Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

17th Report after the Enactment of the
Stem Cell Act (StZG)
for the Reporting Period 1 January to 31 December 2019

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/or use of human embryonic stem cells (hES cells) according to the regulations of the Stem Cell Act, issues an opinion on every application and sends it to the Robert Koch Institute (RKI), the competent authority under the Stem Cell Act. The Committee's activities are based on 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 on 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, 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 Stem Cell Act, 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 import and/or use hES cells, for which an application has been submitted, meets the criteria of section 5 of the Stem Cell Act. Section 5 of the Stem Cell Act requires that an application must demonstrate 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 Stem Cell Act), (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. 2 letter a of the Stem Cell Act), and (c) that the targeted increase in scientific knowledge requires the use of hES cells (section 5 no. 2 letter b of the Stem Cell Act). The ZES summarizes the results of its review in a written opinion and sends it to the RKI.

Pursuant to section 14 of the ZESV, the ZES prepares an annual report which is 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 Clinic for Neurology Georg-August-Universität Göttingen	Prof. Dr Wolfram H. Zimmermann Institute of Pharmacology and Toxicology Georg-August-Universität Göttingen
	Prof. Dr Anthony D. Ho Med. Universitätsklinik und Poliklinik Ruprecht-Karls-Universität Heidelberg	Prof. Dr Beate Winner Department of Stem Cell Biology Universitätsklinikum Erlangen Friedrich-Alexander-Universität Erlangen-Nürnberg
	Prof. Dr Katja Schenke-Layland Natural and Medical Sciences Institute at the Universität Tübingen	Prof. Dr Ricardo E. Felberbaum Gynaecology Clinic Klinikum Kempten Oberallgäu
	Prof. Dr Hans R. Schöler Max Planck Institute for Molecular Biomedicine Münster	Professor Dr Martin Zenke Helmholtz Institute for Biomedical Engineering RWTH Aachen
	Prof. Dr Anna M. Wobus **(Deputy Chair)** Leibniz Institute of Plant Genetics and Crop Plant Research (IPK) Gatersleben	Prof. Dr Maria Wartenberg Molecular Cardiology and Stem Cell Research Universitätsklinikum Jena
Ethics and Theology	Prof. Dr Dr Antonio Autiero **(Deputy Chair)** Faculty of Catholic Theology Westfälische Wilhelms-Universität Münster	Prof. Dr Dr Jochen Sautermeister Faculty of Catholic Theology Rheinische Friedrich-Wilhelms-Universität Bonn
	Prof. Dr mult. Nikolaus Knoepffler Chair of Applied Ethics Friedrich-Schiller-Universität Jena	Prof. Dr Christine Hauskeller Department of Sociology, Philosophy and Anthropology University of Exeter, England
	JProf. Dr Dr Sabine Salloch Institute of Ethics and History of Medicine Universitätsmedizin Greifswald	Prof. Dr Ralf Stoecker Department of Philosophy Universität Bielefeld
	Prof. Dr Klaus Tanner **(Chair)** Theological Seminary Ruprecht-Karls-Universität Heidelberg	Prof. Dr Hartmut Kress Faculty of Protestant Theology Rheinische Friedrich-Wilhelms-Universität Bonn

Table 1. Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES), last revised December 2019.

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

In 2019, the ZES held five meetings and discussed a total of ten applications for the import and use of hES cells. The ZES handed down favourable 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 Stem Cell Act and are ethically acceptable within its intendment (section 9 of the Stem Cell Act).

