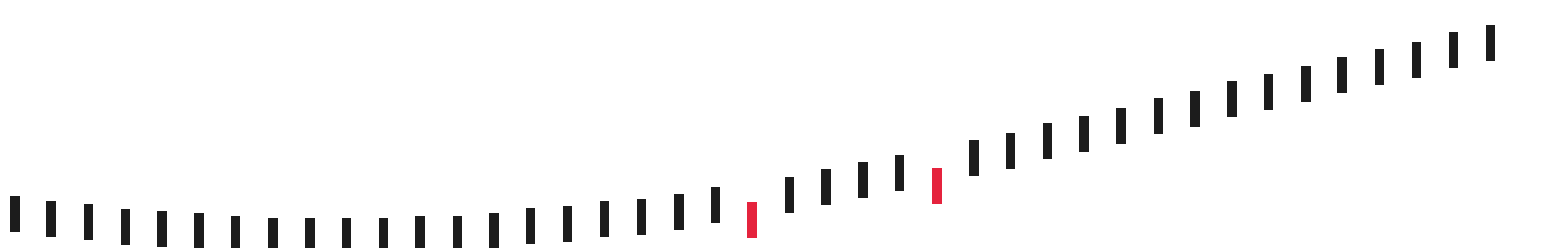


Final Report

Survey and Review on Stem Cell Research

**Survey of researchers and literature review of research
involving human embryos and human embryonic stem
cells**

Basel | 10/22/2025



Imprint

Survey of researchers and literature review of research involving human embryos and human embryonic stem cells

Final Report

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Abbreviations

- **PSC:** pluripotent stem cell, summary term comprising ESC and iPSC
- **hPSC:** human pluripotent stem cell
- **ESC:** embryonic stem cell, subtype of PSC
- **hESC:** human embryonic stem cell, subtype of hPSC
- **iPSC:** induced pluripotent stem cell, subtype of PSC
- **hiPSC:** human induced pluripotent stem cell, subtype of hPSC
- **StRA:** Swiss Stem Cell Research Act
- **IVF:** in vitro fertilization

Please note: As the report focuses on human PSCs (hPSCs), the prefix 'h' is omitted from all abbreviations used in the results section for brevity.

Abstract

The Stem Cell Research Act (StRA) came into force in 2005. In preparation for the act's revision process, this report aims to provide an overview of current and future developments in research involving human pluripotent stem cells (hPSCs) and human embryos. We conducted a scoping review of the literature and interviewed ten experts in the field. Our findings show that both human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs, i.e. adult cells that were reprogrammed to pluripotent states) are widely used in research, with hiPSCs dominating in clinical trials. hPSC-derived models are valuable tools to study embryogenesis, organ development, disease mechanisms, and therapeutic strategies. Nevertheless, research on human embryos and fetuses remains of high value, as embryo models currently do not fully replicate in-utero organization and require validation against natural development. Applications of hPSCs in cell differentiation and organ models include the study of physiological development, pathological processes, drug screening and cell transplantation. While some hPSC-based therapies are already being tested in humans, researchers continue to face several limitations. Expert feedback about their experiences with the StRA was generally positive, although some adjustments were proposed. In conclusion, hPSC research enables scientists to study human biology in human tissue and holds promise for advancing specialized treatments.

1. Introduction

The Stem Cell Research Act (StRA) was passed in 2003 and came into force in 2005. The act regulates the conditions for research on human embryonic stem cells as well as their derivation from surplus embryos. As the field of stem cell research is developing dynamically, it has brought up new research techniques (e.g. embryo models) and applications including precise genetic engineering. The aim of this report is to provide an overview of the current state of stem cell and embryonic research. The report thereby informs the interested parties involved in the revision of the regulatory framework.

1.1 Background

The inner cell mass of the early embryo (blastocyst) contains pluripotent stem cells (PSCs). These cells are characterized by their ability to differentiate into cell types of all the three germ layers as well as by their ability to potentially unlimited in vitro cultivation (O’Leary et al., 2012). Thus, these so called embryonic stem cells (ESCs) are a valuable resource for fundamental research and biotechnological applications. In 1998, the American developmental biologist James Thomson and his team isolated for the first time human embryonic stem cells (hESCs) from human blastocysts (Thomson et al., 1998). This scientific breakthrough inspired other researchers to work with human embryos and hESCs while also raising new ethical questions. In Switzerland, the Stem Cell Research Act (StRA) was passed after long debates and a popular vote in 2003, and came into force two years later in 2005. The act regulates the conditions under which research involving hESCs is permitted. These conditions include regulations on obtaining hESCs (from surplus embryos not used for in vitro fertilization (IVF), not older than 7 days), the scientific use of embryos, and import and export of stem cells.

Stem cells can be categorized into three groups: totipotent, pluripotent and adult stem cells. Totipotent (or omnipotent) stem cells possess the potential to develop into all cell types that the developing embryo needs, including extra-embryonic tissues, and can be found in fertilized oocytes. Pluripotent cells like ESCs lost some of this potential already and can develop into all of the three germ layers that later form the human body. We will describe later, however, that this distinction may not always be clear in laboratory settings, as some pluripotent stem cells (PSCs) can also differentiate into extra-embryonic tissues. Some depict these cells extended PSCs (EPSCs) as they demonstrate some features of totipotency (Yang et al., 2017). Lastly, adult stem cells are either multipotent or unipotent and able to develop into restricted types of cells (e.g. hematopoietic stem cells as precursors of blood and immune cells). Adult stem cells are not regulated under the Stem Cell Research Act, which is exclusively concerned with the regulation of human ESC for research applications.

Since its inception in 2005, minor revisions of the StRA were released in 2014 and 2023, but the regulatory framework for research on hESCs has remained largely constant. However, at the same time, the research conducted on this matter has taken off.

One example is the creation of organoids. The PSCs used for these concepts are modified in vitro so that simplified organs or organ tissues develop. Such organ models are either two- or three-

dimensional and can be used to further study organ development, to understand the course of diseases, or to test pharmaceutical agents (J. Kim et al., 2020; Lancaster & Knoblich, 2014). Research on organoids gained further importance when Shinya Yamanaka et al. used human skin cells to generate human induced pluripotent stem cells (hiPSCs) (Takahashi et al., 2007). This breakthrough allows the generation of human organ models without the use of human embryos or animal models.

This example indicates the rapid advances in the field of research on human embryos and hESCs. In combination with new methods in precise genome editing (i.e. Jinek et al., 2012), further implications need to be accounted for. This illustrates the necessity to consider a revision of the StRA that reflects the current state of research as well as future developments and applications.

1.2 Aims of the study

The aims of this study are to provide an overview of the current research topics and methods in the field of research on human embryos and human ESCs as well as future developments that can be expected. This study focuses solely on the state of scientific research and is agnostic about its ethical assessment. The results derive from a combination of a systematic literature analysis and qualitative interviews of researchers. The study can be used to underpin the planned revision of the StRA.

1.3 Research questions

The study focuses on the current state of research in the field of stem cell and embryonic research and its expected developments over the next years. In particular, the study is centered around three main research questions:

1. Which new technologies in research on human embryos and human ESCs have significantly impacted the state of research in the last five years (i.e. since 2020)?
2. What advances in research and practical applications have been achieved with these new technologies?
3. What future trends are expected regarding the scientific significance and practical application of these technologies?

To address the first two questions, we used a combination of systematic literature analysis and qualitative interviews with researchers. For the third question, interviews conducted with researchers were the primary source of information as the literature mainly focuses on finished projects. However, when future trends were mentioned in the literature (e.g. in the discussion or as limitation), they were also considered.

2. Methods

2.1 Scoping review of the literature

2.1.1 PubMed Search

A keyword search was conducted using PubMed, a meta-database for biomedical publications that is run by the United States National Library of Medicine. The query consisted of several parts to (a) target results according to our research question, and (b) to limit the number of results to the most relevant, high-quality papers.

Table 1: Query used for scoping review of the literature

Prompt	Description
(«human»)	Species
(«embryonic stem cells»[tiab] OR «ESCs»[tiab] OR «hESCs»[tiab] OR «iPSC»[tiab] OR «iPSCs»[tiab] OR «induced pluripotent stem cells»[tiab] OR «induced pluripotent stem cell»[tiab])	Pluripotent stem cells (in title/abstract)
(«embryo»[tiab] OR «embryos»[tiab] OR «blastocyst»[tiab] OR «blastocysts»[tiab] OR «early development»[tiab])	Embryo (in title/abstract)
(«method»[tiab] OR «methods»[tiab] OR «methodology»[tiab] OR «methodologies»[tiab] OR «technique*»[tiab] OR «technology»[tiab] OR «technologies»[tiab] OR «model»[tiab] OR «models»[tiab] OR «protocol»[tiab] OR «protocols»[tiab] OR «analysis»[tiab] OR «experiment»[tiab] OR «experiments»[tiab] OR «tool»[tiab] OR «tools»[tiab] OR «application»[tiab] OR «applications»[tiab])	Content
(«english»[language] OR «german»[language])	Language
(«2020/01/01»[Date - Publication] : «2024/12/31»[Date - Publication])	Publication date
(«cell stem cell»[journal] OR «stem cells»[journal] OR «stem cells transl med»[journal] OR «NPJ regen med»[journal] OR «stem cell reports»[journal] OR «cytotherapy»[journal] OR «development»[journal] OR «cell transplant»[journal] OR «stem cells dev»[journal] OR «regen med»[journal] OR «stem cell res	Journal

Prompt	Description
ther»[journal] OR «stem cell rev rep»[journal] OR «cell»[journal] OR «science»[journal] OR «nature»[journal] OR «cell rep»[journal] OR «mol cell»[journal] OR «cancer cell»[journal] OR «nat cell biol»[journal] OR «genes dev»[journal])	
Additionally for embryo research: ...OR «J stem cells»[journal] OR «stem cell res»[journal] OR «cell reprogram»[journal] OR «anat sci educ»[journal] OR «mol hum reprod»[journal] OR «re- production»[journal] OR «fetal diagn ther»[journal] OR «F S rep»[journal])	
((“review”[pt]) OR (“systematic review”[pt]) OR (“clinical study”[pt]) OR (“clinical trial”[pt]) OR (“classical article”[pt]) OR (“observational study”[pt]) OR (“research support, american re- covery and reinvestment act”[Publication Type]) OR (“research support, n.i.h., extramural”[Publication Type]) OR (“research support, n.i.h., intramural”[Publication Type]) OR (“research sup- port, u.s. gov’t, non-p.h.s.”[Publication Type]) OR (“research support, u.s. gov’t, p.h.s.”[Publication Type]) OR (“research sup- port, u.s. gov’t”[Publication Type]))	Publication type: included
(all others on PubMed)	Publication type: excluded

Put together, the search was built as follows (for the full search command, see A.1):

((Species) AND (Pluripotent stem cells) AND (Content) AND (Journals) AND (Publication date)
AND (Language) NOT (Publication types: excluded))
OR ((Species) AND (Pluripotent stem cells) AND (Content) AND (Journals) AND (Publication
date) AND (Language) AND (Publication types: included))
OR ((Species) AND (Embryo) AND (Content) AND (Journals + additional journal) AND (Publica-
tion date) AND (Language) NOT (Publication types: excluded))
OR ((Species) AND (Embryo) AND (Content) AND (Journals + additional journals) AND (Publi-
cation date) AND (Language) AND (Publication types: included))

To stay within the given time frame, we focused our search on selected journals. For stem cell research, we used Paul Knoepfler’s (UC Davis) journal list and included the journals of the two categories “The stem cell journal list” and “Great journals that often publish stem cell work” but left out “Other stem cell journals” (Knoepfler, 2024). For embryo research, we additionally included papers that were ranked as Q1 in the category “Embryology” by the SCImago Journal Rank Impact Factors for the year 2023 (‘Scimago Journal & Country Rank’, n.d.) and, to increase the number of results, the top three journals of Paul Knoepfler’s “Other stem cell journals” list.

PubMed often omits publication types or assigns more than one. We therefore included desired types with AND and excluded undesired types with NOT. Splitting the queries in this way captured records with missing publication type metadata.

Our search strategy was reviewed by experts from the Federal Office of Public Health (FOPH) as well as by Dr. Arun Sharma (Professor at Cedars-Sinai, LA, California, USA).

The search covering the years 2020-2024 yielded 1,158 results. To reduce this quantity, we retrieved the number of citations for each paper via Crossref as a measure of impact. To adjust for differences in citations due to their time since publication, we sorted papers according to their year of publication and applied a citation correction to standardize based on the month of publication for each year using the statistics software 'R'. Eventually, we retained the 10 most highly cited papers per year from this adjusted list for the screening, totaling 50 papers.

