# Guide to Submission

University of Queensland (formerly Australian Stem Cell Centre)
Submission #2011-ACD-006

# hESC Registry Application Database

**Detailed Listing for Request #: 2011-ACD-006**
November 28, 2011

## hESC Registry Application Search Results

**Request #:** 2011-ACD-006
**Status:** Pending

**Review:** ACD

**Assurance:** Yes (Section II(B))
**Certification:** Yes
**Authority:** Yes

**Cell Lines:** 4
**Available:** 4

**Previous #:**
2010-DRAFT-014
2011-ADM-008

Email
Edit
Delete
Switch to ADM

**Organization:** University of Queensland
**Org Address:** Australian Institute for Bioengineering & Nanotechnology Building 75--Cnr of College and Cooper Road University of Queensland Brisbane QLD 4072 AUSTRALIA
**DUNS:** 000000 **Grant Number(s):**
**Signing Official (SO):** Victoria Turner / 61 7 3346 3472 / v.turner@uq.edu.au
**Submitter of Request:** / /
**Submitter Comments:** (None)

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**Line #1:** MEL-1 Human Embryonic Stem Cell LIne
**NIH Approval #:**
**Available:** Yes
**Embryo from U.S.:** No
**Embryo Donated in Year(s):** 2004
**Provider Name:** StemCore, Stem Cells Ltd
**Provider Phone:** +61 7 3346 3472
**Provider Email:** v.turner@uq.edu.au
**Provider URL:** www.stemcore.com.au
**Provider Restrictions:** Not for clinical use.

**NIH Restrictions:**

**Additional Information:**

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**Line #2:** MEL-2 Human Embryonic Stem Cell LIne
**NIH Approval #:**
**Available:** Yes
**Embryo from U.S.:** No
**Embryo Donated in Year(s):** 2004
**Provider Name:** StemCore, Stem Cells Ltd
**Provider Phone:** +61 7 3346 3472
**Provider Email:** v.turner@uq.edu.au
**Provider URL:** www.stemcore.com.au
**Provider Restrictions:** Not for clinical use.

**NIH Restrictions:**

**Additional Information:**

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**Line #3:** MEL-3 Human Embryonic Stem Cell LIne
**NIH Approval #:**
**Available:** Yes
**Embryo from U.S.:** No
**Embryo Donated in Year(s):** 2005
**Provider Name:** StemCore, Stem Cells Ltd
**Provider Phone:** +61 7 3346 3472
**Provider Email:** v.turner@uq.edu.au
**Provider URL:** www.stemcore.com.au
**Provider Restrictions:** Not for clinical use.

**NIH Restrictions:**

**Additional Information:**

**Line #4: MEL-4 Human Embryonic Stem Cell LIne**
**NIH Approval #:**
**Available:** Yes
**Embryo from U.S.:** No
**Embryo Donated in Year(s):** 2005
**Provider Name:** StemCore, Stem Cells Ltd
**Provider Phone:** +61 7 3346 3472
**Provider Email:** v.turner@uq.edu.au
**Provider URL:** www.stemcore.com.au
**Provider Restrictions:** Not for clinical use.

**NIH Restrictions:**

**Additional Information:**

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**Supporting Documents:**
Document 1: (PDF - 03/29/2011) Provenance of MEL Lines - Elements: 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15
Document 2: (PDF - 03/29/2011) NHMRC verification of MEL derivation and licensing to Australian standards - Elements: 1,2,3,4,7
Document 3: (PDF - 03/29/2011) Consent for disposal or use of excess embryos - Elements: 1,2,3,7
Document 4: (PDF - 03/29/2011) Plain Language statement regarding stem cell derivation research project - Elements: 1,2,4,5,6,8,9,10,11,12,13,14,15
Document 5: (PDF - 03/29/2011) Consent to use excess embryos for stem cell deriviation - Elements: 2,4,5,6,7,8,9,10,11,12,13,14,15
Document 6: (PDF - 03/29/2011) Request for registration of MEL Lines - Elements: 16