No.	Holder of approval	Topic of approved studies	Date of the positive ZES opinion
1 (143, 144)	Dr Katrin Schrenk-Siemens, Universität Heidelberg Dr Claudio Acuna Goycolea, Universität Heidelberg	Establishment of cell models to study signalling pathways and synaptic transmission in human neural networks under the conditions of physiological and pathological pain	16/01/2019
2 (145)	Prof. Dr Michaela Frye, German Cancer Research Institute (Deutsches Krebsforschungsinstitut, DKFZ), Heidelberg	Study of the functions of RNA modifications in the ectodermal and neuronal differentiation of human embryonic stem cells	15/05/2019
3 (146)	Technische Universität Dresden	Differentiation of human embryonic stem cells towards steroid-producing cells of the adrenal cortex	15/05/2019
4 (147)	Dr Leo Kurian, Universität Köln	Studies on the role of RNA-binding proteins in the maintenance of pluripotency and in the differentiation of human embryonic stem cells	17/07/2019
5 (148)	Max Delbrück Center for Molecular Medicine (MDC), Berlin	Studies of further specific functions of the human endogenous retrovirus H (HERVH) in the regulation of the pluripotency of human embryonic stem cells	17/07/2019
6 (149)	Prof. Dr Anne Grapin-Botton, Max Planck Institute for Molecular Cell Biology and Genetics (MPI-CBG), Dresden	Study of molecular processes in the development of different types of pancreatic cells from human embryonic stem cells and the development/optimization of corresponding *in-vitro* differentiation protocols	16/09/2019
7 (150)	RHEINCELL Therapeutics GmbH, Langenfeld (Rhineland)	Use of human embryonic stem cells as reference material for the establishment of a bank of HLA-homozygous induced pluripotent stem cells under conditions of good manufacturing practice	16/09/2019
8 (151)	Professor Dr Dennis Schade, Christian-Albrechts-Universität, Kiel	Study of modulators of mesoderm induction and cardiomyocyte differentiation in human embryonic stem cells	11/11/2019
9 (152)	Dr Micha Drukker, Helmholtz Zentrum München GmbH	Studies on the influence of nuclear RNA-protein aggregates on the pluripotency and differentiation of human embryonic stem cells	11/11/2019
10 (153)	Technische Universität 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 (the approved research work is identical to the 139th approval under the Stem Cell Act)	12/12/2019

Table 2. Overview of research projects that were approved by the RKI during the 2019 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 two approvals in the case of one application (no. 1).

The subject of the first research project listed in Table 2 (143rd and 144th approvals under the Stem Cell Act) is the establishment of human *in-vitro cell models* that allow to study mechanisms involved in pain perception and transmission in neurons of the peripheral and central nervous system. In Germany, approximately 12 to 15 million people suffer from chronic pain; at present, some of them can only be inadequately treated, so that the development of cell models for reproducing the molecular and cellular processes occurring in pain is of great relevance. In the project, neuronal cell types of the peripheral and central nervous system are therefore to be produced from hES cells, and specific neural networks generated by co-cultivating the different neuronal cell types in a microfluidic system consisting of several chambers and thoroughly characterized at the morphological, molecular and functional level. The properties of the neural networks formed on the microfluidic chip are then to be studied, particularly under conditions of experimentally generated chronic pain – by adding pain-inducing substances or by genome editing; the suitability of this *in-vitro* cell model for testing analgesic substances is to be examined. This work may generate new insights into the genetic and cellular mechanisms underlying pathological forms of pain in human neurons. The work may also lay the foundation for the future development of new pharmacological test systems in the development of active ingredients.

The focus of the second research project (145th approval under the Stem Cell Act) is on studying the role of RNA modifications, particularly tRNA modifications, in the maintenance of pluripotency and in (neuro-)ectodermal differentiation. The background of the research work is the fact that some mutations in genes that code for RNA-modifying enzymes are associated with neurological diseases or developmental disorders. Precise genetic modifications are therefore to be introduced into the genes for tRNA-modifying enzymes in hES cells; the effects on the properties of hES-cell-derived (neuro-)ectodermal cells and undifferentiated pluripotent cells will be thoroughly analysed. These studies include, for example, the analysis of differentiation and self-renewal behaviour, the translation rate and protein synthesis. The above-mentioned studies can in all probability lead to new insights on the influence of tRNA modifications on neurological development processes and their importance for severe neurological diseases in humans.

