# Report

## of the

# Central Ethics Committee for Stem Cell Research (ZES)

**13th Report after the enactment of the Stem Cell Act (StZG)**

**for the reporting period**
**1 January to 31 December 2015**

## 1. The Central Ethics Committee for Stem Cell Research

The Central Ethics Committee for Stem Cell Research (ZES) was appointed for the first time when the Stem Cell Act (StZG) came into force in 2002. This independent and interdisciplinary expert body reviews and assesses applications for the import and use of human embryonic stem cells (hES cells) according to the regulations of the Stem Cell Act (StZG), issues an opinion on every application and sends it to the Robert Koch Institute (RKI), the competent authority under the StZG. 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), 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]), 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) of 18 July 2002 (BGBl. I page 2663, http://bundesrecht.juris.de/zesv/index.html).

The interdisciplinary Committee conducts its work on an honorary basis. It is made up of nine members and nine deputies; in accordance with section 8 of the Stem Cell Act (StZG), five members represent the disciplines of biology and medicine, and four members the fields of ethics and theology (see Table 1). In accordance with the ZESV, both the members and the deputy members take part regularly in the meetings and deliberations on the applications.

According to section 9 of the StZG, it is the Committee's task to review the ethical acceptability of the applications submitted to the RKI for the import and use of hES cells. On the basis 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. Section 5 of the StZG requires that an application must prove in a scientifically substantiated manner (a) that the project pursues research objectives of high-level interest for an increase in scientific knowledge (section 5, no. 1 of the StZG), (b) that the scientific issues have already been subject to a preliminary clarification in other systems, for example in animal-cell models (section 5 no. 2a of the StZG), and (c) that the targeted increase in scientific knowledge requires the use of hES cells (section 5 no. 2b of the StZG). The ZES summarizes the results of its review in a written opinion and sends it to the RKI.

The ZES prepares its reports annually (section 14 of the ZESV). They are published by the Federal Ministry of Health (BMG) and 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. Schröder<br>Max-Planck-Institut für Molekulare Biomedizin<br>Münster | Prof. Dr rer. nat. Martin Zenke<br>Institut für Biomedizinische Technologien<br>Abt. Zellbiologie<br>RWTH Aachen |
| | Prof. Dr rer. nat. Anna M. Wobus<br>**(Deputy Chairperson)**<br>Leibniz-Institut für Pflanzengenetik und Kulturpflanzenforschung (IPK)<br>Gatersleben | Prof. Dr rer. nat. Maria Wartenberg<br>Molekulare Kardiologie und Stammzellforschung<br>Universitätsklinikum Jena |
| **Medicine** | Prof. Dr med. Mathias Bähr<br>Neurologische Klinik<br>Georg-August-Universität Göttingen | Prof. Dr med. Wolfram H. Zimmermann<br>Institut für Pharmakologie<br>Georg-August-Universität Göttingen |
| | Prof. Dr med. Marion B. Kiechle<br>**(Deputy Chairperson)**<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. Ursula Just<br>Max-Planck-Institut für Herz- und Lungenforschung<br>Bad Nauheim |
| **Ethics** | Prof. Dr phil. Dr med. h.c. Jan P. Beckmann<br>Institut für Philosophie<br>FernUniversität Hagen | Prof. Dr phil. Ralf Stoecker<br>Professur für Praktische Philosophie<br>Universität Bielefeld |
| | Prof. Dr mult. Nikolaus Knoepffler<br>Lehrstuhl für Angewandte Ethik<br>Universität Jena | Prof. Dr phil Christine Hauskeller<br>Department of Sociology, Philosophy and Anthropology<br>University of Exeter<br>England |
| **Theology** | Prof. Dr theol. Klaus Tanner<br>**(Chairperson)**<br>Wissenschaftlich-Theologisches Seminar<br>Systematische Theologie/Ethik<br>Ruprecht-Karls-Universität Heidelberg | 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>Katholisch-theologische Fakultät<br>Ludwig-Maximilians-Universität München |

**Table 1.** Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES), status: December 2015

## 2. Deliberations on, and reviews of, applications pursuant to section 5 of the Stem Cell Act during the reporting period

In2015, the ZES held four meetings and discussed a total of seven applications for the import and use of human ES cells. The ZES had already assessed and voted on one application (99) in 2014. Since this application was not approved by the RKI until the beginning of 2015, it is included in this report; furthermore, an extension of the corresponding approval was applied for and discussed by the ZES in 2015. The ZES handed down positive opinions on all the applications. In addition, two applications for extensions of already approved research projects using hES cells were assessed and voted on using the written procedure.