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**Administrative Comments:** 1 May_Submitter Response to NIH Admin Rev Questions - uploaded by DHannemann 2 May 2011 Decision to move ASCC submission to WG (7 Jun) - uploaded by DHannemann 24 Jun 2011 IIB Assurance from Submitter (16 Jun) - uploaded by DHannemann 24 Jun 2011 ASCC Submission Compilation (as of 24 Jun 2011) - uploaded by DHannemann 24 Jun 2011 12 July Submitter Response email - by DHannemann 12 July 2011 Added Provider Restriction per submitter - by DHannemann 12 July 2011 SO changed per D. Collins (E.Gadbois 28 Oct 2011)

10 Nov Submitter email re Provider Information update - uploaded by DHannemann 22 Nov 2011

Updated the provider contact information for hESC lines MEL1 - 4 per submitter email received on 10 Nov 2011 - by DHannemann 22 Nov 2011

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**Administrative Attachments:**
Document 1: (DOC - 05/02/2011) 1 May - Submitter Respone to NIH Admin Review Questions
Document 2: (PDF - 06/24/2011) Decision to move ASCC submission to WG (7 Jun)
Document 3: (PDF - 06/24/2011) IIB Assurance
Document 4: (PDF - 06/24/2011) ASCC Submission Compilation (as of 24 Jun 2011)
Document 5: (PDF - 07/13/2011) 12 JUly Submitter Email Response
Document 6: (PDF - 07/22/2011) ASCC response re new SO and institution
Document 7: (PDF - 10/28/2011) ASCC change of SO and ownership
Document 8: (PDF - 11/22/2011) 10 Nov 2011 Submitter Email re Provider Info Update

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**Status History:**
**Draft:** 06/29/2010
**Pending:** 03/29/2011

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**Emails Sent:** 12/08/2010-Six_Month_Reminder_1_Email -- 12/22/2010-

Six_Month_Reminder_2_Email -- 03/29/2011-New_Applicaton_Email

**Previous ADM Request Number:** 2011-ADM-008
**Switched from ADM to ACD Date:** 06/17/2011
**Reason for Switch to ACD Review:**
The embryo donation consent contains borderline exculpatory language similar to an earlier submission from the University of New South Wales that was also referred to the ACD Working Group on the same basis.

**Added By:** Commons\DAVIDCOLLINS **On:** 06/29/2010 | **Last Updated By:** NIH\hannemannd **On:** 11/22/2011 | **Record ID:** 60

## Total Record Count = 1

Administration Page

Logout of NIH Form 2890 Admin Site

IIB Assurance

(4)

**From:** David Collins
**To:** HESCREGISTRY (NIH/OD)
**Cc:** Megan Munsie
**Subject:** RE: New hESC Registry Application Request #2011-ADM-008
**Date:** Thursday, June 16, 2011 3:41:38 PM

Dear Ms Gadbois

Thank you for your and apologies for the delay in responding. Unfortunately both Dr Munsie and I are at a stem cell conference in Toronto this week hence the tardy response.

We would like our submission considered by the Advisory Committee to the Director, NIH under the Section IIB criteria. I can also confirm that the requirements set out in your earlier e-mail were complied with.

Specifically I hereby assure that the embryo from which the cell line(s) identified in item 6 of the form was derived was donated prior to July 7, 2009, and the embryo:
1) was created using in vitro fertilization for reproductive purposes and was no longer needed for this purpose; and
2) was donated by individuals who sought reproductive treatment ("donor(s)") who gave voluntary written consent for the human embryo to be used for research purposes.

We will be back in the office next week and at that point we can provide you with any further information needed and these assurance in writing.

Thank you once again for your assistance in this submission and please do not hesitate to contact me if there is any further information required ahead of the ACD's working group meeting.

Kind regards, David Collins

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**From:** HESCREGISTRY (NIH/OD) [mailto:hescregistry@mail.nih.gov]
**Sent:** Fri 17/06/2011 1:31 AM
**To:** David Collins; Megan Munsie
**Cc:** HESCREGISTRY (NIH/OD)
**Subject:** RE: New hESC Registry Application Request #2011-ADM-008

Mr. Collins and Ms. Munsie,

If you are willing to have this submission considered by the Advisory Committee to the Director, NIH, under the Section IIB criteria, it would be great if you could let us know in the next few days so we can put it on the agenda for the ACD's working group, which meets later this month. Just so you know, this submission is very similar to a submission from the University of New South Wales for Endeavour-2, which was reviewed by the ACD and is now listed on the NIH Registry.

