Human Pluripotent Stem Cell Registry

Standard Operation Procedures (SOPs)

Version 2.1

2019-07-25

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Contents

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1. Registering of Users and Institutions

Generators of human pluripotent stem cell lines or their representatives can register as users at hPSCreg.

i. Each user needs to sign up on the webpage (https://hpscreg.eu/signup) with name, email and her/his institutional affiliation. After registration, a verification email is sent automatically to the user with a verification link that needs to be clicked on in order to activate the account.

ii. After activating the account, the user has two options:

a) If the Institution is not already registered in hPSCreg, users can register a new Institution. The role of the Institutional manager is then automatically assigned to the user who registered the Institution. All new Institutions will be checked by the hPSCreg Team and if the new Institution has been created in error, e.g. the Institution already exists in the database under a similar name, it will be deleted by the hPSCreg Team after contacting the Registrant.

b) A user can apply to get Access privileges to an already registered Institution. If the user applies for Access privileges, an automated email will be sent to the Institutional manager. The application will then be reviewed by the Institutional manager. The reminder mail will be resent every day, until the request has been accepted or rejected. If the Institutional manager does not reply within three working days after the user applied for access, a member of the hPSCreg Team will check the request for an affiliation of the user to the requested Institution, e.g. through the use of Institution's email addresses. In case of doubt, a member of the hPSCreg Team will re-write to the user and ask for a reason why an entry to the Institution is needed.

The user can be assigned the roles "registrant" or "manager" for the respective Institution by the hPSCreg Team or by the institutional manger. The existing Institutional manager(s) will be automatically informed via email about the new role of the user.

2. Soliciting Data on Cell Lines

Here we describe how different sources of cell line data are identified for Submission to hPSCreg:

i. New lines are entered by the users of the respective Institutions themselves.

ii. hPSCreg manually searches for new lines that are of importance to the community and enters the data of the cell line into the database in cooperation with the relevant Provider (see “10. Manual registration of hPSC lines”).

iii. hPSCreg encourages the Generators of hPSC lines and banks to enter their cell lines’ data by providing several advantages:

   a) Creating a Standardized cell line name, which promotes an unambiguous, unique identifier for the hPSC line
   b) The opportunity to publish cell line as a Lab Resource in the journal “Stem Cell Research”
   c) Receiving Cell line certificates that confirms the hPSC line's ethical provenance and allows the line to be used in European Union (EU)-funded research projects
   d) Promoting international visibility of the hPSC line by inclusion in hPSCreg

2.1 Permitted Sources of hPSC Line Data

i. Generators of cell lines: these are the preferred data providers.

ii. Publications from the scientific literature:

   a) The hPSCreg Team can update existing datasets of cell lines with newer data from publications. In this case ,hPSCreg will contact the Registrant of the cell line for verification.

   b) In the case of unregistered cell lines, the hPSCreg Team will contact the authors of the relevant publication and ask them to register the line and offer to do it for the author if the line is of particular interest to hPSCreg (See “10. Manual registration of hPSC lines”)

3. Registering of hPSC lines

i. After the user has received access to an Institution (see “1. Registering of Users and Institutions”), he/she can register lines. First, the following information is required in order to generate a unique Standardized cell line name:

   a) Generator

   b) Other lines from the same donor already registered at hPSCreg (if any)

   c) Information about whether the line is a Subclone or not.

   d) As an additional option, alternative names like other database identifiers (e.g. Cellosaurus) or the name primarily used internally by the Generator can be entered. The collection of these alternative names enhances its findability in hPSCreg, especially when the alternative names are more commonly used (e.g. "H9" as the common name for "WAe009-A")

→ Upon entering the information in the above points, a unique Standardized cell line name will be automatically created, and this information will become immediately publicly visible in hPSCreg.

ii. After the unique standard name has been created, further information can be added, including:

   - General information on the cell line
   - Donor information
   - Ethics
   - Derivation
   - Culture conditions
   - Characterisation
   - Genotyping
   - Genetic Modification

4. Editing of hPSC line data

Cell lines registered in hPSCreg can be edited at any time. Apart from the Generator of the cell line or its representatives, all hPSCreg Team members can edit the cell line's data.