Table 2 provides a summary overview of the applications that were assessed positively by the ZES and approved by the RKI during the reporting period. All the projects listed therein that were discussed by the ZES meet the preconditions of section 5 of the StZG and are ethically acceptable within its intendment (section 9 of the StZG).

| No. | Applicant | Research topic | Date of the positive ZES opinion |
|---|---|---|---|
| 1 (99) | Zentrum für Regenerative Therapien (CRTD), Technische Universität Dresden | Establishment of a cell model for identifying potential substances for treating diseases of the retina and for studying molecular processes in the phagocytosis of photoreceptor outer segments | 10/12/2014 |
| 2 (100) | Prof. Dr. Jürgen Rohwedel Universität Lübeck | Establishment of protocols for the kidney-cell differentiation of human pluripotent stem cells as a model for the characterization of the pathogenesis of polycystic kidney disease | 18/02/2015 |
| 3 (101) | Medizinische Hochschule Hannover | Development of protocols for improved hepatocyte and cholangiocyte differentiation of human pluripotent stem cells | 15/04/2015 |
| 4 (102) | Prof. Dr. Ulrike Nuber Technische Universität Darmstadt | Development of human cell models for Rett syndrome | 15/04/2015 |
| 5 (103) | Dr. Zsuzsanna Izsvák Max-Delbrück-Centrum für Molekulare Medizin Berlin | Identification of target genes of the transcription factor DLX5 in trophoblast cells developed from hES cells and their possible role in the development of pre-eclampsia | 27/05/2015 |
| 6 (104) | Evotec International GmbH Hamburg | Development of robust protocols for the differentiation of human embryonic stem cells to beta cells and the use of the beta cells derived from hES cells in drug discovery studies | 17/06/2015 |
| 7 (105) | Medizinische Hochschule Hannover | Human embryonic stem cells as the initial source for a cell-replacement therapy of diabetes mellitus | 19/10/2015 |

| Extensions of already approved applications | | | |
|---|---|---|---|
| 8 Extension of approval no. (99) | Zentrum für Regenerative Therapien (CRTD), Technische Universität, Dresden | Identification of potential active substances for modulating the phagocytosis activity of RPE cells | 18/02/2015 |
| 9 Extension of approval no. (84) | Dr. David Vilchez, Universität Köln | Studies on the role of cold shock proteins in the life span and differentiation decisions in human ES cells | 30/09/2015 |
| 10 Extension of approval no. (78) | Dr. Micha Drukker, Helmholtz Zentrum München | Differentiation of human embryonic stem cells towards cardiovascular and trophoblast precursor cells | 12/11/2015 |

**Table 2.** Overview of research projects that were approved by the RKI during the 2015 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 aim of the first research project listed in Table 2 (99th approval under the Stem Cell Act) is to use hES cells to identify substances which will make it possible in the future to treat eye diseases related to reduced phagocytosis, e.g. the various forms of macular degeneration. Initially, a procedure for high-throughput analysis is to be developed to identify substances that stimulate phagocytosis using cells of the retinal pigment epithelium (RPE cells). To this purpose, hES cells are to be differentiated into RPE cells, and these are to be used to establish an *in vitro* test system for measuring phagocytosis activity. Subsequently, substance libraries are to be searched for substances that stimulate phagocytosis by RPE cells. The second part of the research work aims to study the poorly understood molecular principles of phagocytosis in RPE cells and to identify genes whose products are involved in the regulation of phagocytosis and participating signalling pathways. To increase the likelihood of identifying drug candidates, in an extension of the application the number of substances to be tested is to be significantly increased by using additional substance libraries. The work is expected to make an important contribution to understanding the molecular processes during phagocytosis in RPE cells. The work is also to be carried out with human induced pluripotent stem cells (hiPS cells) from healthy patients compared with those of patients suffering from macular degeneration.