2.1.2 Literature suggestion by experts

To ensure the most relevant literature is included in our survey, we additionally asked scientists in the field to share up to five papers that they considered as 'seminal' research on hESCs, human embryos, or human iPSCs that have been published since 2020 covering groundbreaking research approaches and thus representing the current frontier in research involving human embryos or human ESCs. We invited 47 researchers to participate and received literature suggestions from ten experts.

We selected the researchers for our invitation list according to the following criteria: (a) they have been granted a project by the FOPH to work with hESCs ('Research Projects and Stem Cell Lines', 2025), (b) they have been recommended to us by other researchers, or (c) we retrieved their names by other recommendations (embryo research, board member of the Swiss Stem Cell Network (SSCN), or the International Society for Stem Cell Research (ISSCR)).

In addition to the PubMed search, we included 41 papers that were sent to us by these researchers. We excluded one suggestion because it was not a scientific publication, but a news article. Of these responses, 5 papers were mentioned by two or more experts:

- Proposed 6 times: Complete human day 14 post-implantation embryo models from naive ES cells, Oldak et al., 2023
- Proposed 4 times: Pluripotent stem cell-derived model of the post-implantation human embryo, Weatherbee et al., 2023
- Proposed 4 times: Human blastoids model blastocyst development and implantation, Kagawa et al., 2022
- Proposed 2 times: Post-gastrulation synthetic embryos generated ex utero from mouse naive ESCs, Tarazi et al., 2022
- Proposed 2 times: An in vitro model of early anteroposterior organization during human development, Moris 2020

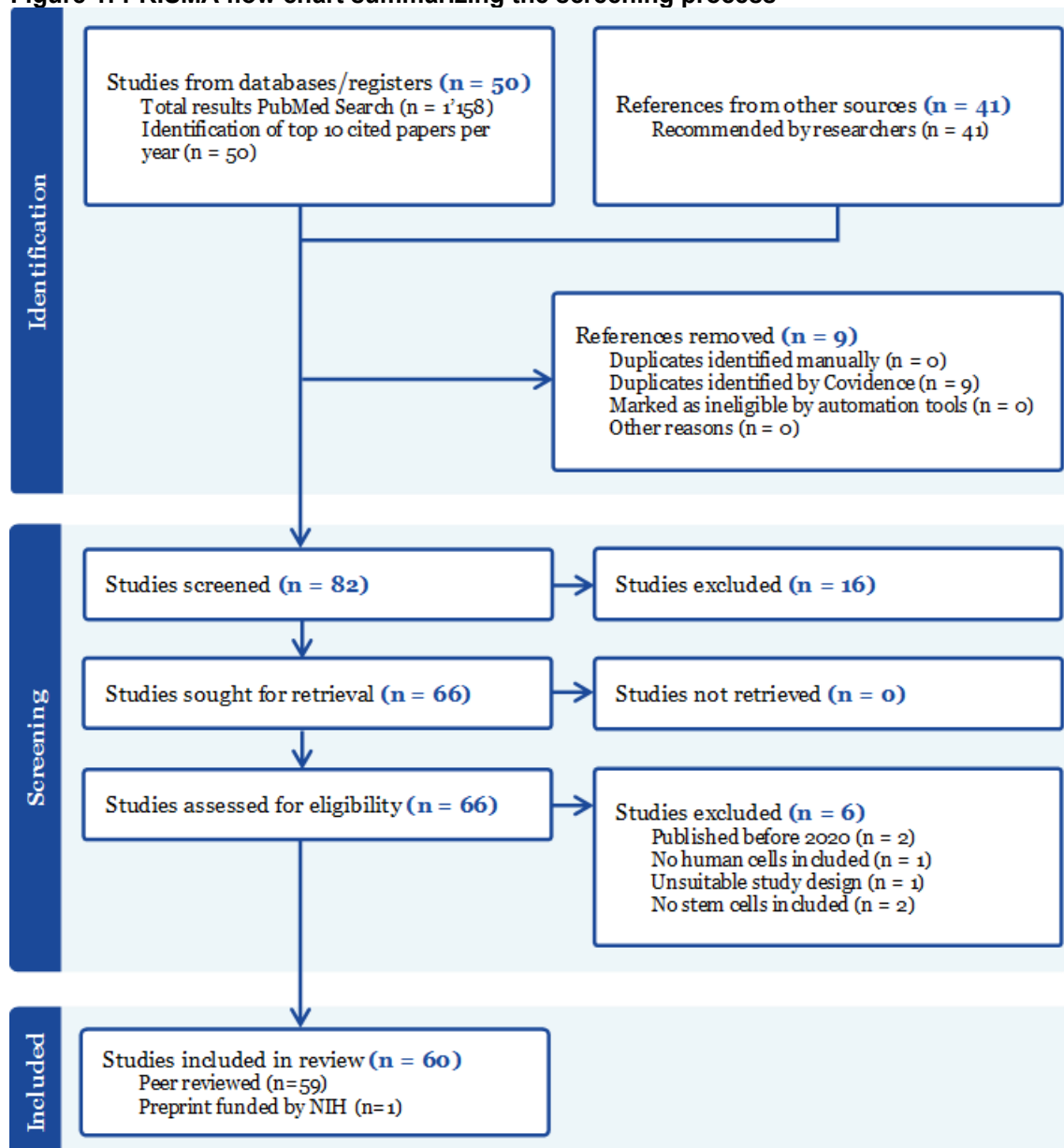
2.1.3 Literature screening

These 91 papers were uploaded to Covidence.org, a platform for systematic reviews following the PRISMA 2020 scheme. Two authors screened all 91 abstracts. The criteria for exclusion were as follows:

- Focus on non-human PSCs
- Focus not relevant for our study
- Incomplete article, unclear methodology
- Not compatible with keyword search: published before 2020, wrong publication type

Figure 1 summarizes the results of the screening process.

Figure 1: PRISMA flow chart summarizing the screening process



2.1.4 Literature extraction

The following data of the 60 remaining papers was extracted systematically in Covidence:

1. Metadata: authors, title, journal, article type, type of research (fundamental/translational/clinical), year of publication
2. Content:
 - a. Research question, results, limitations
 - b. Starting cell types, hESCs or hiPSCs, differentiated cell types and germ layers, age of embryo models
 - c. Approaches: organ models, full models, chimera, generation of hiPSC, source of hESC, other
 - d. Adjacent methods/tools: genome editing and overexpression, somatic cell nuclear transfer, other
 - e. Application, medical field
 - f. Other important aspects

As translational research is not clearly defined, we used this category to label studies and projects focusing on specific diseases and possible treatment applications in humans including preclinical studies without clinical tests in patients.

We extracted the data according to the points 1 – 2f listed above, focusing on what cells were manipulated in which way and the product. We did not, however, trace the use of well-established methods for solely analytical purposes (e.g. single-cell RNA sequencing, immunohistochemistry and fluorescent reporter proteins) as any experiment requires some sort of analytical method. Furthermore, these tools do not constitute the primary focus of the experiment and are commonly used in wet lab research across many specializations, and are therefore not specific to stem cell research. Such extra adaptations to cells are only performed for analytical purposes in the wet lab and the process of data generation usually acts as an end point for the cells.

2.2 Expert interviews

For the second part of the study, we interviewed 10 experts on human PSCs or human embryos. In consultation with our FOPH contact, we invited 29 researchers to participate, drawing on the FOPH ESC project list and peer recommendations. Our goal was to create a diverse array of experts in both academia and industry with different foci and goals of work. Many invitees work in neuroscience, reflecting current interest in PSC-based brain research. Interviews were online, lasted 30–60 minutes, and followed a semi-structured guide distributed on request in advance.

Table 1: List of interview partners

Expert scientist	Institution	Focus
Amiq Gazdhar	Department of Pulmonary Medicine, Allergeology and Clinical Immunology, University Hospital Berne, Switzerland	Lung organoids, pulmonary fibrosis, drug screening
Bernadette de Bakker	Amsterdam UMC; Netherlands	Dutch fetal Biobank
David Suter	EPFL, Switzerland	Cell identity, regulation of gene expression
Ekaterine Berishvili	University of Geneva, Switzerland	Cell-based therapies for type 1 diabetes
Fides Zenk	EPFL, Switzerland	Neurodevelopmental disorders
Jacob Hanna	Weizmann Institute of Science, Israel	Embryo models
Laurence Daheron	Harvard University; United States	iPSC production, genome editing
Marisa Jaconi	University of Geneva, Switzerland	Heart organoids, organoid technology platform
Matthias Lütolf	Roche – Institute of Human Biology, EPFL, Switzerland	Next-generation organoids
Sebastian Jessberger	University of Zurich, Switzerland	Neural plasticity

In this report, each expert was referenced using a randomly assigned number from 1 to 10.

The interviews comprised the following dimensions:

- The researchers' current research questions and goals they are working towards.
- What methods and techniques are being used, their benefits and challenges and expected further technical improvements.
- Which scientific insights and treatments might be developed with these strategies in the next 5-10 years.
- Regulatory challenges they face and their experiences working with the StRA.
- Current research frontier and developments in their field and in pluripotent stem cell and embryo research in general.
- The role and possibilities of artificial intelligence (AI) in future research projects.

The aim of these interviews was to gather the researchers' perceptions of the field, challenges in their research, as well as their personal forecasts of future developments, since such factors cannot exclusively be evaluated from the literature.

3. Results

Please note: As the report is exclusively focused on human PSCs, the prefix 'h' is not included in the abbreviations used throughout the result section except its mention was necessary.

3.1 Techniques

Cell differentiation:

Throughout the differentiation process, stem and progenitor cells express different genes at various time points and develop into their destined cell lineage. Thus, the existence of cell types can be explained even though the genome is the same. The reversal of this process is termed reprogramming. From the literature, three pluripotency states are worth mentioning:

- **Naïve PSCs:** The cells present in the epiblast before implantation into the uterus lining possess unrestricted potential to develop into embryonic tissues (Nichols & Smith, 2009).
- **Primed PSCs:** After implantation, the PSCs are being prepared for commitment to a certain lineage (Nichols & Smith, 2009).
- **Extended PSCs (ePSCs):** In some publications, PSCs that possess totipotent characteristics and can differentiate into embryonic and extra-embryonic tissues are specifically called extended PSCs (Yang et al., 2017).

Genome editing:

Genome editing includes a wide variety of methods to alter the genome. Below, we provide a brief explanation of the most relevant terms. The list contains approaches, techniques and methods for transportation of genetic material inside the body and thus, some can be combined.

- **Knock-in / knock-out:** These approaches refer to the insertion (knock-in) or deletion (knock-out) of a gene or DNA sequence. They are commonly used to study the function of a gene.
- **CRISPR/Cas:** The CRISPR/Cas system, adapted from bacterial immunity. Enables targeted edits in eukaryotic cells. The complex specifically binds with its guide RNA (gRNA) to the desired DNA sequence where the Cas protein (mostly Cas9) then cuts the DNA double strand. In a second step, modifications can be carried out at this position (Jinek et al., 2012).
- **Transduction:** The potential of some viruses (e.g. Lentivirus or Sendai virus) to integrate into the host genome can be methodologically exploited by interchanging their RNA to sequences of one's choice. The engineered RNA still possesses the viral capabilities necessary for entering the cell and integration, but the actual genes are non-viral.

- **Transfection:** Similar to transduction, transfections also insert additional genes in the host cell. Here, however, the genomic material (i.e. plasmids) is produced in bacteria and may not reach the host's nucleus where the genome is stored.
- **Overexpression:** This approach is widely used in stem cell research as transcription factors are crucial for cell differentiation or dedifferentiation. In overexpression, cells are transduced with genes for the desired transcription factors so that they are then read. The produced proteins then activate other gene pathways and therefore ultimately steer the cell's fate. For stem cell research, only few of these factors are required for reprogramming cells to pluripotency state and they were named “Yamanaka factors” after its founder.

3.1.1 Comparison of ESCs and iPSCs

iPSC production is getting better and safer.

According to our interview partners, projects with iPSCs yield more variable results, compared to ESCs (Expert No. 2, personal communication, 2025; Expert No. 9, personal communication, 2025). One factor influencing this variability is the remaining epigenetics after the reprogramming of cells into pluripotent states using conventional methods. Epigenetic factors like the chromatin arrangement influence whether a gene can be reached by the transcription apparatus. As only such activated genome sequences can be read, the epigenetic memory influences the cell's fate even as an iPSC. However, several groups address this problem by working on reprogramming strategies and protocols to delete cell's epigenetic memory and prevent genetic aberrations (Buckberry et al., 2023; Murase et al., 2024). Other studies propose to overcome the epigenetic barrier by chemically reprogramming adult cells in the environment and media for each step required. This external reprogramming approach serves as an alternative to genetic modifications of cells where transcription factors are overexpressed (Guan et al., 2022). Improvements in reprogramming enable to generate not only primed PSCs, but also to go one step further back to naïve PSCs and thus reaching the developmentally earlier state of pluripotency present in nature before implantation into the uterus. (Expert No. 2, personal communication, 2025).