The subject of the third research project (146th approval under the Stem Cell Act) is the generation of steroid-producing adrenal organoids from hES cells with the long-term aim of developing cell-replacement therapies for adrenal diseases. Such organoids are also to be used to study the molecular and cellular processes underlying adrenal insufficiency. The project aims to first establish procedures for the efficient *in-vitro* differentiation of cells of the intermediate mesoderm into steroid-producing cells/organoids and to characterize the steroid-producing cells/organoids comprehensively both *in vitro* and *in vivo*. Another focus of the work is the establishment of a model for genetically caused adrenal insufficiency. To this end, corresponding disease-associated genes in hES cells are to be switched off or modified by genome editing to determine the effects on the properties of the organoids derived from these hES cells. Adrenal insufficiency is a life-threatening condition that requires lifelong hormone-replacement therapy and can lead to significant morbidity in connection with chronic fatigue, muscle weakness, loss of appetite and weight loss. Since the currently available therapeutic options are inadequate, the development of corresponding tissue-replacement therapies is of great relevance; the research project aims to lay the foundations for this. The work could lead to new insights into the properties of adrenal organoids derived from hES cells; furthermore, new *in-vitro* model systems based on human adrenal cells are

to be created, which can be used in the future to study the molecular and cell-biological changes associated with adrenal insufficiency. This is important for understanding the molecular pathogenesis mechanisms underlying this disease.

The fourth research project (147th approval under the Stem Cell Act) aims to clarify the regulatory role of certain RNA-binding proteins (RBPs) in hES cells during the early differentiation of human cells. The first stage will be to study the association of the respective RBPs with ribosomes and to determine their subcellular localization. The next will be to identify interaction partners at the protein and RNA level and to analyse changes in these interactions during differentiation, especially into the cardiac lineage. Furthermore, the genes coding for the respective RBPs are to be functionally switched off in hES cells to determine possible effects on the pluripotency of the cells and on their transcriptome and proteome. An additional task will be to examine whether and to what extent the differentiation of the cells modified in this way is impaired in cells of different germ layers. The research is expected to contribute to a deeper understanding of the importance of the RBP-mediated post-transcriptional regulation of gene expression in early differentiation processes in human cells.

The fifth project (148th approval under the Stem Cell Act) is to investigate whether and how the human endogenous retrovirus H (HERVH) influences the chromatin structure in human pluripotent stem cells and is thus involved in the regulation of (naïve) pluripotency. The first step will be to use hES cells to study whether there is a specific relationship between the HERVH-controlled gene-expression pattern and the chromatin structure, what influence histone modifications have on the HERVH-mediated regulation of pluripotency, and whether and to what extent HERVH is involved in the build-up/reduction and/or in the stabilization/destabilization of so-called topologically associated domains (TADs). Another aim will be to clarify whether and to what extent HERVH also influences the expression of distant genes as a functional enhancer, particularly by establishing TADs. In order to conduct the above-mentioned studies, genetic modifications (using the CRISPR/Cas9 technique) and analyses are to be made at the level of the transcriptome and chromatin structure and organization. The results of this work could yield new insights into HERVH-controlled processes potentially involved in establishing and maintaining the pluripotency of human stem cells.

The focus of the sixth project (149th approval under the Stem Cell Act) focuses on optimizing procedures for obtaining different pancreatic cell types from hES cells *in vitro* – with the aim of gaining a better understanding of the molecular processes involved in the development of the different types of human pancreatic cells. To achieve this, the procedures for developing and expanding pancreatic progenitor cells are first to be optimized and the underlying differentiation processes analysed at the molecular level. Furthermore, approaches to the cell development and maturation of progenitor cells into endocrine and exocrine pancreatic cells are to be further developed and the underlying mechanisms studied. The results obtained in hES cells are then to be verified in human induced pluripotent stem cells (hiPS cells) using hES cells as reference material. This work could led to a better understanding of the molecular and cellular principles of human pancreatic development and to the creation of a basis for future cell-based therapies by developing new effective methods for providing human pancreatic cells.

The aim of the seventh research project (150th approval under the Stem Cell Act) is to build up, under the conditions of *good manufacturing practice* (GMP), a clinically usable stem-cell bank of hiPS cells that are homozygous with regard to the genes for the most important human leukocyte antigens (HLA). hES cells are to be used in the proposed research project to make it possible to estimate whether and to what extent the respective produced hiPS cell lines exhibit properties of pluripotent cells. If the proposed research project is successful, a clinically usable and well characterized cell bank of HLA-homozygous hiPS cells could be made available that enables the production of largely immunocompatible allogenic cell-therapeutic agents. This would be of great importance for the future use of (allogeneic) hiPS cells for treating many patients with different immunological phenotypes.

