Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

Eleventh report since the enactment
of the Stem Cell Act (StZG)
for the period from 1 Jan. – 31 Dec. 2013

1. The Central Ethics Committee for Stem Cell Research

The Central Ethics Committee for Stem Cell Research (ZES) is an independent and interdisciplinary expert body that was appointed for the first time in 2002 when the Stem Cell Act (StZG) came into force. The Committee's activities are governed by this law (the 'Act ensuring the protection of embryos in conjunction with the import and use of human embryonic stem cells' (Stem Cell Act – StZG) dated 28 June 2002 (BGBl. I p. 2277, http://www.gesetze-im-internet.de/stzg/BJNR227700002.html) and by the 'Regulation concerning the Central Ethics Committee for Stem Cell Research and the competent authority pursuant to the Stem Cell Act' (ZES Regulation – ZESV) dated 18 July 2002 (BGBl. I p. 2663) (http://www.gesetze-im-internet.de/zesv/BJNR266300002.html).

The nine members of the Committee and their nine deputy members are appointed by the Federal Government for a term of three years. They represent the fields of biology, medicine and philosophical, medical and theological ethics (see Table 1). Both the members and the deputy members take part regularly in the meetings and in the deliberations of these meetings pursuant to the ZESV. The work of the ZES is conducted in an honorary capacity.

The work of the ZES consists in the review and assessment of applications to import and use human embryonic stem cells (hES cells) according to the regulations of the Stem Cell Act. Based on the documents submitted by the applicants, the Committee determines whether a research project intending to use hES cells for which an application has been submitted meets the criteria of section 5 of the StZG and is ethically acceptable in this sense. Within the framework of the application, it has to be proven in a scientifically substantiated manner that the project pursues research objectives of superior interest for an increase in scientific knowledge (section 5, no. 1 of the StZG), that the scientific issues have already been subject to a preliminary clarification in other systems, for example animal cell models (section 5 no. 2a of the StZG), and that the targeted increase in scientific knowledge requires the use of hES cells (section 5 no. 2b of the StZG). The results of the review of the applications are summed up by the ZES in a written opinion which is sent to the Robert Koch Institute (RKI), the competent authority pursuant to the Stem Cell Act.

The ZES's annual reports are published by the Federal Ministry of Health (BMG; section 14 of the ZESV). They can be accessed via the websites of the BMG (www.bmg.bund.de) and the RKI (http://www.rki.de/DE/Content/Kommissionen/ZES/Taetigkeitsberichte/taetigkeitsbericht_node.html).

Field	Member	Deputy member
Biology	Prof. Dr. rer. nat. Hans R. Schöler Max-Planck-Institut für Molekulare Biomedizin Münster	Prof. Dr. rer. nat. Martin Zenke Institut für Biomedizinische Technologien Abt. Zellbiologie RWTH Aachen
	Prof. Dr. rer. nat. Anna M. Wobus **(Deputy Chairperson)** Leibniz-Institut für Pflanzengenetik und Kulturpflanzenforschung (IPK) Gatersleben	Prof. Dr. med. Ursula Just Biochemisches Institut Christian-Albrechts-Universität Kiel
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 Chairperson)** 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. rer. nat. Maria Wartenberg Molekulare Kardiologie und Stammzellforschung Universitätsklinikum Jena
Ethics	Prof. Dr. phil. Jan P. Beckmann Institut für Philosophie FernUniversität in Hagen	Prof. Dr. phil. Ralf Stoecker Philosophische Fakultät Universität Potsdam
	Prof. Dr. mult. Nikolaus Knoepffler Lehrstuhl für Angewandte Ethik Universität Jena	Priv. Doz. Dr. med. Tanja Krones Klinische Ethik Universitätsspital Zürich
Theology	Prof. Dr. theol. Klaus Tanner **(Chairperson)** Wissenschaftlich-Theologisches Seminar Lehrstuhl Systematische Theologie/Ethik Ruprecht-Karls-Universität Heidelberg	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 Katholisch-theologische Fakultät Ludwig-Maximilians-Universität München

Table 1: Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES), status: December 2013

2. Deliberations on, and review of, applications pursuant to section 5 of the StZG during the reporting period

In 2013, six meetings were held and a total of 13 applications for the import and use of human ES cells were discussed. On some applications the RKI had asked the applicant in advance for further information and more documents. The ZES issued positive opinions on all the applications. On one subject, two identical but independent approvals were issued because two scientists had the same research interest (no. 7 in Table 2). All the projects met the prerequisites of section 5 of the StZG and were ethically acceptable in this sense (section 9 of the StZG).