Other challenges that researchers are currently experiencing (e.g. low efficiencies, low predictability, and difficulty in handling the cells) are being addressed and protocols refined (Buckberry et al., 2023; Expert No. 2, personal communication, 2025; Feyen et al., 2020; Sharma et al., 2020). A persisting problem is the high cost of iPSC production, mainly associated with the time intensity and labor input (Expert No. 5, personal communication, 2025).

Structural differences between iPSCs and ESCs are becoming less relevant.

While some differences between the origin of PSCs might persist, in principle, neither ESCs nor iPSCs are inferior to the other. Some researchers nevertheless suggested that, at least at present time, ESCs and iPSCs should be assigned to different applications for which they are better suited: ESCs for studying early development, and patient-derived iPSCs for modelling diseases and treatment applications (Expert No. 5, personal communication, 2025; Expert No. 7, personal communication, 2025). This separation, however, was not supported by the literature review.

As ESCs have been used for longer time, such cell lines are better characterized and are often used as a preferred control in studies (Expert No. 4, personal communication, 2025). Considering the advances in iPSC production, the two cell types nevertheless can be seen as functionally equal.

There are relevant differences between existing cell lines regarding their behavior during differentiation.

Apart from differences between ESCs and iPSCs, differences among cell lines within these PSC subtypes are larger and more relevant (Expert No. 9, personal communication, 2025). Researchers report the lower potential or even inability to create certain cell types out of certain PSC lines. Variability between PSC lines is at least partially due to genetic differences between donors. This results in the need to repeat experiments in more than one PSC line to demonstrate external validity (Expert No. 6, personal communication, 2025). Additionally, the genome of PSC lines can also be genetically engineered to match another, creating so called isogenic controls (J. Kim et al., 2020). For instance, Liu et al. report reproducible results across both ESC and iPSC lines. However, they also observe variations in the efficiency of model generation among different ESC lines (L. Liu et al., 2023).

Pantazis et al. addressed this matter by creating a reference iPSC line applicable for various research purposes. They examined single cells (or subclones to be precise) from various iPSC lines for their properties as well as their stability over time. After rigorous testing for genetic and phenotypic properties and genetic stability, they distributed the most promising subcloned PSC line to research groups worldwide, asking them to evaluate the cell line's performance using their standard protocols and applications. This approach is intended to standardize fundamental research involving iPSCs and to increase comparability between studies (Pantazis et al., 2022). However, it remains to be seen whether this PSC line will gain widespread adoption.

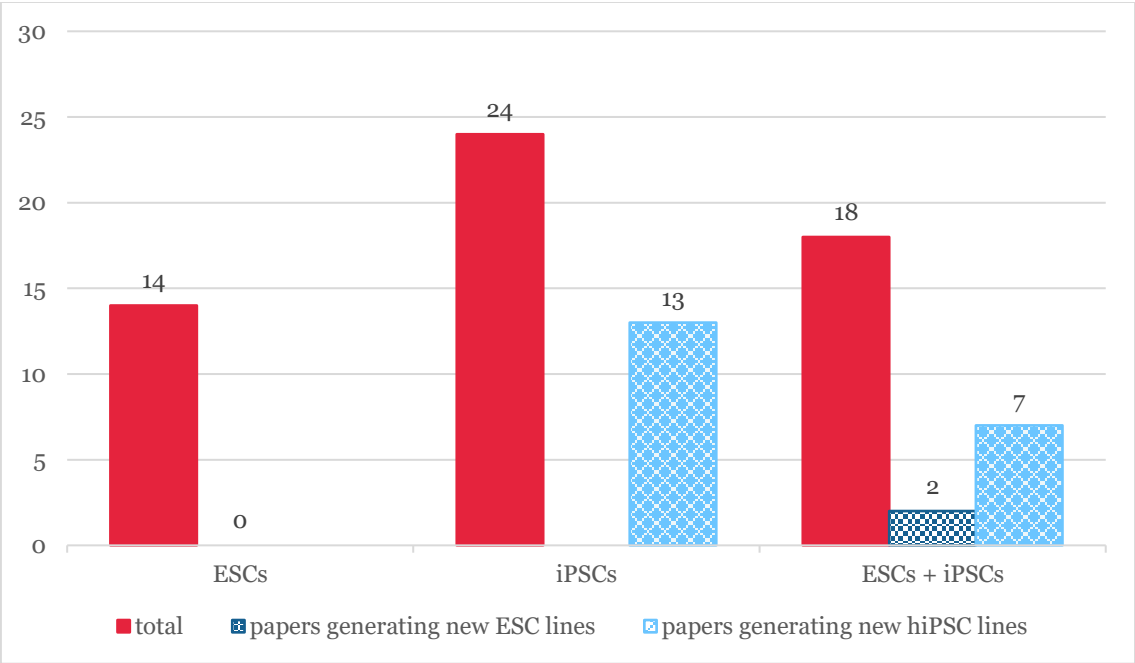
ESCs were seen as a “gold standard” and used in a majority of ongoing Phase I clinical trials. However, iPSCs have overtaken in recent years.

As hESCs were first produced in 1998 by Thomson et al., nine years before hiPSCs by Takahashi et al. (Takahashi et al., 2007; Thomson et al., 1998), a lead in clinical applications is to be expected. In 2020, Deinsberger et al. reported that in registered ongoing interventional clinical trials, 73.3% of the cells used were ESCs. Five years later, Kirkeby et al. showed in their 2025 update a decrease in ESCs entering interventional clinical trials in 2023-2024 while iPSC-derived products have been leading since 2019 (Deinsberger et al., 2020; Kirkeby et al., 2025) (Figure 3), showing a clear trend towards the adoption of iPSC-based applications.

An advantage of iPSCs in clinical trials is the possibility of patient specificity (i.e. using autologous cells), enabling personalized treatment options. In practice, however, the majority of cells used in clinical trials are derived not from the patient, but are iPSCs from another individual of the same species (i.e. allogeneic cells) to allow for using the same product across multiple patients (Kobold et al., 2023). In fundamental and translational research, patient-derived iPSCs facilitate the study of genetic diseases, amongst others. Currently, ESCs continue to be an important reference, and researchers often still conduct their experiments using both PSC types. Research with ESCs is mostly performed using existing cell lines. However some experiments require the creation of new lines from surplus IVF-embryos, unfortunately often without providing clear rationale in their

publications (Kagawa et al., 2022; Yu et al., 2021). This preference for iPSCs was also reflected in our literature analysis, as more experiments were performed using iPSCs than ESCs (Figure 2).

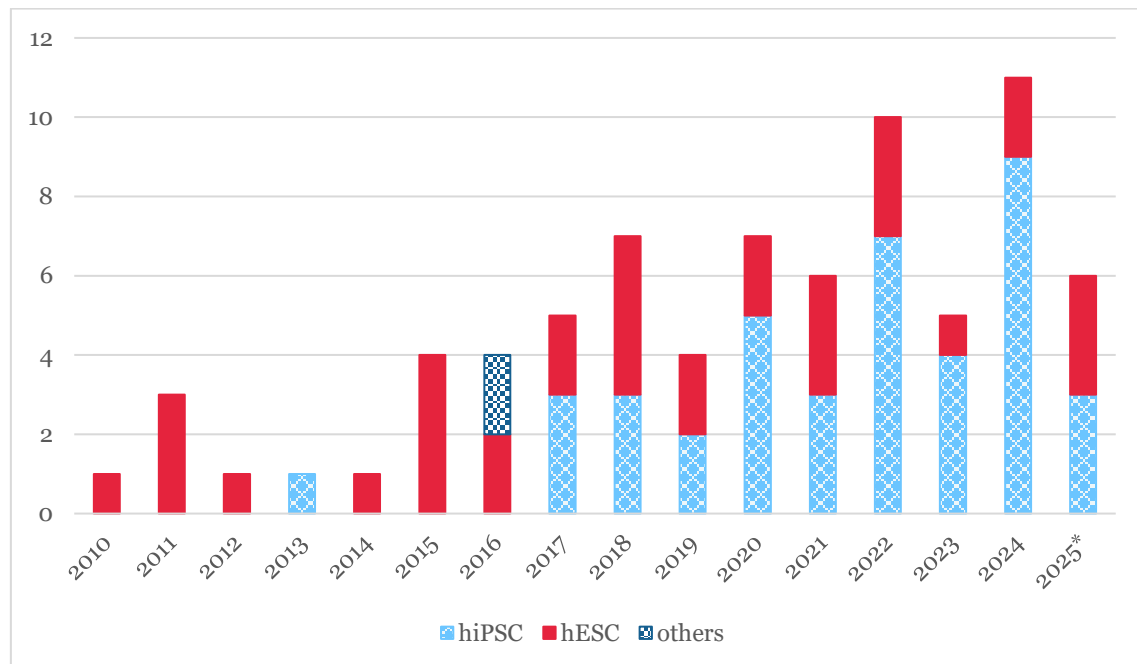
Figure 2: Number of papers included in the literature review by cell type studied



Source: Own computations.

Notes: 56 papers are included in this graph. Three papers from the literature review are excluded here because they were either reviews, an analysis of global trends, or did not work with cell cultures. The papers were divided into three groups depending on whether they used ESCs only, iPSCs only, or both. Within these groups, papers that generated new cell lines may also have used existing cell lines.

Figure 3: Cell source of hPSC-derived products entering clinical trials per year (n=76)



Source: Kirkeby et al., 2025, use of data kindly provided. The data was gathered from analyzing 115 approved interventional clinical trials with hPSC products worldwide. *Numbers for the year 2025 are incomplete as not all trials starting that year had been given approval by the time of publication. The category ‘others’ includes products produced with somatic nuclear cell transfer and parthenogenetic stem cells.

Although PSCs are easily available for purchase, many laboratories still prefer to produce their own iPSCs lines.

Although iPSC production is expensive and time-consuming, about one third of the reviewed studies (20 papers) created new iPSC lines, while 23 papers worked with existing lines, with only one overlap (Figure 2). This continued investment in producing new lines reflects both practical and scientific reasons:

In some countries, import restrictions limit or prohibit access to existing ESC lines. Moreover, the choice between creating new iPSC lines and using established ones depends on the specific research question. The generation of new cell lines allows for a more specific choice of donors, for instance individuals diagnosed with the disease of interest, so that disease-related mutations can be studied directly and potential treatments tested in a personalized setting. One study, for example, reprogrammed peripheral blood cells from a patient with autism spectrum disorder, while another purchased iPSCs from healthy donors as well as patients with schizophrenia or major depression (Li et al., 2023; Qian et al., 2020). Using such autologous iPSCs, after genetic correction of the underlying mutation, also minimizes the risk of immune rejection.

Additionally, a more diverse range of patient-derived cells enables more representative study results. This addresses a self-declared limitation of the above mentioned reference iPSC line derived from a male donor of European origin (Pantazis et al., 2022), whose results may not generalize to other populations or to female donors.

3.1.2 Research on human embryos

Data from human embryos is needed to validate PSC-derived models.

When researchers produce model structures to mimic a naturally occurring embryonic form, they need to validate their structure by comparing them to the biological original. This validation requires reliable and extensive data collected from human embryos. These reference data may be obtained in one of three ways: (a) by accessing existing datasets, (b) by focusing the project specifically on generating new reference data from human embryos, or (c) by producing the relevant reference data from human embryos precisely fitting the stage of the model which is being established. While option (a) suffices for many studies, other research questions require the latter two options.

The source of the validation tissue depends on the endpoint of the study. Commonly, the tissue stems from surplus IVF-embryos (Guo et al., 2021; Taubenschmid-Stowers et al., 2022; Yanagida et al., 2021) or from aborted tissue (Expert No. 3, personal communication, 2025; Yamanaka et al., 2023). Meistermann et al. followed a different aim and worked with 25 surplus embryos staged from morula to blastocysts. The analysis of these embryos resulted in an atlas containing data on which genes are transcribed pre-implantation, aiming to support improvements in IVF treatments (Meistermann et al., 2021). For later developmental stages, however, reference data are extremely limited: Tyser et al. were able to analyze the transcription profile of only one aborted human embryo during gastrulation (at CS7), illustrating the scarcity of material available for studies of these stages (Tyser et al., 2021).

One approach to validation is comparing models to data collected in so called atlases. For instance, Bernadette de Bakker has dedicated her career to the creation of embryo and fetal atlases based on donated human tissues. Other groups have used ESCs to analyze expression of transcription factors used to read genes in single cells and visualized this data in a transcription factor atlas to support other researchers in their differentiation processes (Joung et al., 2023).

Embryo models remain distinct from human embryos.

