Fact sheet for Funders/Regulators

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. In this factsheet, we introduce the topic of human pluripotent stem cells and the roles funders and regulators play in stem cell research.

What are pluripotent stem cells used for in human medical research?

Human pluripotent stem cells, whether embryonic or induced pluripotent stem cells (hESC and hiPSC, respectively) are not only excellent tools to model human development, but are also widely used for testing and development of new drugs and treatment methods. Their use is expected to increase due to new technological developments in the field of stem cell research and an growing attention towards human-derived biological model systems that have multiple benefits (e.g. closer similarity with human genome/cell types, individualised research) over e.g. animal models (3R initiative – which aims to reduce, refine and replace animal experiments in research). The use of human-derived stem cells over animal models is widely promoted and funded and an increasing amount of laboratories worldwide are taking advantage of these developments. Additionally, several clinical trials using stem cell derived products as Advanced Therapy Medicinal Products (ATMPs) are ongoing enabling a regenerative therapy over a conventional disease treatment.

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 stem cells. Because of this high development potential, hESC and hiPSC are the starting point for ever new areas of application: Organoids, germ cells, human and animal chimera, or even combinations of cellular and non-biological structures such as xenobots are already being researched and developed. Particularly the field of regenerative medicine benefits from technological combinations of the stem cell potential together with modern biomaterials but also digital applications such as so called “digital twinning” for personalized medicine.

How do researchers obtain pluripotent stem cells for their research?

All of these research areas rely on the initial donation of human sample material by volunteers. Researchers need biological donor material in order to produce stem cells and stem cell lines. There are for now two different resources to obtain and generate stem cell lines: ESC are derived from very early stage embryos, although their use is seen ethically controversial since the embryo has to be destroyed for this purpose. Less concerning in comparison is the use of iPSC, which can be generated from any somatic cell source, like small skin biopsy, cells isolated from blood or urine etc. by means of the reprogramming technology, which reverses the somatic cell identity back to an embryonic-like stage. 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.

To what extent can funding institutions be research regulators?

By assessing and selecting projects for funding, funders not only influence the projects’ scientific methods, objectives and promise, but increasingly funding agencies uphold ethical standards, particularly in the field of human medical research. Substantial and targeted funding and critical regulation by funders and regulators establish new field specific standards and measures that can critically change a field. As an example, substantial funding for alternatives to animal research, e.g. stem cell based approaches, following the 3R initiative (reduce, refine, replace) has left a significant impact on reducing animal based experiments in human biomedical R&D. This is a direct translation of society’s will into legal and political measures that have left a significant footprint in the stem cell field. Social and ethical values should not be threatened or even contradicted by the research objectives and the methods used. In this way, funders also indirectly represent a regulatory body: by selecting the type of research to be financially supported, they influence the direction that researchers take in their

projects, which has not only scientific but also societal and ethical aspects.

In which areas can funders/regulators demand compliance with ethical standards?

In stem cell research, this relates to two areas: firstly, the biological source material used in the research projects, and secondly, the intended goals/products/methods of the research.

Stem cells for human biological research are derived from human cell source material that comes from donors. Here, Funders/Regulators can attach importance to the fact that the cell donation took place under certain ethical conditions, which were recorded in form of a consent and are verifiable.

Ethical controversies may arise in relation to the research objectives if methods are used or stem cells are applied that are ethically controversial: in the field of human embryos/embryonic stem cells in particular, there are national laws that only permit certain applications. Reproductive cloning with human cells, for example, is prohibited in most countries. In other cases, such as the production of germ cells from hiPSCs or organoids from stem cells, legislation varies from country to country, and funders/regulators must take this into account when regulating research.

Why does the ethical provenance of pluripotent stem cells used in research play such an important role?

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). Free and unrestricted proliferation of such genomic digital information could come with serious validation of the donors' rights if measures to maintain full anonymity are not undertaken. Particularly unforeseen technological developments such as use of Artificial Intelligence and related technologies such as prediction algorithms could lead to unforeseen disadvantages for the donor in the future if the genomic data are not protected. The autonomous decision to voluntarily participate in research by donating a biological sample and the associated digital data requires a clear ethical framework in order to treat the donors in question with respect and on an equal footing.

What other ethical values may need to be considered in stem cell research?

