Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

Twelfth Report after the enactment of the Stem Cell Act (StZG) for the reporting period 1 January to 31 December 2014

1. The Central Ethics Committee for Stem Cell Research

The Central Ethics Committee for Stem Cell Research (ZES) has been carrying out its remit – the review and assessment of applications to import and use human embryonic stem cells (hES cells) in accordance with the Stem Cell Act – since 2002. The Committee's work is governed by the Stem Cell Act (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 Committee, which conducts its work in an honorary capacity, submits opinions on applications to import and use human embryonic stem cells to the Robert Koch Institute (RKI), the competent authority pursuant to the Stem Cell Act.

The independent and interdisciplinary expert body is made up of nine members and their nine deputies (see Table 1). Five members represent the disciplines of biology and medicine, and four members the fields of philosophical, medical and theological ethics (see section 8 of the StZG). The body is appointed by the Federal Government for a term of three years respectively. Since the fourth appointment term expired in July 2014, sixteen members and deputy members were reappointed to the ZES and two deputy members appointed for the first time for what is now the fifth appointment term (2014 to 2017). In accordance with the ZES Regulation, the members and deputy members participate regularly in Committee's meetings and in the deliberations on the applications.

Section 9 of the Stem Cell Act specifies that it is the task of the ZES to review the ethical acceptability (pursuant to section 5 of the StZG) of the applications submitted to the RKI for the import and use of hES cells. An application must prove in a scientifically substantiated manner (a) that the research project pursues research objectives of superior interest aimed at increasing scientific knowledge (section 5, no. 1 of the StZG), (b) that the scientific issues have already been subjected to preliminary studies in other systems, including animal 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). Both scientific and ethical aspects play an important role when reviewing and assessing the applications submitted. Based on four votes which are prepared from among the members and deputy members of the different disciplines, the ZES summarizes the results of the assessment in a written opinion, which is sent to the RKI.

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. Schröder 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 rer. nat. Maria Wartenberg Molekulare Kardiologie und Stammzellforschung Universitätsklinikum Jena
Medicine	Prof. Dr med. Mathias Bähr Neurologische Klinik Georg-August-Universität Göttingen	Prof. Dr med. Wolfram H. Zimmermann Institut für Pharmakologie 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 med. Ursula Just Max-Planck-Institut für Herz- und Lungenforschung Bad Nauheim
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Table 1: Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES) as of their appointment on 8 August 2014

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

Five meetings of the ZES were held during the reporting period at which a total of eleven applications for the import and use of human ES cells and one application for the extension of an already approved research project were discussed. The ZES has already issued positive opinions on nine applications and the application for extension. One application which the ZES had already assessed and discussed using the written procedure in 2013 was approved by the RKI in 2014. These definitively approved projects meet the preconditions of section 5 of the Stem Cell Act and are ethically acceptable within its intendment (section 9 of the StZG). In the case of one application, the ZES asked the RKI to obtain further information from the applicant. Another application that was given a positive opinion during the reporting period had not yet been approved by the RKI by the end of the reporting period and is therefore not part of the report submitted here. Table 2 gives an overview of the applications that were given a positive opinion by the ZES during the reporting period and approved by the RKI by 31 December 2014.

