Facts sheet for research institutions

Research on human embryonic stem cells and their somatically derived counterparts, the human induced pluripotent stem cells, can not only advance scientific knowledge in understanding human development and disease, but has the great promise to be used to develop innovative therapies to treat uncurable diseases. To this end, the European Commission supports and funds human stem cell research under strict ethical guidelines. The following factsheet gives an introduction to pluripotent stem cells and the roles and tasks of research institutions in human pluripotent stem cell research.

What is human stem cell research about and what is its great potential?

Human pluripotent stem cells (hPSCs), whether human embryonic stem cells (hESCs) or induced pluripotent stem cells (iPSCs), play an important role in human biological research. They are not only excellent tools to model human development and disease, but are also widely used in other areas of research, such as the testing and development of new drugs and treatment methods. Current efforts also focus on the use of hPSC-derived cells for therapy, with the first clinical trials in humans already underway. The use of pluripotent stem cells is expected to further increase steadily worldwide as seen by the growing number of publications and patents related to stem cells.

What is the significance of cell donations for the stem cell research community?

All of these research areas rely on the donation of human sample material by volunteers. Researchers need biological donor material in order to produce stem cells and stem cell lines - this donor material can either consist of very early stage embryos or somatic cells from a donor. Whereas embryonic stem cells are derived from an early stage embryos called blastocyst, induced pluripotent stem cells are generated from somatic cells by means of reprogramming. The value of these donations of the source material for these stem cell lines should not be underestimated for research, and the ethical and social framework conditions for these voluntary donations must be observed and considered.

How do cell donations need to be evaluated on an ethical level?

Cell donations from volunteers are to be understood as sensitive, personal entities that should only be used as research objects under very specific ethical conditions. Every single human cell donated for research has its origin in the autonomous decision of a person who not only cedes ownership of parts of their body to the public/research community, but also provides sensitive personal data (e.g. relating to their individual genome). This autonomous decision requires a clear ethical framework in order to treat the donors in question with respect and on an equal footing.

How is the value of freedom of research related to the value of the donor's self-determination?

Freedom of research is a high ethical and social good, not only because of the human desire to seek the truth and accumulate knowledge, but because it can form the basis for greater social prosperity and an increase in the health of society as a whole through scientific progress. In all these considerations, however, other ethical values must not be underestimated: the value of human autonomy and the right of self-determination, the value of protecting personal data and privacy, i.e. the rights of the donor of biological material for research.

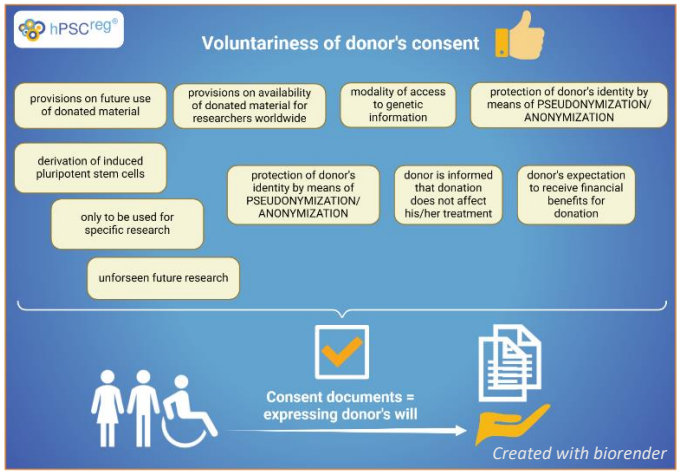
Under what ethical conditions must the process of cell donation take place?

Cell donation must take place under certain ethically defined conditions, for example, it must be voluntary and without pressure, it must be: (i) informed, respectful and include a description of all the risks, opportunities and consequences associated with the donation for the donor; (ii) financial incentives should not have pressured donors to donate; and (iii) means should be used to protect donor's confidentiality. The fact that the cell donation took place in this way is recorded and made comprehensible in a document: the declaration of consent (often combined with a participant information sheet describing the project idea), which the donor signs if he or she agrees to the conditions of the cell donation and is willing to donate.

