Report

of the

Central Ethics Committee for Stem Cell Research (ZES)

21st Report after the Enactment of the Stem Cell Act (StZG) for the reporting period from 1 January to 31 December 2023

1. The Central Ethics Committee for Stem Cell Research

The Central Ethics Committee for Stem Cell Research (Zentrale Ethik-Kommission für Stammzellenforschung, ZES) was convened 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 submits 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 p. 2277), most recently amended by Article 50 of the 'Act on dismantling unnecessary ordinances on the written form in Federal administrative law' (BGBl. I p. 626) dated 29 March 2017 (http://www.gesetze-im-internet.de/stzg/index.html), and on the 'Regulation concerning the Central Ethics Committee for Stem Cell Research and the competent authority pursuant to the Stem Cell Act' (ZES-Verordnung – ZESV) dated 18 July 2002 (BGBl. I p. 2663), most recently amended by Article 51 of the above-mentioned law dated 29 March 2017 (BGBl. I p. 626) (http://www.gesetze-im-internet.de/zesv/index.html).

The Committee conducts its work on an honorary basis; it 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). At the end of the seventh appointment period, Prof. Dr Schicktanz, Prof. Dr Kress and Prof. Dr Schöler left the ZES in August 2023. Of the 18 members and deputy members of the ZES, fifteen members and deputy members were reappointed, and two members (Prof. Dr Moretti and Prof. Dr Dr Friedrich) and one deputy member (Dr Inthorn) were appointed to the ZES for the first time for what is now the eighth appointment term (2023 to 2026). Furthermore, Prof. Dr Felberbaum has now been appointed as a member and Prof. Dr Schrepfer as a deputy member. 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 pursuant to the Stem Cell Act of the applications received by 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 meets the criteria of section 5 of the Stem Cell Act, which requires that an application must demonstrate in a scientifically substantiated manner that (a) the project pursues high-level research objectives for a gain in scientific knowledge (section 5, no. 1 of the Stem Cell Act), (b) the scientific issues have, as far as possible, 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) the targeted gain in scientific knowledge can probably only be achieved by using 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 submits it to the RKI. Pursuant to section 6 (4) no. 3 of the Stem Cell Act, the existence of an opinion by the ZES is a prerequisite for the granting of an approval to import and use hES cells.

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 and the RKI.

Table 1. Members and deputy members of the Central Ethics Committee for Stem Cell Research (ZES), as of December 2023.

Members	Deputy members
Biology	
Prof. Dr Katja Schenke-Layland, **(Deputy Chair)** Natural and Medical Sciences Institute at Tübingen University	Prof. Dr Maria Wartenberg, Universitätsklinikum (University Hospital) Jena, Molecular Cardiology and Stem Cell Research
Prof. Dr Alessandra Moretti Technische Universität München (Technical University Munich) Klinikum rechts der Isar Clinic and Polyclinic for Internal Medicine I: Cardiology	Prof. Dr Martin Zenke, RWTH Aachen, Medical Clinic IV
Medicine	
Prof. Dr Mathias Bähr, Georg-August-Universität Göttingen (Göttingen University), Neurological Clinic	Prof. Dr Wolfram-H. Zimmermann, Georg-August-Universität Göttingen (Göttingen University) Institute of Pharmacology and Toxicology
Prof. Dr Anthony D. Ho, Ruprecht-Karls-Universität, Heidelberg (Heidelberg University), Med. Universitätsklinik und Poliklinik (University Hospital and Policlinic)	Prof. Dr Beate Winner, Friedrich-Alexander-Universität Erlangen-Nürnberg (Erlangen-Nuremberg University), Universitätsklinikum (University Hospital) Erlangen, Department of Stem Cell Biology
Prof. Dr Ricardo E. Felberbaum Klinikum Kempten Oberallgäu Gynaecological Clinic	Prof. Dr Sonja Schrepfer University Heart and Vascular Centre (UKE) Hamburg Clinic and Polyclinic for Heart and Cardiovascular Surgery
Ethics	
Prof. Dr Dr Sabine Salloch **(Deputy Chair)**, Medizinische Hochschule Hannover (Hanover Medical School) Institute of Ethics, History and Philosophy of Medicine	Prof. Dr Dres. h. c. Michael Quante, Westfälische Wilhelms-Universität Münster (Münster University), Department of Philosophy
Prof. Dr Dr Orsolya Friedrich Fernuniversität Hagen Cultural and Social Sciences Department of Philosophy IV	Prof. Dr Christine Hauskeller, University of Exeter, England, Department of Sociology, Philosophy and Anthropology
Theology	
Prof. Dr Dr Antonio Autiero **(Chair)**, Westfälische Wilhelms-Universität Münster (Münster University) Faculty of Catholic Theology	Prof. Dr Dr Jochen Sautermeister, Rheinische Friedrich-Wilhelms-Universität Bonn (Bonn University), Faculty of Catholic Theology
Prof. Dr Thorsten Moos, Ruprecht-Karls-Universität Heidelberg (Heidelberg University), Theological Seminary	Dr Julia Inthorn Centre for Health Ethics (ZfG) at the Protestant Academy Loccum