No.	Applicant	Research topic	Date of positive opinion by ZES
1 (89)	Professor Dr Jürgen Hescheler Universität Köln	Development of a cell-based test system for detecting cardiac toxicity on the basis of cardiomyocytes derived from human embryonic stem cells.	6 December 2013
2 (90)	Dr Anthony Gavalas Technische Universität Dresden	Differentiation of human embryonic stem cells into pancreatic beta cells and motor neurons, and their functional characterization	20 January 2014
3 (91)	Dr Leo Kurian Universität Köln	Study of the role of long, non-coding RNAs in the cardiac differentiation of human pluripotent stem cells	17 February 2014
4 (92)	Dr Jennifer Winter Universitätsmedizin Mainz	Establishment of human cell models for studying pathogenesis mechanisms of the Opitz BBB/G syndrome	17 February 2014
5 (93)	Dr Armin Blesch Universitätsklinikum Heidelberg	Study of the potential of neural derivatives of human pluripotent stem cells for the treatment of spinal-cord injuries in animal models	17 February 2014
6 (94)	Miltenyi Biotec GmbH Bergisch Gladbach	Development of improved conditions for cultivating, differentiating and enriching human pluripotent stem cells	17 February 2014
7 (95)	PD Dr Christine Blattner Karlsruher Institut für Technologie	Study of the properties of p53 in human embryonic stem cells	14 April 2014
8 (96)	Institut für Transfusionsmedizin Universitätsklinikum Essen	Development of an in-vitro cell model for Angelman syndrome	14 April 2014

9 (97)	Prof. Dr Wolfgang Wurst Helmholtz-Zentrum München	Identification of molecular principles of the differentiation of pluripotent stem cells into dopaminergic nerve cells and study of the role of mutations in the development of Parkinson's disease	15 September 2014
10 (98)	Institut für Humangenetik Universitätsklinikum Essen	Differentiation of human pluripotent stem cells into neural retina for the development of an in-vitro model to study the genesis of retinoblastoma	15 September 2014
Extensions of already approved applications			
11 Exten-sion of approval no. (73)	Dr Alessandro Prigione Max-Delbrück-Centrum (MDC) für Molekulare Medizin, Berlin	Study of the mitochondrial metabolic reprogramming of human cells and establishing hiPS-cell-based models for mitochondrial diseases	14 April 2014

Table 2: Overview of research projects that were approved by the RKI during the 2014 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 project listed in Table 2 (89th approval under the Stem Cell Act) is identical to the project of the 80th approval, which was described in the 2013 Report. The aim of the project is to establish and validate an in-vitro test system for determining potential cardiotoxicity based on cardiac cells obtained from hES cells. The ZES voted on the project using the written procedure and rated the research objectives, which are classified as basic research, as being of superior interest.

Two sub-projects were applied for in the second research project (90th approval). The first sub-project aims to obtain mature and functioning beta cells from hES cells in order to explain – and reproduce *in vitro* – the processes that take place during the development of cells of the definitive endoderm into endocrine pancreatic cells and during maturation to insulin-secreting pancreatic beta cells. The properties and functionality of terminally differentiated beta cells are to be studied *in vitro* and after transplantation into a diabetic mouse model. The second sub-project aims to differentiate hES cells into subtypes of motor neurons that are active in different regions of the brain. The first step will be to develop neural precursor cells generated from hES cells into precursor cells of different motor-neuron subtypes. After characterization, the motor-neuron precursor cells are to be terminally differentiated and the resulting cells analysed, particularly with regard to their ability to form synapses *in vitro*. Both research projects pursue goals in basic research that are of superior interest and could furthermore attain a high degree of medical relevance in the long term.

The focus of the third project (91st approval) is on clarifying the function of so-called long, non-coding RNAs (lncRNAs) (a) in maintaining the pluripotency of hES cells, (b) in the differentiation of hES cells into cardiac and vascular cells, and (c) in the regeneration of the heart and the vascular system. Already identified lncRNAs are to be analysed to determine their importance for the pluripotency and differentiation ability of hES cells into different cell types of the cardiac line by modulating their expression. It is known that lncRNAs have accumulated in regenerating zebrafish hearts. LncRNA expression is also to be examined in cardiac precursor cells obtained from hES cells or mature cardiomyocytes to determine their possible role in the proliferation and dedifferentiation of cardiac cells. Finally, another aim is

to determine the molecular mechanisms through which the lncRNAs control cardiovascular development and regeneration. The research project, which is classified as basic research, can help improve our understanding of cardiac regeneration processes and thus, in the longer term, also be of clinical relevance.

