Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

16th Report after the Enactment of the

Stem Cell Act (StZG)

for the Reporting Period
1 January to 31 December 2018

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 connection with the import and use of human embryonic stem cells (Stem Cell Act – StZG)' dated 28 June 2002 (BGBl. I page 2277, which was most recently amended by Article 50 of the law dated 29 March 2017 (BGBl. I p. 626), http://www.gesetze-im-internet.de/stzg/index.html), as amended by the 'Act amending the Stem Cell Act' dated 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) dated 18 July 2002 (BGBl. I page 2663, which was most recently amended by Article 51 of the law dated 29 March 2017 (BGBl. I p. 626), http://bundesrecht.juris.de/zesv/index.html).

The Committee conducts its work on an honorary basis and is made up of nine members and nine deputy members; 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 examine the ethical acceptability of the applications submitted to the RKI for the import and use of hES cells. On the basis of 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 (https://www.bundesgesundheitsministerium.de/service/begriffe-von-a-z/s/stammzellgesetz.html#c1091) and the RKI (http://www.rki.de/DE/Content/Kommissionen/ZES/Taetigkeitsberichte/taetigkeitsbericht_node.html)

Field	Member	Deputy member
Biology and Medicine	Prof. Dr Mathias Bähr Neurologische Klinik Georg-August-Universität Göttingen	Prof. Dr Wolfram H. Zimmermann Institut für Pharmakologie und Toxikologie Georg-August-Universität Göttingen
	Prof. Dr Anthony D. Ho Med. Universitätsklinik und Poliklinik Ruprecht-Karls-Universität Heidelberg	Prof. Dr Beate Winner Nikolaus-Fiebiger-Zentrum für Molekulare Medizin Universitätsklinikum Erlangen
	Prof. Dr Katja Schenke-Layland Naturwissenschaftliches und Medizinisches Institut at the Universität Tübingen	Prof. Dr Ricardo E. Felberbaum Frauenklinik Klinikum Kempten Oberallgäu
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Ethics and Theology	Prof. Dr Dr Antonio Autiero **(Deputy Chair)** Katholisch-Theologische Fakultät Westfälische Wilhelms-Universität Münster	Prof. Dr Dr Jochen Sautermeister Katholisch-Theologische Fakultät Rheinische Friedrich-Wilhelms-Universität Bonn
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	Prof. Dr Klaus Tanner **(Chair)** Theologisches Seminar Ruprecht-Karls-Universität Heidelberg	Prof. Dr Hartmut Kress Evangelisch-Theologische Fakultät Rheinische Friedrich-Wilhelms-Universität Bonn

Table 1. Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES), last revised December 2018

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

In 2018, the ZES held four meetings and discussed a total of eight applications for the import and use of hES cells. The ZES handed down positive opinions on all the applications. 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.	Holder of approval	Topic of approved studies	Date of the positive ZES opinion
1 (133)	Uniklinik Köln	Studies on the potential of human pluripotent stem cells for corneal surface reconstruction in limbal stem-cell insufficiency	17/01/2018
2 (134)	Charité – Universitätsmedizin Berlin	Study on epigenetic principles of the regulation of the proopiomelanocortin (POMC) gene in human neurons	23/02/2018
3 (135,136, 137)	Universitätsklinikum Essen	Epigenetic mechanisms of mental retardation in rare syndromal diseases	18/06/2018
4 (138)	Dr Viet Loan Dao Thi, Universitätsklinikum Heidelberg	Characterization of hepatitis E virus transport pathways in hepatocyte-like cells derived from human embryonic stem cells and complex hepatocyte systems	18/06/2018
5 (139)	Prof. Dr Henrik Semb, Helmholtz Zentrum München	Production of insulin-producing beta cells from human embryonic stem cells on an enlarged scale for future clinical studies on the treatment of type 1 diabetes mellitus	26/09/2018
6 (140)	Max-Delbrück-Centrum für Molekulare Medizin (MDC), Berlin	Local proteome, transcriptome and translatome investigations in motoneuron diseases using hES-cell-derived motoneurons	17/09/2018
7 (141)	Dr Moritz Mall, Deutsches Krebsforschungzentrum (DKFZ), Heidelberg	Study on the role of transcription regulators in the induction and maintenance of human neuronal cell identity	17/10/2018
8 (142)	Dr Claudio Acuna Goycolea, Universität Heidelberg	Study on the role of HAR mutations associated with neuropsychiatric disorders in hES-cell-based neuronal cell models	23/11/2018

Table 2. Overview of research projects that were approved by the RKI during the 2018 reporting period following a 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). For formal reasons, the RKI issued three approvals in the case of one application (no. 3).