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

In 2023, the ZES discussed a total of 7 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).

Table 2. Overview of research projects approved by the RKI during the 2023 reporting period after receiving a positive opinion from the ZES. The numbers in brackets in the left column correspond to the approval numbers in the RKI register.

Serial no.	Holder of approval	Topic of approved research	Date of the positive ZES opinion
1 (185)	Max Planck Institute of Molecular Physiology, Dortmund	Differentiation mechanisms of the human hypoblast and human anterior visceral endoderm.	18 January 2023
2 (186)	Deutsches Krebsforschungszentrum (German Cancer Research Centre), Heidelberg	Development of in-vitro models for paediatric brain tumours.	12 April 2023
3 (187)	Max Delbrück Centre for Molecular Medicine (MDC), Berlin	Differentiation of human embryonic stem cells into organoids for the quantitative study of cortical development and associated human diseases. (The content of the approval is identical to the 161st approval in accordance with the Stem Cell Act)	04 July 2023
4 (188)	Bayer AG, Leverkusen	Development of improved processes for the production of the cell therapy bemdaneprocel.	11 September 2023
5 (189)	Deutsches Krebsforschungszentrum (German Cancer Research Centre), Heidelberg	Development of in-vitro models for human choroid plexus tumours.	11 October 2023
6 (190)	Universitätsmedizin Göttingen (Göttingen Medical School),	Study of the role of CX3CR1 for the development of microglia from human embryonic stem cells.	11 October 2023
7 (191)	Medizinische Hochschule Hannover (Hanover Medical School)	Generation of cytokine-resistant pancreatic beta cells derived from human embryonic stem cells by cytokine receptor knockout.	11 October 2023

The **first** research project (185th approval in accordance with the StZG) aims to develop and optimize procedures for obtaining hypoblast and anterior visceral endoderm (AVE) cells and to elucidate the molecular and cellular mechanisms underlying these early embryonic development processes, which are still poorly understood in humans. The focus is on identifying interactions between the different early embryonic cell types in humans. The research work is expected to contribute to a better understanding of human developmental biology.

The main emphasis of the **second** research project (186th approval according to the StZG) lies on the development of new models for medulloblastoma, the most common malignant tumour in children. In three sub-projects, new model systems based on neuronal precursor cells and cerebellar organoids derived from hES cells are to be established for three tumour subtypes that differ in terms of their cell-biological origin and for which there are currently no or only insufficiently meaningful cell and animal models. These models can be used to study the biology of these tumours on a cell-biological and molecular level and to develop new active substances for treating these tumours. Results from the studies should lead to new human-relevant disease models for medulloblastomas and provide insights into molecular processes that trigger the development of different types of medulloblastoma, which can make an important contribution to understanding the pathogenesis of these tumours.

The 187th approval according to the StZG, which is identical in content to the 161st approval, was granted to the Max Delbrück Centre for Molecular Medicine (MDC), Berlin **(third** research project, see Table 2, serial no. 3). The proposed research work using hES cells aims to establish a cortical organoid model that can be used to study aspects of cortical development in humans, analyse the molecular and cellular basis of neuronal developmental disorders and neurodegenerative diseases, and possibly identify substances that could form a basis for the development of novel therapeutic approaches in the future. The background here is that parts of the work covered by the 161st approval are now also to be carried out at the MDC's Stem Cell Core Facility.