In order to expand knowledge of Opitz BBB/G syndrome, which leads to defects in neural development, the fourth research project (92nd approval) intends to study the effects on neural differentiation of malfunctions of the MID1 gene, which is linked to the form of the disease that is inherited through X-chromosomes. To this purpose, the specific functions of MID1 are to be determined in neural crest cells, neural precursor cells and neurons derived from hES cells. A particular objective is to analyse the effects of different mutations of the MID1 gene at the molecular level and the consequences for the ability of cells to differentiate, as well as for their proliferation, migration and apoptosis. Finally, the project intends to transfer findings obtained from hES cells to hiPS cells taken both from healthy subjects and from subjects with Opitz syndrome, and to compare the results with those from hES cells. The research project, which pursues objectives of superior interest in basic research, aims to develop a disease model for Opitz BBB/G syndrome and to lay the foundations for identifying new active substances for treating this disease in the future.

The long-term objective of the fifth research project (93rd approval) is to develop new approaches to the stem-cell-based treatment of traumatic injuries of the spinal cord. Different as-pure-as-possible populations of glial and neuronal cells are to be obtained from hES cells and transplanted into rodent models for spinal-cord lesions. The therapeutic effects of the transplanted cells on the motor, autonomous and sensory functions are also to be studied using growth factors and carrier materials. Finally, the project aims to transfer the studies to hiPS cells and to examine the extent to which hES and hiPS cells demonstrate comparable potential to differentiate into specific sub-populations of neural cells and are able to bring about comparable therapeutic effects after transplantation into animal models for spinal-cord lesions. It seems likely that the project can explain important issues of basic research, which can create a basis for a tissue-replacement therapy of spinal-cord injuries in humans.

The purpose of the sixth research project (94th approval) is to optimize and standardize the cultivation and differentiation of human pluripotent stem cells and to compare the use of hES and hiPS cells. The first step will be to optimize media and methods for the efficient expansion of pluripotent cells under 2D and 3D conditions, and subsequently to further develop the conditions for differentiation into clinically relevant cell types. The differentiated cells are to be functionally characterized both *in vitro* and after transplantation into corresponding animal models. The processes of cultivating, differentiating and enriching the cells is to be scaled up to new levels that make it possible to provide the quantities of cells required for clinical application and which are also in line with Good Manufacturing Practice (GMP). The aim is to be able to use the cells produced under these conditions not only for translational research in the development of cell-replacement therapies, but also for applications in pharmacology/toxicology and in basic research. The research project thus represents a major step on the road towards laying the foundations of new therapeutic procedures that can be used in humans.

The seventh research project (95th approval) seeks to clarify the function of p53 in hES cells and in their early differentiation stages. p53, which plays a key role in the regulation of the cell cycle in human cells, is also thought to be involved in early embryonic development processes. The first step will be to determine genes regulated by p53 by means of altered expression patterns after siRNA-dependent repression of the p53 gene in hES cells and after induction of differentiation. A further aim is to study the effect of inhibiting p53 gene expression on the proliferation behaviour of hES cells. A final objective is to determine the conformation of p53 in hES cells and in their differentiated derivatives under different conditions, and to study the ability of whatever p53 protein is present to bind to known

interaction partners. The research project promises to extend our knowledge of the properties of the key protein p53.

The eighth research project (96th approval) aims to establish an *in-vitro* cell model for Angelman syndrome, a developmental disorder of the central nervous system involving a defect of the maternal allele of the ubiquitin-protein ligase gene (UBE3A) (the paternal allele is inactivated by imprinting). In order to study the pathogenesis, hiPS cells are to be generated from a patient with Angelman syndrome. Their properties are to be compared with hES cells in which the same mutation has been created using homologous recombination, in order to generate isogenic disease-specific pluripotent cells with a standardized genetic background. After neural differentiation, the project aims to determine those neuronal cell types that are directly affected by the disease. In addition, allele-specific imprinting is to be studied and strategies developed – and tested *in vitro* – for reactivating the paternal, inactive UBE3A allele. The project, which can be classified as basic research, aims to improve our understanding of the cellular and molecular causes of Angelman syndrome and may in the long term lead to new therapeutic strategies for treating the disease.