The subject of the first research project listed in Table 2 (133rd approval under the Stem Cell Act) is the generation of limbal stem cells – and mature limbal epithelial cells derived from them – from hES cells in order to develop new strategies for the reconstruction of the corneal surface in cases of limbal stem-cell insufficiency; the functionality of the cells obtained is also to be tested in animal models. Limbal stem-cell insufficiency is a severe disorder of the regeneration and wound healing of the ocular surface epithelium; it can lead to blindness. No

efficient therapies for this disease are available to date. Therefore, hES cells are to be differentiated into limbal stem cells *in vitro* and under xenofree conditions on the basis of an already established and published protocol, and comprehensively tested to determine their cell identity and degree of maturation. The limbal (stem) cells are subsequently to be applied to different carrier membranes and transplanted into rabbits in which limbal stem-cell insufficiency has previously been induced by manual limbectomy. Using various parameters, it will then be determined to what extent limbal stem cells derived from hES cells (or mature limbal epithelial cells derived from them) can improve the integrity of the ocular surface. In addition, the impact of the immunosuppression used on the result of the transplantation will be investigated. The above-mentioned studies are also to be carried out in comparison with human-induced pluripotent stem cells (hiPS cells). These studies are expected to lead to new insights into the potential of limbal stem cells derived from human pluripotent stem cells (hiPS cells) for the reconstruction of the corneal surface. In addition, questions are already being considered that are directly related to the future use of such cells in the clinic. This would be highly relevant for the treatment of limbal stem-cell insufficiency, especially in cases where the disease affects both eyes, i.e. where no autologous cell material is available for transplantation.

At the centre of the second research project (134th approval under the Stem Cell Act) is the establishment of neuronal cell and organoid models using hES cells in which early processes of the methylation of the proopiomelanocortin gene *(POMC* gene) can be examined *in vitro*. The background to this research work is that increased methylation in certain regions of the gene for POMC is associated in humans with an increased risk of developing obesity. This could be due to the properties of the *POMC* region, which fulfils the criteria of a so-called metastable epiallele. The aim of the work is to clarify how variable the methylation of certain regions of the *POMC* gene is and whether increased methylation is associated with a decreased expression of this gene (and consequently with a decreased secretion of the melanocyte-stimulating hormone, MSH). To this end, suitable hES cells are transferred into the naive status, differentiated in the direction of neurons of the hypothalamus or neuronal organoids, and comprehensively characterized with respect to the methylation of the *POMC* gene and its expression. The next step of the research project will be to determine whether and to what extent the presence of so-called C1-metabolites, and the presence or absence of transposable elements (aluminium elements), influences the methylation of the *POMC* gene region in developing human neurons. In addition, changes in the methylation of the histones associated with the *POMC* gene region and their variability depending on the above-mentioned conditions are to be determined. The results of the approved studies are expected to provide new insights into the possible causes of the inter-individual methylation variability of the *POMC* gene and the associated risk of developing obesity.

The third research project (135th, 136th and 137th approvals) aims to clarify the molecular principles of mental retardation syndromes. The focus of the project is on rare syndromal diseases in which, although mutations in certain genes or regulatory elements are known to be associated with the expression of the disease, they cause a change in the epigenetically controlled gene regulation as a consequence. These mutations comprise on the one hand imprinting disorders (including Angelman and Prader-Willi syndromes), and on the other hand syndromes in which the composition of chromatin-remodelling complexes is altered (e.g. Coffin-Siris and Nicolaides-Baraitser syndromes) and X-chromosome-associated mental retardation in which X-inactivation or compensation mechanisms play a role (Shashi syndrome, IQSEC2 type). In order to establish corresponding cellular disease models, the disease-associated genes in hES cells are to be specifically genetically modified and the effects on the properties of the neuronal (precursor) cells and three-dimensional cortical organoids derived from the corresponding hES cells comprehensively characterized at the molecular, morphological, functional and (epi)genetic level. The research work can contribute to a better understanding of the molecular and cellular processes involved in the pathogenesis of mental retardation syndromes involving disorders in epigenetic processes.