The subject of the eighth research project (151st approval under the Stem Cell Act) is the establishment of chemically defined conditions for the efficient differentiation of hES cells into cells of the mesodermal germ layer using novel small-molecule activators of the bone morphogenetic protein (BMP) signalling pathway; the focus of interest here is the differentiation into cardiac cells via mesodermal progenitor cells. For this purpose, the new BMP activators are to be used either alone or in combination with other cytokines for the differentiation of hES cells; the effects on mesoderm induction, mesoderm structuring and cardiac differentiation, and on the BMP signalling pathway are to be analysed. A further aim is to identify and characterize cellular binding partners of the new BMP activators in hES cells during mesoderm induction. The work will also make comparisons using hiPS cells. Overall, the research may contribute to a deeper understanding of the role and functions of the BMP signalling pathway in early mesodermal and cardiac differentiation processes in human cells. This could contribute to a better standardization of cell production from hES cells and thus have a significant impact on potential applications of cells produced from hES cells. The research work could also be important for the development of new BMP-mimetic substances that might be used in the future for pharmacotherapeutic purposes, for example in the treatment of osteopenic diseases.

The aim of the ninth research project (152nd approval under the Stem Cell Act) consists of research into the role of nuclear RNA-protein aggregates (particularly so-called paraspeckles) in differentiation, especially in the transition from the stage of naïve/primed pluripotency to early differentiation stages, as well as in the development into various differentiated cell types. In order to achieve this, specific *knockouts* are to be carried out of the genes for NEAT1, an essential structural component of paraspeckles, and for other paraspeckle proteins; or else changes in their expression level (e.g. *knockdown*) in hES cells will be made and the consequences of these changes for pluripotency and differentiation ability evaluated at the molecular level. To this end, analyses are to be made i.a. of gene expression at the protein and DNA/RNA level and cellular interaction partners of NEAT1 identified and characterized in undifferentiated hES cells and different cell types derived from hES cells. These studies are also to be extended to other so-called lncRNAs *(long non-coding RNAs*) regulated during development. The aim is for the work to contribute to new insights into the molecular function of nuclear RNA-protein aggregates in maintaining pluripotency and in differentiation processes in human cells. These insights could also be important for explaining diseases associated with the deregulation of e.g. NEAT1 and other lncRNAs, such as cancer or amyotrophic lateral sclerosis.

The 153rd approval under the Stem Cell Act, which is identical to the 139th approval in terms of content, was granted to the Technische Universität München (see no. 10, Table 2). The applied-for research using hES cells aims to develop methods to make sufficient quantities of high-quality functional, mature beta cells available for future regenerative therapies of diabetes mellitus type 1. The background here is that the research conducted in the context of the 139th approval must now also be optimized under conditions of good manufacturing practice in order to define the procedures for producing the cell and tissue material that will be required later for clinical trials of tissue-replacement therapy for diabetes mellitus. This requires specific technical conditions for cultivating and differentiating the cells that the licence holder has.

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 ZES's main arguments justifying the high-ranking status of the research projects, the adequate preliminary clarification of the respective research questions, and the need to use human ES cells were also included in the RKI's assessment of the research projects.

Seven 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 17 years of activity, the ZES has submitted opinions to the RKI on a total of 149 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 153 approvals, some of which have been extended. Thirty of these approvals have expired to date. At present, 86 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

3.1. Research topics in the reporting period

3.1.1 Generation of therapeutically useful cells from hPS cells

The generation of therapeutically useful cells derived from human pluripotent stem cells (hPS cells) is again a central topic among the research projects applied for in 2019. Of the ten research projects evaluated during the reporting period, three projects (146th, 149th and 151st approvals) deal with the establishment and optimization of methods for the *in-vitro* production of potential starting materials that are of the quantity, purity and quality required for a clinical application. Here, diseases of the adrenal gland, the pancreas and the heart are the focus of interest. Methods for the efficient production of steroid-producing adrenal organoids, as well as pancreatic (endocrine and exocrine) and cardiac cells/organoids, from hPS cells are required for their future therapy. In another of these projects (150th approval), in which hES cells are used as a reference material for evaluating the pluripotency of hiPS cells, pluripotent hiPS cells derived from umbilical cord blood are also to be used to establish an HLA-homozygous cell bank; these cells can in future be the starting material for the production of largely immunocompatible allogeneic cell-therapeutic agents. The development of procedures for the provision of cells for clinical application is highly relevant in view of the international developments in this field.