Table 2 gives a summary overview of the applications under the Stem Cell Act that were approved by the RKI during the reporting period and on which the ZES had issued positive opinions.

No.	Applicant	Research topic	Date of positive the ZES opinion
1 (75)	Prof. Dr. Martin Zenke RWTH Aachen	Establishment and characterization of cell models for myeloproliferative neoplasms	11 Feb. 2013
2 (76)	Prof. Dr. Heiko Lickert Helmholtz Zentrum München	Efficient differentiation of human embryonic stem cells to endodermal precursor cells and insulin-producing beta cells	15 April 2013
3 (77)	Medizinische Hochschule Hannover	Characterization, genetic modification and differentiation of patient-specific induced pluripotent stem cells compared with human embryonic stem cells	15 April 2013
4 (78)	Dr. Micha Drukker Helmholtz Zentrum München	Genetic and epigenetic monitoring over time of the differentiation of human embryonic stem cells into cardiovascular precursor cells	15 May 2013
5 (79)	Dr. Alexander Kleger Universitätsklinikum Ulm	Study of the pancreatic differentiation of human ES cells and analysis of the influence of disease-associated mutations on the development and functionality of pancreatic cells	15 May 2013
6 (80)	Prof. Dr. Agapios Sachinidis Institut für Neurophysiologie der Universität Köln	Development of a cell-based test system for detecting cardiac toxicity on the basis of cardiomyocytes derived from human embryonic stem cells.	18 June 2013
7 (81 und 82)	PD Dr. Beate Winner Universitätsklinikum Erlangen und PD Dr. Angelika Lampert Friedrich-Alexander-Universität Erlangen-Nürnberg	Establishing human neural cell models on the basis of pluripotent stem cells	11 July 2013
8 (83)	Prof. Dr. Katja Schenke-Layland Universitätsklinikum Tübingen	Study of the cardioinductive effect of the extracellular matrix on the differentiation of human embryonic stem cells	10 July 2013
9 (84)	Dr. David Vilchez	Study of the regulation of proteostasis in human embryonic stem cells in order to understand the	16 Sept. 2013

	Universität Köln	molecular principles of cellular ageing	
10 (85)	Max-Delbrück-Centrum (MDC) für Molekulare Medizin, Berlin	Study of differential splicing in the cardiac differentiation of human embryonic stem cells	16 Sept. 2013
11 (86)	Dr. Konstantinos Anastassiadis Biotechnologisches Zentrum (BIOTEC), Technische Universität Dresden	Genetic modification of human pluripotent stem cells for efficient differentiation into mesenchymal stromal cells	11 Nov. 2013
12 (87)	Dr. Sophie Pautot DFG Forschungszentrum für Regenerative Therapien Dresden (CRTD), Technische Universität Dresden	Establishing neural three-dimensional networks from human pluripotent stem cells	11 Nov. 2013
13 (88)	Dr. Andreas Kurtz Berlin-Brandenburg Centrum für Regenerative Therapien (BCRT), Charité Berlin	Induction and maintenance of the naive condition in pluripotent human stem cells and differentiation of human pluripotent stem cells into kidney cells	11 Nov. 2013

Table 2: Overview of research projects that were approved by the RKI during the 2013 reporting period following a final positive assessment by the ZES. The numbers in brackets in the left-hand column correspond to the approval numbers in the RKI register (http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html)

