Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

Tenth Report after the enactment of the Stem Cell Act (StZG) for the reporting period 1 January to 31 December 2012

1. The Central Ethics Committee for Stem Cell Research

The members of the Central Ethics Committee for Stem Cell Research (ZES) were appointed for the first time when the Stem Cell Act (StZG) came into force in 2002. The Committee's remit is the review and assessment of applications to import and use human embryonic stem cells (hES cells). It issues an opinion on every application and sends it to the Robert Koch Institute (RKI), the competent authority under the Stem Cell Act. The Committee's activities are governed by the "Act ensuring the protection of embryos in conjunction with the import and use of human embryonic stem cells" (Stem Cell Act – StZG) of 28 June 2002 (BGBl. I page 2277, http://www.gesetze-im-internet.de/stzg/index.html), as amended by the Act amending the Stem Cell Act of 14 August 2008 (BGBl. I page 1708, http://www.bgbl.de/Xaver/start.xav?startbk=Bundesanzeiger_BGBl&bk=Bundesanzeiger_BGBl&start=//*[@attr_id=%27bgbl108s1708.pdf%27]), by the Regulation concerning the Central Ethics Committee for Stem Cell Research, and by the competent authority pursuant to the Stem Cell Act (the ZES Regulation – ZESV) of 18 July 2002 (BGBl. I page 2663, http://bundesrecht.juris.de/zesv/index.html).

The Committee, which performs its duties on a voluntary basis, has a total of 18 members and deputy members and is interdisciplinary in terms of its composition. In accordance with section 8 of StZG, five members represent the fields of biology and medicine and four members the fields of philosophical, medical and theological ethics; one deputy member is appointed for each member (see Table 1). In accordance with the ZES Regulation, the deputy members of the Committee, too, participate regularly in the deliberations on the applications.

The Committee's task (according to section 9 of StZG) is to determine, on the basis of the applicant's documents, whether a research project intending to use hES cells, for which an application has been submitted, meets the criteria of section 5 of StZG and is ethically acceptable within this meaning. Within the framework of the application it must be proven in a scientifically substantiated manner: a) that the project pursues research objectives of superior interest for an increase in scientific knowledge (section 5, no. 1 of StZG), b) that the scientific issues have already been subject to preliminary clarification in other systems, for example in animal models (section 5, no. 2a of StZG), and c) that the targeted increase in scientific knowledge requires the use of hES cells (section 5, no. 2b of StZG). The results of the review of the applications are summed up by the ZES in a written opinion, which is sent to the RKI.

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

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

The ZES held five meetings in 2012; a ZES working group held an additional meeting in September to discuss the programme for the anniversary event. At the meetings a total of five applications for the import and use of human ES cells and two applications for extensions of already approved research projects were discussed. All the applications discussed were reviewed positively by the ZES. They meet the prerequisites of section 5 of StZG and are ethically acceptable within its intendment (section 9 of StZG). A summary overview of the applications under the Stem Cell Act approved by RKI during the reporting period, in respect of which the ZES issued positive opinions, is given in Table 2.

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 2012

No.	Applicant	Research topic	Date of positive the ZES opinion
1 (70)	Prof. Dr. Axel Methner Universitätsklinikum Düsseldorf	Establishing a cell model to study the role of GDAP1 in the pathogenesis of Charcot-Marie-Tooth polyneuropathy type 4a	18.01.2012
2 (71)	Prof. Dr. Suzanne Kadereit Universität Konstanz	Study of the influence of ionizing radiation on human embryonic stem cells and their differentiation	19.04.2012
3 (72)	Dr. Claudia Claus Universität Leipzig	Study of the effects of infection with the rubella virus on mitochondrial function and the differentiation capacity of human embryonic stem cells	14.06.2012
4 (73)	Dr. Alessandro Prigione Max-Planck-Institut für molekulare Genetik, Berlin	Study of the mitochondrial metabolic reprogramming of human cells and establishing hiPS-cell-based models for mitochondrial diseases	11.07.2012
5 (74)	Medizinische Hochschule Hannover	Comparative study of glycosylation during the neuroectodermal differentiation of human pluripotent stem cells	15.10.2012
Extensions of already approved applications			
6 Extension of approval (46)	Dr. Insa Schroeder Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg	Pancreatic differentiation of human embryonic stem cells and induced pluripotent stem cells for the purpose of studying the pathogenesis mechanisms of diabetes mellitus	07.09.2012
7 Extension of approval (48)	Max-Delbrück-Centrum für Molekulare Medizin (MDC), Berlin	Targeted differentiation of human embryonic stem cells into somatosensory neurons for pain sensation	07.09.2012
8 Extension of approval (16)	Prof. Dr. Sigurd Lenzen Institut für Klinische Biochemie der Medizinischen Hochschule Hannover	Generation of reporter-cell lines for the purification of pancreatic precursor cells from differentiated human embryonic stem cell cultures	15.10.2012

