor Dr. Francis Stewart<br>Biotechnologisches Zentrum<br>Technische Universität Dresden | Development and optimisation of methods for the genetic manipulation of human embryonic stem cells | 30.09.2005 |
| 2 (15) | Professor Dr. Heinrich Sauer<br>Physiologisches Institut der Universität Gießen | Tumor-induced angiogenesis in confrontation cultures of tumours with stem cells | 14.12.2005 |
| 3 (16) | Professor Dr. Sigurd Lenzen<br>Institut für Klinische Biochemie der Medizinischen Hochschule Hannover | Differentiation of human embryonic stem cells to insulin-producing cells with the characteristics of pancreatic beta cells | 02.03.2006 |
| 4 (18) | Fraunhofer Institut für Biomedizinische Technik (IBMT), St. Ingbert | Establishment and optimisation of methods for the cryopreservation of therapeutically relevant human stem cells | 14.06.2005 |
| 5 (19) | Fraunhofer Institut für Biomedizinische Technik (IBMT), St. Ingbert | Assessment of bone cell differentiation of human embryonic stem cells using impedance spectroscopic methods | 14.06.2006 |
| 6 (20) | Professor Dr. Jürgen Hescheler<br>Institut für Neurophysiologie<br>Universität Köln | Development of improved cultivation methods and new cryopreservation protocols for human embryonic stem cells | 11.08.2006 |

Table 2: Overview of projects which were approved by RKI following a definitive, positive assessment by ZES during the reporting period. The numbers in brackets in the left column correspond to the approval numbers in the RKI stem cell register.

cells. The research work is part of the EU project CRYSTAL. Another project (Project 1) aims to develop methods for the more effective genetic modification of human ES cells. This project – like another project already approved during the previous reporting period – is being conducted within the framework of another EU integrated project (ESTOOLS). The above-mentioned three projects are all oriented towards creating optimised experimental conditions under which human ES cell research can be pursued. Careful cryopreservation is thus the precondition for cell preparations of consistent quality being available for research. Methods for the targeted insertion of genetic material into human ES cells could, for instance, considerably increase the effectiveness of selection methods for the differentiation of human ES cells. The projects aim to contribute to solving some of the fundamental problems, that have not been sufficiently understood up to now, in research into human ES cells. Furthermore, the reproducible frozen storage of human ES cells, their cultivation without using animal feeder cells or animal serum and their (clonal) cultivation starting from individual cells are the precondition for the future potential use of these cells and their derivatives for human therapies. Hence, some of these projects also map out medium-term goals which are oriented towards “extending medical knowledge of the development (…) of therapeutic methods for use in humans” in line with Article 5 (1) StZG.

Two of the projects assessed during the reporting period focus on the differentiation of human ES cells into therapeutically relevant, defined cell and tissue types. Project 3 involves the establishment of improved protocols for the differentiation of human ES cells into insulin-producing cells whereby novel differentiation protocols established by the applicant in the mouse model are to be transferred to human ES cells. Project 5 seeks to use impedance

spectroscopy to observe the differentiation of human ES cells into bone tissue. In future, this method could pave the way for non-invasive monitoring of this differentiation process. This last project is also part of an integrated project (OSTEOCORD) that receives EU funding.

Another project that was given a positive assessment during the reporting period (Project 2) wishes to examine the mechanisms involved in the formation of blood vessels from human ES cells. Here the focus is to be on modelling the induction of vessel formation through tumours. This research work seeks, amongst other things, to provide insight into whether and, if so, how vessel growth triggered by the tumour can be inhibited in confrontation models of spheroids of human ES cells with tumours. This could perhaps lead to improved assessment of the anti-angiogenesis potential of pharmaceuticals in tumour therapy. If successful, this project would have a foreseeable application horizon.

Further information on these projects supported by the ZES and approved by the RKI can be found in the RKI register (http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html). The main arguments of the ZES on the premium value of research goals, sufficient preliminary clarification of the projects and on the need to use human ES cells have been taken over into the register texts underlining the concurring assessment of the applications by the ZES and the RKI in all cases up to now.