The ninth research project (97th approval) focuses on laying the foundations for a tissue-replacement therapy for genetically determined forms of Parkinson's disease. The first stage will be to establish and optimize protocols for the reproducible *in-vitro* production of as-pure-as-possible populations of dopaminergic neurons from hES cells. The use of hES reporter-cell lines aims to facilitate the characterization and analysis of the different stages of dopaminergic differentiation and of molecules and signalling pathways involved in this. The influence of components of the extracellular matrix (ECM) on the genesis of dopaminergic neurons is also to be investigated. Finally, mutations that are associated with hereditary, early-manifesting forms of Parkinson's disease are to be specifically introduced into hES cells to study their influence on the differentiation of the cells to dopaminergic neurons. In addition, the properties of the genetically modified hES cells are to be compared with those of hiPS cells that have been derived from cells of patients with corresponding genetic defects. The project is designed not only to help extend our knowledge of the differentiation of dopaminergic neurons, but also to contribute to the development of new therapeutic approaches for treating people suffering from Parkinson's disease.

The purpose of the tenth research project (98th approval) is to improve our understanding of the processes that take place at the molecular and cellular level during the development of retinoblastoma, the most common tumour of the eye that occurs in childhood. The first step will be to establish and optimize the differentiation of hES cells (and hiPS cells) into cells of the neural retina and further into optical vesicles. The next will be to generate heterozygous, homozygous and multiple mutations in the retinoblastoma (Rb1) gene, but also outside of the Rb1 gene, and to analyse the effects of the different genetic modifications on the differentiation of the pluripotent cells into the neural retina at the levels of the transcriptome, the proteome and the epigenome – compared with non-modified hES cells. The intention is for this work to also help identify cell types that are the starting point for the development of retinoblastoma. The project aims to contribute towards our understanding of the pathogenesis of the tumour and is expected to advance the development of a targeted therapy for retinoblastoma.

An extension for further research work on the 73rd approval (issued in 2012) was requested during the reporting period; this required a new opinion by the ZES (see no. 11 in Tab. 2). The research project deals with comparative studies of the mitochondria in human pluripotent stem cells; in particular, it analyses the influence of reprogramming somatic cells on the mitochondria's properties. The aim now is to clarify whether possible malfunctions of mitochondria play a role in the pathogenesis of degenerative diseases of the nervous system. The first step will be to study the specific changes that happen to mitochondria in the process of neural differentiation and whether there are differences in this context between

hiPS and hES cells. In addition, using hiPS cells obtained from affected patients, cell models are to be established for human neurodegenerative diseases which, according to the current state of knowledge, are related to a modified mitochondrial function in neural cells. hES cells serve as reference material here. The cell models are to be used for studies of the various mitochondria functions, especially after the induction of cellular stress. This project, which pursues research objectives in the field of basic research, can extend our knowledge of the processes involved in the development of neurodegenerative diseases.

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 11 applications discussed during the reporting period, six were submitted by research groups that had not yet previously received an approval under the Stem Cell Act. Five applications were made by working 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 twelve years of activity the ZES has deliberated on and assessed a total of *100 applications* for the import and/or use of hES cells. In addition, *nine applications for extensions* of already approved projects have been examined. This means that *101 opinions* have been submitted to the RKI to date. The RKI has followed the ZES's recommendation in all cases up to now.
Since the entry into force of the Stem Cell Act, the RKI has issued 98 approvals that also contain extensions. Three of the approvals have expired since 2010. As shown in Table 3, 76 groups of researchers at 50 institutions currently have permission to conduct research with hES cells in Germany. Research with hES cells takes place mainly at universities, university hospitals and institutes of such research organizations as the Max Planck Society, the Helmholtz Association and the Fraunhofer Society. However, eight approvals were also granted to companies conducting hES-cell research in Germany.