Table 2: Overview of research projects that were approved by RKI during the 2012 reporting period following a final positive assessment by the ZES. The numbers in brackets in the left 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 reviewed during the reporting period (70th approval under the Stem Cell Act) involves the study of the gene for the mitochondrial transmembrane protein GDAP1 (ganglioside-induced differentiation associated protein 1) and its activities in motor neurons isolated from human ES cells. The project aims to supply information on the extent to which GDAP1 exerts an influence on the glutathione metabolism and mitochondrial activity of cells and thus contributes to providing resistance to oxidative stress in human motor neurons. Another aim is to examine whether, and to what extent, mutations in the GDAP1 gene play a causative role in the pathogenesis of hereditary Charcot-Marie-Tooth polyneuropathy type 4a (CMT4A). The research work is to be conducted on hES cells and induced pluripotent stem cells (hiPS cells), and the differentiation potential of hES cells and hiPS cells in motor neurons is to be compared. Furthermore, a comparison is also to be made between the properties of motor neurons differentiated either from the hiPS cells of patients with natural mutations of the GDAP1 gene, or from hES cells in which the mutation in the GDAP1 gene has been artificially induced. The project aims to help establish a cell-based disease model for CMT4A.

The studies on the effect of different types of ionizing radiation on hES cells and their differentiation, planned in the second project (71st approval), aim to improve our understanding of the cytotoxic and genotoxic influence of ionizing radiation during early human embryonic development. The work is to be carried out in cooperation with the GSI Helmholtz Centre for Heavy Ion Research, Darmstadt, Germany, which already received an approval under the Stem Cell Act in June 2011 (65th approval). The project applied for is identical to the GSI project.

The third project (72nd approval) aims to establish a cell model for studying the effects of an infection with the rubella virus (RV) on the early human embryo at the molecular and cellular level. An RV infection in early pregnancy is associated with a greatly increased risk of malformations in the child. In the project reviewed here, the initial aim is to determine the immediate consequences of an RV infection of hES cells, for example with regard to the vitality of the cells, their division rates, the expression of marker genes for pluripotency, and their rates of apoptosis or necrosis. Furthermore, the effects of RV infection on mitochondrial functions are to be studied. The final aim is to determine the consequences of an RV infection on the differentiation capacity of hES cells in order to draw conclusions on effects of an RV infection on the early steps of differentiation into the three germ layers.

In the fourth research project (73rd approval), hES cells are to be used as reference material for studying the extent to which the mitochondria of reprogrammed human cells are similar to those of hES cells. In particular, the aim is to determine the influence of the reprogramming of somatic cells to hiPS cells on the functions and properties of the mitochondria, and to examine whether the low level of maturity of the mitochondria, which is typical of hES cells, can be fully achieved in hiPS cells. To study the possible influence of mitochondrial reprogramming on the differentiation of pluripotent cells, hES cells and hiPS cells are to be differentiated into cell types that have a high energy-turnover rate, e.g. post-mitotic neurons and cardiomyocytes. A further aim is to generate hiPS cells from cells of patients suffering from diseases caused by mutations in the mitochondrial DNA, and to compare them with hES cells. The aim here is to develop cell models for diseases that are based on functional mitochondrial gene defects.

Comparative studies of the glycosylation patterns of hES and hiPS cells during neuroectodermal differentiation are the subject of the fifth project (74th approval). A particular objective is to investigate the role of the sugar molecule polysialic acid (PolySia) in neural precursor cells expressing the gene for neuron-glial antigen 2 (NG2). Another aim is to study the hereditary disorder CDG-Ia (congenital disorder of glycosylation Ia), which is caused by a mutation in the gene for phosphomannomutase II (PMM2), using a cellular disease model based on hiPS cells. The idea is to compare disease-specific hiPS cells at the levels of the transcriptome, proteome and glycome with hES cells and with hiPS cells from healthy individuals before and during neuroectodermal differentiation.