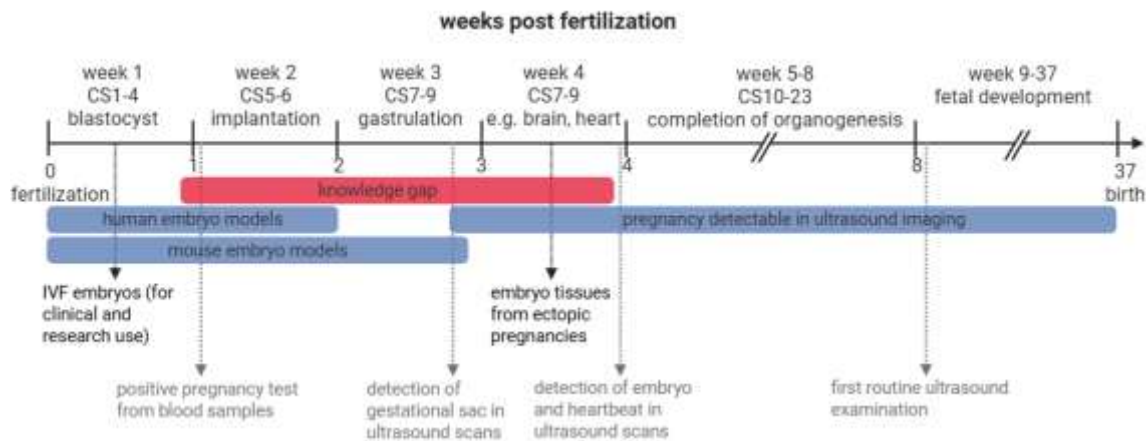
Albeit huge progress in 3D cell cultivation techniques has been made, embryo models still lack the spatial organization of human embryos (Expert No. 1, personal communication, 2025). Additionally, at present, there exist constraints on the embryological age of embryo models that can be reached while still exhibiting enough similarity to human embryos. One of the factors limiting the age and production efficiency named by researchers is the insufficient understanding of intracellular processes during these periods. Consequently, researchers are less accurate in their differentiation protocols (Expert No. 2, personal communication, 2025).

Further developing surplus IVF-embryos enables scientists to bridge the current knowledge gap.

Embryos used in studies that were generated for in vitro fertilization (IVF) treatment but not implanted into a uterus (therefore called surplus embryos) cover a bandwidth of 4-cell-stage to blastocysts, thus usually at week 1 of pregnancy (Kagawa et al., 2022; Taubenschmid-Stowers et al., 2022; Yanagida et al., 2021). The second source of embryo material is after an embryo is donated to scientific use by the parents after an abortion or miscarriage. The earliest stage at which such

tissue can be collected is in ectopic pregnancies at week 4 (Expert No. 1, personal communication, 2025). This results in a gap of data of approximately 2-3 weeks of embryogenesis (Figure 4). This period could be bridged by further culturing surplus embryos to later stages. In comparison to single ESCs, surplus embryos possess more accurate conditions for correct development, leading to more reliable outcomes (Expert No. 1, personal communication, 2025). This data will not only allow scientists to validate their results, but could also help understand the initial stage of pregnancy and causes for miscarriage and organ malformations, upon which one can find ways to prevent such incidents.

Figure 4: Timeline of pregnancy and availability of investigation methods



Sources: Created with biorender.com, (Doubilet et al., 2013; Hill, 2025a, 2025b; Schöni-Affolter et al., 2021; Stiefel et al., 2020; The Virtual Human Embryo, 2025; Universitätsspital Basel - Frauenklinik, n.d.; Yilmaz et al., 2025)

The figure shows the main developments throughout pregnancy and the knowledge gap of 2-3 weeks between research on IVF embryos and research on donated embryo tissues. Please note that the assignment of the Carnegie stages (CS) to the weeks post fertilization and the events at certain weeks are approximated and may vary among sources. Additionally, here, the counting of the weeks starts at fertilization whereas in clinical settings, the gestational age starts at the beginning of the last menstruation 2-3 weeks before fertilization.

The red bar shows the knowledge gap of 2-3 weeks between data from surplus IVF embryos and the first tissue donations from aborted pregnancies. The blue bars show the age of current human embryo models, the development of mouse embryo models transformed to the corresponding human stage, and the window during which the pregnancy can be detected in vivo on a macroscopic level using ultrasound imaging techniques. Even blue and red bars are overlapping, as described elsewhere, embryo models currently cannot fill this knowledge gap.

3.1.3 Animal models and chimeras

The role of animal models is changing in research with pluripotent stem cells.

The 3Rs principle “replace – reduce – refine” serves as a guiding framework for ethical animal research. Human organ models represent a replacement strategy for animal experimentation. Animal experiments are a common choice in research, especially when ethical and safety concerns preclude human studies. However, this approach merely transfers ethical dilemmas to another species. Moreover, the translational value of animal models is limited interspecies differences in physiology and pathology. Studying human diseases in human models promises more clinically relevant results (e.g. Zietek, 2020). In some cases, species-specific differences render animal models inadequate. For example, animal cells lack receptors on their cell membrane that were studied in their human counterparts. Stem cell-based therapies that specifically bind to such a

receptor then cannot be tested in animals. Recognizing these limitations, the US Food and Drug Administration (FDA) Modernization Act 2.0, enacted in 2022, eliminated the mandatory animal testing requirement prior to human clinical trials. This regulatory shift allows regulators to consider data from in vitro models as appropriate alternatives. However, approval still depends on the quality and context of the submitted evidence (Adashi et al., 2023; Expert No. 6, personal communication, 2025).

Yet, animal models may provide valuable research approaches when combined with human models. Researchers employ two primary approaches: co-culturing animal and human cells in vitro, or creating chimeric organisms by transplanting human cells into animal hosts. These chimeric systems allow researchers to assess the differentiation potential, tissue integration, and functional maturation of PSC-derived cells within a living organism. Such in vivo assessments provide information that cannot be obtained from in vitro systems alone. For neurological research, Ciceri et al. co-cultured human PSC-derived neurons with mice astrocytes in vitro to study the timing of maturation in the human cells (Ciceri et al., 2024). Other groups transplanted human cortical organoids into immunodeficient mice to study the neural development and interactions between cell types (Revah et al., 2022; Schafer et al., 2023). To test a potential therapy for Parkinson's disease, human dopamine neurons were transplanted intracranially into mice (T. W. Kim et al., 2024). Similarly, research groups implanted skin organoids in the back skin of mice (Lee et al., 2020) or tested whether their differentiated airway basal stem cells developed into airway epithelium in an in vivo setting, creating a tracheal xenograft model (Hawkins et al., 2021). In cancer research, human cells were either transplanted to study the tumor formation (Baggiolini et al., 2021) or the anti-tumor effect of modified immune cells (Shah et al., 2024; Zhu et al., 2020). The functionality of pancreatic beta cells was tested in mice and monkeys before transplantation into human (Hogrebe et al., 2020; S. Wang et al., 2024). To avoid the need for immunosuppression after transplantation, researchers work on hypimmune iPSC-derived pancreatic islets and their fate in immunocompetent diabetic humanized mice (Hu et al., 2024).

Chimeras are also prevalent in embryo research: Several papers reported on the implantation of human PSCs into mouse embryos at 8 cell stage or into mouse blastocysts (Mazid et al., 2022; Pedroza et al., 2023; Weatherbee et al., 2023; Yu et al., 2021). For a functional test of pluripotency, cells can be injected subcutaneously in mice and be checked for undirected differentiation into cell lines of the three germ layers, so called teratoma formation (Mazid et al., 2022; Shah et al., 2024). In conclusion, in vitro organ(oid) models may increasingly replace animal testing and experiments. At the same time, animal models have been at the heart of many advances in stem cell research and are unlikely to become completely dispensable. In particular, chimera models are frequently used to study in vivo survival and functionality, the need for immunosuppression, anti-tumor reactions and for (legally required) safety testing before application in humans.

3.1.4 Additional methods

Genome editing allows for better understanding and modelling of diseases.

The modification of the genome in cells or animal models is widely used in research to generate pluripotent stem cells and to differentiate them into the desired cell types. Shinya Yamanaka's generated iPSCs by overexpressing four transcription factors that read the genes required for reprogramming the skin fibroblasts back to a pluripotent state. The sequences for these transcription factors were loaded onto viral constructs and then introduced into the cells via transduction

(Takahashi et al., 2007). Methods now allow researchers to reprogram and differentiate cells by adding defined chemical components to the culture medium (Guan et al., 2022). Albeit this possibility to eliminate the need for genome editing for this step, some groups still prefer to use over-expression to modify their cells' fate, presumably because it has been proven feasible and efficacious for a longer time and is therefore currently more established.

Genome editing methods are used for a broad range of applications. Genes, for example, can be targeted and silenced to study their function and the effects of their loss-of-function. The CRISPR/Cas9 system, among other techniques, can be used to conduct knock-out experiments to model diseases or to study developmental processes. For instance, Li et al. followed this approach to study 36 high-risk genes for autism spectrum disorder, separately knocking out these genes in brain organoids (Li et al., 2023). Additionally, knock-outs can identify the transcription factors that are required to differentiate cells into the desired cell lines and can therefore improve further stem cell research (Expert No. 3, personal communication, 2025). The opposite of knock-outs are knock-ins and describe the process to insert a specific gene into an existing sequence. Even though some scientists state that knock-ins are still labor-intensive and can produce inefficient and potentially imprecise results, others report more success so that the technique can nevertheless be found in various experiments (Expert No. 4, personal communication, 2025). A common method is to couple fluorescent reporter genes to the gene to be inserted to measure the knock-in success (Balmas et al., 2023). This approach can, for example, be used in ESCs to analyze the differentiation potential of these cell lines (Guo et al., 2021; Mazid et al., 2022).

As mentioned in a previous chapter, genome editing can reduce variability between cell lines (J. Kim et al., 2020), the research group around Pantazis used CRISPR/Cas9 to correct a mutation when generating their reference iPSC line (Pantazis et al., 2022). Similarly, a Boston-based research group created isogenic iPSCs using CRISPR/Cas to study ApoE4, a type of apolipoproteins (molecules carrying cholesterol), that is a known risk factor for Alzheimer's disease. By doing so, the researchers minimized individual genetic variation, allowing focused investigation into the role of ApoE4 in dementia risk (Tcw et al., 2022).

Moreover, such engineering may be used to minimize the immune response to the injection of new cells, as exemplified in diabetes research. Type I diabetes mellitus is an autoimmune disease in which immune cells attack and kill own pancreatic cells, thus resulting in the inability to produce sufficient amounts of insulin and other hormones. Even if researchers took patient-derived cells, differentiated them into pancreatic islets and transplanted them back into the patient, the autoreactive immune cells would still target the new pancreatic cells. Consequently, patients in ongoing clinical trials still require immunosuppressive medication after receiving their new and functional cells (Ramzy et al., 2021). However, immunosuppression necessitates lifelong therapy, and carries significant risks due to potential adverse side effects. Therefore, researchers are working on genetic immune modifications to minimize or eliminate the need for immunosuppressive therapy after transplantation (Expert No. 10, personal communication, 2025). Considering that transplanted cells must first undergo animal testing or might be derived from unrelated donors, a research team created hypoimmune iPSCs (HIPs) from both human and rhesus macaques by depleting or overexpressing various immune molecules on the cell surface. The primate and human HIPs and HIP-derived pancreatic islets were transplanted into rhesus macaques and humanized mice respectively, and survived and functioned in their respective hosts for several weeks

(Hu et al., 2024). Of note, to keep control of the transplanted allogeneic HIPs, particularly avoiding tumor formation due to their immune evasion, this concept must include safety aspects as well, e.g. genetically introducing “safety switches”.

Even though the CRISPR/Cas system is a widely used tool and well-known, other techniques for gene engineering exist, each having its own benefits and disadvantages. For example, CRISPR/Cas is less effective for editing sequences frequently repeated throughout the genome. In these cases, the TALEN-technique provides a viable alternative (Expert No. 9, personal communication, 2025). Improvements in genome editing technology are expected to continue, further broadening the applicability and precision of gene editing. Taken together, genome editing has become an indispensable tool in PSC research, enabling the targeted modification of cell lines to investigate cell differentiation, developmental processes, and disease mechanisms and with unprecedented precision.

Machine learning and AI models are used both in planning experiments and for analysis.

We included machine learning and artificial intelligence (AI) techniques in our interviews and literature reviews to reflect the rapid progress and adoption of these technologies. The applications that we found can be split into two categories: planning an experiment and analyzing the data.

When planning an experiment, AI models can help to optimize differentiation protocols and to support the decision of which transcription factors are needed at every step of the process (Expert No. 4, personal communication, 2025; Expert No. 7, personal communication, 2025; Expert No. 10, personal communication, 2025). This assistance can reduce experimental errors, increase reproducibility and save time and resources. In the development of Zernicka-Götz's 2023 embryo-like structures, such models were used to predict the activity of transcription factors and ligand-receptor pairings (Weatherbee et al., 2023).