Type of institution	**Number of approvals granted**	**Number of research groups**	**Number of institutions**
Universities and university hospitals	66	51	32
Research organizations (e.g. Max Planck Society, Helmholtz Association, etc.)	20	14	8
Companies	8	7	7
Non-profit limited liability companies	3	3	2
Federal authorities	1	1	1
Total	**98**	**76**	**50**

Table 3: Type and number of institutions that have been awarded approvals under the Stem Cell Act since 2002.

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

1. Some of the new applications filed during the reporting period were concerned with the differentiation of hES cells into certain cell types. They aim to explain and reproduce the processes and function of molecules and signalling pathways that are important for the course of differentiation into pancreatic, cardiac, vascular cells and neuronal cell types such as motor neurons and dopaminergic neurons. In some cases the intention is to study the influence of external components or carrier materials. Other projects aim to establish cell models for genetically caused diseases in order to improve our understanding of the pathogenesis mechanisms of these diseases, and to be able to develop new therapeutic strategies in the long term. Furthermore, the targeted development of automated methods of producing, enriching and expanding defined derivatives of human pluripotent stem cells is a prerequisite for the use of such cells in future tissue-replacement therapies.

2. Comparative studies on hiPS cells and hES cells are another subject of the research projects. It is still the case that these pluripotent cell types are being studied in parallel in approx. two thirds of the research projects approved in Germany since 2007 under the Stem Cell Act (see Figure 1).
Four of the research projects applied for and reviewed by the ZES intend to use exclusively hES cells. In the other seven projects, hES cells are used for comparison with hiPS cells; four of these deal with the development of cell models for genetically caused diseases. As described in recent publications, disease-specific hiPS cells are used here for the purpose of modelling disease models and elucidating the cellular pathogenesis mechanisms of hereditary diseases. In some cases the projects aim to also generate in hES cells the respective mutations that are present in the patient-specific hiPS cells. Such disease-specific hES cells can then be studied and compared with non-modified hES cells using an isogenic background. Vice versa, the mutation can be corrected in disease-specific hiPS cells in order to conduct a comparative study of both disease-specific hiPS cells and genetically corrected hiPS cells using the same patient-specific genetic background. Comparative studies of the properties of these two cells, which only differ in the gene of interest, can yield information on aberrations during the differentiation processes which, in turn, can advance our knowledge of the genesis of genetically caused diseases and perhaps lead to the development of new therapies. In addition, hES cells are needed in general as a control in order to estimate the success of reprogramming into hiPS cells and the differentiation procedure used.
In addition to their use as reference material in research projects aimed at gaining insights into hiPS cells, hES cells remain a subject of research in their own right. Neither German research activities nor international scientific developments currently provide evidence to support the assumption that hES cells are only needed for a transitional period and only as reference material for other pluripotent cell types.

3. As mentioned in the Committee's 2012 report, research on hES cells does not only relate to basic research; at the international level it is also moving in the direction of a clinical application. In 2012 seven Phase I/II clinical trials were ongoing worldwide, mostly approved by the US Food and Drug Administration (FDA); another four clinical trials had been added by the end of 2014. The approved studies are examining the suitability, safety and tolerability of cells differentiated from hES cells for the treatment of diseases for which no adequate therapeutic options are currently available (see Table 4).
The first clinical study was launched in 2010 by the Geron Corporation; however, it was terminated in November 2011 because the company decided to discontinue its activities in the field of stem cells. The results of the study using oligodendrocytes differentiated from hES cells, and including five patients with subacute spinal-cord injuries, showed the tolerability and safety of cells derived from hES cells. The study has been continued by Asterias Biotherapeutics since 2014; the patients are now being administered a 10-times higher dose of oligodendrocytes differentiated from hES cells than in the Geron study.