During the reporting period, permission to conduct three further research projects using hES cells was applied for involving research activities which required an extension of approvals already issued by the RKI and a further discussion by the ZES.

6th project:
The research project approved up to now (46th approval) studies the pathogenesis mechanisms of diabetes mellitus and the development and examination of anti-diabetic drugs. This requires functioning pancreatic cells. The aim of the work is to help optimize protocols for the *in-vitro* differentiation of hES cells into mature pancreatic beta cells. One plan is to differentiate endothelial, exocrine or ductal cells from hES cells in order to isolate a sufficient quantity of the corresponding cell types of reproducible quality and the required specificity. These would then be used in co-culture with hES cells that are differentiating into beta cells. Another aim is to examine the influence of specific micro-RNAs (miRNAs) on the differentiation of hES cells into pancreatic beta cells. The studies are to be conducted in a comparative way on hES and hiPS cells.

7th project:
The research project approved in November 2009 (48th approval) intends to pave the way for studies of signalling pathways that are important for pain perception and pain processing. It deals with the development and optimization of protocols for isolating somatosensory neurons from hES cells. In the meantime, neural crest cells have been isolated *in-vitro* from hES cells in the approved project. The objective now is to examine their potential to also differentiate into other sensory neurons, e.g. thermo- and chemosensitive neurons, after being transplanted into chicken embryos. This *in-vivo* niche was chosen because there are no *in-vitro* protocols for such differentiations. Once the proof-of-concept has been established, other, already approved *in-vitro* studies on the development of somatosensory neurons are to follow. The studies will compare hES and hiPS cells.

8th project:
The development and testing of selection processes for the enrichment and purification of pancreatic cells is planned as part of the work on the differentiation of human ES cells into insulin-producing pancreatic beta cells (16th approval). hES cells are therefore to be provided with expression cassettes for reporter genes in which the expression of the reporter gene is under the control of promoters that are active in cells in pancreatic differentiation. After the hES reporter cell lines have differentiated into pancreatic precursor-cell populations, attempts are to be made to use flow-cytometric methods and cell sorting to enrich – and subsequently comprehensively characterize – specific endodermal, pancreatic and endocrine precursor-cell populations. The cells are then also to be transplanted into immunodeficient diabetic mice to assess their functionality and degree of maturity.

Further information on the content of the research projects is available from RKI's register (http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html).
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 five applications discussed during the reporting period, three were submitted by research groups that had not yet received an approval under the Stem Cell Act. Two applications were made by groups that had already been given a corresponding approval in the past. All the applications were approved by the RKI after examination by the ZES. The ZES has deliberated on a total of *77 applications* for import and/or use of hES cells during its ten years of activity. In addition, *eight applications for extensions* of already approved projects were examined. This means that *85 opinions* have been submitted to RKI to date. RKI has followed the Committee's recommendation in all cases up to now.

At present 56 groups at 41 research institutions may conduct approved research work with hES cells in Germany. According to knowledge available to the ZES, results originating from the approved research projects of 21 research groups have been the subject matter of 83 scientific original publications in which holders of approvals under the Stem Cell Act are mentioned as authors in charge. Further original publications have resulted from cooperation projects at the international level in which holders of approvals under the Stem Cell Act were involved.

3. Event to mark the 10th anniversary of the ZES

The Stem Cell Act had been in force for ten years by the summer of 2012. By this time the ZES had also been working for ten years. Its task is to examine and assess applications to conduct research projects under this Act, before a decision on the application can be made by the competent authority, the RKI. A symposium was held on 6 September 2012 at the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW) to mark the 10th anniversary of the existence of the ZES. Invited participants included representatives of the *Bundestag's* parliamentary groups and committees, the responsible government ministries, the regional ethics committees of the *Länder* (federal states), the National Ethics Council and the scientific organizations, as well as scientists currently engaged in research projects with hES cells under the Stem Cell Act. The aim of the event, entitled "10 Years of Research on Human Embryonic Stem Cells in Germany", was to offer an opportunity to relate the research situation in Germany to new international developments in stem cell research.