Please let us know if you have any questions regarding this request.

Sincerely,
Ellen Gadbois

*Ellen L. Gadbois, Ph.D.*
*Office of Science Policy Analysis*
*Bldg 1 Room 218D*
*National Institutes of Health*
*voice: 301-594-2567*
*fax: 301-402-0280*

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**From:** HESCREGISTRY (NIH/OD)
**Sent:** Monday, June 13, 2011 2:41 PM
**To:** david.collins@stemcellcentre.edu.au; megan.munsie@stemcellcentre.edu.au
**Cc:** HESCREGISTRY (NIH/OD)
**Subject:** RE: New hESC Registry Application Request #2011-ADM-008

Mr. Collins and Ms. Munsie,

Thank you again for this submission. NIH administrative review has determined that this submission does not meet the Section IIA criteria in the NIH Guidelines for Human Stem Cell Research, but is eligible for review under Section IIB of the Guidelines by the Advisory Committee to the Director, NIH.

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# Provenance of the MEL Human Embryonic Stem Cell Lines

In Australia, it has been legal since 2002 to use human embryo generated by assisted reproductive technology for stem cell derivation and in other areas of research provided certain criteria are met. Only embryos that were created by in vitro fertilisation (IVF) procedures for infertility treatment in an accredited clinic, and were subsequently declared to be in excess to the reproductive needs of the couples for whom the embryos had been originally created, can be used in research. Furthermore, prior to the use of a donated, excess human embryo, the researcher must obtain a licence from the Embryo Research Licensing Committee (the Licensing Committee) of the National Health and Medical Research Council (NHMRC) and in accordance with the relevant Australian legislation - *Research Involving Human Embryos Act 2002* and the *Prohibition of Human Cloning for Reproduction Act 2002*.

Under the Australian regulatory framework, it is essential that excess IVF embryos are only donated to licensed research project after proper consent was obtained to the satisfaction of the Licensing Committee. It is specifically prohibited under the Australian legislation for embryo donors to be offered any inducements for the donation of their embryo. Additional information on the Australian regulatory framework can be found on the NHMRC website or in the attached documentation (Document 2).

## Regulatory Approval of MEL Derivation

The MEL human embryonic stem cell lines (MEL lines) were derived in Australia during 2004 (MEL-1 and MEL-2) and 2005 (MEL-3 and MEL-4) from human embryos donated from patients of the infertility clinic, Melbourne IVF Pty Ltd. The use of the excess, donated IVF embryos for this research project was approved by the Licensing Committee, under Licence 309709. A copy of the licence, the standard and special conditions associated with Licence 309709, together with a covering letter from the Chair of the Licensing Committee has been included in the submission (see Document 2).

In this collaborative project, the licence holders, Melbourne IVF, were specifically responsible for obtaining consent from their patients and embryo culture; whilst the then biotechnology company, Stem Cell Science Ltd, as an authorised participant, were responsible for the isolation and identification of the embryonic stem cell lines (see Document 4). The ASCC's role was to provided financial support specifically for the research undertaken by Stem Cell Sciences in support of the derivation and initial characterisation of the MEL lines, as well as to assist in characterisation, and importantly, the distribution of the MEL lines to Australian and international researchers.

### *Consent process*

The consent process that was approved by the Licensing Committee for the derivation of the MEL lines involved written and oral communications. Specifically, the IVF clinic provided couples who had indicated that they had completed their infertility treatment, but had embryos frozen in storage with a consent form to confirm that they no longer required their embryo/s for treatment and to indicate whether the embryos should be discarded, made available for research, or donated to another couple (see Document 3). This consent also indicates that additional consent will be required if donation for research or to another couple is selected.

The next step in the consent process was to provide couples who indicated that they were interested in donating their excess, frozen IVF embryos to research with a plain language statement (see Document 4) that provided information on the project to derive embryonic stem cell lines.