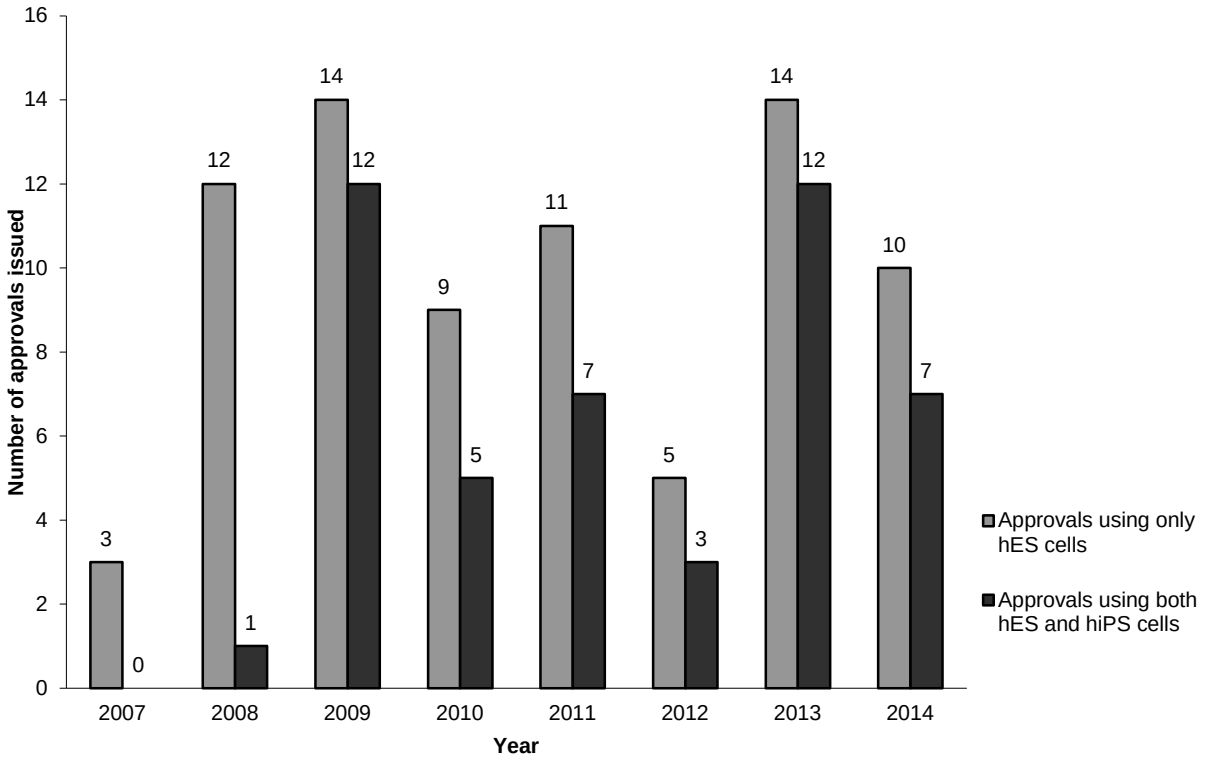

Figure 1: Overview of approved research projects between 2007 and 2014 using either only hES cells (grey) or both hES and hiPS cells (black) (status: December 2014)

Disease	***Cell type differentiated from hES cells (product name)***	***Responsible for the studies***	***Regulatory authority ClinicalTrials.gov identifier***	***Study phase Expected duration of study period***
Spinal-cord injuries	Oligodendrocytes (GRNOPC1)	Geron Corporation, USA, until 2013 Since Jan. 2014: Asterias Biotherapeutics, Inc., USA	Food and Drug Administration (FDA), USA. NCT01217008	Phase I October 2010 – July 2013
Inherited juvenile form of macular degeneration (Stargardt's disease)	Retinal pigment epithelial cells (MA09-hRPE)	Ocata Therapeutics, USA; formerly Advanced Cell Technology (ACT)	FDA NCT01345006	Phases I and II April 2011 – December 2014
Age-related macular degeneration (AMD)	Retinal pigment epithelial cells (MA09-hRPE)	Ocata Therapeutics, USA	FDA NCT01344993	Phases I and II April 2011 – December 2014