The **fourth** research project (188th approval according to the StZG) aims to develop and optimize procedures for establishing a process for the production of the cell-based therapeutic agent bemdaneprocel – which is to be used for the treatment of Parkinson's disease and is already being tested in clinical trials conducted outside Germany – on a larger scale than hitherto. The intention is to optimize the first stage of the bemdaneprocel production process, during which the (pluripotent) hES cells are removed from a working cell bank and expanded into large quantities of cells. To this end, the culture medium for the expansion of the pluripotent stem cells is to be optimized and, in particular, the harvesting step at the end of the expansion phase, which includes the dissociation, centrifugation, filling and cryopreservation of the cells, is to be improved. The optimized cryopreservation of the cells should also make it possible to decouple stem-cell expansion – in terms of space and time – from the subsequent differentiation of the cells into the cell product. The research work is intended to contribute to the further development of a cell-replacement therapy for the treatment of Parkinson's disease in humans.

The purpose of the **fifth** research project (189th approval according to the StZG) is to develop *in-vitro* disease models for choroid plexus tumours (CPT), in which the cellular and molecular basis of tumour development and biology will be elucidated. There are currently no – or only an insufficient number of – meaningful cell or animal models available for studying these tumours. The project focuses on studying the effects of mutations in genes whose products are associated with the activation/regulation of the Wnt signalling pathway, which is believed to be involved in the development of CPT. However, the changes in the Wnt signalling pathway that underlie tumour development are still unknown. The project therefore initially aims to establish hES reporter-cell lines for Wnt to monitor the activation of Wnt signalling and to differentiate these into choroid plexus organoids (ChP organoids). In order to induce tumourigenesis *in vitro*, genes for the activation/regulation of the Wnt signalling pathway will then be functionally switched off or overexpressed in these organoids. The effects of the genetic changes on the development and properties of the ChP organoids will subsequently be determined in detail at the cell-biological and molecular level, particularly with regard to the development of tumours. The results of the studies may lead to new human disease models for CPT and provide insights into the molecular processes that trigger the development of CPT, which in all likelihood will make an important contribution to understanding the pathogenesis of the tumour.

Against the background that missing or dysfunctional microglia can play a role in the development of neurodegenerative diseases of the central nervous system and that the transplantation of functional microglia represents a conceivable therapy option for these diseases, the **sixth** research project (190th approval under the StZG) intends to use hES cells to clarify the functional significance of the CX_3C motive chemokine receptor 1 (CX_3CR1) for the development of human microglia. To this end, during the project hES cells carrying fluorescent reporters for the expression of the CX_3CR1 receptor gene, or hES cells in which the gene for CX_3CR1 is functionally deleted, will be differentiated *in vitro* into microglia precursor cells, and their ability to develop into microglia-like cells after transplantation into the CNS of microglia-depleted mice will be studied depending on the expression of the gene for CX_3CR1. Subsequently, the microglia cells differentiated from hES cells will be removed from the mouse at different times after transplantation and comprehensively characterized at the molecular level. As a result of this work, the molecular and cellular mechanisms of human glial development are likely to be better understood than before. The work could also yield results that are important for future cell therapies with functional microglial cells produced from hES cells and may be relevant for the treatment of patients with missing or dysfunctional microglia.

The aim of the **seventh** research project (191st approval in accordance with the StZG), is to clarify whether and to what extent a functional deletion of specific cytokine receptors in hES cells can reduce the toxic effect of proinflammatory cytokines on pancreatic beta cells differentiated from these hES cells and thus promote the survival of these cells *in vivo*. To this end, genes for cytokine receptors whose gene products are strongly expressed in beta cells derived from hES cells are to be functionally deleted. After comprehensive characterization of the genetically modified hES cells, these will then be differentiated into pancreatic organoids, their phenotype analysed in detail, and the effect of various cytokines on the vitality, functionality and molecular properties of the pancreatic organoids determined. The research work is intended to provide new insights into immunological issues associated with type 1 diabetes and to contribute to the creation of a basis for cell-replacement therapy for the treatment of type 1 diabetes.

Further information on the content of the research projects is available (in German) from the RKI's register (http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register-inhalt.html). The main arguments of the ZES justifying the high-ranking status of the research projects, the sufficient preliminary clarification of the respective research questions, and the need to use human ES cells were also included in the assessment of the research projects by the RKI.