The user who has registered a cell line is the one who is primarily responsible for maintaining the record. Upon request, it is also possible to set up group access to cell line data for several people. Users interested in group access should contact the hPSCreg Team via email (hpscreg-contact@charite.de) or use the contact form (https://hpscreg.eu/contact).

In the event that the hPSCreg Team finds new information about an already registered cell line (e.g. from publications), this can also be added by the hPSCreg Team to the cell line record. If the new information is not clear or contradicts already registered information, hPSCreg will contact the Generator to discuss how to proceed. If the Generator is no longer available, the hPSCreg Team will try to reach the contact person of the institute. If no one is available, the information can be added by the hPSCreg Team to the best of their knowledge to the cell line record.

5. Finding new publications related to a cell line

hPSCreg reviews current publications to see if they are related to already registered cell lines. This is done using the Standardized cell line name that each cell line automatically receives from the registry. This automatic check uses existing APIs from EuropePMC (https://europepmc.org/RestfulWebService) and Elsevier (SCOPUS: https://dev.elsevier.com/sc_apis.html) and ScienceDirect: https://dev.elsevier.com/sd_apis.html). Found entries are automatically added to the cell line. A daily overview of new publications is sent to the hPSCreg Team, who checks whether the publication is related to the cell line (primarily based on title, abstract and journal).

Furthermore, each user with access rights to a registered cell line in hPSCreg can add new publications to this cell line. Alternatively, a user can also register a new publication directly at hPSCreg (https://hpscreg.eu/user/publication/edit) and assign already registered cell lines to that publication.

6. Visibility of cell lines

After a pluripotent stem cell line has been registered with a standard name at hPSCreg, only some basic information is public:

- Standardized cell line name
- alternative names
- cell line type (hiPSC or hESC)
- user feedback
- Generator
- Distributor
- publications

After all mandatory information (see “10. Manual registration of hPSC lines”) has been provided, the line can be submitted. Submission of a cell line means that the cell line data should be reviewed by the hPSCreg for validation (see 7. Validation of cell lines).

Upon Submission, the cell line data will be publicly accessible on hPSCreg. However, in accordance to the EU General Data Protection Regulation, cell line sensitive genetic information (e.g. STR and HLA data), as well as confidential documents relating to the field of Ethics (e.g. Donor Consent and Donor Information Sheets) are not made public in order to safeguard donor’s personal data.

Additionally, information on all users who have edited or registered the cell line data is not displayed in the public version of the cell line record on the hPSCreg website.

7. Validation of cell lines

After all mandatory information have been entered (see Appendix 2: Mandatory fields for the registration of hPSC lines), users can submit the cell line for validation. The validation of the lines is done by the hPSCreg according to well defined criteria (see 7. Validation of cell lines).

Users have the opportunity to write a comment to the Validators when submitting the line to support the validation process.

The validation of the cell lines is based on a decision tree, which can also be found under the following link:

hiPSC: https://hpscreg.eu/docs/downloads/hiPSC_Validation.svg

hESC: https://hpscreg.eu/docs/downloads/hESC_Validation.svg

Two areas are crucial for the validation of the hPSC line: ethics and the evidence of pluripotency. Changes to the cell line data after a cell line has been validated may affect the validation status. Please see 8. How to handle previously existing data in the face of a dynamic database structure for details.