The same group published a new paper in 2025 using an AI-based approach to study the differences among their mice embryo models (Caldarelli et al., 2025). Analysis of embryo models or organoids enables researchers to selectively pursue only the most promising cell clusters (Expert No. 1, personal communication, 2025; Expert No. 2, personal communication, 2025). Doing this in thousands of petri dishes without computational support is simply impossible. Other data profit from high-throughput analyses as well, for example to study gene regulation, to track cells or to analyze or reconstruct images (Expert No. 2, personal communication, 2025; Expert No. 4, personal communication, 2025; Wahle et al., 2023). In drug research, AI models may assist in drug design, efficacy screening, dose optimization, toxicity testing, and checking for interactions with other drugs (Expert No. 5, personal communication, 2025). Additionally, Bernadette de Bakker's team is currently training an AI model to recognize organs and to detect abnormalities in ultrasound images of embryos, leading to a possible diagnostic application in gynecology (Expert No. 1, personal communication, 2025).

The main challenge to such applications is, however, the lack of high-quality data sets of sufficient size for training these AI models, which significantly limits model development in many cases. In

particular, AI models cannot replace research with embryos or embryo models because the underlying data for key stages of human development are lacking. This is especially important for the window between the stage of IVF-embryos and the availability of further developed aborted embryos or fetuses. Without empirical data from this intermediate period, AI models cannot be trained and validated to simulate or predict developmental processes. As a result, experimental work with embryos or embryo models in the wet lab remains necessary to advance our understanding of early human development (Expert No. 1, personal communication, 2025; Expert No. 5, personal communication, 2025).

3.2 Applications

3.2.1 PSC-derived models

A short overview of embryogenesis in human:

The result of the fertilization of the oocyte with a sperm is a **zygote**, comprising the full genetic dataset. The zygote starts dividing and the number of cells doubles each time. At 16 cells, the structure is called morula. The cells on the outside start to form the **trophoblast** while the inner cell mass at one pole gives rise to the **embryoblast**. As development proceeds, the **blastocyst** (or blastula) forms between these two structures.

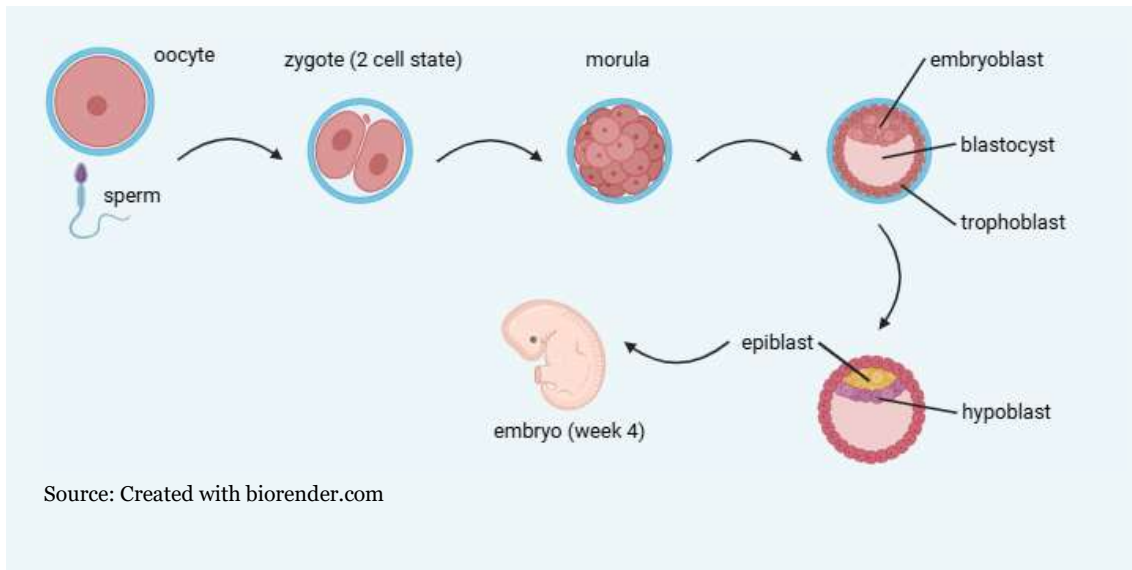
The embryoblast forms two layers of cells: **epiblasts** and **hypoblasts**. Then, the cells are **implanted** into the endometrium of the uterus. The embryo develops from the epiblast, the other blasts will form extra-embryonic tissues (e.g. placenta, amnionic membrane). At the beginning of forming the embryo, the epiblast becomes the embryonic disc. **Gastrulation** explains the process from a bilaminar into a trilaminar germ disc, from which consequently the three **germ layers** (ectoderm, mesoderm, endoderm) are formed.

The embryonal period spans the first 8 weeks of development and is marked by organ formation. It is followed by the fetal period that is characterized by organ growth and further development. To classify embryonic development:

- **Carnegie stages (CS)** divide the 56 days of the embryonal period into 23 stages, based on the embryo's morphologic features.
- Other classification systems include **days post fertilization** (dpf) and the **embryonic day** (E, used for mice).

(Schöni-Affolter et al., 2021)

Figure 5: overview of embryogenesis



PSCs have played an essential role in understanding COVID-19 by studying the consequences of virus infection of lung and brain tissues.

In response to the COVID-19 pandemic, researchers rapidly deployed PSCs to study SARS-CoV-2 infection across multiple organ systems. Huang et al. studied the inflammatory response in infected PSC-derived alveolar epithelial type 2 cells, the lung cells responsible for gas exchange. Their 2D air-liquid interface lung culture also served as a model for testing remdesivir, a known antiviral drug (Huang et al., 2020).

Recognizing that COVID-19 affects organs beyond the lungs, other groups focused on the brain. Jacob et al. (2020) studied brain cells infected with SARS-CoV-2 and characterized their cell fate. Even though their results needed validation in human tissue and their experiments built on direct exposure of immature (fetal-like) brain cells to the virus, the results were of high value for understanding the disease (Jacob et al., 2020). Building on these neurological studies, Wang et al. examined the role of ApoE4, a risk factor for Alzheimer's disease, in SARS-CoV-2 infection and severity of the disease in self-generated iPSC-derived brain organoids. Like other groups, they also simultaneously tested remdesivir on organoids (C. Wang et al., 2021). Addressing the question of viral neuroinvasion, Krasemann et al. used blood-brain-barrier models to demonstrate how the virus migrates from the blood stream into the brain and identified potential prevention strategies (Krasemann et al., 2022).

Apart from research groups adding a single antiviral drug to their experiment, Riva et al. performed a drug screening of approximately 12,000 FDA-approved drugs on ESC-derived lung cells and found several promising candidates for potential off-label use. Here, the PSCs enabled the researchers to work on a scale not realizable with animal models or other methods (Riva et al., 2020). Collectively, these studies demonstrate how PSC technology enabled researchers to rapidly model COVID-19 pathogenesis across multiple organ systems and accelerate therapeutic screening efforts.

Embryo models¹ have shown promise in addressing key knowledge gaps in embryo development.

One in three papers identified in our literature review focuses on modeling early development, indicating that the landmark 2023 studies by Hanna and Zernicka-Götz represent part of a broader research trend rather than isolated breakthroughs. The majority of these studies target specific developmental stages rather than attempting to model complete embryogenesis.

Early-stage models have typically targeted the blastocyst stage. For instance, Mazid et al. started with PSCs and reprogrammed them further until they reached the 8-cell stage to study the genome for totipotency loci. Similarly, Taubenschmid-Stowers used 8-cell stage cells from surplus embryos, but both groups then differentiated them into blastocysts (Mazid et al., 2022; Taubenschmid-Stowers et al., 2022). Blastocyst stages were also the endpoints of several other studies, with models compared to data from human blastocysts (Guo et al., 2021; Kagawa et al., 2022; Karvas et al., 2022; X. Liu et al., 2021; Meistermann et al., 2021; Yanagida et al., 2021; Yu et al., 2021). Such blastocyst-models are commonly called blastoids. Kagawa et al. generated ESCs from surplus embryos and differentiated them into blastoids before combining them with non-stem cell-derived 2D endometrial organoids representing the uterus lining. This model was then used to study the implantation of the blastoids under hormonal stimulation. Their post-implantation model, however, did not match their references, so that they focused on their blastoids at 5-7 days post fertilization (dpf) for the rest of their project, whose gene expression resembled *in vivo* blastocysts (Kagawa et al., 2022). When talking about mechanisms underlying implantation, an extra publication is noteworthy here as it diverges from others in its emphasis, shifting the focus from the biochemistry to the mechanical aspects. While mechanotransduction is already known to influence gene expression in adult stem cells, the generation of a deformable *ex vivo* platform allowed scientists to study traction forces of the embryo during implantation (Godeau et al., 2025).

Building on these blastocyst-stage achievements, researchers have extended their models to capture gastrulation, the next critical developmental milestone. Liu et al. specifically mentioned using extended PSCs to study the potential of self-organization into embryoblasts and then undergoing gastrulation. Their peri-gastruloids at CS8 contained both embryonic tissues (epiblast) and extra-embryonic tissues (hypoblast) derived from embryoblasts, and showed signs of early organogenesis (L. Liu et al., 2023). Other uses for such gastrulation models are to study effects of growth factors on molecular pathways or to study the spatial or self-organization, where not all models require the presence of extraembryonic tissues (Jo et al., 2024; Pedroza et al., 2023; Moris et al., 2020).

Rather than focusing on specific developmental milestones like gastrulation, other research groups have targeted broader post-implantation periods to study particular biological processes. During development, several organs are sequentially involved in the production of blood cells. In early development, the extra-embryonic yolk sac is responsible for hematopoiesis, which can be studied in iPSC-derived CS7-9 post-implantation models (Hislop et al., 2024). Other groups are interested in the early embryo structures that later form the skeletal apparatus or parts of the spine (Rito et al., 2025; Yamanaka et al., 2023) or in tissues necessary to compare metabolic and

¹ In this report, the term ‘embryo model’ is used for multicellular constructs modeling embryological processes. We acknowledge that some models lack structures that are crucial for *in vivo* embryological development and the current discourse in the scientific community on what qualifies as an embryo model.

thus developmental rates in mice and human (Diaz-Cuadros et al., 2023). Differentiation of PSCs into the germ layers can also be done undirected, creating random clusters of different tissues. While such teratomas can occur in humans as tumors, in research they are deliberate tools to validate the behavior of one's cells. This is often done as a safety check before implanting the cells into humans or animals. Depending on the application, the experiment resulting in a teratoma can be either desired or not (Hu et al., 2024; Mazid et al., 2022; Ramzy et al., 2021; Shah et al., 2024; Sharma et al., 2020; S. Wang et al., 2024; Yu et al., 2021).

While the studies above focused on specific developmental processes or time windows, the ultimate goal for many researchers has been creating comprehensive embryo models that capture multiple developmental stages. This possibility gained public attention in 2023 when two labs published their papers: Zernicka-Götz's lab created post-implantation embryo models via combining wild-type ESCs with two extraembryonic-like cell types that were created by targeted transcription-factor overexpression. Subsequently, the mixed populations self-organized into embryo models. Hanna's group, on the other hand, chose to create embryo models using the intrinsic self-organization capacity of wild-type ESCs under the right culture environment, such as external stimulators and rotating culture systems. Both groups compared their models to data derived from human embryos (Oldak et al., 2023; Weatherbee et al., 2023). Hanna's 14 dpf (CS6a) embryo model had remarkable resemblances to embryos, in part due to the invention of cell culturing systems which rotate the bottles and thus, allow to adjust and control air pressure and effects from gravity. Despite this advancement, however, 3D organization remains an ongoing challenge (Expert No. 1, personal communication, 2025).

In succession of this project, where they limited themselves to 14 dpf in their application to the ethics committee, Hanna and coauthors are currently working on generating older models while maintaining close mimicry of their natural counterparts. In their plans to create models at day 30-40 or even up to day 70 (after completion of organogenesis), they are focusing on cell differentiation and self-organization of the cells (Expert No. 2, personal communication, 2025). These models offer several advantages, including the potential to understand why most pregnancies fail at early stages before clinical detection (Macklon, 2002; Weatherbee et al., 2023).

Although these models share features with embryos, including secretion of hCG detected by pregnancy tests, they remain incomplete. Zernicka-Götz' models, for example, lack trophoblast-like cells that could later develop into placental tissues. Trophoblast-like cells are found in Hanna's model, though their spatial organization differs from natural embryos (Mallapaty, 2024; Weizmann Wonder Wander, 2023). To improve human embryo models, researchers are working on mouse embryo models, where models have reached embryonic day 13 of a 20-day gestation. Size wise, this roughly corresponds to day 70 in human, when organogenesis is largely complete and the heart has started to beat (Ansedé, 2024). To mitigate ethical concerns, some research groups have started working on models with inactivated genes critical for brain and heart development (Mallapaty, 2024).