Of the applications discussed during the reporting period (Table 1, serial nos. 2-7), five were submitted by researchers or institutions that had not yet previously received an approval in accordance with the Stem Cell Act. Six applications were made by researchers or institutions that had already received approvals in accordance with the Stem Cell Act in the past. All the applications were approved by the RKI after receipt of the ZES's opinion. During its 21 years of activity, the ZES has submitted opinions to the RKI on a total of 185 applications for the import and/or use of hES cells. In addition, a total of 42 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 granted 191 approvals, some of which have been extended [1]. Fifty-seven of these approvals have expired to date. Currently, 95 groups at 52 research institutions in Germany are in possession of approvals in accordance with the StZG and can conduct research using hES cells (as of 31 December 2023).

[1] The discrepancy between 185 favourable opinions of the ZES and 191 approvals of the RKI to date is due to the occasional joint application by more than one person. In these cases, two or three approvals were granted on the basis of only one opinion on the respective application.

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 hES cells

Of the seven research projects evaluated during the reporting period, two projects deal with the establishment of methods for the *in-vitro* production of potential starting materials for a clinical application. One of these research projects (Table 2, serial no. 4) focuses on the neurodegenerative condition Parkinson's disease; any future therapy will require methods for the efficient production of dopamine-producing neurones from hES cells. In another of these projects (Table 2, serial no. 7), cytokine-resistant pancreatic beta cells from hES cells are to be provided, which could in future be the starting material for the production of cell therapeutics for treating patients with type 1 diabetes. The development of procedures for the provision of cells for clinical applications is highly relevant in view of the international developments in this field.

3.1.2 In-vitro disease models using hPS cells

Three of the research projects approved during the reporting period aim to provide human cell models for clarifying molecular and cellular causes of diseases, and to determine the relation between genetic modifications and the pathogenesis of human diseases at the cellular level. Two of the research projects focus on the establishment of cell models for studying tumours of the central nervous system (Table 2, serial nos. 2 and 5). Another research project concentrates on neuronal developmental disorders and neurodegenerative diseases (Table 2, serial no. 3). Insights are expected into changes in processes that take place at the cellular level in the respective disease of interest, hopefully leading to a better understanding of the molecular pathogenesis of the diseases in question than has been the case to date. Authentic human disease models that depict the disease *in vitro* can be important for research into the disease and the development of new drugs.

3.1.3 Regulation of differentiation processes and early human embryonic development

Two of the research projects approved during the reporting period aim to clarify research questions relating to the importance of specific molecular processes in early embryonic development and microglial differentiation processes of human embryonic cells. One project will study the molecular and cell-biological principles of the differentiation of human embryonic cells in the direction of hypoblast cells and cells of the anterior visceral endoderm (AVE) (Table 2, serial no. 1). The aim of another research project is to gain new insights into the molecular function of CX_3CR1 in the development of micoglia from hES cells (Table 2, serial no. 6). The findings of this research work are expected to contribute to a deeper understanding of the control of basic development-biological processes in humans.

3.2. ELSA (Ethical Legal and Social Aspects) symposium organized by the Federal Ministry of Education and Research (BMBF)

The BMBF's ELSA symposium on 'Human embryos in medical research, taboo? - Justifiable? - Chance?' took place on 9-10 October 2023; members of the Committee took part as speakers. Two working groups prepared position papers on ethical and legal issues relating to reproductive medicine and research with human embryos, which are to be forwarded to the BMBF. The work of the ZES was mentioned positively several times, and the desiderata regarding a reform of the Stem Cell Act, as set out in the ZES's annual reports in recent years, were also explained in short presentations by members of the Committee.

3.3. Comparative studies on hiPS cells and hES cells

Comparative studies using iPS and hES cells are the subject of two of the seven research projects approved during the 2023 reporting period (Figure 1). In one project, hES cells are used as reference material to assess the potential of hiPS cells to differentiate into medulloblastoma cells of origin (Table 2, serial no. 2). Different hiPS cell lines vary considerably in terms of their differentiation ability. This can be caused by the genetic background of the donors, the properties of the somatic cells used for reprogramming, the reprogramming method and the factors used in this context for reprogramming, or by a possible epigenetic memory of the cells.

In another project (Table 2, serial no. 3), which aims to model developmental disorders and neurodegenerative diseases (autism spectrum disorders and Alzheimer's disease) *in vitro* and to clarify pathogenesis mechanisms at the cellular level, hiPS cells are compared with hES cells in which the mutation causing the disease has respectively been generated, as well as with corresponding isogenic wild-type controls. The aim here is to identify disease-specific signatures in order, in the further course of the project, to be able to include in the studies cases of illness that are not based on known individual mutations and for which, therefore, no isogenic cell lines can be produced and used for the study. These studies can contribute to our understanding of the molecular causes of these diseases and to the development of new therapeutic processes.