7.1 Ethics

The hPSCreg Team has adopted mechanisms to verify whether the cell line was obtained under a robust informed donor consent. In detail, we request a copy of the donor information sheet and a copy of the (redacted) donor consent form as attestation of the informed consent process. These documents are only requested for validation purposes and will not be made available to third parties (see 6. Visibility of cell lines).
If these documents are not available, it is also possible to provide alternative documents to demonstrate that donor informed consent was obtained. These alternatives are checked manually by the hPSCreg Validators and it is decided on a case-by-case basis whether the information is sufficient for validation. If no documents could be provided, attestation could be done by answering the questionnaire available in the Ethics section. This is generally the preferred way, as it is possible in this way to automatically evaluate the given answers. If the hPSCreg Validator cannot reach a decision on whether the given information is sufficient for validation, the Validator will contact the Ethics advisor for guidance.

As part of due diligence, the Ethics advisor of hPSCreg randomly checks 10% of all

uploaded donor consent forms and related documents to ensure that these documents comply with hPSCreg requirements. This is carried out as follows: twice a year, 10% of all newly uploaded documents are selected and sent encrypted by email to the Ethics advisor. In the event that there are unredacted (e.g. signed) donor consent forms among the selected documents, the documents will be redacted in advance to ensure donor anonymity.

In the event of any discrepancies in reviewing the documents, the Ethics advisor will contact the hPSCreg Validator to discuss the individual cases and to work with the cell line Provider to find a solution.

7.2 Characterisation

For the validation of a hPSC line, the pluripotency of the line must be demonstrated. HPSCreg accepts two ways to show the pluripotency:

1. hPSCreg accepts these pluripotency assays:

- EpiPluriScore
- PluriTest
- hPSC Scorecard

For validation, one of these tests must be show evidence of pluripotency. Furthermore, hPSCreg requires the proven expression of at least two pluripotency markers:

- OCT-4
- SOX2
- NANOG
- KLF4
- TRA-1-60
- TRA-1-81
- SSEA1
- SSEA4

2. If no pluripotency assay is available, it is also sufficient to show the differentiation of the cell line into all three germ layers (endoderm, mesoderm and ectoderm).

7.3 Subclones

If the cell line is a Subclone of an already registered cell line, the Parental cell line needs to be validated according to the newest standards (see 8. How to handle previously existing data in the face of a dynamic database structure).

Furthermore, the information on the genetic modifications will be checked for completeness, including information on:

- Type of modification
- Target gene
- Chromosome Location

8. How to handle previously existing data in the face of a dynamic database structure

hPSCreg is a dynamic data resource for hPSC lines and aims to keep up-to-date with the current developments involving hPSC lines in research and clinical settings. Therefore, hPSCreg will introduce new data fields and adjust the validation criteria accordingly to accommodate this rapidly changing field. Due to the dynamic nature of hPSCreg, previously entered data in hPSCreg are dealt with in the following ways:

- If new data fields have been introduced, which make previous data fields obsolete, the hPSCreg Team will try to map the existing data to the new fields.
- In the case that the cell line has already been validated:
  - If the validation criteria have changed since the cell line was first validated, the cell line will not lose the validation status.
  - If changes are made to the cell line data, the line will be checked again for mandatory fields (see Appendix 2: Mandatory fields for the registration of hPSC lines). If all mandatory fields are filled the cell line will not lose the validation status.
  - If some mandatory information is missing, the cell line will lose the validation status after the cell line has been saved. In such cases, the user will be informed before saving the data that the changes could alter the validation status of the cell line. In any case, a certificate that has already been issued using previous validation criteria will still be available. If the users enters the missing mandatory data, the cell line can be submitted again for validation (see 7. Validation of cell lines) by the hPSCreg Validator.
- In the case that the cell line has been submitted, but not yet validated:
  - If any changes have been made after Submission, the cell line will be evaluated for validation by the hPSCreg Validator based on the most recent validation criteria.

9. hPSCreg certificates

9.1 Cell line certificates

Human pluripotent stem cell lines used in EU-funded research projects require a certificate that confirms that the cell line has been derived with full informed consent of the donor and no undue inducement has been provided for donation. hPSCreg is authorized to issue these certificates.