The plain language statement described:

- background information about embryonic stem cells and their use in research
- the participants involved in the project
- the aim of the project
- the licensing process in Australia
- the fact that the embryo will be destroyed in the process of deriving the stem cell line
- that the line will be frozen, stored and distributed to researchers in Australia and overseas
- the offer of a verbal explanation of the research project
- how confidentiality would be protected
- statement that withdrawal of consent would not affect the couples' future treatment at the IVF clinic
- timeframe for project
- that the donation must be altruistic
- there is no commercial gain to be derived from participants in the project

- that couples can not expect to claim any share of financial benefits that may be generated from the use of these cell lines in the future.

Couples interested in donating their excess IVF embryos for the derivation of embryonic stem cell lines were also provided with a consent form that specifically restated the key points addressed in the plain language statement (see Document 5).

Employees of Stem Cell Sciences were not involved in obtaining consent from donors. Similarly, employees of the Australian Stem Cell Centre were not involved in obtaining consent from donors.

Embryos were only used in this project upon receipt of full written consent as demonstrated by signed consent forms – one generic for disposal or use of excess embryos, and one specifically for the use of the excess embryo for the research project - the derivation of embryonic stem cell lines. All couples who indicated an interest in participating in this research project were also offered a verbal explanation of the project as part of the consent process (see Document 4). Prior to the use of any donated embryo, the IVF clinic was also required to notify the Licensing Committee that appropriate consent had been obtained.

## Derivation and characterisation

Donated embryos were thawed and cultured to the blastocyst stage by Melbourne IVF staff in their laboratory. The inner cell mass (ICM) was extracted from blastocyst stage embryos following immunosurgery and placed on fibroblast feeder layers (of mouse origin for MEL-1 and MEL-2 and human origin for MEL-3 and MEL-4). The ICMs were cultured in the Melbourne IVF laboratory before transfer to the laboratory of Stem Cell Sciences for further culture and initial characterisation. Samples of the putative stem cell lines were shared with researchers at the Australian Stem Cell Centre laboratories for additional characterisation and expansion.

The MEL-1 and MEL-2 lines have been demonstrated to have a normal human diploid karyotype, express immunologically defined markers and genes specific of human embryonic stem cells and in vitro and in vivo differentiation characteristics consistent with pluripotent stem cells. Both MEL-1 and MEL-2 were characterised as part of the International Stem Cell Initiative with the results appearing in a subsequent publication[1]. The MEL-3 and MEL-4 lines have also been demonstrated to have a normal human diploid karyotype, express immunologically defined markers and genes specific of human embryonic stem cells and in vitro and in vivo differentiation characteristics consistent with pluripotent stem cells. However it was noted that following injection into NOD-SCID mice, the resulting teratomas consisted mostly of immature cell types with limited representation of ectoderm and mesoderm germ layers observed (not published).

## Distribution of the MEL lines

From the instigation of this project, it was always envisaged that all human embryonic stem cell lines derived in the MEL research project would be widely available through this service on a not-for-profit basis to researchers in Australia and overseas. As foreshadowed in the plain language statement, the initial collaborating parties, Melbourne IVF and Stem Cell Sciences, expected that a national stem cell bank would be established in Australia and that this organisation would be responsible for the distribution of the MEL lines. However, given a national stem cell bank was not established in Australia, nor has been established since, Stem Cell Sciences formed a collaboration with the Australian Stem Cell Centre to assist in the characterisation of the lines and to be the key distributor of any lines. Fundamental to the objectives of the collaboration was that the provision of new human embryonic stem cell lines was without intellectual property encumbrance.

The Australian Stem Cell Centre provides the MEL lines to Australian researchers through its StemCore facility. International researchers can obtain the MEL-1 and MEL-2 lines through the UK Stem Cell Bank or through Millipore.

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[1] Adewumi O et al (2007) Characterization of human embryonic stem cell lines by the International Stem Cell Initiative. *Nat Biotechnol* 25(7):803-16.