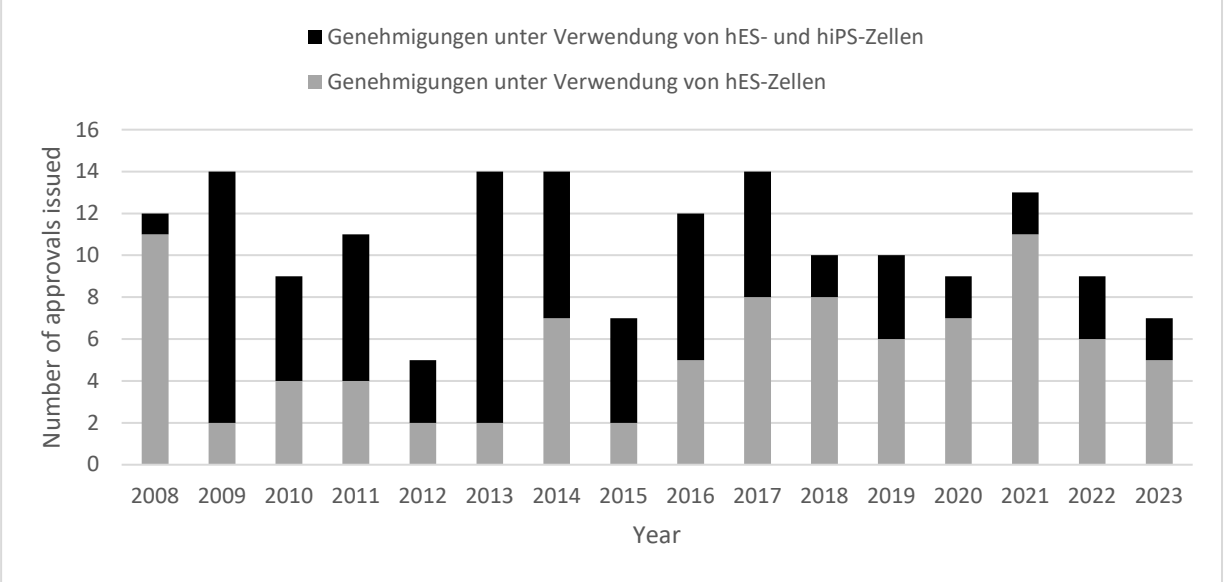

Figure 1. Approvals using hES and hiPS cells
Approvals using hES cells only

Use of hES and hiPS cells in approved research projects 2008-2023. The chart shows the number of research projects in which hES cells are used (grey) and the number of research projects in which not only hES but also hiPS cells are used (black).

3.4. Increase in the number of clinical trials using hPS cells

As shown in the Committee's reports in recent years, research on pluripotent stem cells since 2010 does not only involve basic research; at the national and international level it is also continuously moving in the direction of clinical applications. Table 3 provides an overview of the hPS-cell-based clinical trials conducted worldwide in the period from 2010 to 2023. Their number now totals 135 studies (as of the end of 2023). In such studies, cells derived from hPS cells are being tested to determine their suitability for treating diseases for which no adequate therapy options currently exist. Their safety and tolerability are also being examined in long-term studies in the meantime. Furthermore, over time there has also been a continuous

expansion in the spectrum of diseases for whose treatment cell therapeutics derived from hPS cells are being clinically tested. For example, clinical trials based on hiPS cells targeting the therapy of ischaemic heart diseases, atopic eczema and HIV disease were initiated for the first time in the reporting period.

The clinical studies listed in Table 3 are predominantly conducted using cell therapeutic agents derived from hES cells (58/135) or hiPS cells (74/135), whereby the proportion of studies with hiPS-cell-derived cell therapeutic agents predominates in the meantime. Two studies use cells based on human, parthenogenetically produced pluripotent stem cells (hpPS cells), and one study uses cells (NT-hES cells) derived from embryos created by nuclear transfer (SCNT).