The first research project assessed in the 2013 reporting period (75th approval under the Stem Cell Act) aims to help determine the molecular mechanisms leading to the emergence of certain diseases of the haematopoietic system. The work deals in particular with establishing cell models for myeloproliferative neoplasms (MPN) based on human induced pluripotent stem cells (hiPS cells) from patients affected by MPN. Using hES cells as reference material, the first step will be to investigate the properties of these iPS cells. Should it prove impossible to obtain hiPS cells with genetic changes that are known to be associated with MPN from patients, these mutations are to be specifically introduced into hiPS cells from healthy test subjects and into hES cells. In parallel, protocols for an efficient haematopoietic differentiation of pluripotent human stem cells are to be developed and optimized using hES cells; these are then to be transferred to hiPS cells of healthy test subjects and MPN patients. Haematopoietically differentiated MPN hiPS cells are then to be characterized in terms of their molecular properties and compared with haematopoietically differentiated hES cells and hiPS cells from healthy test subjects. The work aims to create the basis for the development of in-vitro test systems which can be used to identify new active substances for treating MPN diseases using high-throughput procedures.

The aim of the second project (76th approval) is the reproducible in-vitro production of, if possible, mature and functional ß cells for the development of knowledge for a future cell-replacement therapy and research into the causes of diabetes mellitus. To this end, initially hES cells are to be genetically modified in such a way that endodermal differentiation can be tracked via the activity of corresponding reporter genes. Using the modified hES cells, libraries of low-molecular substances are then to be searched for molecules that can trigger or intensify the endodermal differentiation of human ES cells. Proliferation-competent subpopulations of endodermal precursor cells are to be differentiated into pancreatic and endocrine precursor cells and into insulin-producing ß-like cells, and their molecular and functional properties comprehensively characterized. The knowledge gained is then to be transferred to hiPS cells from healthy test subjects and to hiPS cells from patients with monogenetic forms of diabetes.

The third project (77th approval) focuses on the production of patient-specific iPS cells using a wide range of reprogramming strategies, in order to identify efficient and safe methods for a later application in gene correction and gene therapy. This includes the comparative characterization of hiPS cells from patients with genetic diseases and hES cells. The planned analyses relate both to the properties of the pluripotent cells in their undifferentiated state and to the characterization of cell types derived from them, in particular neurons, keratinocytes, melanocytes, hepatocytes, cardiomyocytes and various cell types of the blood and immune system. In addition, hES cells are to be genetically modified in such a way that they show genetic defects that cause certain monogenetic disorders. The subsequent aim is to check whether the properties of hiPS cells obtained from patients with the corresponding disease differ from the genetically modified hES cells.

The fourth research project (78th approval) aims to help expand knowledge of the processes that take place in the differentiation of hES cells to mesodermal precursor cells and further to precursors of cardiac cells. The intention is to differentiate hES cells along the mesodermal line into cardiovascular cells and to identify signalling cascades that participate in this. Subsequently, the cardiac precursor cells are to be differentiated in vitro and in vivo into the heart's three main cell types (cardiomyocytes, smooth muscle cells and endothelial cells) and studied in mice to determine their therapeutic potential in a heart-attack model.

The fifth research project (79th approval) deals with studies on the differentiation of hES cells into pancreatic precursor cells with the aim of providing as-pure-as-possible populations of pancreatic cells with the help of new differentiation protocols. The aim in this context is to study molecular processes during pancreatic differentiation and to identify and characterize signalling pathways, molecules and transcription factors with relevance to endodermal and pancreatic differentiation. An additional aim is to establish cell models for diseases of the pancreas, such as certain types of diabetes mellitus. Finally, mutations associated with genetic diseases of the pancreas are to be generated in hES cells. One of the aims of the study of the endodermal and pancreatic differentiation of the modified hES cells and analyses of the pancreatic cells obtained from them (also compared to pancreatic cells derived from disease-specific hiPS cells) is to help clarify the genetic causes of human diseases of the pancreas.

The aim of the sixth project applied for (80th approval) is to establish and validate an in-vitro system based on human cells for testing potential cardiotoxicity. To this purpose, hES cells are first to be differentiated into cardiomyocytes; then the cardiac cells are to be treated with reference substances with known cardiac effects and with substances that inhibit mitochondrial ATP synthesis. The aim is to determine possible biomarkers for substance-induced cardiotoxicity by analysing the changes caused by the respective substances in the electrophysiological properties, in the gene expression pattern, in the epigenome of the cells, and in the signal and metabolic pathways. The development of the test system and the studies are to be carried out comparatively between hES cells and hiPS cells.