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), United Kingdom NCT01469832	Phases I and II November 2011 – December 2015
Inherited juvenile form of macular degeneration (Stargardt's disease)	Retinal pigment epithelial cells (MA09-hRPE)	CHABiotech Co., Ltd, Korea; formerly CHA Bio & Diostech, Korea	Food and Drug Administration, Korea. NCT01625559	Phase I September 2012 – June 2015
Age-related macular degeneration (AMD)	Retinal pigment epithelial cells (MA09-hRPE)	CHABiotech Co., Ltd, Korea	Food and Drug Administration, Korea. NCT01674829	Phases I and II September 2012 – April 2016
Wet age-related macular degeneration (AMD)	Membrane-bound retinal pigment epithelial cells (PF-05206388)	Pfizer in collaboration with University College, London	MHRA, United Kingdom NCT01691261	Phase I May 2015 – September 2017
Myopic macular degeneration (due to severe short-sightedness)	Retinal pigment epithelial cells (MA09-hRPE)	University of California, Los Angeles, in collaboration with Ocata Therapeutics, USA	FDA NCT02122159	Phases I and II April 2014 – April 2015
Ischemic heart disease	Cardiac precursor cells embedded in fibrin (CD15+ Isl-1+)	Assistance Publique - Hôpitaux de Paris, France	Comités de Protection des Personnes, France NCT02057900	Phase I June 2013 – June 2016
Diabetes mellitus Type 1	Encapsulated pancreatic precursor cells (VC-01)	ViaCyte, USA	FDA NCT02239354	Phases I and II September 2014 – August 2017
Age-related macular degeneration (AMD)	Retinal pigment epithelial cells (OpRegen)	Cell Cure Neurosciences Ltd., Israel	FDA NCT02286089	Phases I and II February 2015 – August 2017
	Cell type differentiated from hiPS cells			
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 WHO ID: JPRN-UMIN000011929	September 2014 – 2018

Table 4: 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 December 2014

The treatment of different forms of macular degeneration is being tested in another eight studies. Patients with age-related macular degeneration (AMD) or a hereditary juvenile form of macular degeneration (Stargardt's disease) in the USA, Korea and the United Kingdom are being treated with retinal pigment epithelium (RPE) cells produced from hES cells. Many people around the world are affected by these incurable eye diseases which lead to complete blindness; AMD affects one in five people over the age of 70. The ongoing studies aim to test issues relating to the clinical safety of the cell derivatives and to how well the transplant is tolerated by the recipient. RPE cells can be obtained from hES cells as very pure cell populations, and a relatively small number of cells (50,000 to 100,000) is sufficient for a cell transplant into the easily accessible eye. After two years, Schwartz et al. (Lancet 2014; doi: 10.1016/S0140-6736(14)61376-3) reported again on the first results of two studies by Ocata Therapeutics approved in the USA. The safety of the procedure was confirmed, and visual acuity improved in half of the patients who had small numbers of RPE cells transplanted into their eyes – compared to untreated patients. However, certain questions have not yet been sufficiently clarified, e.g. relating to the biological activity of the transplanted cells, the safety of the transplanting technique, and possible immunological reactions. Because of the clear evidence of the effectiveness of the therapy, Ocata Therapeutics plans to extend the studies and to recruit 100 patients with Stargardt's disease for another Phase II clinical trial.
In addition to subacute spinal-cord injuries and macular degeneration, clinical studies to test the safety of cells derived from hES cells were also approved last year for the treatment of ischemic heart diseases and diabetes mellitus. In a study conducted in France cardiac precursor cells derived from hES cells are being used to treat heart-attack patients. A study being carried out by ViaCyte in the USA aims to examine the safety, tolerability and efficacy of pancreatic precursor cells produced from hES cells by implanting the encapsulated cells under the skin of diabetes patients.
Further clinical trials using hES cells can be expected in the next few years.
hiPS cells were also used in a first clinical study last year. In a study being carried out in Japan, six patients with AMD are to receive a transplant of autologous RPE cells derived from hiPS cells. The therapeutic benefit of such transplants is also to be assessed if their safety is confirmed.