Studies based on hES-cell-derived cells are primarily aimed at treating diseases of the eye and the ocular adnexa (26/58 studies), and metabolism (11/58). Other studies focus on the treatment of diseases of the nervous system (8/58 studies), the circulatory system (3/58), the genitourinary system (2/58), the digestive system (1/58), the musculoskeletal system (1/58), as well as the therapy of malignant neoplasms (1/58), spinal cord injuries (3/58) and COVID-19 infections (2/58). Clinical studies using hiPS-cell-derived cells are primarily aimed at the development of therapies for (malignant) neoplasms (23/74), diseases of the circulatory system (18/74) and diseases of the eye and the ocular adnexa (10/74). Clinical studies using cells derived from NT-hES cells or hpPS cells are in the minority and focus on the treatment of age-related macular degeneration and Parkinson's disease.

Table 3. Overview of clinical trials conducted or initiated worldwide on the basis of human pluripotent stem cells (2010-2023), 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. Source: Robert Koch Institute, unpublished data from various sources, *inter alia*: ClinicalTrials.gov, a service of the U.S. National Institutes of Health (NIH), and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO); data last revised on 31 December 2023).

	Disease (according to ICD-10)	Number of studies	Participants (does not correspond to the number of patients treated)*
hES-cells	**Endocrinal, nutritional and metabolic diseases**	**11**	**484**
	Type 1 diabetes mellitus	9	451
	Primary ovarian insufficiency	1	28
	Urea cycle disorders	1	5
	Diseases of the eye and the ocular adnexa	**26**	**369**
	Age-related dry macular degeneration	12	186
	Retinitis pigmentosa	2	22
	Stargardt's disease	5	53
	Other eye disorders	7	108
	Diseases of the circulatory system	**3**	**58**
	Ischaemic heart disease	1	10
	Cerebral infarction, unspecified	1	30
	Left heart failure	1	18

	Diseases of the digestive system	**1**	**5**
	Acute and subacute liver failure	1	5
	Diseases of the musculoskeletal system and connective tissue	**1**	**18**
	Meniscus damage due to an old tear or an old injury	1	18
	Diseases of the nervous system	**8**	**134**
	Motor neuron disease	1	16
	Primary Parkinson's disease	5	48
	Multiple sclerosis	1	30
	Epilepsy	1	40
	Diseases of the urogenital system	**2**	**35**
	Interstitial cystitis (chronic)	1	3
	Intrauterine synechiae	1	32
	Neoplasms	**1**	**8**
	Malignant neoplasm of the bronchi and lungs	1	8
	Injuries, poisonings and certain other consequences of external causes	**3**	**35**
	Injury of the spinal cord, level unspecified	3	35
	Provisional classifications of diseases with unclear aetiology and unassigned code numbers	**2**	**29**
	COVID-19	2	29
	Total studies with hES cells	***58***	***1175***
hiPS cells	**Diseases of the eye and the ocular adnexa**	**10**	**167**
	Age-related wet macular degeneration	2	7
	Age-related dry macular degeneration	1	20
	Hereditary retinal dystrophy: retinitis pigmentosa	1	2
	Retinal affection, unspecified	3	121
	Other corneal affections described in more detail	1	4
	Bullous keratopathy	1	3
	Degeneration of the macula and the posterior pole	1	10
	Diseases of the blood and blood-forming organs and certain disorders involving the immune system	**3**	**15**
	Beta thalassemia	2	14
	Other aplastic anaemias	1	1

Diseases of the circulatory system	**18**	**319**
Ischaemic cardiomyopathy	6	56
Cerebral infarction, unspecified	4	72
Cardiac insufficiency, unspecified	6	185
Dilated cardiomyopathy	2	6
Diseases of the nervous system	**6**	**74**
Primary Parkinson's disease	6	74
Neoplasms	**23**	**2825**
Malignant neoplasms	5	636
Head, face and neck	2	15
Myeloid leukaemia	1	234
B-cell chronic lymphatic leukaemia	2	948
Malignant neoplasms of the mammary gland [mamma]	1	32
Malignant neoplasm of the ovary	1	33
Acute myeloblastic leukaemia (AML)	4	281
Other and unspecified types of non-Hodgkin's lymphoma	1	50
Malignant neoplasm of other and unspecified female genital organs	1	3
Carcinoma in situ of other and unspecified genital organs	1	18
Thrombocytopenia, unspecified	1	10
Multiple myeloma	1	168
B-cell lymphoma, unspecified	2	397
Injuries, poisonings and certain other consequences of external causes	**5**	**88**
Graft-versus-host disease	2	76
Tear of the knee-joint cartilage, acute	1	4
Injury of the spinal cord, level unspecified	2	8
Provisional classifications of diseases with unclear aetiology and unassigned code numbers	**2**	**29**
COVID-19	2	29
Endocrinal, nutritional and metabolic diseases	**3**	**53**
Type 1 diabetes mellitus	2	23
Unspecified diabetes mellitus – with diabetic foot syndrome	1	30