The seventh research project (81st and 82nd approvals) is concerned with clarifying the cellular and molecular principles of pain disorders, such as genetic pain syndrome and polyneuropathies. Different differentiation strategies are to be used to initially establish efficient procedures for differentiating hES cells into neural crest cells. These cells are then to be differentiated into peripheral neurons, in particular sensory neurons, the emphasis lying on the generation of pain receptors. After characterization of their biochemical, molecular and functional properties, the generated neural cells are to be examined for the presence of certain sodium channels, which can play a role in hereditary neuropathies. It is also planned to mutate genes in hES cells whose products are involved in the development of hereditary pain syndromes, in order to be able to determine a possible influence of genetic modification on the differentiation of the cells into sensory neurons. The aim is to provide cell models of neuropathic pain disorders. Furthermore, hES cells and hiPS cells obtained both from

patients with hereditary pain syndromes and from healthy test subjects are to be differentiated in parallel into different sensory neurons and their properties studied and compared.

The focus of the eighth project (83rd approval) is on studying the influence of components of the extracellular matrix (ECM) on early cardiac differentiation. hES cells are first to be differentiated to embryoid bodies (EBs), a high proportion of which have spontaneously contracting cardiac cells, and to cardiovascular precursor cells, in order to obtain the ECM at different times during differentiation and to study its composition. Identified ECM components are to be examined in an hES-cell-based in-vitro model to determine their relevance to early cardiac differentiation. In addition, receptors and signalling pathways are to be studied that are connected with the identified ECM components and possibly relevant for cardiac differentiation. Subsequently, the ECM obtained from hES cells during cardiac differentiation and an artificial ECM containing the previously identified components of the early cardiac ECM are to be studied and compared to determine their ability to support and improve the cardiac differentiation of hES cells.

The aim of the ninth research project (84th approval) is to improve the understanding of the molecular processes that help maintain the dynamic balance of the proteome (proteostasis) of hES cells. This is expected to provide knowledge on the molecular principles of how the lifespan of cells and cellular senescence are regulated. Proceeding on the basis of data showing that hES cells have a much higher proteasome activity than cells differentiated from them and somatic cells, further factors and signalling pathways are to be identified that are responsible for the increased proteasome activity in hES cells and are involved in the regulation of proteostasis. The importance of the proteins identified in this process for maintaining the pluripotency of hES cells is to be determined by modulating the expression of the corresponding genes. An additional aim is to analyse the role of these genes in reprogramming somatic cells to human induced pluripotent stem cells, and in transdifferentiation into neural cells.

The tenth research project (85th approval) aims to study the molecular principles of the regulation of the differential splicing of cardiac transcripts. Another aim is to help clarify the molecular causes of cardiac diseases that lead to modified isoforms of cardiac proteins as a result of splicing defects. To this purpose, genes for cardiac splicing factors are to be introduced into hES cells, and hES cells are differentiated into cardiac cells or to so-called engineered heart tissue (EHT). The next step will be to analyse the interactions between splicing factors and their substrates, identify the substrate specificity of splicing factors, and determine what role they play in the splicing of specific isoforms of cardiac transcripts. Another aim is to identify further molecules and signalling pathways that are essential in particular for a differential splicing during the development of human cardiac cells under the 3D conditions of EHT. The work will be carried out partly in comparison with murine ES cells, partly in comparison with hiPS cells.

The purpose of the eleventh research project (86th approval) is to develop and optimize methods for the targeted genetic modification of human pluripotent stem cells in order to strengthen differentiation into mesenchymal cell types and provide suitable original cells for differentiation into mesenchymal stromal cells. The project is embedded in the EU project entitled 'Pluripotent Stem Cell Resources for Mesodermal Medicine' (PluriMes), whose aims include the detailed characterization of mesodermal precursor cells derived from human pluripotent stem cells and the provision of reproducible, genetically stable and well-characterized mesenchymal stromal cells that can be obtained in sufficient quantities for cell therapies.

The objective of the twelfth research project (87th approval) is to establish a three-dimensional in-vitro cultivation system for creating a network of different interacting neural

cells from neural precursor cells generated from pluripotent, embryonic stem cells. This 3D network is meant to serve as a long-term reference model for comparisons with 3D networks constructed from human iPS cells and patient-specific iPS cells and, in the medium term, for studying the pathogenetic mechanisms of neurodegenerative diseases.