The second research project (100th approval) deals with the establishment of a human kidney-cell model for studying the molecular and cell-biological processes of cilia formation in renal epithelial cells and their malfunction as a result of genetic defects in the genes *Pkd1* and *Pkd2,* which are related to polycystic kidney disease (PKD). First, suitable differentiation protocols for hES cells are to be established which will initially be developed into cells of the intermediary mesoderm, and then into more differentiated kidney cell types, particularly into tubular renal epithelial cells. The differentiation methods are to be transferred to hiPS cells obtained from patients with PKD. hES cells are also to be used to produce pairs of isogenic pluripotent stem cells that are carrying patient-specific mutations in the *Pdk1*or *Pdk2* gene or are genetically unchanged. These cells are to be studied and compared with isogenic pairs of patient-specific and genetically corrected hiPS cells, particularly with regard to their ability to form cilia. The project aims to help broaden understanding of the renal differentiation processes in humans, particularly in cilia formation. It may also make an important contribution towards clarifying the molecular principles of the pathogenesis of polycystic kidney disease.

The purpose of the third research project (101st approval) is to obtain mature and functioning human hepatic and cholangiocytic cells from pluripotent stem cells, to aggregate them to organoids in a 3D culture and subsequently – after transplantation into suitable mouse

models – to study their functionality *in vivo*. The *in vitro* maturation of hepatic precursor cells into functional hepatocytes has not been sufficiently successful up to now. Therefore, the first aim will be to optimize various protocols for differentiating hES cells to liver parenchyma cells and bile-duct cells and to comprehensively characterize the differentiated cells. Another aim is to clarify the question of which miRNAs are involved in the differentiation, and in particular in the maturation of hepatic cells; if necessary, genes for transcription factors and *long non-coding RNAs* (lncRNAs) involved in hepatic and cholangiocytic differentiation are to be identified which are differentially regulated during hepatic differentiation. The hepatic cells derived from hES cells are also to be aggregated in 3D culture to organoids, together with endothelial cells and mesenchymal stromal cells also derived from hES cells. Finally, the hepatocytes and cholangiocytes derived from hES cells are to be transplanted into immunodeficient mice and the properties of the transplanted cells examined. The work is also to be carried out with hiPS cells. hES cells will be used for the purpose of comparison. The project can contribute to the provision of a sufficient quantity of functioning, mature human hepatocytes and, in the long term, contribute to the development of transplantable liver organoids, which is of great medical relevance.

The fourth research project (102nd approval) aims to establish a human cell model for Rett syndrome. There is currently no causal therapy for this severe neurological disease mediated by mutations in the X-chromosomally encoded gene for MECP2 (*methyl CpG binding protein 2*) and therefore occurring almost exclusively in girls. First, hiPS cells are to be generated from patients with corresponding mutations and – for reference purposes – the same mutations created in hES cells. The genetically modified hES cells, patient-specific hiPS cells and unchanged hES cells are to be differentiated via neural precursor cells into granule cells of the dentate gyrus, and these are to be examined in terms of their morphology and functionality. Another aim is to identify potential target genes of MECP2 in the mutant cells and to study the role of the glucocorticoid signalling pathway in the manifestation of Rett syndrome. On the one hand, these studies can help better understand the molecular and cellular changes in the case of Rett syndrome; on the other hand, they can also lead in the long term to the development of new approaches for treating Rett syndrome. Furthermore, the project aims to develop processes by means of which different sub-populations of neural precursor cells that have been differentiated from human pluripotent stem cells can be separated from each other and enriched; this is important for the development of improved neural differentiation protocols.

The focus of the fifth research project (103rd approval) is on clarifying the role of the homeobox-transcription factors DLX5 (coded from *distal-less homeobox 5 gene)* in the development of trophoblast cells from human pluripotent stem cells. The background is a possible role of the DLX5 gene product during the formation of pre-eclampsia, a sometimes difficult disease that occurs during pregnancy. After establishing protocols for differentiating hES cells in cells of the trophoblast, the aim is to identify genes in whose regulation DLX5 is involved, in particular in differentiation towards trophoblast cells. Their specific role in trophoblast differentiation is then to be studied by the overexpression or repression of the identified genes. Since it is now known that DLX5 is expressed to a significantly higher extent in the placental tissue of patients with pre-eclampsia than in normal placental tissue, overexpression or repression of the expression of DLX5 aims to clarify what effects this has on the properties of the evolving trophoblasts, particularly on the proliferation and invasion ability of its cells. The research work, which is regarded as being of high-level interest, could contribute to improving understanding of the early molecular and cellular processes in the formation of the trophoblast from pluripotent stem cells, and to improving the assessment of the possible consequences of a false regulation of DLX5 for this process, particularly with regard to the development of pre-eclampsia.