4. Research on hES cells and cells derived from them also make it possible to establish test systems for identifying and/or examining medicinal products, as well as examining the toxicity of environmental chemicals. Test systems based on animal experiments are expensive and, above all, can only partially predict effects in humans. Adverse effects of potential medical active substances cannot be detected very reliably in advance using common methods, and not all rare, serious side effects are known, even if in the case of approved drugs. Furthermore, the effects of untested environmental chemicals cannot be predicted; these are believed to number 70,000 under the EC regulation REACH. New, better and more informative test systems are therefore needed. These are currently being developed, and in some cases are already in use. They are based, for example, on *in-vitro* test systems with human cells, 3D *in-vitro* models which are being further developed as '*organs on a chip*', high-throughput screening processes, and computer-aided toxicity evaluations. hES cells and cells differentiated from them are used worldwide for testing developmental neurotoxicity, neurotoxicity, reproductive toxicity, cardiotoxicity and hepatotoxicity. In particular, it is possible to analyse – under the influence of potentially toxic substances – early embryonic development processes taking place in humans at the cellular level. The required test systems are complex, however. The potential toxicity of substances for early development processes must be investigated in several development stages. In addition, there is the complicated process of standardizing *in-vitro* test systems, i.e. for example defining the time period and the concentration in which the substance impacts on the system, testing suitable endpoints, and determining the point in time in development when the substance must be applied into the system. Batteries of tests and automated test procedures are needed for tracking *in vitro* the different biological steps in the cells at

different points in time of early human development. In this context, hES cells are regarded as an indispensable reference model because of their characteristics as original early cells, according to the current state of knowledge. It is still unclear whether studies with hiPS cells will lead to the same results, because high-precision comparative analyses are not yet available.
Corresponding toxicity test systems are also used in industry. Foreign pharmaceutical companies are already examining their substances in *in-house* test series in the preclinical field with cells developed from pluripotent stem cells. The SEURAT-1 programme was initiated in 2011 within the framework of the 7th European Framework Programme for Research with the aim of developing methods for testing the safety of substances, in order to restrict animal testing.

5. The German Ethics Council held a public hearing on 8 May 2014 to discuss the issue of whether the cloning of humans for reproductive purposes using new methods is perhaps not unequivocally regulated by German laws in general, and by the Act for the Protection of Embryos (EschG) and the Stem Cell Act (StZG) in particular. Subjects discussed included new developments in the production of human embryonic stem cells by nucleus transfer and in the production of induced pluripotent stem cells. ZES members Messrs Schöler and Tanner were invited to take part as experts. They informed the participants about the current state of research and presented thoughts on a possible need for regulation from an ethical perspective. In the view of the invited legal expert Mr Müller-Terpitz, although the new research methods were covered by the applicable laws, there were inconsistencies and ambiguities with respect to different legal definitions of such key terms as "embryo" and "totipotency" in the ESchG and StZG. The German Ethics Council has published an ad-hoc recommendation to accompany the hearing. It is available at:
http://www.ethikrat.org/dateien/pdf/empfehlung-stammzellforschung.pdf.

The twelfth report was unanimously adopted at the 79th ordinary meeting of the ZES on 18 February 2015.