NHS Blood and Transplant

RINTAG
09 May 2018

Consent for the creation of cell lines

1. Status – Public

2. Executive Summary

This paper sets out the requirements for obtaining consent from families of deceased organ donors for material that will be used to create immortalised cell lines. It is intended to provide background to inform discussions at RINTAG. The final decision relating to NHSBT's position on the level of consent required of donors of such material rests with the CARE group chaired by Dr Gail Miflin, Medical and Research Director, NHSBT. RINTAG are asked to provide their thoughts and recommendation to feed in to discussions regarding consent for the creation of cell lines which are ongoing in NHSBT.

3. Action Requested

RINTAG is asked to:

- ***Discuss the level of consent required from donor families before donated material is used to create cell lines;***
- ***Provide recommendations to NHSBT on this issue.***

4. Proposal

This paper presents background on the current consenting and regulatory requirements relevant to the creation of cell lines from donated material. It considers these in the context of using organs from deceased organ donors which have been removed for transplantation but which are subsequently deemed unsuitable for transplant. Best practice is that specific consent should be obtained when material will be used to create cell lines.

5. Background

It is possible to create a permanent cell culture which will indefinitely proliferate when maintained under appropriate culture conditions. So-called *cell lines* are developed from single cells, are genetically uniform and can be established using several techniques.

Relevant material under the HT Act includes tissues and cells removed directly from a person. The cell division which occurs during the process of creating cell lines means that no original cells from the person remain. This means that the cells have been replaced by cells generated outside the body and cell lines are therefore not considered relevant material under the HT Act. HTA licences under the HT Act are therefore not required for either the storage of cell lines for research or primary cell cultures that have divided sufficiently to replace original cells with new cells.

The main issues regarding providing material from deceased organ donors to produce immortalised cell lines are therefore ethical. They focus on the inherent creation of long-lived cells which are genetically identical to the donor. The controversy surrounding HeLa cells, captured in the book *The Immortal Life of Henrietta Lacks*[1], demonstrates the sensitivity of the ethical issues associated with the creation of immortalized cell lines and their subsequent use in research.

The creation of cell lines can be achieved by several methods, including the introduction of viral genes which deregulate the cell cycle or the expression of proteins required for immortality. Induced pluripotent stem cells (iPSCs), which are capable of propagating indefinitely and giving rise to every cell type in the body, can be generated from adult cells by introducing specific transcription factors. They hold great promise for the future understanding and treatment of disease, including those relevant to organ transplantation. Compared with embryonic stem cells, iPSCs have the advantage that they do not require the use of embryos.

Surveys of patients indicate that altruism often motivates support for iPSC research.[2] The primary concerns of patients' centre on privacy, immortalisation, commercialization, and the potential to create gametes. Privacy concerns expressed by patients were linked to the potential for reidentification through genetic analysis. Some patients find it unnerving that donated cells would live forever, with concerns focused on inappropriate use and any future profit which their material may lead to. Consent, transparency and trust all act to mitigate the concerns which patients express. Proper informed consent, taken with full transparency over the potential uses of donated material, allayed patient concerns.

A process of informed consent in stem cell research must provide sufficient baseline information to enable participants to decide whether to give permission for iPSC research to proceed using their donated material. Any

[1] The Immortal Life of Henrietta Lacks, R. Skloot, Random House LLC, New York (2010)
[2] Patients' attitudes toward the donation of biological material for the derivation of induced pluripotent stem cells, Dasgupta, I *et al*¸ Cell Stem Cell 14, January 2, 2014

consent process should be designed to respect participant autonomy by giving reasonable control over the use of their specimens.[3]

Multiple bodies and organisations involved in stem cell research and the creation of cell lines provide guidance on obtaining informed consent from donors of biological material. These include the International Society for Stem Cell Research (ISSCR) and the Human Induced Pluripotent Stem Cell Initiative (www.hipsci.org). An extract of the ISSCR sample consent form for somatic cell donation for iPSC research is shown in Appendix 1. This highlights the need to be transparent with potential donors about the immortal nature of the created cells. The sample consent form also states that consent cannot be withdrawn once the cell line has been created and that the cell line may be widely distributed.

RINTAG aims to support high-quality research studies which will be published in leading academic journals. The Nature group of journals has recently published its policy relating to stem cell research which encourage scientists to embrace the ISCCR guidelines.[4] Nature journals will require authors to provide an ethics statement when papers "involve human embryos or gametes, and for clinical studies of cells derived from pluripotent stem cells." It is expected that the statement highlights "ethical oversight of the work, including the review boards specialized in embryo research that approved it, and *details of the consent process for cell donors and recipients.*" It is not clear whether the generic consent process in place in ODT will meet these requirements.