The focus of the sixth research project (104th approval) is on identifying and developing new active substances for treating type 1 and type 2 diabetes. In order to develop the required *in-vitro* test system, a standardized differentiation protocol is initially to be established for deriving large quantities of mature and functioning beta cells from hES cells via different

pancreatic precursor cells. The proposed study of the molecular processes that take place in the development of pancreatic precursor cells to insulin-secreting beta cells, can be expected to provide new insights into pancreatic differentiation in humans, which is regarded as a research goal of high-level interest. By using these beta cells developed from hES cells, the aim is to establish an *in vitro* test system by means of which various libraries of small molecules and potentially therapeutic proteins can be tested in high-throughput analyses. The objective of these studies is to identify substances by means of which insulin-producing beta cells can be protected from apoptosis, substances that slow down or prevent the differentiation and function losses mediated by stress, or which stimulate the proliferation of beta cells. This research could lead to the identification of substances that are starting points for the development of new drugs. These are of great relevance for the development of new therapeutic methods in the treatment of diabetes mellitus.

The seventh research project (105th approval) aims to help improve understanding of the cell-biological principles of pancreatic differentiation in humans and to contribute to the development of methods for providing sufficient quantities of cells for future cell therapies for diabetes mellitus. First, the signalling pathways are to be studied that are involved in the differentiation and specification of cells of the definitive endoderm derived from hES cells towards pancreatic precursor cells, and in the formation of the different cell types of pancreatic islets. Furthermore, the methods for enriching pancreatic precursor-cell populations are to be improved, for example by coupling reporter genes to genes that are characteristic of certain pancreatic precursor cells. Moreover, the role of miRNAs during the segregation of the mesodermal and endodermal lines and during the pancreatic differentiation of hES cells is to be analysed. Since, in the case of type 1 diabetes, insulin-producing beta cells are destroyed by an autoimmune process in the islets of Langerhans, it is necessary for the development of tissue-replacement therapies to study the potential toxicity of soluble pro-inflammatory cytokines in relation to the viability of beta cells. Another aim, therefore, is to examine to what extent and in what way an apoptosis mediated by cytokines occurs in pancreatic beta cells derived from hES cells, and how this might be prevented. The research work will also make use of hiPS cells. The research project is expected to contribute to improving understanding of pancreatic differentiation in humans, and to gaining knowledge that is of considerable importance for a targeted future tissue-replacement therapy for type 1 diabetes.

Applications were made in the reporting period for the extension of research work relating to two approvals granted in 2013 (approvals 78 and 84) on which the ZES commented (see nos. 9 and 10 in Table 2).

During the implementation of the research project listed under no. 9, which aims to clarify the mechanisms for maintaining the dynamic balance of the proteome (proteostasis) in hES cells, when comparing the proteomes of undifferentiated and neurally differentiated hES cells, it was found that genes coding for so-called cold shock proteins (CSPs) are strongly expressed in hES cells. Since CSPs, as components of ribonucleoprotein complexes, evidently influence the translation rate of various mRNAs via the binding of RNA, they play a role in maintaining the proteostasis of hES cells. The aim now, therefore, is to examine the importance of various cold shock proteins for the life span and for differentiation decisions of hES cells. This work can contribute towards clarifying further molecular mechanisms that lead to maintaining the proteome. They can help improve the current understanding of the molecular principles for the regulation of proteostasis in hES cells.

In the project listed under no. 10, which studies the early differentiation steps from hES cells to cardiovascular precursor cells, an additional aim is to clarify the cause of the highly diverse success of differentiating human pluripotent stem cells towards cardiac cells. Following the hypothesis that, in the initial phase after triggering the *in vitro* differentiation of pluripotent stem cells towards the mesodermal cells, two mutually exclusive differentiation pathways can be pursued – one towards mesodermal cells, and one towards cells of the trophoblast – hES cells are now also to be differentiated into trophoblast cells. Using a newly developed method for sequencing the entire transcriptome of individual cells, the causal

differences in the transcriptomes of differentiated cells are to be clarified. This should lead to new findings about the order of the gene expression events that ultimately lead to differentiation decisions on the single-cell level after induction of mesodermal differentiation. This can be expected to lead to improved differentiation strategies for the *in vitro* generation of cardiac cells, and expand understanding of early differentiation processes in humans.

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-inhalt.html).

In each case, the essential arguments made by the ZES justifying the high-level interest 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.