The thirteenth research project (88th approval) aims to use the imported hES cells for two sub-projects. The intention of the first sub-project is to develop culture conditions under which it is possible to establish and maintain a 'naive' pluripotency status in human ES cells. By systematically studying factors that are supposed to increase reprogramming efficiency in human somatic cells or improve the maintenance of the naive pluripotency phenotype in murine ES cells – as well as by modelling intracellular signalling pathways by means of bioinformatics – the aim is to identify the factors that can contribute to the establishment and maintenance of the naive pluripotency status in human cells. The second sub-project deals with the differentiation of pluripotent human cells into different kidney precursor cells and endothelial cells which are to be developed into terminally differentiated kidney-cell types. This sub-project can provide new findings on molecular processes in kidney development and, in the long term, also be of importance for therapeutic approaches in regenerative medicine. The work will also make use of 'naive' hES cells and involve comparisons with hiPS cells.

Further information on the content of the research projects is available from the RKI's register (http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html). In each case, the essential arguments made by the ZES justifying the high-ranking status of the research projects, their sufficient preliminary clarification and the necessity to use human ES cells were also included in the RKI's assessment of the research projects.

Of the 13 applications discussed during the reporting period, eight were submitted by research groups that had not yet received an approval under the Stem Cell Act. Five applications were made by groups/institutions that had already been given an approval in the past. All the applications were approved by the RKI after examination by the ZES. During its eleven years of activities the ZES has deliberated on a total of 90 applications for import and/or use of hES cells. This means that 91 opinions have been submitted to the RKI to date. The RKI has followed the ZES's recommendation in all cases up to now. Figure 1 shows the number of opinions compiled by the ZES on applications under the Stem Cell Act each year. It shows that significantly more applications than before have been submitted to the RKI and endorsed by the ZES since the amendment of the Stem Cell Act in 2008 and the extension of the cut-off date for the isolation of hES cells in the country of origin from 2002 to 1 May 2007.