The aim of the fourth research project (138th approval) is, on the one hand, to establish and optimize cell models for infecting human polarized liver cells with the hepatitis E virus (HEV) and, on the other hand, to identify and characterize molecular mechanisms of the polarized intracellular transport and secretion of HEV that are not yet known in full detail. Selected genes are to be modified to clarify how cellular components of the host and viral determinants control polarized HEV transport. To perform the above-mentioned studies, mutation approaches (using CRISPR/Cas9 systems), immunofluorescence stainings, qRT-PCR and Western-Blot analyses, fluorescence *in-situ* hybridizations (FISH), and live-cell imaging techniques will be used. HEV infections are considered the most common cause of hepatitis; at present, around 20 million people worldwide are infected with HEV, leading to approximately 3.3 million acute hepatitis cases with about 56,000 deaths per year, mostly in developing and threshold countries. If the research project approved here is carried out successfully, authentic human infection models for the hepatitis E virus could be created which could be used to gain new insights into the molecular mechanisms of the assembly, transport and release of HEV particles in human polarized liver cells. This would be of considerable importance for the further clarification of HEV pathogenesis and the identification of suitable therapeutic substances.

The aim of the fifth research project (139th approval) is to develop methods to provide sufficient amounts of high-quality functional mature beta cells derived from hES cells for future regenerative therapies of type 1 diabetes mellitus (T1D). Currently, it is not possible to cure T1D, and efficient cell-replacement therapies have not been available hitherto. Therefore a differentiation protocol for the generation of glucose-inducible and insulin-secreting pancreatic beta cells that the applicant has already established is to be adapted to GMP conditions and further optimized in order to be able to provide the material required for clinical Phase I trials. In particular, an efficient approach for enriching multipotent pancreatic progenitor cells is to be developed to produce sufficient cell material for clinical application, and to achieve a better maturation of the pancreatic beta cells *in vitro*. The work can create the prerequisites for cell-replacement therapy in the treatment of diabetes mellitus in humans, but may also produce important findings for basic research. In particular, it is expected that the molecular processes involved in beta-cell development in humans can be further clarified.

The subject of the sixth research project (140th approval) is the clarification of common molecular mechanisms involved in the development of degenerative motoneuron diseases such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), which are still insufficiently known at the genome-wide level. The degeneration of motoneurons leads to paralysis of the arms and legs, but also of respiratory muscles and the muscles used for swallowing. No curative therapy exists at present. First, precise genetic modifications in genes associated with different motoneuron diseases are to be introduced into hES cells using genome editing (CRISPR/Cas9 technology); then the effects of the genetic modifications on the properties of hES-cell-derived motoneurons after fractionating the cells obtained into cell bodies (soma) and cell extensions (neurites) will be determined. Analysis of the local proteome, transcriptome and translatome will aim to determine whether and to what extent changes in the subcellular localization and translation of RNA in motoneurons contribute to the development of the disease. Furthermore, identified signalling pathways, which are the underlying common cause of motoneuron diseases, will be further analysed. The studies will also be carried out in comparison with hiPS cells obtained from patients with degenerative motoneuron diseases. The results of the studies may lead to new knowledge about dysregulated signalling pathways or processes that play a central role in the pathogenesis of motoneuron diseases of different genetic aetiology. This could be relevant for the future development of new therapies, such as those aimed at restoring dysregulated signalling pathways or processes.