Five of the new applications discussed during the reporting period were submitted by researchers or institutions that had not yet previously received an approval under the Stem Cell Act. Two applications were made by working groups at an institution that had already received approvals under the Stem Cell Act in the past. All the applications were approved by the RKI after review by the ZES. During its 13 years of activities the ZES has issued opinions on a total of 107 applications for import and/or use of hES cells and sent them to the RKI. In addition, a total of 27 applications for extensions of already approved projects, on which the ZES was asked for an opinion, have been approved by the RKI to date. In its decisions on the eligibility of applications for approval, the RKI has followed the ZES's recommendations in all cases up to now.

Since the Stem Cell Act came into force, the RKI has issued 105 approvals, some of which were extended. Seven of these approvals have expired to date. At present, 75 groups at 53 research institutions are conducting approved research work with hES cells.

## 3. Developments and trends in research using human embryonic stem cells in Germany

1. In the reporting period, the research projects applied for deal primarily with the development of cell models from human pluripotent stem cells. These models aim on the one hand to facilitate the study of molecular processes at the cellular level, or to make it at all possible to study the principles of the differentiation of precursor cells into different human cell types. On the other hand, they aim to help clarify molecular processes in illnesses which are triggered, for example, by mutations in certain genes or occur as a result of a change in the regulation of signal transmission. In some cases they are also to be used for testing substance libraries, which can contribute to the identification of potential active substances and thus ultimately to the development of new therapeutic procedures for treating diseases such as diabetes mellitus or macular degeneration. In addition, several new applications are concerned with improving differentiation protocols of hES cells into specific cell types and their enrichment and expansion. This is a prerequisite for the development both of efficient *in vitro* test systems with human cells and of future cell-replacement therapies in humans, e.g. in the form of organoids.
2. In five of the newly approved research projects, hiPS cells are to be compared with hES cells (Figure 1). In this context, hES cells are used in some cases as a reference material for assessing reprogramming success in the generation of hiPS cells and for estimating the differentiation potential of the respectively generated hiPS cells. Some of the hiPS cells are derived from cells of ill people in order to use them for modelling diseases and to clarify pathogenesis mechanisms at the cellular level. Particularly in the case of diseases that are caused by singular genetic modifications, hES cells in which the mutation that causes the disease is generated are a valuable comparison and reference material. The consequences of the respective genetic modification can be studied and compared with non-modified hES cells against an otherwise identical genomic

background. Conversely, genetic defects in disease-specific hiPS cells can be corrected, and the properties of genetically deficient hiPS cells compared with those of the repaired hiPS cells, again against the same genetic background. On the one hand, these comparative studies make it possible to draw conclusions on the stage in which the mutations associated with diseases become phenotypically effective and, perhaps, lead to undesirable developments. On the other hand, the consequences of certain mutations for the cellular phenotype can be precisely analysed. This can help expand knowledge of the molecular causes of (genetic) diseases and thus has relevance for the development of new therapeutic approaches for treating these diseases.

In addition, the applicants have pointed out that research results that are not adequately based on hES cell lines may not be publishable under certain circumstances.