3.1.2 Molecular basis of pluripotency and differentiation processes

It is evident that research into the molecular basis of pluripotency and differentiation processes in human cells has not been completed and is therefore still of considerable interest more than 20 years after the first establishment of human embryonic stem cells. The purpose of one project (145th approval) is to clarify the importance of RNA modifications, particularly tRNA modifications, for the maintenance of pluripotency and for (neuro)ectodermal differentiation Two other projects (147th and 152nd approvals) aim to provide fresh insights into possible functions of RNA-binding proteins and nuclear RNA-protein aggregates in the pluripotency of human ES cells and in early differentiation processes at the molecular level. A further project seeks to answer questions concerning the role of the human endogenous retrovirus H (HERVH) in the regulation of the pluripotency of hES cells. These projects aim not only to achieve a better understanding of the molecular basis of pluripotency maintenance and of development into different differentiated cell types, but also to enable conclusions to be drawn about early human development processes.

3.1.3 In-vitro disease models using hES cells

Another topic of the research projects evaluated in the reporting period was the provision of human cell models for the study of human diseases. In one project (143rd and 144th approvals), neural networks based on human nerve cells and consisting of neurons of the peripheral and central nervous system are to be established and characterized. These

networks are then to be used to analyse the genetic and cellular basis of physiological and pathological pain and to study the causes of pain hypersensitivity and pain tolerance. In the future, the established neuronal cell models are also to be used as pharmacological screening systems, which will help identify new analgesic drug candidates and thus contribute to the development of new therapeutic procedures for the treatment of pain disorders. In addition, in a further research project (146th approval) a model system for genetically determined adrenal insufficiency is to be established using adrenal (cortex) cells derived from hES cells to gain a better understanding of the molecular basis of this disease.

3.2. Comparative studies on hiPS cells and hES cells

In four of the eleven new research projects approved in the reporting period, hES cells are also needed as reference material or for comparison purposes to clarify research questions using hiPS cells. In most cases, the respective question of interest is also to be clarified for hES cells (Fig. 1). In some projects, hES cells are used together with hiPS cells to estimate the differentiation potential of hiPS cells into pancreatic and/or mesodermal/cardiac cell types compared to hES cells (149th and 151st approvals). Another project aims to clarify whether there are differences between the two cell types in the expression of ribosomal binding proteins and in their function in the regulation of gene expression (147th approval). The purpose of this study is thus to evaluate in each case whether the findings obtained in hES cells can be confirmed in hiPS cells, and consequently whether they apply generally to human pluripotent cells. In a further project to establish a cell bank made up of HLA-homozygous hiPS cells, however, hES cells are to be used exclusively as reference material for the evaluation of the properties of hiPS cells; it is assumed here that hES cells are more original than hiPS cells with regard to the properties determining pluripotency and can therefore be used as reference material (150th approval).