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## Commonality in Australian and NIH regulatory framework

The stringent Australian regulatory process governing the use of human embryos in research is in accordance with key points of the NIH guidelines. Specifically, the MEL series of human embryonic stem cells were derived in conditions consistent with the following statements:

- the embryo from which the cell lines was derived was donated prior to July 2009;
- the embryo was created using in vitro fertilization for reproductive purposes and was no longer needed for this purpose;
- the embryo was donated by individuals who sought reproductive treatment ("donor(s)") who gave voluntary written consent for the human embryo to be used for research purposes, and
- during the consent process, including written and oral communications, the donors:

  (1) were informed of other available options pertaining to the use of the embryo;

  (2) were NOT offered any inducements for the donation of the embryo; and

  (3) were informed about what would happen to the embryos after the donation for research.

To assist in the evaluation of our application to list the MEL cell lines on the NIH Human Embryonic Stem Cell Registry. We have included a table below that links additional supporting documentation (Documents 2-5) against the Section II(A) elements.

It is also worth noting that the Endeavour-2 cell line recently listed on the NIH Human Embryonic Stem Cell Registry was derived under the same Australian regulatory framework (Licence 309708) as the MEL lines.

| | EVIDENCE IN ACCORDANCE WITH NIH ASSESSMENT CRITERIA – Section II(A) | | | |
|---|---|---|---|---|
| | Document 2 – NHMRC confirmation of derivation conditions | Document 3 – Consent for the disposal or use of excess embryos | Document 4 – Plain language statement about stem cell derivation research project | Document 5 – Consent to use excess embryos for stem cell derivation |
| **Section II (A) Element 1** - hESCs should have been derived from human embryos that were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose | Page 1,Paragraph 3 | Whole document | Page 2,Paragraph 2 | N/A as addresses by first phase of the consent process (see Document 3) |
| **Section II (A) Element 2** - hESCs should have been derived from human embryos that were donated by individuals who sought reproductive treatment (hereafter referred to as "donor(s)") and who gave voluntary written consent for the human embryos to be used for research purposes | Page 1,Paragraphs 3 & 4 | Whole document | Page 2,Paragraph 2 | Whole document |
| **Section II (A) Element 3** - All options available in the health care facility where treatment was sought pertaining to the embryos no longer needed for reproductive purposes were explained to the individual(s) who sought reproductive treatment | Not specifically addressed but note this in an essential aspect in determining embryo to be "in excess" under Australian regulations (see Page 1, Paragraph 3) and for Proper Consent to have been obtained pursuant to NHMRC guidelines (section 2.3) | Page 2 | N/A as addresses by first phase of the consent process (see Document 3) | N/A as addresses by first phase of the consent process (see Document 3) |
| **Section II (A) Element 4** - No payments, cash or in kind, | Page 2,Paragraph 3 | N/A as addressed in second phase of | Page 2,Paragraphs 4 & 6 | Page 1, dot point 5 |

| | EVIDENCE IN ACCORDANCE WITH NIH ASSESSMENT CRITERIA – Section II(A) | | | |
|---|---|---|---|---|
| | Document 2<br>NHMRC confirmation of derivation conditions | Document 3<br>Consent for the disposal or use of excess embryos | Document 4<br>Plain language statement about stem cell derivation research project | Document 5<br>Consent to use excess embryos for stem cell derivation |
| were offered for the donated embryos | | consent process (see Documents 4 & 5) | | |
| **Section II (A) Element 5** - Policies and/or procedures were in place at the health care facility where the embryos were donated that neither consenting nor refusing to donate embryos for research would affect the quality of care provided to potential donor(s) | Not specifically stated but approved as part of the Australian licensing process | N/A | Page 2, Paragraph 4 | Page 2, dot point 1 |
| **Section II (A) Element 6** - Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize hESCs in research. The attending physician responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize hESCs should not have been the same person unless separation was not practicable | Not specifically stated but approved as part of the Australian licensing process. In addition there is a segregation of duties between MIVF, responsible for obtaining Proper Consent, Stem Cells Science, responsible for deriving and characterizing the lines and the Australian Stem Cell Centre, primarily responsible for distributing the lines for research purposes. This segregation provides a natural firebreak between donors and the derivation and research community. | N/A | Page 1, Paragraph 5 outlines the division of responsibility in the project<br>+<br>Page 2, Paragraph 2 outlines the role of MIVF staff in obtaining consent (not clinicians)<br>+<br>Page 2, Paragraph 4 note that this information/opportunity to donate is only provided at the completion of the infertility treatment | Page 2 – note opportunity to discuss implications of research with MIVF counselor or scientist |
| **Section II (A) Element 7** - At the time of donation, consent for that donation should have been obtained from the individual(s) who had sought reproductive treatment. That is, even if potential donor(s) had given prior indication of their intent to donate to research any embryos that remained after reproductive treatment, consent for the donation for research purposes should have been given at the time of the donation | Page 2, Paragraph 1 +<br>+ General statements on Page 1, Paragraphs 3 & 4<br>In addition NHMRC guidelines state that proper consent must be in writing and must include the names of those consenting, the dates of signature and include provision to record which embryos are being declared as excess including the date that they were frozen NHMRC guidelines | Initial first phase indication followed up by subsequent second phase consent (see Documents 4) | N/A | Whole document |
| **Section II (A) Element 8** - Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable | N/A | N/A | Page 2, Paragraph 4 | Page 2, dot point 1 -3 |