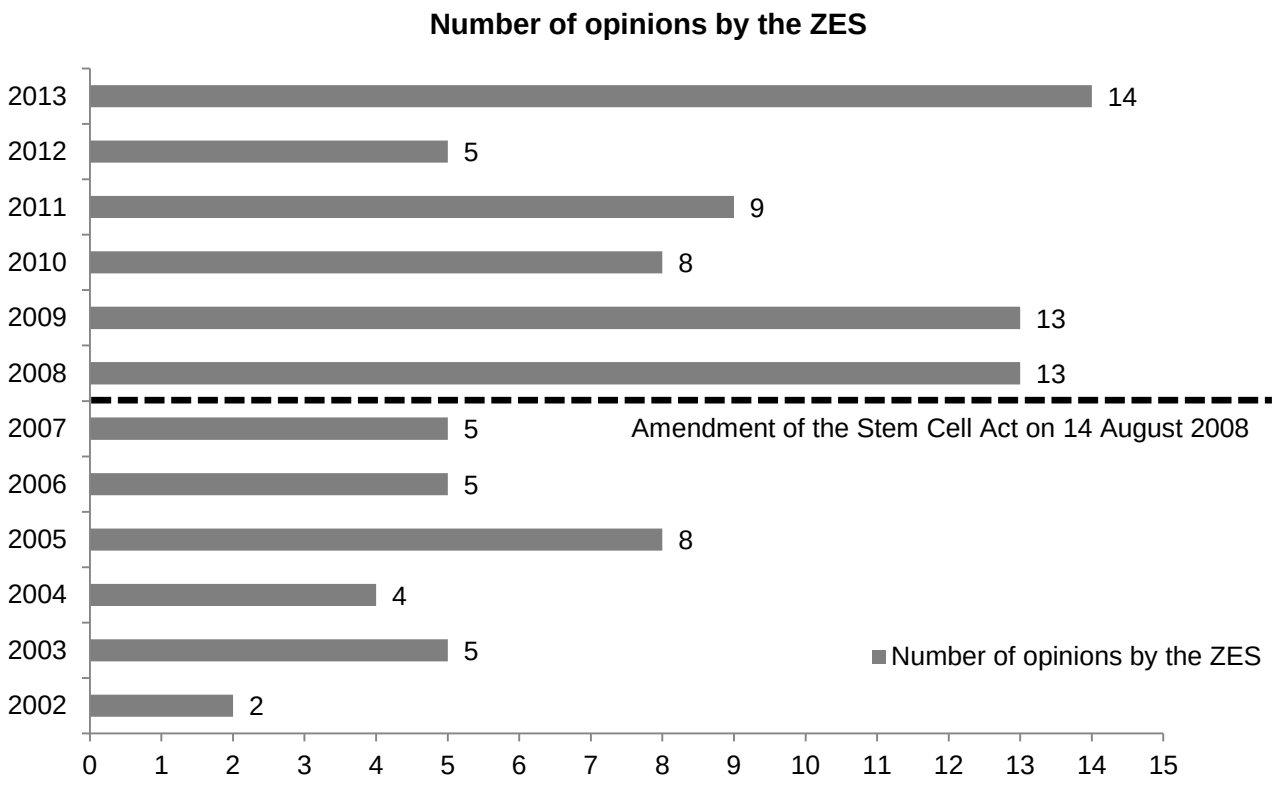

Figure 1: Number of opinions compiled by the ZES and submitted to the RKI in the years 2002 to 2013

At present, 68 groups at 45 research institutions may conduct approved research work with hES cells. According to information available to the ZES, results originating from the approved research projects of 23 research groups have been the subject matter of 102 original scientific publications in which holders of approvals under the Stem Cell Act are mentioned as responsible authors. Figure 2 shows the development of publications by German researchers on their research with hES cells during the term of the Stem Cell Act. Many more original publications have resulted from cooperation projects at the international level in which holders of approvals under the Stem Cell Act were involved.

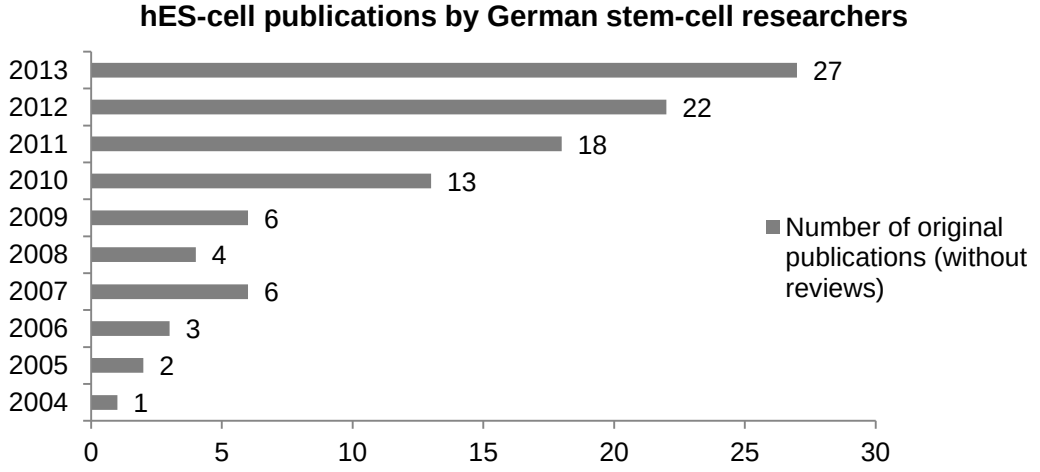

Figure 2: Publications by German stem-cell researchers using hES cells, only taking into account publications where the author responsible for the study works in Germany

3. Developments and trends in stem-cell research

1. In the period under review, some of the research projects applied for aimed to improve the differentiation of hES cells into cell types such as neural, cardiac, haematopoietic, pancreatic or renal cells and their subtypes. These projects are intended in particular to help clarify molecular processes that take place in these cell types during differentiation. The findings can also form the basis for new cell models that are relevant to examining the effectiveness or toxicity of drugs, or to studying the causes of pathological processes at the cellular level. In the long term, the work on hES cells can also yield principles for developing cell-replacement therapies in humans.

