Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

Fifth report after enactment of the Stem Cell Act (StZG)

Reporting period: 1 December 2006 to 30 November 2007

1. The Central Ethics Committee for Stem Cell Research

The Central Ethics Committee for Stem Cell Research (ZES) was convened for the first time with the entry into force of the Stem Cell Act on 1 July 2002. It reviews and assesses applications for the import and use of human embryonic stem cells (hES) and makes recommendations on the applications to the competent authority, the Robert Koch Institute (RKI). The activities of the Committee 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 Stammzellenforschung - ZESV) of 18 July 2002 (BGBl. I p. 2663) (http://www.gesetze-im-internet.de/zesv/index.html). According to these provisions, 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. It must examine whether the proposed use of human embryonic stem cells serves research purposes of superior interest for increasing scientific knowledge (Article 5 (1) StZG), whether the required preliminary clarifications have been submitted and the results justify the use of human embryonic stem cells (Article 5 (2) a StZG) and whether the desired knowledge can only be obtained with human embryonic stem cells (Article 5 (2) b StZG). ZES summarises the results of the application review, which is prepared in each case on the basis of four votes from the circle of members and deputy members, in a written opinion.

The independent, interdisciplinary expert body consists of nine members and their deputies. In accordance with the ZES Regulations the deputy members also regularly attend the deliberations. At the present time, two members and their deputies are from the field of biology, three members and their deputies from the field of medicine and four members and their deputies from the fields of philosophical, medical and theological ethics (Table 1). The members and deputy members of ZES perform their duties on a voluntary basis. They were appointed, last time round, in July 2005 by the federal government for a period of three years.

ZES prepares an annual report which is published by the Federal Ministry of Health (BMG) (Article 14 ZESV). The previous ZES Reports can be accessed on the BMG website (http://www.bmg.bund.de/).

Besides reviewing applications, ZES' activities also involve the monitoring of the latest scientific developments in the field of stem cell research. The Committee is supported by the secretariat within RKI.

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

During the reporting period ZES held six meetings at which a total of six applications for the import and use of human embryonic stem cells were extensively discussed. All the applications were viewed positively by ZES. They all met the preconditions of Article 5 StZG and were, therefore, ethically acceptable pursuant to Article 9 StZG. Table 2 gives an overview of these applications; two of them are extensions to already approved projects.

Field	Member	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 Leibniz-Institut für Pflanzengenetik und Kulturpflanzenforschung (IPK) Abteilung Zytogenetik Gatersleben	Prof. Dr. rer. med. Ursula Just Biochemisches Institut Christian-Albrechts-Universität Kiel
Ethics	Prof. Dr. phil. Ludwig Siep **(Chairman)** Philosophisches Seminar Westfälische Wilhelms-Universität Münster	Prof. Dr. phil. Jan Beckmann Institut für Philosophie FernUniversität in Hagen
	Prof. Dr. med. Claudia Wiesemann Institut für Ethik und Geschichte der Medizin Georg-August-Universität Göttingen	Prof. Dr. med. Giovanni Maio, Institut für Ethik und Geschichte der Medizin 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 Chairman)** 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 deputies of the Central Ethics Committee for Stem Cell Research (ZES), Status November 2007

In the first project a library of low-molecular substances is examined for the ability to induce the differentiation of human embryonic stem cells in dopaminergic neurons and/or to influence the differentiation process. Human embryonic stem cells modified by a reporter gene are to be examined by means of high throughput screening for a differentiation- inducing effect on the substances to be analysed. Identified substances are then to be examined on the molecular level for their effect, in particular on the Wnt signalling pathway.

Number	Applicant	Research area	Date of positive ZES opinion
1 (21)	Universität Rostock Medizinische Fakultät Klinik und Poliklinik für Neurologie	Induction of dopaminergic differentiation of reporter gene-transfected human embryonic stem cells by low-molecular substances and underlying molecular mechanisms	14.02.2007
2 (22)	Max-Planck-Gesellschaft Max-Planck-Institut für Molekulare Biomedizin, Münster	Reprogramming of somatic cells through fusion with human embryonic stem cells	16.07.2007
3 (23)	Universitätsklinikum Bonn Institut für Rekonstruktive Neurobiologie	Production of human microglia cells from human embryonic stem cells for the analysis of human-specific molecules	16.07.2007
4 (24)	Prof. Dr. Marcel Leist Universität Konstanz	Development and characterisation of model systems for the neurotoxicological safety testing of medicinal products and chemicals using *in vitro* methods	21.11.2007
Extensions to approved applications			
5 Extension to approval (2)	Prof. Dr. Jürgen Hescheler Institut für Neurophysiologie der Universität zu Köln	Comparative pharmacological and toxicological characterisation of embryonic stem cells and derived heart cells of the mouse, rhesus monkey and cynomolgus monkey with human embryonic stem cells	28.08.2007
6 Extension to approval (9)	Max-Planck-Gesellschaft Max-Planck-Institut für Molekulare Genetik, Berlin	Identification, functional characterisation and epigenetic regulation of genes and associated signaling pathways for maintaining the pluripotency of human embryonic stem cells	21.11.2007