	Diseases of the musculoskeletal system and connective tissue	**2**	**444**
	Gonarthrosis, unspecified	2	444
	Diseases of the skin and subcutaneous tissue	**1**	**20**
	Atopic [endogenous] eczema	1	20
	HIV disease	**1**	**34**
	HIV disease	1	34
	Studies with hiPS cells, total	***74***	***4068***
NT-hES cells	Diseases of the eye and adnexa	1	3
	Age-related dry macular degeneration	1	3
	Studies with NT-hES cells, total	***1***	***3***
hpPS cells	**Diseases of the nervous system**	**2**	**62**
	Primary Parkinson's disease	2	62
	Studies with hpPS cells, total	***2***	***62***
	Studies using pluripotent stem cells: Total	**135**	**5308**

See Table 4 for an overview of the countries in which the clinical trials were/are being carried out. It becomes clear here that between 2010 and 2023 clinical trials based on hES cells were carried out mainly in the USA, China, Canada and the UK; trials using cell products derived from hiPS cells took place mainly in Japan, the USA and China. Furthermore, the range of countries in which clinical trials based on hES cells are being conducted has expanded: these now include the Netherlands, Germany, Belgium, Iran, Italy, Norway, Sweden and Switzerland.

Table 4. Overview of the countries in which clinical trials based on human pluripotent stem cells have been or are being conducted or initiated (2010-2023), including long-term studies with patients from previous clinical trials. * Some studies are being carried out in several countries. Source: Robert Koch Institute, unpublished data from various sources, *inter alia*: ClinicalTrials.gov, a service of the U.S. National Institutes of Health (NIH), and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO); data last revised on 31 December 2023.

	Country	Number of studies
hES cells	USA	25
	China	13
	Canada	9
	UK	9
	Korea	5
	France	3
	Israel	2
	The Netherlands	2
	Belgium	1
	Brazil	1
	Germany	1
	Iran	1
	Italy	1
	Japan	1
	Norway	1
	Sweden	1
	Switzerland	1
hiPS cells	Japan	27
	China	20
	USA	20
	Australia	5
	Germany	1
	Iran	1
	UK	1
NT-hES cells	Korea	1
hpPS cells	Australia	1
	China	1
	Total	**155***

3.5. Final remarks

The statements repeatedly made in the previous ZES reports on the desiderata of the Stem Cell Act remain valid. Twenty-one years after the StZG came into force, it is the ZES's view that the following problems – which are above all delaying and/or preventing the development of new therapies for treating patients with hitherto incurable diseases – continue to exist:

- The cut-off date, now 17 years ago, which prevents imports of newer stem-cell lines, even those necessary for clinical research, is a significant constraint on research. There is no objective basis for retaining the cut-off date and the related restriction of freedom of research. To the knowledge of the ZES, no other country in which research using hES cells is permitted has a similarly restrictive cut-off-date regulation.
- The contradiction inherent in the Stem Cell Act's exemption for research, i.e. that hES cells may be used in research projects but not for the subsequent application of research results, is no longer justifiable in view of therapeutically promising hES-based cell products If hES cells are required to produce such therapeutic agents, the results of hES cell research carried out in Germany may not be used for this purpose in Germany. Similarly, the use of hES cells for pharmacological and toxicological purposes apart from research is still not permitted.
- The fact that the results of research with hES cells, some of which have been achieved using considerable public funds, may not be used in Germany to manufacture therapeutic products for the benefit of patients also represents a significant contradiction that urgently needs to be resolved.
- The inadmissibility of important research whose sole aim is to develop procedures that could make it possible to reduce the number of animal experiments or replace them, is difficult to justify in view of the growing status of animal welfare in Germany.

There is an ongoing urgent need for clarification and reform on these points.

The 21st Report was adopted at the 114th ordinary meeting of the ZES on 15 April 2024.