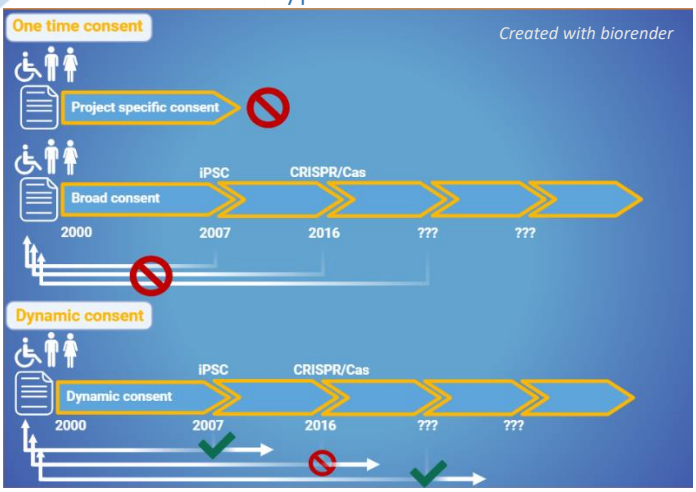
Freedom of research is a high ethical and social good, not only because of the human urge to seek the truth and accumulate knowledge, but also because it can form the basis for greater social prosperity and an increase in the health of society as a whole through scientific progress. In all these considerations,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

How are the personal rights of the donor respected?

In order to take into account and respect the personal rights of the donor, the cell donation process is subject to a clear ethical framework: cell donation must take place under certain ethically defined conditions, for example, it must be voluntary and without pressure, it must be informed, respectful and include a description of all the risks, opportunities and consequences associated with the donation for the donor. Explanations by e.g. medical staff to the donor must be clear and understandable to a broad audience and inform about the process of retrieving the sample towards producing the stem cell. 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 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.

Stem cell researchers 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.

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 are the advantages of formulating and demanding ethical standards for donors and researchers?

The formulation and enforcement of ethical standards in stem cell research by funders/regulators, ideally based on a global discourse, has advantages for both the donors of cell material used for the production of stem cell lines and for researchers in this field: donors can be sure that their autonomous decision will be respected and that their donated cell material will be used under clear ethical rules. Researchers can be sure that they are not contravening the wishes of the donor by adhering to ethical standards and are given clear instructions on how to handle the donated cells and associated data. This gives them security. It is important for acceptance of and trust in science and scientific research that the public can see that clear ethical standards are being adhered to. This trust will ultimately also increase the willingness of volunteers to contribute to successful research through donations, which will also benefit research community.

How can funders support stem cell research and donors?

As a funder of stem cell research, it is important to realise the strong role that funding institutions play in shaping and directing developments in human biological research: in addition to scientific content, funders should demand ethical standards, define benchmarks and minimal criteria for ethical aspects of the funded research and make their financial support dependent on compliance with these standards, rigorous reporting and transparency and thus implement them to an increasing extent.

How can regulatory bodies support stem cell research and donors?

Regulators also have this power at the level of binding laws, but often, especially in the case of international requirements, they are limited on the creation of legally non-binding recommendations/guidelines. However, these ethical guidelines/recommendations can be used as the basis for binding rules and requirements by funders if they want ethical standards to be met in the projects they fund.

How can hPSCreg® support regulators and funders?

For funders/regulators, the hPSCreg registry (www.hpscreg.eu) is a tool with various functions:

Firstly, hPSCreg provides 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 links them with data on the stem cell lines used and a database of clinical trials that use hPSC-derived cell products for therapy (https://hpscreg.eu/browse/trials).

In addition to these purely scientific tasks, hPSCreg also offers support to Funders/Regulators and guidance from an ethical perspective: the donation of cells and use of human biological material in research is 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 origin and their proof of pluripotency and, if necessary, even certified if they fulfil the ethical and scientific requirements specified by the European Commission. This means that any funding agency, e.g. national funding agencies of Member States can take a look at the website of certain stem cell lines to see what ethical background these cell lines have and can use the hPSCreg certificates as proof of the ethical provenance of the cell lines, as the EU funding institution already does.

How does hPSCreg deal with cell lines that do not have consent?

If such declarations of consent are missing for cell lines, then approvals issued by ethics committees can also be saved as alternatives in the Ethics Section of the cell line concerned. This is of course done confidentially and the approval is not publicly visible - however, should questions about the ethical background of these cell lines arise at a later date, the relevant information can be traced in the form of the stored ethics committee approvals, is not lost and remains available for future clarification. In this way, the approvals are not only stored locally (i.e. where they were issued or by the person who requested them), but also in an internationally networked database that manages this information confidentially. Cell lines with such an alternative proof of ethical provenance can also receive an hPSCreg certificate.

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