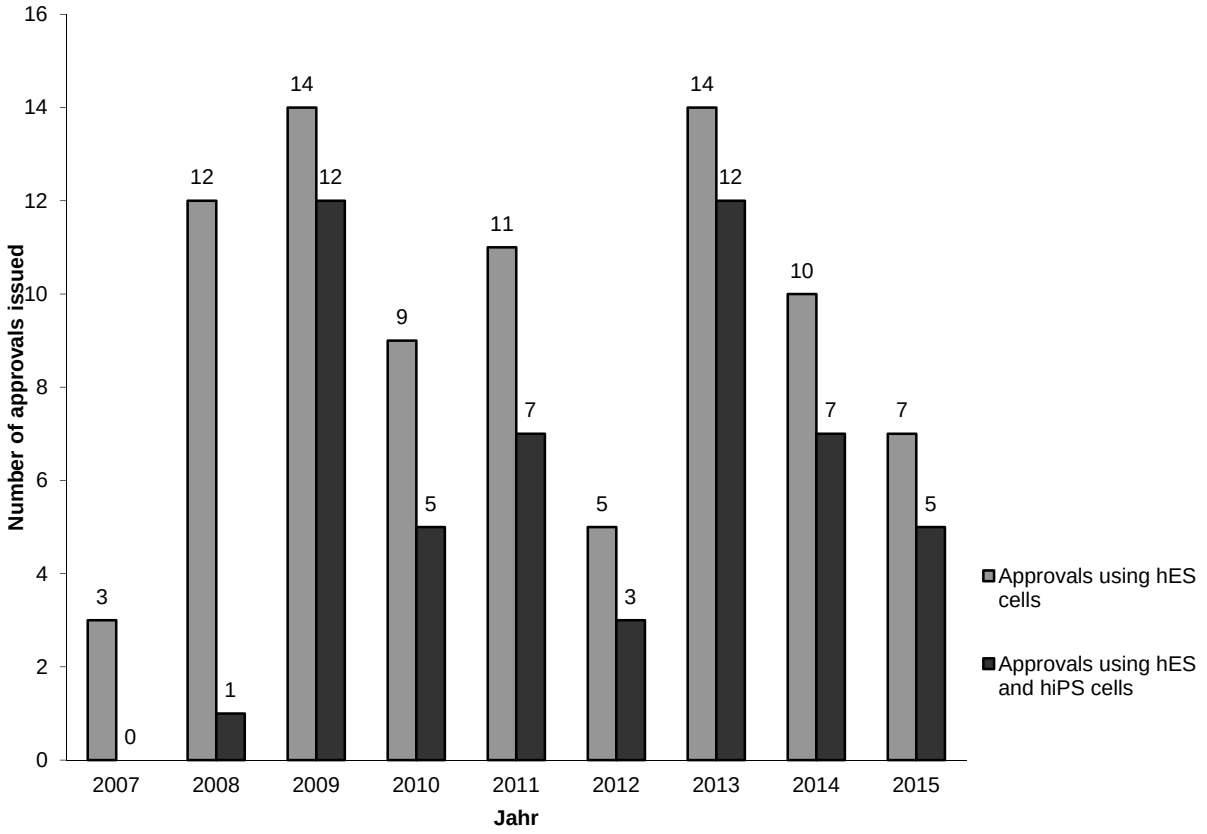


**Figure 1.** Use of hES and hiPS cells in approved research projects, 2007-2015. The chart shows the total number of approved research projects (grey) and the number of research projects in which not only hES but also hiPS cells were used (black).

3. At its 82nd meeting held on 19 October 2015, the ZES was informed about the novel processes developed over the last few years for the targeted genetic modification of cells: so-called *genome editing* procedures. They are used worldwide in the field of biotechnological and biomedical research, as well as in animal and plant breeding. Of these procedures, the modification method known as CRISPR (*clustered regulatory interspaced short palindromic repeats*) / Cas9 in particular has proved to be extremely precise and efficient, as well as cost-effective, and has been widely adopted in the field of research involving human pluripotent stem cells. Apart from its great importance for basic research with human pluripotent stem cells, the use of CRISPR/Cas9 technology opens

up new possibilities for somatic gene therapy, for example by correcting genetic defects. *Genome editing* methods can also be used for the targeted modification of the human germ line. Chinese scientists have already generated mutations in the beta-globin gene from non-viable human embryos with the help of *genome editing* (protein cell, 6(5):363-72, 2015). The methodology was not very efficient and accompanied by numerous so-called o*ff-target* effects. The publication by the Chinese working group and the possibilities of the controversial application of *genome editing* in the human embryo, or as germ-line gene therapy, triggered controversial discussions among the public and a call for a moratorium on the application of this method for modifying the human germ line. In the ZES's opinion, what is necessary is a critical discussion on the open questions relating to the risks and benefits of the application of this method in humans, but without impeding the advancement and development of new application possibilities of *genome editing* for research.

4. In view of the latest developments in connection with the establishment and progressive characterization of so-called 'naive' pluripotent human stem cells, the ZES at its 79th meeting held on 18 February 2015 dealt comprehensively with this issue, which is also the subject of research with hES cells in Germany. Human and murine ES cells are not the same in terms of their degree of development. mES cells are in a so-called '*naive*' condition corresponding to an earlier embryonic stage than that of hES cells, which are in a so-called *'primed'* condition. By applying different culture conditions and using different factors, cytokines, kinase inhibitors and so-called small molecules, it is possible to obtain pluripotent hES cells which are similar to the 'naive' condition of mES cells. 'Naive' hES cells can have beneficial properties. This concerns in particular the ability to differentiate efficiently in all directions. Conventional, so-called *'primed*' hES cells are already more configured to developing into certain cell types like cardiomyocytes or neuronal cells. Furthermore, their potential to differentiate into germ cells is evidently limited. Basic research with 'naive' hES cells is necessary to be able to investigate questions of germ-cell development and very early embryonic development processes in humans. However, this would necessitate another amendment of the cutoff date – the last was in 2008 – since 'naive' hES cells were only produced and published in 2010, i.e. **after** the current cutoff date. Furthermore, the ZES was also informed that, in advance of the submission of applications, various queries were put to the RKI on whether it is possible to import and use certain hES cell lines, which the RKI already knew to have been derived after the StZG cutoff date (1 May 2007). Since the RKI replies to such queries with the information that the import and use of such hES cells cannot be authorized under the Stem Cell Act, the corresponding applications were not submitted. Also in view of such queries, but primarily because of the great dynamics of the research field, a dynamization of the cut-off date would still be meaningful to avoid Germany being left behind in new developments in the field of stem cell research.