Parallel to hES cells, the majority of the projects also use human reprogrammed somatic cells (hiPS), which are studied and compared with hES cells. In this context, several projects use not only hiPS cells derived from healthy test subjects, but also hiPS cells from patients with various diseases, in order to determine changes in the molecular properties of the hiPS cells and cells differentiated from them. The objective here is to gain new insights into the molecular causes of the respective diseases. As in the previous years, there is still a great deal of interest in clarifying the pathogenesis mechanisms of genetically caused diseases at the cellular level. To this purpose, disease-specific human iPS cells are generally used, which are then compared with hES cells or with hiPS cells from healthy test subjects. However, the targeted mutation of genes that cause certain monogenetic disorders in hES cells is increasingly being regarded as an option for the production of disease-specific hES cells. This work is based on the availability of significantly improved methods for genetically modifying human pluripotent stem cells. The analysis of the effects that occur during the differentiation of the modified hES cells makes it possible to draw conclusions on the stage at which the mutations associated with disorders become phenotypically active and perhaps cause aberrations. Furthermore, the comparison with patient-specific hiPS cells can make it possible to detect differences in the various disease-specific cell models that are based on hES and hiPS cells. Moreover, genetic defects in cells can be corrected using various gene-transfer techniques and the 'repaired' cells compared (e.g. with regard to their differentiation behaviour) with genetically unchanged hES or hiPS cells that have the same genomic background as the 'repaired' cells.

2. Since the first publications in 2006 and 2007 describing the reprogramming of somatic cells into the embryonic state, international activities in the field of stem-cell research, studies on hiPS cells, and the comparison of their properties with hES cells have increased continuously. The fact that research on pluripotent stem cells comprises comparative studies of both hiPS cells and hES cells can also be seen in Germany by looking at the research projects that have been approved since 2007 (see Figure 3). In approx. two-thirds of the research projects approved under the Stem Cell Act since 2007, hiPS cells and hES cells are studied in parallel. In some of the studies, hES cells are needed as reference material for the study of hiPS cells. This is because, despite extensive international research activities, it is currently not sufficiently clear to what extent hiPS cells and hES cells are comparable in terms of their properties – for example their epigenetic characteristics or their ability to differentiate into certain cell types. This is also due to the great variability of the various hiPS cell lines, which can be related, inter alia, to the reprogramming method chosen in each case, to the cell type used as the starting material for the reprogramming, and to the age and properties of the cell donor. The epigenetic memory of hiPS cells also has an influence on the properties of the cells. However, hES cells are used not only for the purpose of comparison, but continue to represent an object of research in their own right. This relates to questions of basic research (e.g. into the principles of cellular pluripotency or developmental issues) as well as to projects relating to methodological questions, e.g. the development of differentiation protocols or possibilities of the genetic modification of human pluripotent stem cells.