Organ models enable the study of human physiology and human diseases using human tissue.

Currently, human diseases are predominantly studied in non-human animal models, but organ models derived from human cells offer a new alternative. These models can be generated from

PSCs and subsequently manipulated to reach the physiological or pathological conditions of interest.

Understanding the disease requires knowledge of both, the underlying physiological mechanisms and the embryonic/fetal development of the affected organ. Thus, as a first step, many research groups focus on establishing robust protocols for organ models that can then be applied to study either organ development (healthy or pathological) or disease mechanisms.

Physiology: In the study of physiological processes, experiments focus on single organ systems or specific cell types. In neural development, the timing of developmental processes and the role of microglia, a type of neural resident immune cells, were analyzed (Ciceri et al., 2024; Xu et al., 2021). Due to their importance in brain function, phenotypes of microglia were described in detail elsewhere (Schafer et al., 2023). Other examples include developmental studies on spatiotemporal organization in the retina (Wahle et al., 2023) and on the interaction between the hematopoietic system and the embryonic heart (Dardano et al., 2024). Hair-bearing skin organoids provided information on the influence of immune cells on hair follicle formation, scarless wound healing and skin angiogenesis in prenatal skin (Gopee et al., 2024). At a more fundamental cellular level, studies in undifferentiated PSCs revealed information about chromosome folding and chromosome organization (Krietenstein et al., 2020).

Pathophysiology: Experiments focused on the pathology of a disease might explore disease-associated genes and genetic risk factors (e.g. Baggiolini et al., 2021; Li et al., 2023; Qian et al., 2020; Tcw et al., 2022), while for others concentrating on intracellular or external influences might be a better fit (e.g. Giacomelli et al., 2022). In neurodegenerative diseases, protein turnover within cells can be decelerated or impeded otherwise, leading to accumulation of non-degraded protein and a decline in cell functionality (Expert No. 4, personal communication, 2025).

Some examples of disease models include:

- **Central nervous system (CNS):** Brain organoids are commonly used to study both neurodevelopmental disorders (e.g. autism spectrum disorder (ASD), Rett syndrome) and neurodegenerative disorders (e.g. Parkinson's disease, Alzheimer's disease and other tauopathies, amyotrophic lateral sclerosis (ALS)) (Expert No. 3, personal communication, 2025; Expert No. 4, personal communication, 2025; Li et al., 2023; Parra Bravo et al., 2024; Schafer et al., 2023; Tcw et al., 2022). Studies also investigated signaling pathways in psychiatric diseases in neocortex and forebrain organoids, using iPSCs derived from healthy donors and patients with schizophrenia and major depression (Qian et al., 2020). Additionally, brain organoids were employed to study the effects of Zika virus infection on brain cells, especially during neural development (J. Kim et al., 2020; Xu et al., 2021).
- **Heart:** One group improved the culture medium to generate more mature and longer-surviving heart muscle cells and their electrolyte channels. These models were then used to study two genetic heart diseases, i.e. long QT syndrome type 3 and dilated cardiomyopathy (Feyen et al., 2020). Other researchers have used microtissue platforms to study the influence of non-cardiac cells on cardiac diseases (Giacomelli et al., 2022).
- **Lung:** iPSC-derived airway basal cells can be structured into airway organoids to study respiratory diseases such as asthma, cystic fibrosis or primary ciliary dyskinesia, a disorder

in which the secrete transport is impaired (Hawkins et al., 2021). Other pulmonology laboratories have created patient-derived models of lung fibrosis that are used in two ways: to study the disease mechanisms and for personalized drug screening applications (Expert No. 5, personal communication, 2025).

- **Skin:** Researchers have created a prenatal human skin atlas based on hair-bearing skin organoids, providing a platform to “explore genes that cause congenital hair and skin disorders” (Gopee et al., 2024).
- **Others:** Additional organ models include retinal organoids for eye disorders (e.g. glaucoma) (Wahle et al., 2023), single cell line models to study genes and immune responses in tumors (Baggiolini et al., 2021; Zhu et al., 2020), gut organoids for better understanding of inflammatory bowel diseases (IBD) (Expert No. 6, personal communication, 2025).

Organoid systems have increased in complexity and physiological relevance.

Conventional cell cultures grow as 2D structures in culture dishes. Organoids, however, are typically meant to be structured 3D constructs of organ-specific cells. Gel matrices and scaffolds can facilitate the cellular organization and support the formation of more physiologically relevant architectures. Several different cell types can be differentiated together to form more advanced and realistic organ tissues. For example, researchers have produced skin organoids consisting of a dermal and epidermal layer including even hair follicles, melanocytes, and neural cells. The cells were ESC-derived and embryonically differentiated from two germ layers (ectoderm and mesoderm) (Lee et al., 2020). Similarly, most brain organoids integrate different cell types to better capture brain tissue complexity (e.g. Jacob et al., 2020). Some projects assemble previously generated simple organoids or tissues in a second step (Birey et al., 2017), resulting in structures often referred to as “assembloids”. This modular strategy allows researchers to combine different organ regions or tissue types.

The size of organoids typically ranges from micrometers to millimeters in diameter (Berishvili et al., 2021). A major constraint in creating bigger cell clusters is the need to supply all cells with sufficient oxygen and nutrients. Without proper delivery networks, especially cells in the interior regions would die as a consequence of insufficient supplies. Researchers therefore are working on vascularization strategies to generate more realistic organoids and overcome size constraints.

Mimicking natural blood flow requires several critical components: vessel walls that function as selective permeable barriers, a source to provide essential molecules, mechanisms to excrete cellular waste products, and systems to prevent blood clotting, etc.. Once these factors are operational, vascular flow can be used, for example, to link several organoids together and to study potential impact of mechanic force (e.g. shear stress), allowing experiments in more systemic environments. In such set-ups, the individual tissues are often referred to as ‘organ-on-a-chip’, thus linking chips with their individually fit condition together results in multi-organ-chips. Ronaldson-Bouchard and colleagues demonstrated this approach by combining heart, liver, bone and skin through vascular flow, incorporating monocytes that could migrate between organs. While bone and skin cells were generated from adult cells rather than from PSCs (as used for heart and liver), this study exemplifies how different approaches can be combined into unified systems (Ronaldson-Bouchard et al., 2022).

Apart from blood flow, the integration of other physiological properties is being studied. In the brain, it is critical to regulate which components in the blood are allowed to enter brain tissue. Studying how pathogens or pharmaceutical agents penetrate this barrier in humans requires robust blood-brain-barrier models (Krasemann et al., 2022). In the lung, perfusion only addresses half the challenge, oxygenation constitutes the other half. Currently, only air-liquid interfaces exist and these do not sufficiently model gas exchange (Burgess et al., 2024; Expert No. 5, personal communication, 2025; Huang et al., 2020). The integration of immune system components represents another critical advancement. Gut models, for instance, must incorporate the interplay between immune cells and the microbiome. Such combinations facilitate, for example, the study of inflammatory bowel diseases (IBD) (Expert No. 6, personal communication, 2025).

Further developments are needed to overcome current limitations.

Cellular maturation represents a fundamental challenge. Cells in organoids are frequently described as resembling fetal cells rather than their fully matured adult counterparts (Balboa et al., 2022; Burgess et al., 2024; Expert No. 3, personal communication, 2025; Expert No. 6, personal communication, 2025; Jacob et al., 2020; Sharma et al., 2020; C. Wang et al., 2021). This raises the question whether organoid research based on quasi-fetal cells is informative for typical medical application in human adults. For fundamental research, immature states additionally prohibit researchers from studying aging processes in their cells (Expert No. 6, personal communication, 2025; Parra Bravo et al., 2024; Tcw et al., 2022). The lack of understanding of intracellular processes and transcription profiles limits embryo models to reach further milestones (Expert No. 2, personal communication, 2025).

Problems with differentiation concepts further include (a) receiving undesired or, conversely, lacking desired cell types (Hawkins et al., 2021; Huang et al., 2020), (b) hugely varying results and derivation processes (Meistermann et al., 2021; Oldak et al., 2023; Yu et al., 2021), (c) failing to precisely match embryonic and extra-embryonic temporal developments with one's culture conditions (Karvas et al., 2022), and (d) the lack of accepted and standardized protocols as a solution to today's contradicting reports (J. Kim et al., 2020). Even when differentiation succeeds, many papers report deviations between their model and human data (Burgess et al., 2024; Dardano et al., 2024; Expert No. 1, personal communication, 2025; Gopee et al., 2024; Jacob et al., 2020; Kagawa et al., 2022; Karvas et al., 2022; Krasemann et al., 2022; Li et al., 2023; L. Liu et al., 2023; Mazid et al., 2022; Meistermann et al., 2021; Moris et al., 2020; Oldak et al., 2023; Qian et al., 2020; Revah et al., 2022; Taubenschmid-Stowers et al., 2022; Xu et al., 2021; Yanagida et al., 2021; Yu et al., 2021) and low and variable efficiencies (i.e. positive results) (Guan et al., 2022; J. Kim et al., 2020; L. Liu et al., 2023; Oldak et al., 2023; Sharma et al., 2020; Weatherbee et al., 2023; Yu et al., 2021). Consequently, validation requires human tissues from work in human embryos or organ samples from deceased patients (Expert No. 1, personal communication, 2025; Expert No. 3, personal communication, 2025; Jacob et al., 2020; Tcw et al., 2022). However, embryos donated for scientific use are limited in number and may be compromised in quality. For example, the time of death of an embryo or fetus in miscarriages, and thus its embryonic age is often unknown (Expert No. 1, personal communication, 2025; Guo et al., 2021).

Genetic instability of both iPSCs and ESCs poses an ongoing challenge. Scientists report culture-adapted phenotypes and thus heterogeneity among different ESC-derived lines with somatic mutations and epigenetic alterations leading to differences in gene readouts (J. Kim et al., 2020; Y.-

J. Kim et al., 2024). However, current issues are being addressed by several research teams working on improving adult cells reprogramming into iPSCs to overcome inefficiencies, enhance consistent results across cell sources, and to find alternatives that eliminate the need for oncogenes (Expert No. 9, personal communication, 2025; J. Kim et al., 2020; L. Liu et al., 2023). Still, established iPSC lines might be limited in diversity and thus not representing minorities (Pantazis et al., 2022). Advancements in the field of genome editing are also required. While in some experiments the struggle to delete the global epigenetic memory continues (Pedroza et al., 2023), other projects fail to include specific epigenetic influences (Tcw et al., 2022). In genes whose effect on organ development is transient, the exact timing might be missed and with it the consequence of mutations in high-risk genes. Additionally, the knowledge on whether the cells carry each mutation on only one or on both alleles might not be available (Li et al., 2023).

As a further shortcoming, systemic processes remain poorly modeled. Current models lack or simplify systemic processes and interactions such as vascularization (including the blood brain barrier), integrated immune systems, and inter-organ communication (Expert No. 6, personal communication, 2025; Expert No. 7, personal communication, 2025; J. Kim et al., 2020; C. Wang et al., 2021). One approach to overcoming lack of oxygen in central cells and thus the organoid development is to slice the tissues into discs, accepting the risk of damaging cells through such repeated manipulation (Qian et al., 2020). Besides overall progress, differences between organs exist, such as lung tissue is reported to be challenging to cultivate (Expert No. 5, personal communication, 2025).

Other reported limitations include that brain organoids are highly reductionistic, thus lacking the ability to build complex neural circuits (Expert No. 8, personal communication, 2025). In all of these organoids, cell types present in human brains are missing (Krasemann et al., 2022; Li et al., 2023; Qian et al., 2020; Revah et al., 2022). In infection studies, direct exposure of the cells to the (potentially) pathogenic virus may not reflect reality where virus first need to enter the body through epithelial layers (Jacob et al., 2020; Krasemann et al., 2022). For pharmaceutical studies, organs influencing the pharmacokinetics (absorption, distribution, metabolism, and excretion in e.g. gut, fat, kidney and liver) and pharmacodynamics (effect on the body) of a drug need to be included in studies. Validations of drug testing models should consider different drug administration routes and dosing schemes (Ronaldson-Bouchard et al., 2022). Transplantations of human tissue into animals might put the cells into an immunologic hostile environment that may additionally lack specific factor to interact with the graft (e.g. ligands only being present in humans to receptors on the transplanted human cells). Further studies to examine the external influence of host cells on the graft development/maturation are needed (Schafer et al., 2023). After transplantation into humans, which is currently being done with pancreatic cells in clinical trials, the need for immunosuppressive medication persists. Additionally, small sample sizes and heterogeneous outcomes currently limit the informative value of the study (Ramzy et al., 2021; S. Wang et al., 2024).