Research projects using human material must obtain ethical approval, and additionally the PIS and ICFs must be approved by an ethics committee. Samples are

always obtained within a framework of a research project.

Which aspects can be addressed and agreed with the donor at the time of cell donation and set down in writing in the consent document?



The process of consent at the time of cell donation is recorded in the consent form. This document also confirms, with the donor's signature, that the donation was made voluntarily and that the donor has been informed about the process of the donation, the future use of the cells and the handling of his/her data and cells. Various aspects can be addressed in this consent process, but not all aspects always have to be mentioned explicitly. In general, the consent form includes the confirmation that the donation was made voluntarily and defines the provisions of future use of the donated material (e.g. iPSC generation, only for scientific research or also for commercial use, open for „unforeseen future research"). In addition, the donor is informed whether and how his/her genetic information is accessed, whether his/her cells can be used worldwide and how his/her identity is protected (pseudonymization or anonymization). In addition, he/she must have been informed that participation will not directly influence his/her treatment and that he/she will not receive financial benefit for donation. In hPSCreg®, donor consent forms and information sheets deposited must not contain the donors signature for anonymization purposes.

Examples for consent templates can be found here:

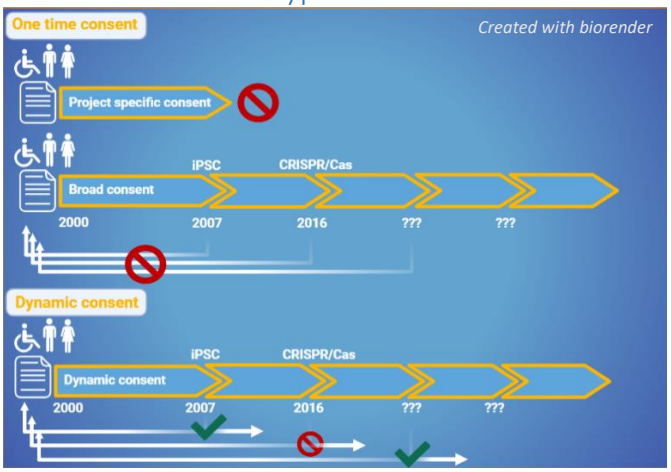
https://www.gscn.org/german-stem-cell-network/strategic-working-groups/elsa

https://ebisc.org/docs/ebisc/EBiSC_CONSENT_TEMPLATE.docx

How binding are the terms of use of the donated material specified in the consent form?

As a stem cell researcher, you are obliged to respect the donor's autonomy. If, for example, the declaration of consent contains restrictions on the use of the donated material, these must be respected, since the donor consent is a legally binding document. The institution providing the donor information sheet and consent form is legally obliged to follow the aspects written and documented in the signed paper. Thus, ensuring that the actions written in the consent form are taken in place is necessary and should be undertaken with utmost care.

Are there different types of consent forms?



Consent forms can have different formats: from project-specific consents, which restrict the use of the donated material to a specific project, to so-called broad consents, which allow cells to be used for any research purpose in the future, there is a whole range. From case to case, from cell line to cell line, the associated consent must therefore be carefully read and taken into account. With increasing digitalisation, new, more dynamic forms of declarations of consent are emerging, so-called dynamic consent approaches: Here, the donor is put in a position to decide repeatedly whether and for what purpose material donated by them may be used. By contacting the donor again, the researcher can enquire whether the donor consents to new research projects/objectives or wishes to object to them.

In which cases can the donor be represented by others in the consent process?

For the production of embryonic stem cell lines, surplus embryos created during artificial fertilisation that have

to be discarded are usually used. In this case, parental consent is required if the embryo is to be used and destroyed for research purposes. Particular care should be taken with regard to cell donation by children/minors: Children are also capable of donating cells for research and should also be given an information and consent process appropriate to their understanding, but the consent of the custodian (parents) is also required here. This may also be the case for people with limited cognitive abilities (guardians).

What can I do, if no consent forms are available?