**Final comments**

In its activities now spanning more than four years, the ZES has deliberated on a total of 22 applications for the import and/or use of human ES cells. Positive opinions were given for a total of 20 applications, in some cases after repeated further questions and corresponding modifications to the projects. All the projects supported by the ZES have been approved by the RKI. In the applications deliberated during the reporting period, the potential for fundamental research and the, in some cases, already therapy-oriented direction of the research in human ES cells in Germany is visible. At present, 14 German research groups are working on human ES cells in 20 projects whereby the experimental results from 4 groups have since been taken over into 11 scientific publications in English journals.

However, in the second half of 2006 only one application for the use of human ES cells, already under discussion, has been reviewed by the ZES. No new applications were submitted during this period. This stagnation in the submission of applications in Germany is undeniable and is in marked contrast to the major growth and extremely fast development of research into human ES cells in other countries. There are several reasons for this and there is an urgent need for their further independent analysis. The ZES already drew attention in its last report to the problems facing German hES cell researchers and attributed them partly to the provisions of the German Stem Cell Act. These problems are still persisting. They partly result from the current cut-off date provision in the StZG as a consequence of which only a few cell lines may be used in Germany. Of the approximately 400 human ES cell lines established around the world at the end of 2005, 73 are listed in the NIH stem cell register. When the StZG was adopted, it was assumed that these 73 lines would be available to German researchers. Most (52) of the cell lines originally entered in the NIH register are not, however, available, could not be replicated in culture or were withdrawn by the depositors for unexplained reasons. In fact, a maximum of 21 human ES cell lines from the NIH register are currently available to German researchers. Furthermore, doubts have arisen recently about the genetic and epigenetic stability of some of the 21 cell lines. More recent cell lines, which were, for instance, prepared without the cultivation of animal feeder cells and could, therefore, be used for therapy in future, are barred from import to Germany as a consequence of the Stem Cell Act. The same holds for human ES cell lines which inherently carry specific hereditary disease traits and could, therefore, be suitable examination models

for cellular changes in the case of severe genetic diseases. Consequently, not all questions of fundamental research can currently be addressed with the human ES cell lines admissible in Germany. Given the expected transition in international research to more recent cell lines and the restrictions imposed on some suppliers of the cut-off date compliant cell lines, it is very questionable whether research in Germany with the admissible cell lines is deemed to have sufficient prospects of success. This probably applies in particular to research that, in the long run, aim for clinical applications. It is currently open whether and, if so, to what extent research work would have to be repeated later or elsewhere with more recent stem cell lines because the properties of the (probably clinically unusable) cut-off compliant and possible later clinically usable cell lines might differ. In its deliberations of the applications the Committee is also confronted with demands from research to change the cut-off date. However, this should be done in such a way that the ethical-legal intent of StZG is respected, i.e. that German researchers should not create any additional incentive for greater embryo use in other countries.

Furthermore, it is clear from the applications that networking in ES cell research activities - for instance within the EU - is very much on the increase. Two-thirds of the projects approved during the reporting period are part of integrated EU projects. Some of these projects which use cut-off date compliant cells in Germany are explicitly designed to include activities elsewhere in Europe involving non-cut-off date compliant human ES cell lines. Hence, German researchers are excluded, from the very outset, from addressing certain questions within these projects. Moreover, the current German legal situation means that German researchers might develop innovative techniques and methods in their own country using cut-off date compliant cells which are then transferred by cooperation partners to better and, perhaps, medically, pharmacologically and toxicologically usable cell lines that are not admissible in Germany. These hES cells could not be imported into Germany under any circumstances. Nor could they be used here to develop stem cell-based applications. In light of the scientific developments in hES cell research, that are also reflected in the 7$^{th}$ EU Framework Research Programme (2007-2013), the ZES expects these problems to become even more aggravated.

The major involvement of German research in EU integrated projects, obvious from the applications discussed, which involve scientists from countries with very different ethical-legal conditions for human ES cell research, currently leads to a climate of considerable legal uncertainty for German research scientists. This applies in particular to projects in which non-cut-off date compliant cells may be used outside Germany. There is above all uncertainty about whether and, if so, on what scale participation is punishable. The Committee believes that there is an urgent need to remove this legal uncertainty about work carried out by German researchers abroad in the framework of the legal and ethical-legal provisions in force there.

The Fourth report was approved at the 27$^{th}$ ordinary meeting of ZES (9 yes votes).