Already issued Cell line certificates can be downloaded from the cell line page (for example https://hpscreg.eu/cell-line/WAe009-A) in the upper right corner below the registration summary. If a user wants to acquire a new certificate, the user must contact the hPSCreg validation team via email (hpscreg-contact@charite.de) or by using the contact form (https://hpscreg.eu/contact).

In order to acquire a cell line certificate, all mandatory information must be filled (see Appendix 2: Mandatory fields for the registration of hPSC lines) and the cell line must have been validated.

9.2 Project certificates

hPSCreg also issues project certificates for the EU-funded projects that use pluripotent stem cell lines.

To obtain a project certificate, the project has to be registered at hPSCreg, including the following information:

- Title
- Summary
- Start and end date
- Sponsor
- Institution
- Principal Investigator
- hPSC lines to be used in the project

Already issued certificates from projects can be downloaded on the project edit page for the user who registered the project in the “Certificates” - section. If a user wants to acquire a new certificate, the user must contact the hPSCreg validation team via email (hpscreg-contact@charite.de) or by using the contact form (https://hpscreg.eu/contact).

10. Manual registration of hPSC lines

The main goal of hPSCreg is to encourage the Generators of hPSC lines to register cell lines in hPSCreg. But in some cases, it has been proven to be difficult to motivate the Generators to register the pluripotent stem cell lines themselves. The hPSCreg Team will therefore complement the holdings of hPSCreg by actively registering PSC lines according to the following steps.

1) Retrieve information from reliable data sources

Reliable data sources include:

- Peer-reviewed journals
- Cellosaurus
- Cell banks

2) Double-checking information

If some information of interest for hPSCreg has been found, the hPSCreg Team will verify whether the cell line has already been registered in hPSCreg, taking into account:

- Name
- Synonyms
- Provider
- Disease
- Donor information

3) Contacting the Generator

If the cell line could not be found in hPSCreg, the hPSCreg Team will contact the Generator directly.

a) Each contact with the Generators will be documented by hPSCreg in order to make sure not to contact the same person twice for the same cell line.

b) If the Generator replies:

1) hPSCreg will ask him/her to register cell line in hPSCreg and offer support.

2) If the Generator does not want the cell line to be registered in hPSCreg, it will be documented by hPSCreg (see 3.a)

3) If the Generator does not want to register line him/herself but gives the hPSCreg Team permission to register cell line:

I. The hPSCreg Team will register line and enter as much data as possible.

II. Permission to register the line and contact details of the person giving hPSCreg permission to register the cell line will be recorded in the "Comments for Editors" free text box.

11. Contact provider of unsubmitted cell lines

The aim of hPSCreg is to give an overview of the cell lines used in research and clinical applications and to describe them as detailed as possible. To this end, hPSCreg reserves the right to re-contact Providers of unsubmitted lines in order to encourage Generators of unsubmitted lines to complete the cell line data Submission and to make their data fully accessible in hPSCreg. hPSCreg promotes FAIR data practices (see https://www.force11.org/group/fairgroup/fairprinciples).

hPSCreg frequently checks for new publications that mention cell lines, which have already been registered in hPSCreg (see 5. Finding new publications related to a cell line). If a new publication is found that refers to an unsubmitted cell line, a member of the hPSCreg Team will contact the cell line Provider and ask to complete the cell line entry.

Each contact is documented by hPSCreg to ensure that Providers are not contacted too often for the same cell line.

12. Mass data import

hPSCreg provides a publicly available API to create a Standardized cell line name (https://hpscreg.eu/about/api/create). This API enables the creation of Standardized cell line names in hPSCreg.

Currently hPSCreg does not provide an API for data import; however, the hPSCreg Team is able to provide support for semi-automatic import of large datasets on a case-by-case basis.

The decision to carry out a data import is made by the hPSCreg Team based on the number of cell lines and the quality of the data.