In his introduction, the Chairman of the ZES gave a summary of the controversial public debates at the time when the Stem Cell Act was being formulated and during the run-up to the Act's amendment in 2008. He then gave the floor to two German stem cell researchers, who gave an insight into recent research using human pluripotent stem cells and their potential applications, especially in drug development. They also presented results from their approved research with hES cells and emphasized the need to continue conducting research on hES cells in the future. Two subsequent lectures discussed constitutional aspects of the Stem Cell Act and explained the ethical aspects of the debate on hES cells (see programme in Table 3). The ensuing discussion addressed issues relating to research on hES cells that are still topical among the public today. The event was rounded off with speeches by Ms von Renesse and Mr Catenhusen, who had been instrumental in the creation of the Stem Cell Act and accompanied its beginnings.

Welcoming speeches
Prof. Dr. Günter Stock, President of Berlin-Brandenburg Academy of Sciences and Humanities (BBAW)
Prof. Dr. Reinhard Burger, President of the Robert Koch Institute
Lectures
Prof. Dr. Klaus Tanner, Universität Heidelberg, Theologische Fakultät, Chairperson of the Central Ethics Committee for Stem Cell Research (ZES) **Close restrictions on hES cell research – a history of conflict**
Prof. Dr. Oliver Brüstle, Universität Bonn, Institute of Reconstructive Neurobiology **Biomedical applications of pluripotent stem cells**
Prof. Dr. Thomas Eschenhagen, University Clinic, Hamburg-Eppendorf **Artificial cardiac tissue from human pluripotent stem cells for use in drug development**
Prof. Dr. Jochen Taupitz, Universität Mannheim, Faculty of Jurisprudence and Macroeconomics **Constitutional conflicts of objectives in the Stem Cell Act**
Prof. Dr. Ludwig Siep, Universität Münster, Department of Philosophy **Ethical justification of stem cell research in Germany**

Table 3: Programme of the event to mark the 10th anniversary of the ZES

All the symposium contributions can be found on the RKI website at: http://www.rki.de/DE/Content/Service/Veranstaltungen/ZES_Jubilaeum.html.
There are plans to publish an anthology of the contributions together with articles on the work of the ZES and how it has changed over the past ten years.

4. Technical and legal developments and trends in stem cell research

4.1.
Some of the new applications received during the reporting period dealt with the establishment of cell models for studying damaging environmental influences – in particular ionizing radiation or infection with the rubella virus – on early human cells. Here, hES cells are still regarded as the most suitable cell model because of their close proximity to the cells of the early human embryo. In addition, it can be seen that attention is concentrating increasingly on issues that serve the development of disease models on the basis of hiPS cells which have been generated from somatic cells from patients with genetic or metabolic defects. hES cells are needed as reference material for this work. The work aims to broaden our understanding of the pathogenic mechanisms of these diseases and to lay the foundations for the future development of new therapeutic strategies. In international research, too, an intense interest can be observed in patient-specific hiPS cells, usually from patients with rare genetic diseases, but also from patients with frequent occurring metabolic diseases. Furthermore, literature repeatedly describes new, disease-specific hES cell lines from embryos that have been examined in the course of pre-implantation genetic screening and are no longer being used for reproductive purposes due to the results, but have been made available for research. These hES cell lines (which number more than 220 in the meantime) could contribute in particular to explaining molecular pathogenesis mechanisms of genetic diseases and be compared with corresponding disease-specific hiPS cells. However, they may not be imported into Germany under the current legal situation and interpretation of the law.

4.2.
The 2008 amendment to the Stem Cell Act made it possible for researchers working in Germany to also import and use hES cells that had been established after 1 January 2002 and before 1 May 2007. Since then, applications to import and use such “new” cell lines has been made and approved, both in the context of newly applied-for research projects and to implement research projects already approved in the past. A study of the hES cell lines used in the approved research projects shows that the number of approved applications to import and use “new” cell lines has been rising since 2009. However, applications were also still being approved to import and use “old” hES cell lines, i.e. hES cells that were isolated before 1 January 2002, which could already be imported and used before the change in the cut-off date regulation under the Stem Cell Act. Only one research project intends to use exclusively “new” hES cell lines (see Figure 1). The continued use of “old” lines may have to do with their easy availability, the considerable experience gained in the cultivation of these lines, and their extensive characterization in numerous publications. It is also conceivable that they are also used as an internal reference when more “new” hES cell lines, or other pluripotent stem cells, are to be studied and characterized.