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

Another project (Project 4 in Table 2) aims to produce sufficient numbers of human neurons and astrocytes from human embryonic stem cells in a reproducible manner, in order to examine the question whether, on the basis of these cells, new, improved *in vitro* systems can be established for testing neurotoxicity and embryoneurotoxicity in man. In the course of the project important questions are to be examined, in particular those concerning the factors and signalling pathways which play a role in neuronal and glial differentiation.

Another project (Project 3) focuses on the characterisation of signalling pathways in human microglia cells which are to be differentiated from human embryonic stem cells. Of special interest is the effect of the human signalling molecule Siglec-11 on the production of inflammation mediators in microglia cells. It is assumed that Siglec-11 mediated inflammation processes could play a major role in the pathogenesis of neurodegenerative diseases.

One research project (Project 2) aims to reprogram human cells in a quasi-pluripotent state. The intention is to fuse different somatic cell types and adult stem cells with human embryonic stem cells in order to induce pluripotency. The goal is to elucidate the molecular processes which lead to reprogramming and to identify factors involved from the human embryonic stem cells. This project is part of international research trends involving the conversion of somatic cells into pluripotent cells.

Applications were submitted for work in conjunction with already approved research projects which required renewed discussion by the Committee and an extension to the approval by RKI:

- 2. Approval: The application approved in 2003 described the research goal of superior interest of differentiating cardiomyocytes from human embryonic stem cells. They were examined electrophysiologically and pharmacologically by testing various known cardial medicinal products. In the extension to approval applied for (Project 5 in the Table), the effects of cardiac substances on cardiomyocytes derived from the embryonic stem cells of various species are to be compared. Based on comparative studies, these experiments are to permit statements about the suitability of various stem cell types for the development of a test system to determine toxic (side) effects on the heart.

- 9. Approval: The research work approved in 2005 examines the molecular mechanisms which contribute to maintaining the pluripotency of human embryonic stem cells. In the extension to this work (Project 6) the molecular basis for different growth and differentiation behaviour of human embryonic stem cells are to be systematically analysed in different culture media. The examinations are to be extended to the epigenome of human embryonic stem cells and the cells that differentiate from them.

Further information on the projects supported by ZES and approved by RKI can be found in the RKI register (www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html). The main ZES arguments on the superior interest of research projects, their sufficient preliminary clarification and on the need to use human embryonic stem cells have been taken over into the assessment of the research projects by RKI.

3. Further activities of ZES

3.1. Colloquium to mark the 5th anniversary of ZES

On the occasion of its 5th anniversary ZES staged a colloquium in the Berlin-Brandenburg Academy of Sciences (BBAW) on 17 September 2007. It extended an invitation to representatives of the Bundestag factions and commissions, ministries, scientific organizations and scientists engaged in research into human embryonic stem cells pursuant to StZG. Committee members commented on the previous expert opinion and advisory activities of ZES (see Programme in Table 3) and were then available for discussions with guests.

Welcome address
by the President of the Berlin-Brandenburg Academy of the Sciences, Günter Stock and the President of the Robert Koch Institute, Reinhard Kurth

Papers
Ludwig Siep, Philosophisches Seminar, Westfälische Wilhelms-Universität Münster
"Ethically acceptable in this sense" – on the understanding of ethics of the Central Ethics Committee for Stem Cell Research

Jan Beckmann, Institut für Philosophie, FernUniversität Hagen
The criteria of superior interest, preliminary clarification and “lack of an alternative” in Article 5 StZG from the ethical angle

Marion Kiechle-Bahat, Frauenklinik und Poliklinik, Technische Universität München
Assessment of the research applications from the medical and natural scientific angle

Anna M. Wobus, Leibniz-Institut für Pflanzengenetik u. Kulturpflanzenforschung (IPK), Gatersleben
Current aspects of stem cell research