Appendix 1: Glossary of terms

Access privileges
The access privileges in hPSCreg allow the user to register cell lines on behalf of an Institution. These privileges are given by the Institutional manager or by the hPSCreg Team. They do not allow to edit data from any cell lines of the corresponding institute.

Acronym
A Generator acronym is a unique institutional code of 2-6 (uppercase) letters. Each (sub-)Institution registering cell lines can self-assign an acronym. Only Institutions having such an acronym can be set as Generator for a new cell line. The acronym must be unique in hPSCreg. Even sub-Institutions are not allowed to have the same acronym as their parent Institution.

The Generator acronym is an integral part of the hPSCreg standard name / unique identifier. More information can be found online (https://hpscreg.eu/about/naming-tool) and in our publication "*A Standard Nomenclature for Referencing and Authentication of Pluripotent Stem Cells*" (PubMed: 29320760). You can set the parental Institution as the Generator to use the corresponding acronym and set your sub-Institution as the contact Institution.

Cell line certificates
The hPSCreg certificate for a hPSC line is issued when evidence has been provided to hPSCreg showing that a set of minimal ethical and scientific standards have been met by the cell line. The ethical standards include documentation of informed consent procedures for the donation of the source material used for derivation of the hPSC line. Scientific standards include the documented testing of a line's pluripotency using established and accepted assays. The hPSCreg cell line certificate is essential for projects using the cell lines in EU-funded research.

Cellosaurus
Cellosaurus is a knowledge resource for cell lines that attempts to describe all cell lines used in biomedical research (see https://web.expasy.org/cellosaurus/). HPSCreg is working together with Cellosaurus to exchange data on hPSC lines.

Distributor
The distributor of an hPSC line registered in hPSCreg is the person or organisation who can be contacted to obtain the physical hPSC line. In some cases, the hPSC line may be readily available from commercial sources or a cell line bank.

Ethics advisor
An independent ethics advisor ensures that all activities of hPSCreg are in compliance with the fundamental ethical principles applicable to the field of hESC and hiPSC research and clinical use.

Generator
The generator is the Institution that generated or derived the cell line. It is not an individual person. Example: A cell line was generated at PSC-University by Dr. Yaka. Consequently, the cell line's generator is the PSC-University and the contact person is Dr. Yaka. The generator of a Subclone cell line may differ from the Institution that generated this cell line. Each generator must choose an Acronym. The generator Acronym becomes integral part of the standard name / identifier of all lines registered from that generator. For Subclone the Acronym of the Parental cell line is chosen for the name.

Genetic Modification
Genetic modifications are defined to be any changes in the genomic DNA, which are not detected in the parental clone. These modifications include variants (spontaneously arising with respect to the parental clone) **and** engineered modifications (changes made through human intervention by genetic engineering techniques).

hPSCreg Team
The hPSCreg team consists of biotechnologists, molecular biologists, computer scientists, ethicists and bioinformaticians. They can be contacted via https://hpscreg.eu/contact.

Institution
In hPSCreg, all organisations generating cell lines are regarded as institutions. Examples are: research organisations, universities, companies etc.

Institutional manager
Usually, the person registering a new Institution becomes per default the hPSCreg manager of that Institution. The hPSCreg manager can accept or decline access requests from other users. The institutional manager can also appoint additional institutional managers or withdraw as institutional manager. However, each registered Institution must have at least one institutional manager.

It is beneficial if the institutional manager on hPSCreg has some insight into the actual Institution. However, in case that nobody from the Institution is available on hPSCreg, other users can act as the hPSCreg manager until a suitable replacement is found.

Owner
The owner is the individual or Institution that holds intellectual property rights over the cell line.

Parental cell line
In hPSCreg, a pluripotent stem cell line, that is the precursor of another (genetically modified) cell line (=Subclone) is called parental cell line.

Provider
The provider is a synonym for the Generator.

Registrant
The registrant is the user who registers a cell line in hPSCreg.