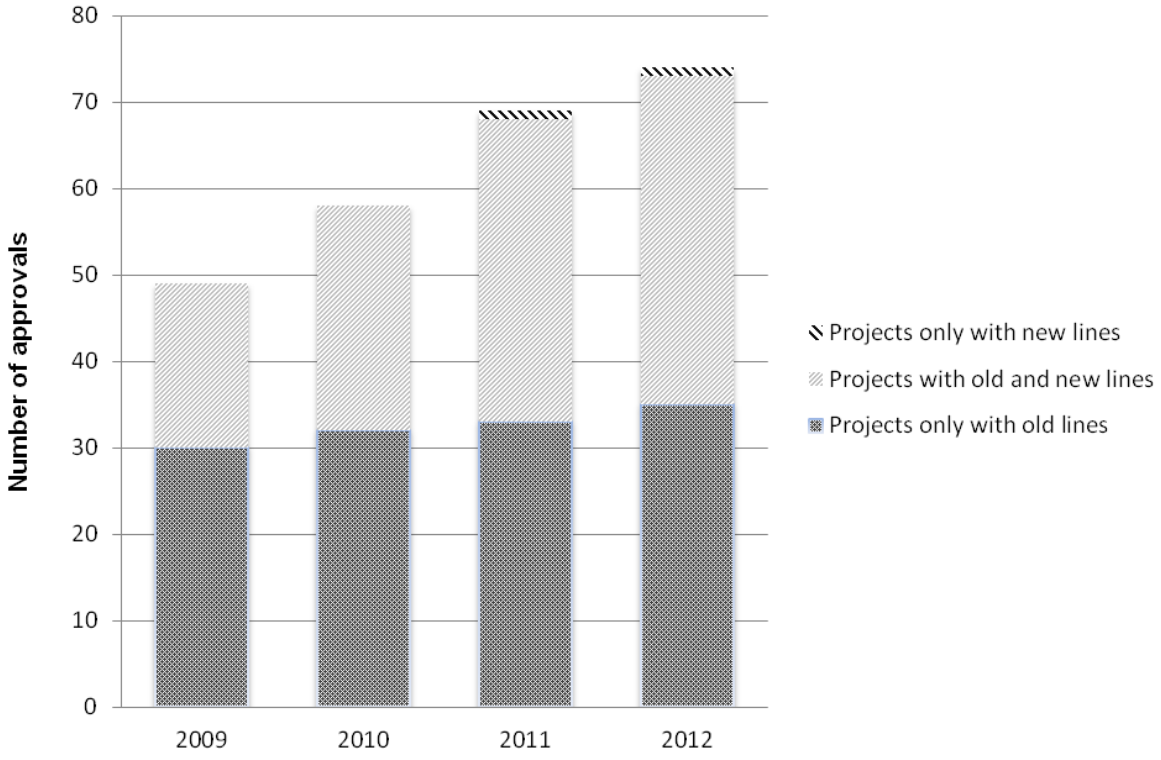

Figure 1: Overview of the number of projects approved between 2009 and 2012 for which hES cell lines were permitted which were generated before 1 January 2002 (old lines) or between 1 January 2002 and 1 May 2007 (new lines).

4.3.
One aim of research with hES cells is to contribute to the development of new therapeutic procedures. Growing international activities substantiate this. The first application of cells differentiated from hES cells in humans in a clinical trial was begun by the Geron Corporation in October 2010 after approval by the US Food and Drug Administration (FDA). This Phase I study examined the tolerability and safety of oligodendrocytes differentiated from hES cells for the treatment of subacute injuries of the spinal cord. Although Geron announced a year later that it was discontinuing this study, along with and other activities in the stem cell field, because it was focusing on other business, BioTime, an American company operating in the field of regenerative medicine, is currently considering whether to continue the study.

The American Advanced Cell Technology, Inc. (ACT), has been conducting further Phase I clinical trials since 2011 in the USA and the UK. After approvals by the FDA and the British regulatory authority, patients with age-related macular degeneration (AMD) and a hereditary juvenile form of macular degeneration (Stargardt's disease) have been treated with retinal pigment epithelial cells made from hES cells. Macular degeneration is a group of incurable eye disorders, and AMD is currently the most common cause of age-related blindness in the industrialized countries: 25 to 30 million people are affected worldwide. Initial results giving first indications of the safety of the procedure were presented in an interim report on these clinical studies published at the beginning of 2012 (Schwartz et al., Lancet 2012; 379: 713). A South Korean company, CHA Bio & Diostech, was also given permission in 2012 to test the cells developed by ACT in a Phase I trial in humans. In 2013, furthermore, Pfizer intends to implant membranes coated with retinal epithelial cells differentiated from hES cells into the eyes of patients with wet macular degeneration. Although the clinical use of hES cells is still at the trial stage and currently only relates to a very small area of possible clinical applications, a possible first therapeutic use of hES cells is now taking shape in this specific area.