NHSBT currently obtains specific consent from blood donors for studies which involve the creation of cell lines from donated material.

6. Points for consideration

6.1 The current generic consent process in place for the use of donated organs for research does not sufficiently address the specific ethical issues relevant to the creation of immortalised cell lines. It is therefore proposed that studies requesting material for the creation of cell lines are only approved if specific consent for a Research Ethics Committee approved study is obtained from donor families.

6.2 Reviewing best practice in the field it is recommended that when consent is sought from donor families the following issues should be explained in the patient information leaflets:

- What cell lines are, where they come from and for iPSCs a statement that animal testing is required to verify that the cell line is pluripotent;
- That cells which are genetically identical to the donor may be kept forever and multiply indefinitely;

[3] What makes clinical research ethical? Emanuel *et al,* JAMA, 2000 283(20):2701-2711
[4] http://www.nature.com/articles/d41586-018-05030-2

- That the donated material and cell lines derived from it may be used for future purposes not yet known and unrelated to the present study;
- That the donated material and cell lines derived from it may be. may be widely distributed;
- That it will not be possible to withdraw consent once a cell line has been established;

7. Next steps

7.1 NHSBT's CARE Committee will be asked to consider the issue of consent for the creation of cell lines to agree a corporate position on this issue.

7.2 RINTAG are asked to discuss the issue and provide recommendations to feed in to the discussion at CARE. A separate paper is provided which highlights the potential impact on the organ donation process for the three options being considered in relation to this issue, namely obtaining specific consent, generic consent or not supporting such studies.

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Appendix 1: ISSCR Sample Research Consent Form (extract)

WHAT WILL HAPPEN TO THE CREATED STEM CELLS?

It is likely that the stem cells, which would be genetically matched to you, will be stored for many years. Stem cells have the ability to grow and make limitless copies of themselves, and they are likely to be used by researchers at other institutions and for many other research purposes.

One possible research use of these stored stem cells might involve changing some of their genes. Another possible research use might be to study the stem cells by putting them into laboratory animals. These are just common examples of what might happen to the stored stem cells. But there are many other future possible research uses that are simply unknown at this time.

[As applicable: It is likely that researchers will perform Whole Genome Sequencing (WGS) on the stem cells. WGS looks for random changes (mutations) in the DNA of the cells. Because the created stem cells will be genetically matched to you, this may reveal genetic information about you and your family. Efforts will be made to protect your genetic privacy, which will be explained in the Privacy section of this form.]

[As applicable: Genetic testing could show unexpected information to researchers that may be important for your health. There (is/is not) a plan in place to share this found information with you.]

**[*Point to consider. The return of health-related incidental findings* - *Researchers and institutions may decide to have a plan in place regarding the return of incidental findings. This plan should include what kinds of conditions will be reported and how the results will be validated in a clinical laboratory. Donors should be made aware of this policy during the consent process, including what kinds of conditions may be found and whether they can opt out of receiving such information.*

Example: "Research on the stem cells created from your donated cells may reveal information that could be important to your health. If you wish to be contacted in the future about any such information, please check yes at the end of this form. If you answered "yes" to this question, (name of institution) will, to the extent possible, pass to you any information that it is given from other researchers or other institutions regarding health information revealed through research on the stem cells."]

You will not be able to say which institutions or researchers can share the stem cells that were created using your cells. If stem cell transplantations are developed in the future, you will not be able to say who should get the transplants **[as applicable: except in the case of autologous transplantation].**

Future uses of stored stem cells must be approved by ethical and scientific review committees to make sure that they are used in scientifically, ethically, and legally appropriate ways. Please contact the individuals listed on the last page of this form if you have any questions or concerns about the future possible uses of the stem cells collected through this research project.

[*Point to consider. Future research involving the creation of gametes and/or embryos* - *Researchers should assess the likelihood that a donor's cells may be used in potentially controversial future research. Donors may be uncomfortable with the creation of research embryos or gametes, especially when they would be genetically matched to them. If the donor's disease or other factors make this kind of future research a foreseeable possibility, it may be reasonable to inform donors and/or provide an opt-out.*

*Example: "Some stem cell researchers studying early human development or reproduction may want to use stem cells to create gametes (sperm and egg cells) or embryos. These gametes and embryos would be genetically connected to you. Embryos created will be allowed to develop for a maximum of 14 days before being destroyed. None of the embryos or gametes created from your cells will be used to produce a baby or pregnancy."***]**