3.2.2 Clinical applications

PSC differentiation can be limited to the cell types of interests, or these cells can be taken from an embryo model (embryo model cell harvesting).

During in vitro differentiation of PSCs, researchers can steer the development pathways to generate specific cell types of interest. This directed differentiation is achieved through overexpression and regulation of specific transcription factors and/or by providing the optimal culture conditions. The cell types of interest are eventually available for further use (Balboa et al., 2022; Giacomelli et al., 2022). Such directed differentiation enables the generation of specific cells from all three germ layers, including precursor cells for gametes such as oocytes and spermatocytes (Mura et al., 2024). To change the genome of one's oocytes, a group recently published their work in which they have further developed the process of somatic cell nuclear transfer (SCNT). Previously, the nucleus of an adult cell was implanted into a denucleated oocyte. However, the group has established a protocol for production of oocytes that contain only one set of alleles that can then be fertilized with sperms. In a second step, the resulting zygotes were cultured to assess their embryonic developmental process and thus, exploring the initial potential for IVF applications (Marti Gutierrez et al., 2025).

Other groups have adopted a second approach for cell generation: Specific cell types such as primordial germ cells or hematopoietic stem cells can be harvested from an embryo model and then potentially used for reproductive medicine or blood transfusions, respectively (Expert No. 2, personal communication, 2025). This method leverages the natural developmental organization within embryo models to access cell populations that may be challenging to generate through directed differentiation protocols.

Current diseases of major interest in PSC research are diabetes mellitus type 1 and neurodegenerative diseases.

Stem cell-based therapies show promise for treating type 1 diabetes mellitus, an autoimmune disease typically manifesting in adolescence where immune cells destroy pancreatic cells and, with them, the ability to produce insulin and other hormones. Patients require a lifelong substitution therapy and lifestyle changes to avoid fatal consequences. New treatment options include the transplantation of iPSC-derived pancreatic islets (Balboa et al., 2022; Expert No. 10, personal communication, 2025; Hoglebe et al., 2020; Hu et al., 2024; Ramzy et al., 2021; S. Wang et al., 2024). While the insulin-producing beta cells play a key role in these tissues, some groups are attempting to incorporate other endocrine pancreatic cells such as alpha cells for glucagon and delta cells for somatostatin (Balboa et al., 2022; Hu et al., 2024; Ramzy et al., 2021). In ongoing clinical trials, patient cells were reprogrammed to a pluripotent state, differentiated into pancreatic cells before being injected under the patient's skin. In their report one year after the transplantation, the researchers stated that the cells were able to secrete insulin according to the patient's blood glucose level. However, even though the transplanted cells stemmed from the same individual, the autoimmune nature of the disease necessitates the continued use of immunosuppressants (Ramzy et al., 2021; S. Wang et al., 2024). A similar trial using ESC-derived allogeneic islet cells could provide similarly promising results after one year follow up in 14 patients (clinicaltrials.gov, 2025; Reichman et al., 2025).

Neurodegenerative diseases represent another major therapeutic focus for PSC research. For Parkinson's disease, the leading therapeutic hypothesis involves the implantation of PSC-derived dopamine neurons into the respective brain regions to replace degenerated cells and restore motor function (Expert No. 8, personal communication, 2025; T. W. Kim et al., 2024). Similar neuronal replacement strategies are being investigated for stroke recovery, where transplanted neurons

could regenerate lost brain functions by integrating into damaged neural circuits (Expert No. 8, personal communication, 2025). Beyond cell replacement therapies, researchers have created a disease modeling platform that facilitates drug discovery for neurodegenerative diseases involving certain forms of the tau protein (e.g. Alzheimer's disease, Pick's disease, corticobasal degeneration) (Parra Bravo et al., 2024).

These two (groups of) diseases have at least two things in common: cell functionality is lost, and that current therapeutic strategies focus on treating symptoms rather than the underlying pathomechanisms. Cell replacement therapy represents a promising therapeutic alternative. Importantly, the brain belongs to the few immune-privileged organs, meaning that implanted cells may evade immune recognition and rejection.

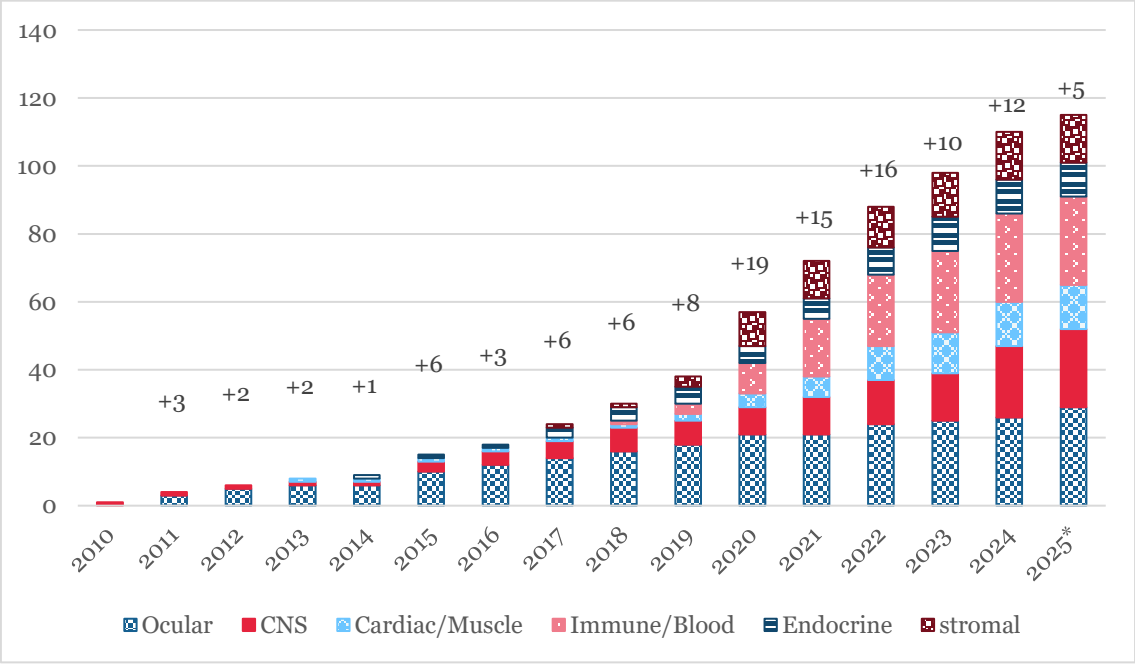
Other promising applications include a broader spectrum of organs and diseases.

Our analysis included treatment approaches for a wide range of indications. In cardiology, in vitro produced cardiac valve replacements for children improve conventional products because they can grow together with the child's heart after transplantation (Expert No. 7, personal communication, 2025). In oncology, new immunotherapy agents are becoming feasible (Expert No. 6, personal communication, 2025; Shah et al., 2024). One approach is to develop induced macrophages with a chimeric antigen receptor (CAR-iMacs) that are ought to fight pancreatic cancer. The concept is similar to treatments using CAR-T cells which currently do not include stem cells, but are already integrated in clinical use (Shah et al., 2024). Transplantation of PSC-derived tissues can include artificial skin for reconstructive surgery (Lee et al., 2020). Organs produced in this way might reduce the need for strong immunosuppression after transplantation, as the cells can be either patient-derived and therefore autologous or be engineered to be hypoimmunogenic, thus not initiating immune responses (Hu et al., 2024). Pharmaceutical industry representatives additionally mentioned the potential of PSC-derived therapies for widespread diseases like chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (IBD) (Expert No. 6, personal communication, 2025). In reproduction medicine, research on PSCs and embryo development have the potential to improve in vitro fertilization (IVF) treatments, prevent miscarriages, and develop new contraceptives (Expert No. 1, personal communication, 2025; X. Liu et al., 2021; Meistermann et al., 2021; Yu et al., 2021). Overall, production of "fetal-like" tissues and utilizing the full potential of cellular reprogramming could play important roles in the future of regenerative medicine (Guan et al., 2022; L. Liu et al., 2023).

In their comprehensive analysis of hPSC-derived therapies in clinical trials, Kirkeby et al. reviewed products from 115 previous and ongoing clinical trials registered by December 2024. The trials included 83 different PSC products for 34 medical indications and were conducted in 19 countries in over 1'200 patients. The majority of trials were in phase I or IIa, therefore focused on safety and dosage finding and that they were "so far showing no generalizable safety concerns", like tumor formation due to contamination with undesired cell types or undifferentiated PSCs. The indications covered seven major categories: (a) ocular products (for e.g. macular and retinal diseases), (b) central nervous system (CNS) products (for e.g. spinal cord injury, Parkinson's disease, stroke, amyotrophic lateral sclerosis (ALS), epilepsy), (c) cardiomyocytes and muscle products (for e.g. heart failure, Duchenne muscular dystrophy), (d) endocrine products (for e.g. type 1 diabetes mellitus, liver failure), (e) immunotherapies (immune cells for e.g. various solid and hematological tumors, COVID-19, systemic lupus erythematosus, thrombocytopenia), (f) blood

products (platelets and red blood cells e.g. for thrombocytopenia or anemia) and (g) stromal products (e.g. for some orthopedic, immunological or gynecological diseases) (Kirkeby et al., 2025) (Figure 6). This broad therapeutic scope, combined with the encouraging safety profile, demonstrates the ongoing maturation of PSC-based medicine.

Figure 6: Cumulative number of clinical trials from 2010 to 2025 by therapeutic area



Source: Kirkeby et al., 2025, use of data kindly provided. The data was gathered from analyzing 115 approved interventional clinical trials with hPSC products worldwide. *Numbers for the year 2025 are incomplete as not all trials starting that year had been given approval by the time of publication.

Technology enables high production rates of cells for further use.

With improving differentiation protocols, efficiencies will increase and the production of cells and organoids at high numbers will become more accessible. Therefore, sufficient cell numbers for clinical and research applications can be reliably generated (Hogrebe et al., 2020). Cells, tissues, or organ chips can then be used, for example, to screen potential drugs without exposing patients to harmful side effects, and when derived from patient-specific cells, they can pave the way for personalized medicine approaches (Expert No. 5, personal communication, 2025; Hislop et al., 2024; Riva et al., 2020; Ronaldson-Bouchard et al., 2022; Sharma et al., 2020).

3.3 Feedback on the StRA

The process to apply a project under the StRA at the FOPH is straightforward.

Six of our interview partners have either a completed or ongoing project using ESCs in Switzerland². Satisfaction with the current FOPH application process was very high³, only one researcher mentioned not applying due to the bureaucratic hurdle (Expert No. 3, personal communication, 2025; Expert No. 5, personal communication, 2025; Expert No. 6, personal communication, 2025; Expert No. 8, personal communication, 2025; Expert No. 10, personal communication, 2025). Nevertheless, a few amendments and potential needs for action were proposed:

- For the researchers, there was currently no need to produce new ESC cell lines. However, one researcher suggested a domestic biobank which stores 5-10 ESC lines to avoid the need to import such cell lines. These lines would then be stored for approximately 20 years before they were then, if still required, replaced by new lines (Expert No. 5, personal communication, 2025). Additionally, one researcher suggested that some of the ESC lines should fulfill Good Manufacturing Practice (GMP) criteria, so that these cell lines could be used for development of therapies.
- One researcher requested more clarity if cells from the trophoblast can be used (and thus extraembryonic cells from surplus IVF-embryos) and regarding human-animal chimeras, and reported ambiguities across language versions (Expert No. 7, personal communication, 2025).
- The process could be streamlined for low-risk projects with long-established cell lines (Expert No. 4, personal communication, 2025).
- The separation of the StRA and the Human Research Act (HRA) leads to uncertainties on which regulations apply and the necessity of legal advisors at their university (Expert No. 3, personal communication, 2025).
- As previously seen, genome editing is a common method used in stem cell research, but its use is too tightly regulated (Expert No. 10, personal communication, 2025).
- The need for international harmonization of regulations was emphasized (Expert No. 9, personal communication, 2025). As a useful additional tool for researchers, the International Society for Stem Cell Research (ISSCR) has published version 1.2 of their 2021 guidelines for stem cell research and clinical translation. The update, released in August 2025 incorporates embryo models in more detail. In a press release, they recommend “enhanced oversight of stem cell based embryo models in response to rapid technological advances” and published a perspective paper advocating for appropriate review, clear scientific rationale, and limited timelines in experiments involving 3D embryo models (Clark et al., 2025; ISSCR, 2025a, 2025b).

Two additional regulatory problems were raised that are indirectly linked to the StRA:

- Problems were reported with the cantonal ethic committees as this process requires a separate application and the committees were said to have insufficient expertise in biomedical research in some cases, causing delays (Expert No. 3, personal communication, 2025). It would be desirable if the StRA-project application could be combined with the project application to the ethics committee.

² Matthias Lütolf's project was as a professor at EPFL and not for his role at Roche. The rest of the interview focused on his work at Roche, while still considering his overall experience in the field.

