Fact sheet for industry

Decades after the initial derivation of human embryonic stem cells and human induced pluripotent stem cells, advances in technology and automation have made it possible for human pluripotent stem cells to be used in increasing scale for not only academic medical research, but also for industrial applications. In the following fact sheet, we introduce human pluripotent stem cells and outline some guidance for use of human pluripotent stem cells by industrial organizations.

Why are pluripotent stem cells interesting research objects for human biomedical research?

Human pluripotent stem cells, whether embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs), play an important role in human biomedical research. They are not only excellent models for basic research, but are also widely used in applied research such as research and development of drug screening, and treatment of human diseases by means of their clinical application.

What does "pluripotency" mean and how is this ability used in research?

Pluripotency describes the ability of stem cells to differentiate into any type of body cell: muscle cells, nerve cells, kidney cells etc. can be formed from pluripotent stem cells. Thus, ESCs/ iPSCs are the starting point for ever new areas of application: organoids, germ cells, cell human / animal chimera, or even combinations of cellular and non-biological structures such as xenobots are already being researched and developed. The massive increase in peer-reviewed stem cell related publications, commercial stem cell products e.g. culture media, growth and differentiation factors, matrices and other stem cell related applications such as bioprinting and lab-on-chip devices underlines their huge potential for modern and efficient biomedical research and application. The stem cell market is expected to steadily increase and biomedical applications requiring stem cells for generation of hPSC derived cell types as Advanced Therapy Medicinal Products (ATMPs) will be a major aspect of modern personalized medicine.

What requirements must pluripotent stem cells fulfil for research?

Stem cell researchers need biologically well defined and highly characterized stem cell lines for their expensive research, but the ethical background of these cell lines, which goes back to the process of donating the biological source material for the cell lines at first hand, must also be transparent and traceable. Especially funding bodies representing tax payers money or driven by high ethical and moral standards pay increasingly attention to ethical aspects and all related issues. Companies that produce and/or distribute such stem cell lines should therefore recognise and implement ethical standards in addition to purely scientific quality standards in order to increase the value of their products. In fact, several examples from researchers' daily lives exist that show that an unclear ethical provenance of commercial stem cell lines used for research purposes dramatically complicates, delays and sometimes even hinders a publication process or the fulfilment of funding body requirements during project reporting. The importance of legal and ethical framework conditions is being increasingly recognised in the industrial stem cell community and companies involved in generating and/or distributing stem cell lines for commercial purposes increasingly implement ethical standards into their documentation routines to make these products more usable for the end-users.

What needs to be considered when using pluripotent stem cells on an industrial scale?

The industrial development and distribution of human stem cell lines for commercial purposes (mostly on an international level) is subject to a number of considerations that need to be taken into account:

(i) awareness of the existence of different legislations, not only in the countries from which the donor material for the commercial cell products originates, but also in the countries to which these products are to be distributed,

(ii) the donor material is derived from embryos or somatic cells of the donor and may be

subject to certain restrictions on use, which are articulated in the consent form,

(iii) the commercial use of donated cells must not be excluded in the consent and must also be taken into account for the associated data (clinical or genetic).

What is the ethical status of cell donation in the industry?

Cell donations from volunteers should be understood as sensitive, personal entities that should only be used as objects of industrial development and economic interests under very specific, ethical conditions. Every single donated human cell has its origin in the autonomous decision of a person who not only cedes ownership of parts of their body to the general public, 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.

What procedure can the industry use to respect the rights of cell donors?

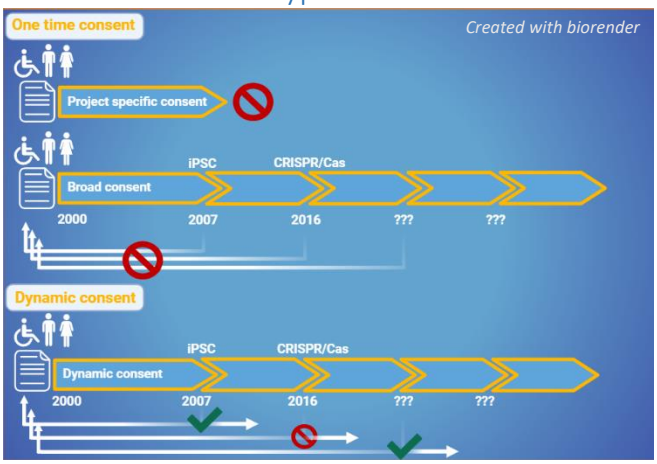
In order to take into account and respect the rights of the donor of the biological material (their right of autonomy and self-determination, the right of protection of their personal data and privacy), the process of cell donation is subject to a clear ethical framework: cell donation must take place under certain ethically set conditions, it must be voluntary and without pressure, it must be informed, respectful and with an explanation of all the risks, opportunities and consequences associated with the donation for the donor. The production of cell products by modifying the originally donated material (e.g. reprogramming or genetic modification) must not have been objected to in the consent, nor must the commercial distribution of these products. The donor must have been informed that any profit sharing is excluded.

Why are the consent forms in compliance with ethical framework conditions so important?

The fact that the cell donation was carried out in accordance with ethical standards and legal requirements is recorded and made traceable in a document: the declaration of consent (often combined with a patient/donor information sheet), which the donor signs if he or she agrees to the conditions of the cell donation and is willing to donate.

A company that manufactures and distributes products made from human biological material is obliged to respect the autonomy of the donor. If, for example, the declaration of consent contains restrictions on the use of the donated material, the company is responsible for respecting these restrictions. It is important that the donor can prove that he/she agrees that commercially available products will be made from his/her cells and that he/she will not participate in any profits from the sale of these products. The donor must also have been informed about how access to their personal data associated with the cells will be handled (e.g. genomic data, clinical information).

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 him/her 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).

How can hPSCreg® support my organization?

For organizations with interests in the pluripotent stem cell sector, the hPSCreg registry (www.hpscreg.eu) is a tool with a dual function: on the one hand from a research-relevant point of view and on the other hand from an ethical point of view.

Firstly, hPSCreg offers providers of pluripotent stem cell lines the opportunity to register their cell lines in order to make them visible to the scientific community and share the information worldwide. Upon registration, each cell line is assigned a unique identifier that makes it unmistakable and findable worldwide (https://hpscreg.eu/about/naming-tool). The provider can also use the database to obtain an overview of human stem cell lines generated worldwide. hPSCreg also contains a of publicly funded research projects that use hPSC lines (https://hpscreg.eu/browse/projects) and a database of clinical studies that use hPSC-derived cell products for therapy (https://hpscreg.eu/browse/trials). hPSCreg a data resource for pluripotent stem cell lines and is not a stem cell bank nor does it distribute stem cell lines; however, researchers can still use hPSCreg to find the institutions that own or distribute cell lines.

In addition to these purely scientific tasks, hPSCreg also offers the provider support and guidance from an ethical perspective: cell donation and the use of human biological material in research are subject to international guidelines and recommendations and national legislation, which can vary greatly internationally, particularly in the area of research with human embryos and hESCs. To help categorise 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 ethical origin and their proof of pluripotency and, if necessary, even certified if they fulfil the ethical and scientific requirements specified by the European Commission. Every company in the stem cell sector can therefore view the ethical background of certain stem cell lines at a glance and can also increase the commercial value of its own cell lines by entering this information and providing proof of the ethical origin of its stem cell lines.

Where can I find further information?

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

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

https://www.isscr.org/guidelines