5. Since 2010, clinical studies using cells differentiated from hES cells are being carried out worldwide, most which were approved by the U.S. Food and Drug Administration (FDA). At the end of 2015, 17 clinical studies were being carried out. In the approved studies, cells derived from hES cells are being tested to determine their suitability for the treatment of diseases for which there are currently no adequate treatment options available. Their safety and compatibility in particular are being reviewed .

| ***Disease*** | ***Cell type differentiated from hES cells (product name)*** | ***Responsible for the studies*** | ***Regulatory authority ClinicalTrials.gov Identifier*** | ***Study phase Expected study launch date*** |
|---|---|---|---|---|
| Spinal-cord injuries | Oligodendrocytes (GRNOPC1) | Geron Corporation, USA, until 2013<br>Since Jan. 2014: Asterias Biotherapeutics, Inc., USA | Food and Drug Administration (FDA), USA<br>NCT01217008 | Phase I<br>Oct. 2010<br>Study ended |
| Inherited juvenile form of macular degeneration (Stargardt's disease) | Retinal pigment epithelial cells (MA09-hRPE) | Ocata Therapeutics, USA; formerly Advanced Cell Technology (ACT) | FDA<br>NCT01345006 | Phases I and II<br>April 2011<br>Study ongoing |
| Age-related macular degeneration (AMD) | Retinal pigment epithelial cells (MA09-hRPE) | Ocata Therapeutics, USA | FDA<br>NCT01344993 | Phases I and II<br>April 2011<br>Study ongoing |
| Inherited juvenile form of macular degeneration (Stargardt's disease) | Retinal pigment epithelial cells (MA09-hRPE) | Ocata Therapeutics, USA | Medicines and Healthcare Products Regulatory Agency (MHRA), UK<br>NCT01469832 | Phases I and II<br>Nov. 2011<br>Study ongoing |
| Inherited juvenile form of macular degeneration (Stargardt's disease) | Retinal pigment epithelial cells (MA09-hRPE) | Ocata Therapeutics, USA | FDA<br>NCT02445612 | Phases I and II<br>July 2012 Longitudinal study<br>Participants are being invited |
| Age-related macular degeneration (AMD) | Retinal pigment epithelial cells (MA09-hRPE) | Ocata Therapeutics, USA | FDA<br>NCT02463344 | Phases I and II<br>July 2012 Longitudinal study<br>Participants are being invited |
| Age-related macular degeneration (AMD) | Retinal pigment epithelial cells (MA09-hRPE) | Ocata Therapeutics, USA | FDA<br>NCT02563782 | Phase II<br>Aug. 2015<br>Participants are being recruited |
| Inherited juvenile form of macular degeneration (Stargardt's disease) | Retinal pigment epithelial cells (MA09-hRPE) | CHABiotech Co., Ltd, Korea | Food and Drug Administration, Korea<br>NCT01625559 | Phase I<br>Sept. 2012 |
| Age-related macular degeneration (AMD) | Retinal pigment epithelial cells (MA09-hRPE) | CHABiotech Co., Ltd, Korea | Food and Drug Administration, Korea<br>NCT01674829 | Phases I and II<br>Sept. 2012<br>Participants are being recruited |