Wolfram-H. Zimmermann, Universitätsklinikum Hamburg-Eppendorf
Use of human embryonic stem cells to produce human heart tissue

Hartmut Kreß, Evangelisch-Theologische Fakultät, Rheinische Friedrich-Wilhelms-Universität Bonn
Research on human embryonic stem cells regarding options for their medical or pharmacological use

Discussions with the Committee
Chair: Henning M. Beier, Institut für Anatomie und Reproduktionsbiologie, Rheinisch-Westfälische Technische Hochschule Aachen

Table 3: Programme of the colloquium on the occasion of the 5th anniversary of ZES.

In their short presentations Committee members commented on the Committee’s understanding of ethics and addressed various aspects of the ethical and natural-scientific assessment of applications for the import and use of human embryonic stem cells. The papers did not always reflect the opinion of the Committee as a whole. The latest scientific developments in the field of stem cell research und their importance for future research were also presented. Reference was likewise made to the current public debate about the need to amend the Stem Cell Act. Special attention was paid to the prospects of gaining a better understanding of the developmental biological processes and mechanisms in the onset of disease, of identifying new ways forward in tumour research and of reprogramming somatic cells with the help of human embryonic stem cell research. The latter could lead, in future, to new medical options requiring no human embryonic stem cells. There was also discussion of the goal of achieving safety for consumers and patients through improved systems of active substance examination on the basis of differentiated human embryonic stem cells.

One of the short presentations looked at the use of human embryonic stem cell lines in pharmacological and toxicological tests from the ethical and legal aspects. In vitro studies of this kind can lead to more reliable test systems for medicinal products and, by extension, to a reduction in medicinal risks. Improved toxicity and active substance testing based on human cell systems constitute a step forward in medicinal product safety. In addition, one contentious issue discussed by the Committee was the ethical relevance of the usability of human embryonic stem cells with a view to reducing the number of animal experiments.

The comments by the Committee members were supplemented by a short presentation on an approved project which reported on the results of the development of heart tissue from human embryonic stem cells. In future, this tissue could be used to identify pharmacologically active substances in toxicity testing and, in the long term, to replace heart tissue as well.

3.2. Experience and developments

Over the last five years the Commission has handed down positive opinions on 24 out of 26 applications, in some cases after repeated further questions to and corresponding modifications by the applicants. All the projects supported by ZES have been approved by RKI. At present, 18 German research groups are working on human embryonic stem cells. Experimental results from the approved research projects of five groups have been taken over into 13 scientific publications.

In 2007 three applications have been submitted so far by research groups who had not worked with human embryonic stem cells previously and three applications by groups who have already been granted approval to work with human embryonic stem cells which were definitively assessed by the Committee. In its previous report ZES had already highlighted the problems facing German researchers already working or wishing to work with human embryonic stem cells. In some cases, they are attributed to the provisions of the German Stem Cell Act (cut-off date, risk of prosecution in the case of international cooperation). These problems still exist. The Committee sought out further information through lectures by external experts on some controversial questions concerning research with human embryonic stem cells (risk of prosecution, relationship between research and application, patenting problems).

Committee members had had several opportunities to input their expertise during various opinion-forming processes in the parliamentary and scientific arenas, for instance in the Bundestag research and health commissions and at various public events. In this context they were able to address questions of stem cell research which were raised in the debate about amendments to the Stem Cell Act. They had an opportunity to share their knowledge about scientific developments and ethical problems of stem cell research.

Important research work has identified new and unexpected ways of reprogramming murine and human somatic cells during the course of last year. Initial results seem to indicate that the reprogrammed cells are pluripotent. This would mean that induced pluripotent stem cells (iPS cells) reprogrammed from adult somatic cells could open up therapeutic opportunities in future without using human embryonic stem cells, even if induced pluripotent cells developed at the present time cannot yet be used in man. Independently of this, it is foreseeable that induced pluripotent cells could take on major relevance for fundamental research. Although these research findings are important, it is not yet known, based on the current level of information regarding their characterisation and validation, whether these cells have all the properties of human embryonic stem cells. This means that with the various cell types – in line with their varying suitability for specific questions – parallel characterisation as well as fundamental and applied research will be necessary, including comparative research with human embryonic stem cells in future, too.

The Fifth Report was unanimously approved at the 34th ordinary meeting of ZES (8 yes votes) on 14 January 2008.