The focus of the seventh research project (141st approval) is on the detailed study of the hitherto unexplored role of certain transcription regulators (MYT1L and related factors) that suppress differentiation into non-neuronal cell types during neuronal differentiation processes

and ensure the maintenance of cell identity in terminally differentiated human neuronal cells. Mutations in the *MYT1L* gene are associated in humans with neurological developmental disorders and mental diseases such as autism and schizophrenia, but also with brain tumours. This suggests that errors in switching off genes from other (non-neuronal) cell differentiation programmes can cause severe diseases in humans. To further investigate the role of MYT1L in neuronal development and the maintenance of neuronal cell identity, genetic alterations are to be introduced into the gene and the effects on the corresponding hES-cell-derived neuronal cells or cerebral organoids comprehensively analysed at the molecular and functional level. Another aim is to clarify which factors the transcription repressor MYT1L interacts with and/or which (target) genes it regulates in order to permanently suppress alternative differentiation processes in neurons and thus maintain neuronal cell identity. This research may contribute to new knowledge on the molecular function of certain transcription regulators in the induction of neuronal differentiation processes and the maintenance of neuronal cell identity in human cells. Furthermore, the results may provide new insights into processes leading to changes in neuronal cell identity and consequently to the development of neurological developmental disorders and mental illnesses such as autism and schizophrenia, or to the development of brain tumours, which may also lead to new therapeutic approaches for treating these diseases in the long term.

The purpose of the eighth research project (142nd approval) is to clarify the role of mutations in non-coding genome segments known as *human accelerated regions* (HARs) in the development of psychiatric illnesses from the spectrum of autism disorders at the cellular level. HARs are characterized by the fact that they have remained intact throughout the evolution of vertebrates, but differ significantly in humans from those in other vertebrates. For the most part, they function as regulatory elements. It is striking that HARs have high mutation rates in children with autism and mental disabilities; there is also a correlation between the occurrence of certain HAR mutations and the pathogenesis of autism spectrum disorders (ASD). However, there has not yet been enough research up to now into how HAR mutations contribute to the pathogenesis of ASD and what basic functions HARs have. To gain a better understanding of the mode of action of HARs, homology-directed repair (CRISPR-HDR) HAR mutations associated with ASD are to be first introduced into hES cells using CRISPR/Cas9. The modified hES cells will then be differentiated into cortical neurons, and these will be comprehensively examined at a transcriptional, morphological and electrophysiological level in comparison with neurons derived from wild-type hES cells. In particular, the consequences of different HAR mutations on the structure and function of the synapses will be analysed. The results of the studies may provide new insights into the extent to which HAR mutations are significant for the development of psychiatric disorders from the spectrum of autism disorders 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-ranking status of the research projects, their adequate preliminary clarification and the need 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. Three applications were made by researchers or institutions that had already received approvals under the Stem Cell Act in the past. All the applications were approved by the RKI after receipt of the ZES's opinion. During its 16 years of activity, the ZES has submitted opinions to the RKI on a total of 139 applications for the import and/or use of hES cells. In addition, a total of 36 applications for extensions of already approved projects have been approved by the RKI to date. The ZES issued an opinion on each of these. 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 142 approvals, some of which were extended. Twenty nine of these approvals have expired to date. At present, 80 groups at 51 research institutions are conducting approved research work with hES cells.

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

1. Development of in-vitro disease models using hPS cells

Of the eight research projects evaluated during the reporting period, five (see Table 2, nos. 2, 3, 6, 7, 8) are concerned with the development of neural *in-vitro* cell models for various diseases such as obesity, autism, schizophrenia and amyotrophic lateral sclerosis (ALS), and for diseases associated with mental retardation, using neuronal cells and/or brain organoids derived from human pluripotent stem cells (hPS cells), in order to contribute to understanding the molecular foundations of the respective disease and to develop new therapeutic methods in the long term. In addition, another research project (see Table 2, no. 4) focuses on establishing and optimizing cell models for infecting human polarized liver cells with the hepatitis E virus (HEV) in order to gain a better understanding of the molecular foundations of infection with HEV, and possibly to contribute to the identification of targets for new antiviral therapies.

2. Research on the generation of therapeutically useful cells from hPS cells

In two of the research projects evaluated during the reporting period, studies are being carried out which aim to establish methods for generating potential starting materials for future clinical applications and to test the therapeutic cells generated in corresponding preclinical (animal) models (see Table 2, nos. 1 and 5). In one of these projects, hES cells are to be used to generate limbal stem cells and mature limbal epithelial cells derived from them in order to develop new strategies for corneal surface reconstruction in cases of limbal stem-cell insufficiency. In the other project, the research work using hES cells aims to develop methods for providing high-quality functional beta cells produced under GMP conditions in sufficient quantities for clinical purposes. This serves the preparation of a clinical Phase I trial for treating type 1 diabetes mellitus (T1D) and, pursuant to section 5 (1) of the StZG, is considered to be research of high-ranking status since it aims to develop new therapeutic procedures for use in humans. The approval holder already seeks the routine use of hES cells for the production of a clinically usable cell product after the approved research project.