³ Please note that it was after the last interviews had been completed that the FOPH changed their website, and information on the application process seem to be more readily available in the new version.

- “In Switzerland, clinical research with PSC-derived products such as pancreatic islets requires not only the standard Swissmedic authorization for a clinical trial under the Therapeutic Products Act, but also—when transplantation provisions apply—additional authorization from the Federal Office of Public Health (FOPH) under the Transplantation Act. This dual oversight creates a parallel layer of regulation that differs from the framework for classical tissue or organ transplantation. The result is a process that can appear fragmented and administratively heavy, particularly when compared with the European framework under Regulation (EC) No 1394/2007, which offers a more consolidated regulatory pathway, even if multiple steps remain in practice. These structural complexities do not prevent research, but they slow down translation by creating multiple approval points and uncertainty about the applicable regulatory route. From the investigator’s perspective, the system would greatly benefit from harmonized guidance and a clearer allocation of responsibilities across the different regulatory layers” (Expert No. 10, personal communication, 2025).

4. Discussion

4.1 Conclusions

This report shows that both hESCs and hiPSCs are currently used in a variety of research applications, ranging from fundamental research to clinical trials. While most research groups work with existing hPSC lines, the authors of 2 out of 60 papers still opted to produce new hESC lines, although there are no recent cases of such practices from Switzerland. In embryology, researchers emphasize the need for validation of their models using data from human embryos, which requires not only aborted tissues but also surplus IVF-embryos to provide comprehensive reference material.

hPSCs enable the creation of organ models, including organoids, which can be used to study organ development, disease mechanisms and to develop potential therapies. For clinical applications, allogeneic hiPSC or hESC-derived products in clinical trials currently predominate over the injection or transplantation of patient-derived iPSC derivatives. While preclinical studies focus primarily on neurological applications, interventional clinical trials include a broader range of diseases, targeting organs such as the pancreas and eye. Currently, significant effort is invested to overcome the limitations hindering progression of this field. While AI models are used to support the planning of experiments and data analysis, the need for generating training data in the wet lab continues. This necessity is particularly acute for human embryo research, given the existing knowledge gap covering approximately three weeks of embryogenesis due to the limited availability of human tissues from this period. Overall, research with hPSCs holds substantial promise for major medical advances. However, despite numerous therapeutic approaches under development, broadly available therapies have yet to be successfully translated to the market.

4.2 Limitations

This report faces two types of limitations: (a) self-imposed design and analysis we had to impose constraints; (b) limits in the available information. For the first category, in the scoping review, we implemented a journal restriction to reduce the number of papers in the PubMed search results, aware that important work can appear elsewhere. Similarly, we used citation counts to reduce the number of papers included in the screening. However, citations might be an imperfect measure of relevance, especially for the most recent papers considered. Citations were standardized for the month of publication within each year. Because counts for 2024 were retrieved in April 2025, they are less stable than for earlier years. In the content analysis of the literature, we focused on the handling and manipulation of cells for the main research questions and did not investigate standard analytical methods that are widely used in biomedical research such as immunohistochemistry, adding genes encoding fluorescent reporter proteins, and analysis of the total of a group of biological molecules (OMICS) as well as single cell sequencing.

The expert interviews exhibit a strong reliance on Switzerland-based researchers owing to the background of our study. No principal investigators from Asia were included, although especially China and Japan account for a significant share of stem cell research. Additionally, not all organs on which hPSC research is performed were covered by our experts. This includes the eye, blood vessels, liver and research on IVF surplus embryos.

Importantly, this report addresses scientific possibilities in stem cell and embryo research, whereas ethical considerations are out of scope and treated in a separate FOPH-mandated study.

For the second category of limitations concerning restrictions on the available information, research articles often omit the rationale for choosing a given approach (e.g. why hESCs rather than hiPSCs were chosen for an experiment or why to generate new PSC lines). Interviewees could not resolve such project-specific decisions but only explain potential trade-offs based on their own research. Accordingly, we describe experiments and the state of research rather than being able to provide the motivation behind all choices.

Taken together, these constraints favor well-cited, English-language, and Switzerland-centric work, with incomplete rationales for methodological choices. Our synthesis report should therefore be read as a map of dominant directions rather than an exhaustive census. Quantitative analyses remain provisional, particularly for the most recent years of publication covered.

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A. Annex

A.1 PubMed keyword search

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A.2 List of papers included in the review

First Author	Year	Full Title	Journal	Source
Baggiolini, Arianna	2021	Developmental chromatin programs determine oncogenic competence in melanoma	Science	Researchers
Balboa, Diego	2022	Functional, metabolic and transcriptional maturation of human pancreatic islets derived from stem cells	Nature Biotechnology	Researchers
Buckberry, Sam	2023	Transient naïve reprogramming corrects hiPS cells functionally and epigenetically	Nature	Researchers
Burgess, Claire L.	2024	Generation of human alveolar epithelial type I cells from pluripotent stem cells	Cell Stem Cell	PubMed
Ciceri, Gabriele	2024	An epigenetic barrier sets the timing of human neuronal maturation	Nature	both
Dardano, Miriana	2024	Blood-generating heart-forming organoids recapitulate co-development of the human haematopoietic system and the embryonic heart	Nature Cell Biology	PubMed
Deinsberger, Julia	2020	Global trends in clinical trials involving pluripotent stem cells: a systematic multi-database analysis	npj Regenerative Medicine	Researchers
Diaz-Cuadros, Margarete	2023	Metabolic regulation of species-specific developmental rates	Nature	PubMed
Feyen, Dries A.M.	2020	Metabolic Maturation Media Improve Physiological Function of Human iPSC-Derived Cardiomyocytes	Cell Reports	PubMed
Giacomelli, Elisa	2020	Human-iPSC-Derived Cardiac Stromal Cells Enhance Maturation in 3D Cardiac Microtissues and Reveal Non-cardiomyocyte Contributions to Heart Disease	Cell Stem Cell	PubMed
Gopee, Nusayhah Huda	2024	A prenatal skin atlas reveals immune regulation of human skin morphogenesis	Nature	PubMed

First Author	Year	Full Title	Journal	Source
Guan, Jingyang	2022	Chemical reprogramming of human somatic cells to pluripotent stem cells	Nature	PubMed
Guo, Ge	2021	Human naive epiblast cells possess unrestricted lineage potential	Cell Stem Cell	PubMed
Hawkins, Finn J.	2021	Derivation of Airway Basal Stem Cells from Human Pluripotent Stem Cells	Cell Stem Cell	Researchers
Hislop, Joshua	2023	Modelling post-implantation human development to yolk sac blood emergence	Nature	both
Hogrebe, Nathaniel J.	2020	Targeting the cytoskeleton to direct pancreatic differentiation of human pluripotent stem cells	Nature Biotechnology	Researchers
Hu, Xiaomeng	2023	Hypoimmune induced pluripotent stem cells survive long term in fully immunocompetent, allogeneic rhesus macaques	Nature Biotechnology	both
Huang, Jessie	2020	SARS-CoV-2 Infection of Pluripotent Stem Cell-Derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response	Cell Stem Cell	PubMed
Jacob, Fadi	2020	Human Pluripotent Stem Cell-Derived Neural Cells and Brain Organoids Reveal SARS-CoV-2 Neurotropism Predominates in Choroid Plexus Epithelium	Cell Stem Cell	PubMed
Jo, Kyoung	2024	Endogenous FGFs drive ERK-dependent cell fate patterning in 2D human gastruloids	eLife	Researchers
Joung, Julia	2023	A transcription factor atlas of directed differentiation	Cell	PubMed
Kagawa, Harunobu	2021	Human blastoids model blastocyst development and implantation	Nature	both
Karvas, Rowan M.	2023	3D-cultured blastoids model human embryogenesis from pre-implantation to early gastrulation stages	Cell Stem Cell	PubMed
Kim, Jihoon	2020	Human organoids: model systems for human biology and medicine	Nature Reviews Molecular Cell Biology	Researchers

First Author	Year	Full Title	Journal	Source
Kim, Tae Wan	2024	TNF-NF- κ B-p53 axis restricts in vivo survival of hPSC-derived dopamine neurons	Cell	Researchers
Krasemann, Susanne	2022	The blood-brain barrier is dysregulated in COVID-19 and serves as a CNS entry route for SARS-CoV-2	Stem Cell Reports	PubMed
Krietenstein, Nils	2020	Ultrastructural Details of Mammalian Chromosome Architecture	Molecular Cell	PubMed
Lee, Jiyeon	2020	Hair-bearing human skin generated entirely from pluripotent stem cells	Nature	Researchers
Li, Chong	2023	Single-cell brain organoid screening identifies developmental defects in autism	Nature	PubMed
Liu, Lizhong	2023	Modeling post-implantation stages of human development into early organogenesis with stem-cell-derived peri-gastruloids	Cell	both
Liu, Xiaodong	2021	Modelling human blastocysts by reprogramming fibroblasts into iBlastoids	Nature	PubMed
Mazid, Md. Abdul	2022	Rolling back human pluripotent stem cells to an eight-cell embryo-like stage	Nature	PubMed
Meistermann, Dimitri	2021	Integrated pseudotime analysis of human pre-implantation embryo single-cell transcriptomes reveals the dynamics of lineage specification	Cell Stem Cell	PubMed
Moris, Naomi	2020	An in vitro model of early anteroposterior organization during human development	Nature	both
Murase, Yusuke	2024	In vitro reconstitution of epigenetic reprogramming in the human germ line	Nature	Researchers
Oldak, Bernardo	2023	Complete human day 14 post-implantation embryo models from naive ES cells	Nature	Researchers
Pantazis, Caroline B.	2022	A reference human induced pluripotent stem cell line for large-scale collaborative studies	Cell Stem Cell	PubMed

First Author	Year	Full Title	Journal	Source
Parra Bravo, Celeste	2024	Human iPSC 4R tauopathy model uncovers modifiers of tau propagation	Cell	PubMed
Pedroza, Monique	2023	Self-patterning of human stem cells into post-implantation line-ages	Nature	PubMed
Qian, Xuyu	2020	Sliced Human Cortical Organoids for Modeling Distinct Cortical Layer Formation	Cell Stem Cell	PubMed
Ramzy, Adam	2021	Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes	Cell Stem Cell	PubMed
Revah, Omer	2022	Maturation and circuit integration of transplanted human cortical organoids	Nature	Researchers
Rito, Tiago	2024	Timely TGF β signalling inhibition induces notochord	Nature	Researchers
Riva, Laura	2020	Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing	Nature	PubMed
Ronaldson-Bouchard, Kacey	2023	A multi-organ chip with matured tissue niches linked by vascular flow	Nature Biomedical Engineering	Researchers
Schafer, Simon T.	2023	An in vivo neuroimmune organoid model to study human microglia phenotypes	Cell	PubMed
Shah, Zahir	2024	Human anti-PSCA CAR macrophages possess potent antitumor activity against pancreatic cancer	Cell Stem Cell	PubMed
Sharma, Arun	2020	Multi-lineage Human iPSC-Derived Platforms for Disease Modeling and Drug Discovery	Cell Stem Cell	PubMed
Taubenschmid-Stowers, Jasmin	2022	8C-like cells capture the human zygotic genome activation program in vitro	Cell Stem Cell	PubMed
TCW, Julia	2022	Cholesterol and matrisome pathways dysregulated in astrocytes and microglia	Cell	PubMed

First Author	Year	Full Title	Journal	Source
Tyser, Richard C. V.	2021	Single-cell transcriptomic characterization of a gastrulating human embryo	Nature	PubMed
Wahle, Philipp	2023	Multimodal spatiotemporal phenotyping of human retinal organoid development	Nature Biotechnology	Researchers
Wang, Cheng	2021	ApoE-Isoform-Dependent SARS-CoV-2 Neurotropism and Cellular Response	Cell Stem Cell	PubMed
Wang, Shusen	2024	Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient	Cell	Researchers
Weatherbee, Bailey A. T.	2023	Pluripotent stem cell-derived model of the post-implantation human embryo	Nature	both
Xu, Ranjie	2021	Developing human pluripotent stem cell-based cerebral organoids with a controllable microglia ratio for modeling brain development and pathology	Stem Cell Reports	PubMed
Yamanaka, Yoshihiro	2022	Reconstituting human somitogenesis in vitro	Nature	PubMed
Yanagida, Ayaka	2021	Naive stem cell blastocyst model captures human embryo lineage segregation	Cell Stem Cell	PubMed
Yu, Leqian	2021	Blastocyst-like structures generated from human pluripotent stem cells	Nature	both
Zhu, Huang	2020	Metabolic Reprograming via Deletion of CISH in Human iPSC-Derived NK Cells Promotes In Vivo Persistence and Enhances Anti-tumor Activity	Cell Stem Cell	PubMed