Standardized cell line name
We developed a nomenclature for the European human pluripotent stem cell registry (hPSCreg), which serves to: 1) unambiguously identify a registered cell line; 2) allow tracing of Subclones of a particular line; and 3) enable the assignment of different lines to a specific donor origin.

The implementation of this nomenclature is the standardized hPSCreg cell line name.

Subclone
A subclone in hPSCreg is a derivative of a specific Parental cell line. A subclone is distinct from the Parental cell line because it carries a stable defined Genetic Modification, which was induced (e.g. transgene) or occurred spontaneously (e.g. mutation) in Parental cell line. Naturally, Parental cell line and subclones have the same human donor.

Submission
After all mandatory information has been given for a cell line data entry, the user can click “Submit” to publish the cell line record in hPSCreg and to request a validation of this data entry.

Validator
The validators of hPSCreg are responsible for checking the mandatory data fields for cell lines that have been submitted to hPSCreg. The validators check the mandatory fields in accordance with the validation criteria (see 7. Validation of cell lines) to ensure that the cell lines listed on hPSCreg comply with the fundamental ethical principles for hESC and hiPSC research and fulfil a minimum scientific criteria that will qualify them to have characteristics of human pluripotent stem cells.

Appendix 2: Mandatory fields for the registration of hPSC lines

Most mandatory fields apply to both iPSC and ESC lines:

General

- Biosamples ID of cell line (can be created by hPSCreg if it does not already exist)
- Is the cell line readily obtainable for third parties?
    - Restrictions

Donor

- (Biological) Sex
- Biosamples ID of Donor (can also be created by hPSCreg)
- Is there a disease diagnosed?

Ethics

- Has consent been obtained from the donor of the embryo/tissue from which cells have been derived?
- Was the consent voluntarily given?
- Has the donor been informed that participation will not directly influence their personal treatment?
- Can you provide us with a copy of the Donor Information Sheet provided to the donor?
    - Yes: Upload
    - No: Provide contact information of the holder of the original Donor Information Sheet:

- Do you (Depositor/Provider) hold a copy of the SIGNED Donor Consent Form?
    - Yes: Upload
    - No:
        - If you do not hold the SIGNED Donor Consent Form, do you know who does?
            - Yes: Contact information / weblink
        - If you do not hold the SIGNED Donor Consent Form, have you obtained a copy of the unsigned Donor Consent Form from the holder?
            - Yes: Upload
- Please indicate whether the donated material has been pseudonymised or anonymised.
- Does consent expressly prevent derivation of pluripotent stemcells?
- Does consent prevent CELLS DERIVED FROM THE DONATED BIOSAMPLE from being made available to researchers anywhere in the world?
- How may genetic information associated with the cell line be accessed?
- Will the donor expect to receive financial benefit, beyond reasonable expenses, in return for donating the biosample?
- Has a favourable opinion been obtained from a research ethics committee, or other ethics review panel, in relation to the Research Protocol including the consent provisions?
- Has a favourable opinion been obtained from a research ethics committee, or other ethics review panel, in relation to the PROPOSED PROJECT, involving use of donated embryo/tissue or derived cells?

Culture Conditions

- Medium

Genotyping

- Has the cell line karyotype been analysed?
    - Yes: Cell Line Karyotype
- STR / Fingerprinting

There are also mandatory fields that only apply to iPSC or ESC lines:

IPSC

Derivation

- Cell type of the source cells that were used for reprogramming (if available)
- Vector type for reprogramming

ESC

Ethics

- Was the embryo established purely for research purposes?
- Have both parents consented to the use of the embryo for ESC derivation?

Derivation

- Date of derivation
- Supernumerary embryos from IVF treatment?
- PGD Embryo

There are also some mandatory fields that only apply to Subclones, which by definition in hPSCreg are genetically modified Subclones of Parental cell line:

- Type of modification
- Target Gene
- Disease name if the modification is associated to a disease