In this context, the consequences of the restrictions on the use of hES cells enshrined in the Stem Cell Act become clear. The conduct of clinical studies in which cells or tissue produced from hES cells are to be transplanted into patients in Germany is likely to be permissible under the StZG, as this would be clinical research. The routine use of hES cells (i.e. no longer primarily for the purpose of obtaining research results) to produce a corresponding cell product and its therapeutic application after completion of the clinical trial is not permissible, however. This has led to the paradoxical situation that, although research objectives can be considered to be of high-ranking status because they help create the foundations for new therapeutic methods for use in humans, the long-term objective of such research, which would ultimately be the production of cell products for clinical purposes and would therefore include the routine use of hES cells for the production of this cell product, would then – although not yet the direct subject matter of the application – not be eligible for approval. According to the StZG, the immediate objectives of the respective research project are decisive for its evaluation. However, even a prospective subsequent use of the research findings achieved, which can certainly be of considerable importance, e.g. for treating hitherto incurable diseases, can still make a considerable contribution to the high-ranking nature of the research objectives, even if an approval were not possible for such studies to be approved in the current legal situation.

Furthermore, in one of the above-mentioned research projects (no. 5), the cut-off date regulation meant that studies already carried out with hES cells abroad had to be carried out

again using hES cells compliant with the cut-off date. The hES cell line whose suitability for the research work applied for was already proven does not comply with the cut-off date conditions of the StZG. Redundant studies using hES cells are required to confirm the suitability of a different hES cell line which this time is compliant with the cut-off date for the research project. This leads to an increased use of hES cells.

In addition, applications submitted to the ZES revealed another fact, i.e. the prospect that, in the future, cells derived from hES cells can contribute to significantly reducing the number of animals currently used for medical or pharmaceutical purposes. According to the StZG, research on hES cells with this aim in view is currently not eligible for approval if this is the exclusive purpose of the research project. Furthermore, a standard application of previously developed methods substituting animal experiments based on hES cells that goes beyond research is currently not permitted under the StZG, if hES cells need to be used in Germany for this purpose. In substance, however, the concern to reduce the use of animals now carries a lot of weight, partly through the inclusion of animal welfare as a national goal in the Basic Law and partly as a result of EU initiatives. In addition, experience has shown that the use of human cell material for human medical and pharmacological purposes produces further relevant results. In view of the progress of international research in the field of replacing animal cells with stem-cell-based *in-vitro* models, it also becomes clear that the Stem Cell Act is reaching its limits in this respect, too.

3. Comparative studies on hiPS cells and hES cells

Comparative studies on hiPS cells and hES cells were not a key topic of the research projects in 2018. This could be an indication that fields of research using hES cells and/or hiPS cells are increasingly developing as independent research fields. In only 2 of the 10 new research projects approved in the reporting period are hiPS cells and hES cells examined in parallel (Figure 1). In one project, hES cells are used as reference material for assessing the differentiation potential of hiPS cells in the cell type that is the subject of interest (Table 2, no.1). The various hiPS cell lines differ considerably in terms of their differentiability. Such differences may be due to the derivation of hiPS cells from genetically different donors, each of whom has a different genetic background; but it may also be due to the donor's age. Even where the donor is the same, strong line-specific differences may be caused by reprogramming artefacts such as incomplete reprogramming or reprogramming-related *de novo* mutations, by the cell type used for reprogramming (blood cells, fibroblasts, keratinocytes, etc.), or by the method chosen for reprogramming. In the other project (Table 2, no. 6) which aims to model diseases *in vitro* and to clarify pathogenesis mechanisms at the cellular level, hiPS cells are derived from cells of ill people and compared with hES cells in which the mutation causing the disease has been generated, as well as with non-modified hES cells. Here, hES cells represent valuable reference material because they enable the effects of the respective genetic modification to be studied and compared with non-modified hES cells against an otherwise identical genomic background.