| | EVIDENCE IN ACCORDANCE WITH NIH ASSESSMENT CRITERIA – Section II(A) | | | |
|---|---|---|---|---|
| | **Document 2** NHMRC confirmation of derivation conditions | **Document 3** Consent for the disposal or use of excess embryos | **Document 4** Plain language statement about stem cell derivation research project | **Document 5** Consent to use excess embryos for stem cell derivation |
| **Section II (A) Element 9** - During the consent process, the donor(s) were informed that the embryos would be used to derive hESCs for research | N/A | N/A | Page 1, Paragraphs 4-7 + Page 2, Paragraphs 1, 4-6 | Page 1, dot points 2-4 |
| **Section II (A) Element 10** - During the consent process, the donor(s) were informed of what would happen to the embryos in the derivation of hESCs for research | N/A | N/A | Page 1, Paragraphs 4 | Page 1, dot point 1 |
| **Section II (A) Element 11** - During the consent process, the donor(s) were informed that hESCs derived from the embryos might be kept for many years | N/A | N/A | Page 1, Paragraphs 7 + Page 2, Paragraphs 4&5 | Page 1, dot point 3 & 4 |
| **Section II (A) Element 12** - During the consent process, the donor(s) were informed that the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the hESCs, such as who may be the recipients of cell transplants | N/A | N/A | Page 2, Paragraph 6<br>Page 2 Paragraph 4 which states clearly that once the donated embryos have been used to establish stem cell lines it is not possible to retrieve or withdraw consent fore the use of the stem cell lines. | Page 1, dot point 5<br>Page 2 dot point 2 |
| **Section II (A) Element 13** - During the consent process, the donor(s) were informed that the research was not intended to provide direct medical benefit to the donor(s) | N/A | N/A | Page 2, Paragraphs 1,2 & 6 | Page 1, dot point 5 and declaration that the nature of the project has been explained to the donors |
| **Section II (A) Element 14** - During the consent process, the donor(s) were informed that the results of research using the hESCs may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development | N/A | N/A | Page 1, Paragraph 7<br>Page 2, Paragraphs 6 | Page 1, dot points 3 & 5 |
| **Section II (A) Element 15** - During the consent process, the donor(s) were informed of whether information that could identify the donor(s) would be available to researchers | N/A | N/A | Page 2, Paragraphs 2 & 3 | This consent includes an acknowledgement that the plain language statement (Document 4) has been received and understood |

MELBOURNE IVF

# CONSENT TO THE DISPOSAL OR THE USE OF EXCESS FROZEN EMBRYO(S)

**Patient Number:** _____

**We,** _____ ___/___/___
(Woman, full name) (date of birth)

**and** _____ ___/___/___
(Partner, full name) (date of birth)

**of** .....
(Current Address)

.....

.....
(Address during treatment)

.....

**state that:**

1. We understand that we have (number) ..... embryo(s) frozen in storage at Melbourne IVF/The Royal Women's Hospital (delete one) (date) ...../...../.....

2. Such embryo(s) was / were frozen for the purpose of transfer to the woman.

3. We no longer require the embryo(s) to be transferred to the woman.

4. We request that the embryo(s) be – (*please cross out what is not required)*

- thawed and discarded
- made available for research* .
- donated to another couple*

* We understand that further consents will be required in this situation.