Sometimes stem cells or cellular material are used in research for which no informed consent form is available: either the generator that produced or distributes the cells can not or does not want to give the consent, or the consent has been lost over time, or the cell donation took place in a country or at a time when international good practices on informed consent and donor information were not installed. In fact, many commercial stem cell lines exist and are still regularly used for different purposes, where a consent document is missing. In these cases, the ethical provenance of the stem cells is incomplete and undetectable. As an alternative, institutional reviewing board (IRB) approvals can be obtained: here, an independent ethics committee, that is typically affiliated with the institution at which the dedicated research shall be conducted, decides, whether the cells in question may be used for this particular research by that particular researcher. It is only valid for this one moment in time and for the specific project mentioned and can not cover the use for any other project following the described research. It must be re-issued in this case and again the purpose and the intended use must be specified and justified for the particular project.

If the cells come from a generator that holds the consent form but does not want to share this document, e.g. due to maintain the anonymity of involved persons or e.g. if third parties are involved, a written proof from that generator confirming that the consent exists and allows the use of the cells in question could also be sufficient.

Can donors withdraw donated cells at a later date and withdraw their participation?

In most current consent processes at the time of cell donation, the donor's consent to the scientific use of their cells is obtained once and is then valid. As long as the donated cells are still available at the institution that carried out the cell donation, the donor can usually withdraw their consent for their cells to be made available for research. However, once the cells have been modified, further developed and transferred to other research institutes (in accordance with the relevant conditions set out in the consent), it is often no longer possible to revoke consent.

Once the identity of the donor has been protected by anonymisation, it is no longer possible to establish a link between the cell material and the corresponding donor. This means that if it is no longer possible to identify which donor donated which cells, the donor can no longer withdraw and revoke the use of their cells for previously consented purposes. However, the donor should be informed of this fact at the time of cell donation. The conditions of withdrawal are outlined in the consent form.

One exception is the newly emerging concept of "dynamic consent", where the donor can be recontacted.

How can hPSCreg® support my research?

For stem cell researchers, the registry hPSCreg (www.hpscreg.eu) is a tool with a dual function: on the one hand in a research-relevant way and on the other hand in an ethical sense.

Initially, hPSCreg offers stem cell researchers the opportunity to feed their developed stem cell lines into the database in order to make them visible to the scientific community and share the information worldwide. During registration, each cell line is assigned a unique identifier that makes it unique and discoverable worldwide (https://hpscreg.eu/about/naming-tool). The researcher can also use the database to get an overview of human stem cell lines developed worldwide. hPSCreg also includes a database of stem cell-related projects (https://hpscreg.eu/browse/projects) and a database of worldwide clinical trials (https://hpscreg.eu/browse/trials). Even though hPSCreg is a pure database that does not offer cell lines

for sale or purchase, it is still possible to find out the owner/distributor of certain stem cell lines with its help.

In addition to these purely scientific tasks, hPSCreg also offers the researcher support and guidance from an ethical point of view: cell donation and the use of human biological material in research is subject to international guidelines and recommendations and national legislation, which can vary greatly internationally, especially in the field of research with human embryos and hESCs. In order to better classify national differences and legislation, hPSCreg offers a legislation world map (https://hpscreg.eu/map).

To assess the ethical background of stem cell lines, hPSCreg collects the declarations of consent regarding the biological source material in a confidential manner.

In a careful process of checking the ethical background of stem cell lines, these are validated with regard to their origin and their proof of pluripotency and, if necessary, even certified if they fulfil the ethical and scientific requirements specified by the European Commission. Thus, every researcher can see the ethical background of these cell lines by looking at the page of certain stem cell lines, and can also increase the value of their own cell lines by entering this information by proving the ethical origin of their stem cell lines.

Where can I find further information?

https://hpscreg.eu/about/documents-and-governance

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52021AP0124

https://www.isscr.org/guidelines

https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/common/guidance/how-to-complete-your-ethics-self-assessment_en.pdf

https://www.eurogct.org/theme/factsheets