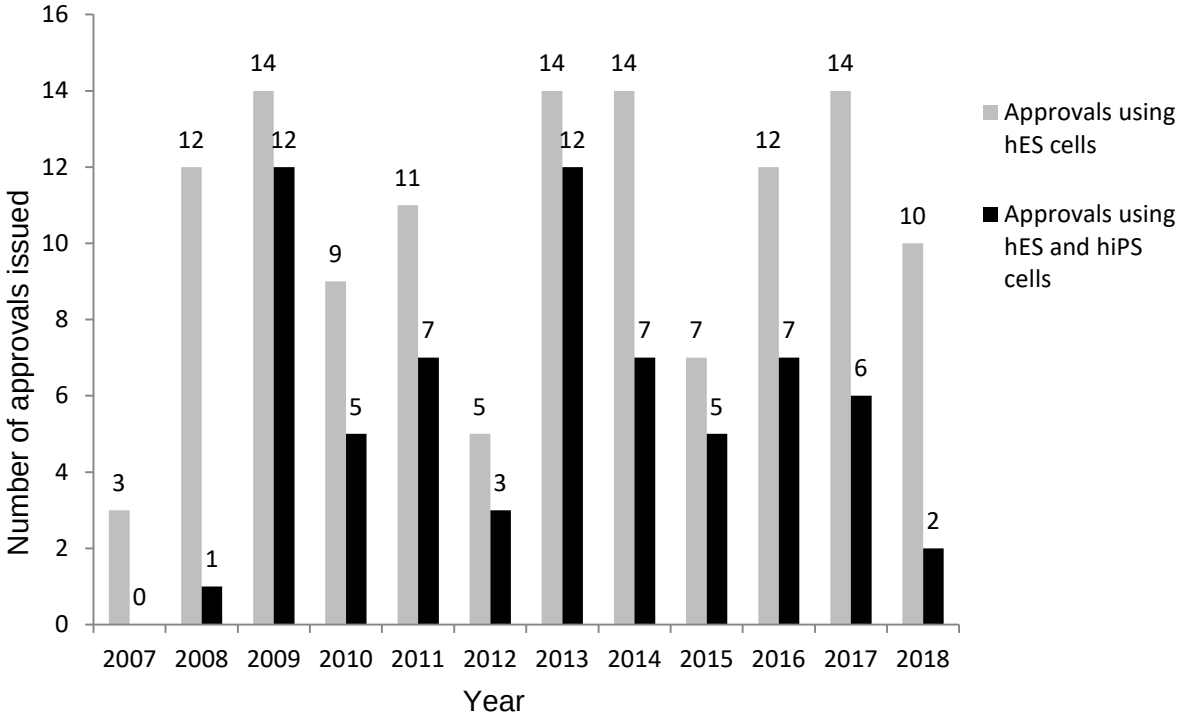

Figure 1. Use of hES and hiPS cells in approved research projects, 2007-2018. The chart shows the total number of approved research projects (grey) and the number of research projects in which not only hES but also hiPS cells are used (black).

4. Increase in the number of clinical trials with hPS cells abroad

Since 2010, an increasing number of clinical studies have been conducted worldwide using cells differentiated from hPS cells. An overview of the studies conducted hitherto, or currently being conducted, in the period 2010 to 2018 is shown in Table 3; the total number of studies now amounts to 42. This represents an increase of 27% compared to the previous year. In such studies, cells derived from hPS cells are being tested outside of Germany to determine their suitability for treating diseases for which no adequate therapy options currently exist. In the meantime, their safety and tolerability are also being examined within the framework of long-term studies. The majority of clinical trials listed in Table 3 are being carried out using cells that have been derived from hES cells (33 studies). Material derived from hiPS cells is currently being used in seven clinical trials, while one study respectively is using cells based on parthenogenetic stem cells (hpPS cells) or stem cells (NT-hES cells) derived from embryos produced by nuclear transfer (SCNT). Most of the studies conducted with cells derived from hES cells (18) focus on the treatment of different forms of macular degeneration. Other studies target the development of therapies for other eye diseases (5), type I diabetes mellitus (4), ischaemic heart diseases (1), diseases of the nervous system (4) and lung cancer (1). Studies using hiPS cells focus on the treatment of age-related macular degeneration (2) (one of these studies was suspended in 2015 because of genetic changes in the hiPS cells), on graft-versus-host disease (1), ischaemic heart disease (2) and Parkinson's disease (2). It is striking that none of the studies currently being conducted with hiPS cells are being carried out on the basis of autologous cells; all the studies are using cell products obtained from allogenic hiPS cells. The clinical study using cells derived from NT-hES cells targets the treatment of age-related macular degeneration, while the only study to date using parthenogenetic stem cells (hpPSC), in which neural stem cells are transplanted, targets the treatment of Parkinson's disease.