Disease	**Cell type differentiated from hES cells (product name)**	**Responsible for the studies**	**Regulatory authority and ClinicalTrials.gov Identifier**	**Expected duration of study period**
Spinal cord injuries	Oligodendrocytes (GRNOPC1)	Geron Corporation, USA	Food and Drug Administration (FDA), USA. NCT01217008	Begin: 10/2010. Geron withdrew from the study in 11/2011.
Inherited juvenile form of macular degeneration (Stargardt's disease)	Retinal pigment epithelial cells (MA09-hRPE)	Advanced Cell Technology (ACT), USA	FDA. NCT01345006	04/2011 – 09/2013
Age-related macular degeneration (AMD)	Retinal pigment epithelial cells (MA09-hRPE)	ACT, USA	FDA. NCT01344993	04/2011 – 07/2013
Inherited juvenile form of macular degeneration (Stargardt's disease)	Retinal pigment epithelial cells (MA09-hRPE)	ACT, USA	MHRA, UK. NCT01469832	11/2011 – 04/2014
Inherited juvenile form of macular degeneration (Stargardt's disease)	Retinal pigment epithelial cells (MA09-hRPE)	CHA Bio & Diostech, Korea	Food and Drug Administration, Korea. NCT01625559	09/2012 – 10/2014
Age-related macular degeneration (AMD)	Retinal pigment epithelial cells (MA09-hRPE)	CHA Bio & Diostech, Korea	Food and Drug Administration, Korea. NCT01674829	09/2012 – 04/2016
"Wet" age-related macular degeneration (AMD)	Membrane-bound retinal pigment epithelial cells (PF-05206388)	Pfizer in collaboration with University College, London	MHRA, UK. NCT01691261	05/2013 – 10/2015

Table 4: Approved Phase I/II clinical trials with cells developed from hES cells.

4.4.
Another subject for discussion in the ZES were the many national and international reactions to the decision by the European Court of Justice (ECJ) on a patent application by Prof. Brüstle in 1997 for the production of human neural precursor cells from hES cells. The methods for differentiating embryonic stem cells into neural precursor cells described in the litigious patent are the subject of the first approval granted under the Stem Cell Act. According to the judgement of the ECJ, patentability is excluded, "… if they require the prior destruction of human embryos or their use as base material" (judgement dated 18 October 2011, C-34/10, Brüstle vs. Greenpeace). Although the ECJ has emphasized that the legal significance of its decision relates exclusively to patent law, this ruling has been cited by various parties to substantiate the view that research with human embryonic stem cells must not be funded under the research and innovation programme of the European Commission for the years 2014 to 2020 (Horizon 2020). The ECJ's interpretation of Article 6 of the European Directive 98/44/EC on the legal protection of biotechnological inventions in the Brüstle vs. Greenpeace case, which had been requested by the German Federal Supreme Court, was also the basis for the German Federal Supreme Court's decision dated 27 November 2012. According to this the patent is void if the precursor cells are derived from hES cells whose production required the prior destruction of embryos. Patent protection for the recovery of neural precursor cells can be granted for such procedures only if methods were used in the original preparation of the pluripotent cell lines that do not impair the viability of the embryo, or if the cells were produced from an early embryo that is no longer viable, or if neural precursor cells were developed from pluripotent stem cells that do not come from embryos. Further discussion is needed on how significant the German Federal Supreme Court's ruling might be for a possible use of hES cells in Germany in the development of routinely conducted diagnostic studies in the context of pharmacological or toxicological tests, and on whether – or to what extent – the development of therapeutic procedures will be affected.

4.5.
During the reporting period, the Nobel Prize for Physiology and Medicine was awarded not only to John Gurdon, but also to and Shinya Yamanaka. The Japanese researcher had succeeded in reverting somatic cells into the embryonic state using four factors, thus creating induced pluripotent stem cells. Research on hES cells was and is an essential prerequisite for the development and characterization of hiPS cells. hES cells are still needed as a reference for the induced pluripotency, epigenetic properties, or differentiation capacity, of hiPS cells, as well as for basic research.

The tenth report was unanimously approved at the 68th ordinary meeting of the ZES on 11 February 2013.