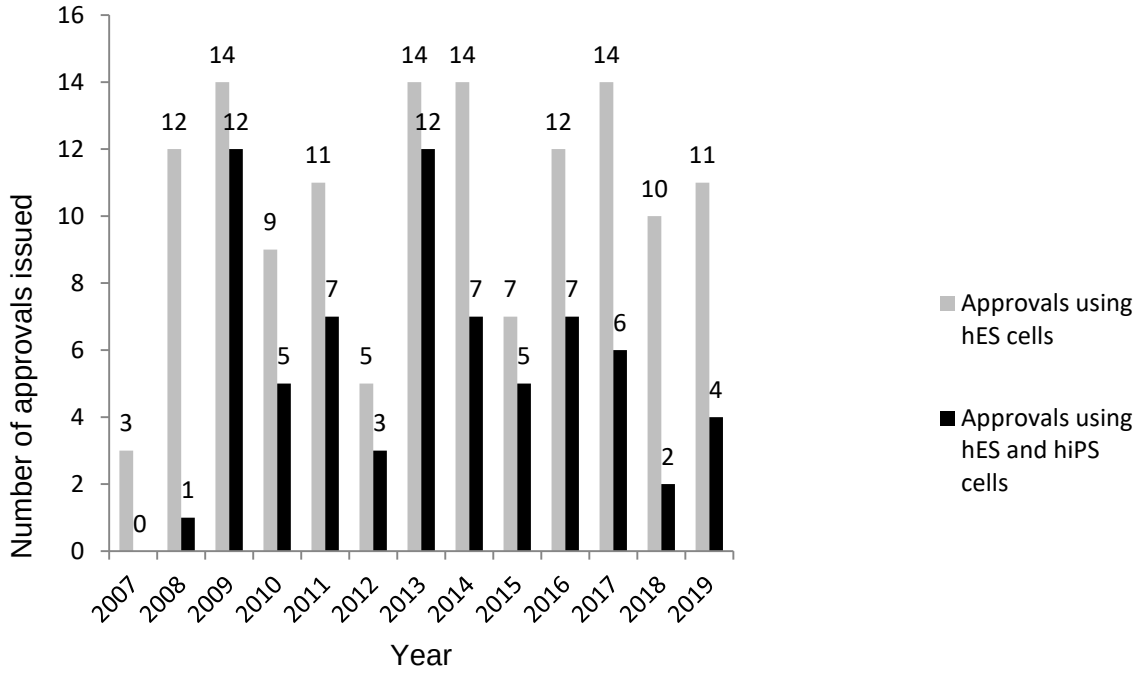

Figure 1. Use of hES and hiPS cells in approved research projects 2007-2019. The chart shows the total number of approved research projects (grey) and the number of research projects in which not only hES but also hiPS cells are used (black).

3.3. Increase in the number of clinical trials using hPS cells abroad

It can be observed that, compared to the previous year, there has been a marked increase in the number of clinical trials conducted abroad using cells derived from hPS cells – from a total of 42 studies at the end of 2018 to 54 studies at the end of 2019. Furthermore, the spectrum of diseases to be treated using hPS-cell-derived cell therapeutics has also expanded significantly. For example, clinical trials with hPS cells have been initiated with the aim of treating primary ovarian insufficiency, meniscal ganglion, affections of the sclera, cornea, iris and ciliary body, thalassemia or cerebrovascular diseases and malignant tumours. Table 3 gives an overview of clinical studies based on hPS cells that have been (or are being) conducted since 2010.

The majority of the clinical trials listed in Table 3 are still being conducted using cell-therapeutic agents derived from hES cells (32 of 54 studies). Nineteen clinical studies are currently using material derived from hiPS cells. Two studies use cells based on human parthenogenetically produced pluripotent stem cells (hpPS cells), and one study uses cells derived from embryos created by nuclear transfer (SCNT) (NT-hES cells).

In the studies with cells derived from hES cells, whose number has remained almost the same as in the previous year, the treatment of diseases of the eye and adnexa predominates (21 of 32 studies); this is followed by studies on the treatment of metabolic diseases (5 of 32 studies) and diseases of the nervous system (3 of 32 studies). By contrast, the number of studies based on hiPS cells has increased markedly compared to the previous year (from 7 studies at the end of 2018 to 19 studies at the end of 2019). These studies are mainly aimed at the development of therapies for diseases of the circulatory and nervous systems, the eye and for the treatment of malignant tumours (15 of 19). An almost equal number of the studies conducted with hiPS cells are based on autologous and allogeneic cells. Clinical studies using cells derived from NT-hES cells or hpPS cells are still in the minority and focus on the treatment of age-related macular degeneration and Parkinson's disease.