**Signed:**

| | |
|---|---|
| (Woman) | (Partner) |
| (Witness) | (Witness) |
| (Date) | (Date) |

Freemasons Hospital

THE ROYAL WOMEN'S HOSPITAL

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MELBOURNE IVF

**DERIVATION OF EMBRYONIC STEM CELL LINES FROM IVF EMBRYOS**
**PLAIN LANGUAGE STATEMENT**

*Project Aim*

The aim of this project is to derive Embryonic Stem cell lines for stem cell research.

*Background Information*

Embryonic Stem (ES) cells are very primitive cells that can be isolated from IVF embryos. ES cells are unique because they are able to grow into all of the different types of cells that make up the human body. For example, ES cells can be grown into nerves, heart, muscle or blood cells in the laboratory. ES cells can also be maintained in their more primitive state in which they can be grown to form continuously growing cell lines consisting of many identical stem cells.

These two attributes make ES cells, and the ES cell lines they form, a very valuable resource for many areas of medical research. ES cells may have an important role in the development of new treatments for many currently incurable conditions such as diabetes, Parkinson's disease and spinal cord injury. ES cells can also be used to develop potential new drug treatments and to investigate how genes regulate early human development. However, at present, very few human ES cell lines are available to Australian researchers, greatly hampering scientific progress in these fields.

*Project Description*

The derivation of human ES cell lines will involve thawing frozen IVF embryos and culturing the embryos for 2-3 days until they reach the blastocyst stage of development. ES cells will then be isolated from the embryo by initially collecting a sub-set of cells called the inner cell mass, then growing these cells in the laboratory for several weeks under specialised conditions. The embryo will be destroyed in the process of isolating these cells.

Not all embryos donated for research will survive the thawing process. Not all surviving embryos will develop to a stage where ES cells can be isolated. Even when ES cells can be isolated, not all cells will continue to grow and form individual ES cell lines.

As the isolation of ES cell lines requires specialised skills, Melbourne IVF has formed a collaborative partnership with Melbourne-based biotechnology company, Stem Cell Sciences Ltd (SCS). In this project, Melbourne IVF will undertake the embryo thawing and culture, while SCS will perform the ES cell isolation and identification. All embryo culture and initial ES cell isolation will be performed on-site at Melbourne IVF. No embryo donated for this research project will leave the laboratory of Melbourne IVF.

Once an ES cell line has been identified, samples will be frozen and stored by SCS. Once established, SCS intends sending the cell line to the planned National Stem Cell Bank for distribution to approved stem cell scientists, including commercial companies, in Australia or overseas where permitted by appropriate Australian authorities. SCS

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scientists plan to use the ES cell lines derived in this project to optimise the laboratory conditions for growing these cells.

The embryos to be used would only be used with the proper consent of the donating couple and after they sign a consent form specifically for this research. All couples who have indicated they wish to donate their excess embryos for research purposes will be contacted by a Melbourne IVF staff member and offered a verbal explanation of the research project. This work has been approved by the National Health and Medical Research Council Licensing Committee [Licence number 309709] and is lawful under the Research Involving Human Embryos Act 2002 (CWLTH No.145), the Prohibition of Human Cloning Act 2002 (CWLTH No.144) and the Infertility Treatment Act 1995 (VIC) as amended. NHMRC compliance inspectors may request access to view patient records in order to confirm that the research is being carried out in accordance with the above Acts.

Embryos for this project will be coded to protect patient confidentiality. Any identifying information will be securely stored at Melbourne IVF. Information about the progress of the work will be available if requested and the information provided by a Melbourne IVF counsellor at no cost. Non-identifying information may also be published in scientific journals or presented at scientific conferences.

A cooling off period of two weeks is provided after signing the consent form. Embryos will not be used during this period. Withdrawal of consent by the donating couple at any time prior to the use of the embryos will not affect the donating couple's current or future treatment at Melbourne IVF. However, once the donated embryos have been used to establish stem cell lines and the derived lines disseminated, it will not be possible to retrieve or withdraw consent for the use of the stem cell lines.