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| 'Wet' age-related macular degeneration (AMD) | Membrane-bound retinal pigment epithelial cells<br>(PF-05206388) | Pfizer in collaboration with University College, London | MHRA, UK<br>NCT01691261 | Phase I<br>Feb. 2015<br>Study ongoing |
| Myopic macular degeneration (due to severe short-sightedness) | Retinal pigment epithelial cells<br>(MA09-hRPE) | University of California, Los Angeles, in collaboration with Ocata Therapeutics, USA | FDA<br>NCT02122159 | Phases I and II<br>March 2013<br>Participants are being recruited |
| Age-related macular degeneration (AMD) | Retinal pigment epithelial cells<br>(OpRegen) | Cell Cure Neurosciences Ltd., Israel (subsidiary of BioTime, USA) | FDA<br>NCT02286089 | Phases I and II<br>April 2015<br>Participants are being recruited |
| Serious ocular surface disorders | Epithelial cells | Eye Institute of Xiamen University, China | ChiCTR<br>ChiCTR-OCB-15005968 | Jan. 2015<br>Participants are being recruited |
| 'Dry' age-related macular degeneration (AMD) | Retinal pigment epithelial cells<br>(CPCB-RPE1) | Regenerative Patch Technologies, LLC | FDA<br>NCT02590692 | Phases I and II<br>Oct. 2015<br>Participants are being recruited |
| Ischemic heart disease | Cardiac precursor cells embedded in fibrin<br>(CD15+ Isl-1+) | Assistance Publique-Hôpitaux de Paris, France | Comités de Protection des Personnes, France<br>NCT02057900 | Phase I<br>June 2013<br>Participants are being recruited |
| Diabetes mellitus type 1 | Encapsulated pancreatic precursor cells<br>(VC-01) | ViaCyte, USA | FDA<br>NCT02239354 | Phases I and II<br>Sept. 2014<br>Participants are being recruited |
| Spinal-cord injuries | Oligodendrocytes<br>(AST-OPC1, formerly GRNOPC1) | Asterias Biotherapeutics, Inc., USA | FDA<br>NCT02302157 | Phases I and II<br>March 2015<br>Participants are being recruited |
| **Cell type differentiated from <u>hiPS cells</u>** | | | | |
| 'Wet' age-related macular degeneration (AMD) | Retinal pigment epithelial cells differentiated from autologous hiPS cells | Riken Center for Developmental Biology, Japan | University Hospital Medical Information Network (UMIN) Center, Japan<br>WHO ID: JPRN-UMIN000011929 | Sept. 2014<br>Study suspended in 2015 |

**Table 3**. Phase I/II clinical trials with cells developed from pluripotent stem cells, sources: ClinicalTrials.gov, a service of the U.S. National Institutes of Health (NIH), and International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO); data status: 31/12/2015

The first clinical trial, which was carried out by the Geron Corporation in 2010, was completed in 2013. It showed that, in the case of patients with subacute spinal-cord injuries, treatment with oligodendrocytes derived from hES cells is well tolerated and safe. Since March 2015, the study is being continued by the company Asterias Biotherapeutics as a Phase I/II trial using the same cell product. The aim is to transplant different quantities of oligodendrocytes differentiated from hES cells into patients with sensorimotor spinal-cord injuries.

Several studies on the treatment of different forms of macular degeneration were launched in 2015. In China, a study is being conducted on the transplantation of epithelial cells derived from hES cells in cases of ocular surface disorders. Furthermore, the company Ocata Therapeutics plans to conduct a double-blind study to assess the extent to which certain immunosuppressive preparations are effective in the prophylaxis of organ-rejection reactions after the transplantation of RPE cells derived from hES cells in patients with age-related macular degeneration (AMD). The company Regenerative Patch Technologies has begun a further study on the subretinal implantation of RPE cells differentiated from hES cells in AMD patients.

Two long-term studies (15 years) by Ocata Therapeutics are dealing with the safety and tolerability of transplanted RPE cells derived from hES cells both in patients with the juvenile form of macular degeneration and in patients with AMD.

All the other studies with cells derived from hES cells mentioned in Table 3 were already mentioned in the last report. They are being conducted on the treatment of various forms of macular degeneration, ischemic heart disease, and diabetes mellitus. The only study using cells derived from hiPS cells – in which autologous retinal pigment epithelium cells differentiated from hiPS cells were transplanted into a patient – was suspended. Although the safety and tolerability of the treatment was evidently confirmed in this patient, genetic changes were detected in the hiPS cells of a second patient which could not be detected in the starting material. Because of the considerable process-related technical challenges in the quality management of autologous cell products, a continuation of the study is being considered using allogeneic cell-therapy medicinal products. Further clinical trials using pluripotent stem cells are expected in the next few years.

The 13th Report was adopted at the 84th ordinary meeting of the ZES on 14 March 2016.