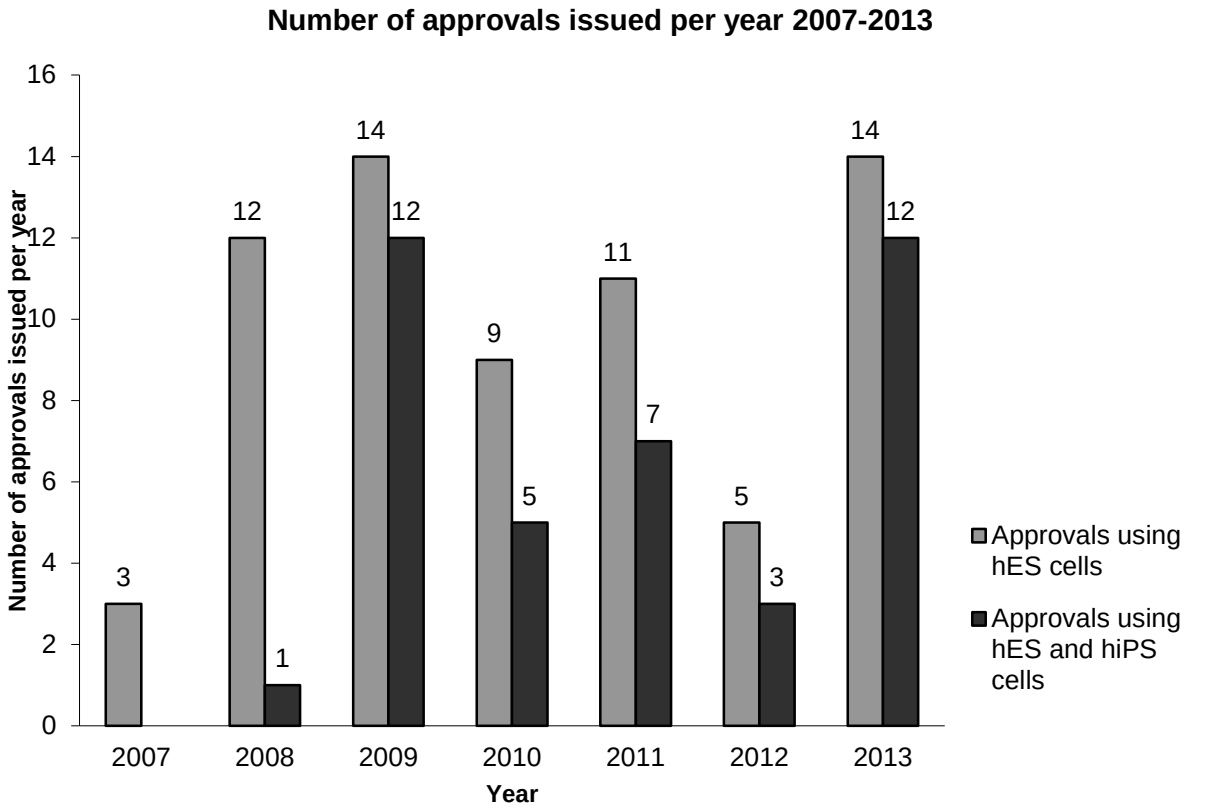

Figure 3: Overview of approved research projects 2007-2013 using either only hES cells (grey) or hES and hiPS cells together (black) (status: December 2013)

3. Studies published in recent years demonstrate that different stages of pluripotency also exist for human ES cells. Two states have been described: 'naive' (more original) and 'primed' (already further developed). hES cells are usually in a 'primed' state under established culture conditions. It was recently shown that 'naive' ES cells can be isolated from human blastocysts and propagated in culture, and that existing ('primed') hES cells can be transferred into a quasi-'naive' status (Gafni et al., Nature 2013). As early as 2010, furthermore, hES cells were successfully obtained under reduced oxygen pressure, which corresponds to the physiological conditions of the blastocysts (Lengner et al., Cell 141, 872; 2010). To some extent, properties of 'naive' hES cells also developed in these cells. The properties of 'naive' hES cells are currently being intensively studied. Because of the cut-off date regulation, new, 'naive' hES cells derived under optimized conditions cannot be imported into Germany and used here in research projects.

4. One trend in international stem-cell research is the use of hES cells, or hES-derived cells, to test new active substances for embryotoxicity. With differentiating hES cells it is scientifically possible for the first time to analyse early embryological development processes in human cells under the influence of teratogenic, embryotoxic substances and/or environmental chemicals. Furthermore, cells differentiated from hES cells can also be developed as test systems for determining potential cardiac, neural or liver-specific effects of substances. Although in-vitro models based on human ES cells are still under development, the test systems published to date are extremely promising.

Due to their ability to develop, human ES cells offer unique possibilities for analysing the effects of substances and their mechanisms of action, and thus to detect potential side effects of medicinal products at a very early stage. With the medical findings obtained in this way, health dangers and risks to the patients and test subjects are more likely to be recognized earlier, and thus more effectively avoided. To this extent, the safety of subjects in

clinical studies in the field of drug development could be improved by in-vitro studies of human cells derived from hES cells in the context of preventive health protection.

The further development of these toxicity test systems can help largely to overcome the lack of suitable human cells and tissues for toxicity assessments. Moreover, such research could also contribute towards reducing the number of animal experiments.

5. The German Stem Cell Network (GSCN) was set up on 7 May 2013 with the aim of pooling German activities and initiatives in stem-cell research, networking better with international researchers, building strategic specialist groups, and acting as a contact centre for politicians. The GSCN's first conference was held from 11 to 13 November 2013 in Berlin.

The eleventh report was unanimously approved at the 74th ordinary meeting of the ZES on 20 January 2014.