The number of clinical trials based on hES cells has been increasing since 2010 – for example by 18% from 28 at the end of 2017 to 33 at the end of 2018 alone. This clearly shows that hES cells have left the field of basic research in many places and are increasingly being

translated into clinical applications. The research reservation of the Stem Cell Act is a central obstacle to making corresponding developments also possible in Germany. To this end, the Stem Cell Act should be revised with regard to the research reservation.

Overview of clinical trials based on human pluripotent stem cells conducted world-wide (2010-2018)

	Disease (ICD-10)	Number of studies	Participants (does not correspond to the number of patients treated)*
hES cells	**Diseases of the eye and adnexa**	**23**	**419**
	Age-related macular degeneration (AMD)	13	286
	Stargardt's disease (hereditary juvenile form of macular degeneration)	5	52
	Retinitis pigmentosa	1	10
	Other eye disorders	4	71
	Endocrinal, nutritional and metabolic diseases	**4**	**327**
	Type 1 diabetes mellitus	4	327
	Diseases of the circulatory system	**1**	**10**
	Ischaemic heart disease	1	10
	Diseases of the nervous system	**4**	**111**
	Spinal-cord injuries	2	40
	Parkinson's disease	1	50
	Amyotrophic lateral sclerosis	1	21
	Neoplasms	**1**	**48**
	non-small cell lung cancer	1	48
hiPS cells	**Diseases of the eye and adnexa**	**2**	**11**
	Age-related macular degeneration (AMD)	2	11
	Injuries, poisonings and certain other consequences of external causes	**1**	**16**
	Graft-versus-host disease	1	16
	Diseases of the circulatory system	**2**	**25**
	Ischaemic heart disease	2	25
	Diseases of the nervous system	**2**	**14**
	Parkinson's disease	2	14
NT-hES cells	**Diseases of the eye and adnexa**	**1**	**3**
	Age-related macular degeneration (AMD)	1	3
hpPS cells	**Diseases of the nervous system**	**1**	**12**
	Parkinson's disease	1	12
	Total	**42**	**996**

Table 3. Clinical trials with cells developed from human pluripotent stem cells (including long-term studies with patients from previous clinical trials). *'Participants' refers to the number of people who have been or are to be recruited for the respective study. The number of people who are already being

treated or have been treated is currently only partly known to the public. Robert Koch Institute, unpublished data from various sources, i.a. 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 last revised: 31/12/2018.

See Table 4 for an overview of the countries in which the clinical trials are being carried out. In summary, it can be stated that between 2010 and 2018 clinical trials using hES cells were carried out mainly in the USA, China and the UK, while trials using hiPS cells took place mainly in Japan. At present, no clinical trials on the basis of pluripotent stem cells are being carried out in Germany.

Overview of the countries where clinical trials with human pluripotent stem cells are carried out (2010-2018)

	Country	Number of studies
hES cells	USA	15
	China	7
	UK	6
	Korea	2
	Brazil	1
	France	1
	Israel	2
	Canada	4
hiPS cells	Australia	1
	China	1
	UK	1
	Japan	5
NT-hES cells	Korea	1
hpPS cells	Australia	1
	Total	42*

Table 4. Overview of the countries participating in clinical trials (including long-term studies with patients from previous clinical trials). *Some trials are being carried out in several countries. Robert Koch Institute, unpublished data using various sources i.a. 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 last revised 31/12/2018.

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