Overview of clinical trials based on human pluripotent stem cells conducted worldwide (2010-2019)

	Disease (according to ICD-10)	Number of studies	Participants (does not correspond to the number of patients treated)*
hES cells	**Diseases of the eye and adnexa**	**21**	**414**
	Age-related macular degeneration (AMD)	10	250
	Stargardt's disease (hereditary juvenile form of macular degeneration)	5	53
	Retinitis pigmentosa	2	22
	Other eye disorders	4	89
	Endocrinal, nutritional and metabolic diseases	**5**	**355**
	Type 1 diabetes mellitus	4	327
	Primary ovarian insufficiency	1	28
	Diseases of the nervous system	**3**	**51**
	Spinal-cord injuries	2	30
	Amyotrophic lateral sclerosis	1	21

	Diseases of the circulatory system	**1**	**10**
	Ischaemic heart disease	1	10
	Neoplasms	**1**	**48**
	Tar lung cancer *(non-small cell lung cancer)*	1	48
	Diseases of the musculoskeletal system and connective tissue	**1**	**18**
	Meniscus ganglion	1	18
hiPS cells	**Diseases of the circulatory system**	**6**	**45**
	Ischaemic heart disease	4	21
	Cerebrovascular diseases	2	24
	Diseases of the eye and adnexa	**3**	**11**
	Age-related macular degeneration (AMD)	2	7
	Affections of the sclera, cornea, iris and ciliary body	1	4
	Diseases of the nervous system	**3**	**24**
	Parkinson's disease	3	24
	Neoplasms	**3**	**212**
	Malignant neoplasms	3	212
	Endocrinal, nutritional and metabolic diseases	**1**	**20**
	Type 1 diabetes mellitus	1	20
	Injuries, poisonings and certain other consequences of external causes	**1**	**16**
	Graft-versus-host disease	1	16
	Diseases of the blood	**2**	**14**
	Thalassemia	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**	**2**	**62**
	Parkinson's disease	2	62
	Total	**54**	**1,303**

Table 3. Clinical trials with cells derived from human pluripotent stem cells (including long-term studies with patients from previous clinical trials). *The term '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 on 31/12/2019.

See Table 4 for an overview of the countries in which the clinical trials are being carried out. It can be stated here that between 2010 and 2019 clinical trials based on 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 human pluripotent stem cells are being carried out in Germany.

Overview of the countries where clinical trials with human pluripotent stem cells are carried out (2010-2019)

	Country	Number of studies
hES cells	USA	13
	China	7
	UK	6
	Canada	4
	France	2
	Israel	2
	Korea	2
	Brazil	1
hiPS cells	China	8
	Japan	7
	USA	3
	Australia	1
NT-hES cells	Korea	1
hpPS cells	Australia	1
	China	1
	Total	59*

Table 4. Overview of countries in which clinical trials based on hPS cells have been or are being conducted or initiated by the end of 2019 (including long-term studies with patients from previous clinical trials) * Some trials are being carried out in several countries. 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 on 31/12/2019.

4. Conclusion

Basic research using hES cells is still essential for understanding the biology of human pluripotent stem cells – and also, both directly and indirectly, for many other areas of research ranging from developmental biology to research into the causes of diseases. For specific questions of basic research it would be meaningful and necessary to make available newer stem-cell lines derived after the cut-off date currently in force in Germany (i.e. after 1 May 2007) and modified to a lesser extent by improved culture conditions.

The increase in the number of clinical trials based on hES cells, all of which are conducted abroad (from 6 studies at the end of 2012 to 32 studies at the end of 2019), is an indication that in several cases steps are already being taken towards translation into clinical research on the basis of successful basic research using hES cells.

The Stem Cell Act's exemption for research is the decisive reason why there are no corresponding developments in the direction of translation in Germany, since the use of hES cells beyond research for the production of cell products is not possible in Germany by law. The research exemption of the Stem Cell Act would have to be dropped to make such production possible and thus to even lay the foundations for the domestic provision of such cell-therapeutic agents. This would also be logical and consistent, because the research exemption of the Stem Cell Act reflects the scientific situation as it was in 2002, when there was little knowledge of hES cells and medical applications were still a long way off.

On the other hand, the legal regulation of research using hES cells was explicitly justified by the need to "take into account sick people's interest in the development of new chances of a cure" (Deutscher Bundestag, Drucksache 14/8394, 27 February 2002). As a result, therefore, it would be contradictory to continue in the future allowing only research of high-ranking status aimed at expanding medical knowledge in the development of diagnostic, preventive or therapeutic procedures for application in humans, while still not allowing the implementation of the knowledge thus gained to develop therapeutic products in Germany.

The 17th Report was adopted using the written procedure.