It is anticipated that this project will be conducted over a 3-4-year period commencing in June 2004. However, as ES cell lines can remain frozen indefinitely, and potentially be maintained in culture for many years, the isolated ES cell lines may be available for approved research projects indefinitely.

Excess embryos must be donated altruistically for the project. While no commercial gains will result from the derivation of ES cell lines, the embryo donors will have no claim now or in the future on any financial benefits that may be generated from the use of these cell lines.

Both Melbourne IVF and Stem Cell Sciences adhere to all Privacy Laws. If you wish to view the privacy policies you can contact their respective privacy officers.

Further information about this project can be obtained from:

- [redacted] Senior Counsellor, MIVF [redacted]
- [redacted] Scientific Director, MIVF, [redacted]
- Your IVF consultant

(14)

MELBOURNE IVF

# CONSENT FOR THE USE OF EMBRYOS FOR THE DERIVATION OF EMBRYONIC STEM CELL LINES

Names: ..... DOB:.....

..... DOB:.....

Address:.....

.....

**We consent to the use of our embryos for the following purpose:**

Name of research project:.....

We had .....number of embryos frozen at Melbourne IVF on _____/_____/_____

The nature of the project has been explained to us and we have had the opportunity to ask questions.

Written information in the form of the attached plain language statement has been given to and is understood by us:

- We understand that our embryos will be destroyed in this process.
- We understand that Embryonic Stem (ES) cell lines will be created in this project and the cells and cell lines will be used for basic stem cell research.
- We understand that the ES cell lines will be frozen and deposited in a stem cell bank where samples will be available for general stem cell research to approved researchers, including commercial companies, in Australia and may be made available to overseas researchers where approved by the appropriate authorities.
- We understand that once ES cell lines are established the ES cells and cell lines will be available for approved research projects indefinitely.
- ß We understand that we are donating our excess embryos for altruistic purposes. We acknowledge that while no commercial gains will result from the derivation of ES cell lines, we have no claim now or in the future on any financial benefits that may be generated from the use of these cell lines.

- We understand that we can refuse to participate in this project and that we can withdraw our consent at any stage prior to the use of the embryos.
- We understand that once the embryos have been used to establish stem cell lines and the lines disseminated we cannot retrieve or withdraw our consent.
- We understand that there will be a two week cooling off period from the date of signing this document before the embryos will be used for research.
- We understand that in accordance with the legislation governing the use of our excess embryos, NHMRC inspectors may request access to our patient records.

We have had the opportunity to discuss the implications of this research with a Melbourne IVF counsellor and/or scientist.

**Signed:**

| | |
|---|---|
| (Woman) | (Partner) |
| (Witness) | (Witness) |
| (Date) | (Date) |

***Office use only:***

**Embryos Formed Before 5th April, 2002** **YES/ NO**

THE ROYAL WOMEN'S HOSPITAL

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Dr Megan Munsie
Director Government Affairs and Policy
Australian Stem Cell Centre
PO Box 8002
Monash University L.P.O. Victoria 3168 Australia

Dear Dr Munsie,

I refer to your request for official confirmation that the MEL series of human embryonic stem cell lines were derived under the following circumstances:

- the lines must have been obtained from embryos created during IVF procedures;
- there must be verifiable informed consent on the part of the donors; and
- the donors were not financially compensated for their donation.

In response, I confirm that the MEL human embryonic stem cell lines were derived under Licence 309709 issued on 11 June 2004 by the Embryo Research Licensing Committee (the Licensing Committee) of the National Health and Medical Research Council (NHMRC) of Australia in accordance with the requirements of the *Research Involving Human Embryos Act 2002* (RIHE Act). The version of the licence current at 15 November 2007 is provided as Attachment 1 and consists of the Licence, the Standard Conditions and the Special Conditions.

The licence authorised the use of excess ART embryos to derive human embryonic stem cell lines (refer to Item 7 of the Licence). An excess ART embryo is defined in section 9 of the RIHE Act as

> A human embryo that:
> (a) was created by assisted reproductive technology, for use in the assisted reproductive technology treatment of a woman; and
> (b) is excess to the needs of:
> (i) the woman for whom it was created; and
> (ii) her spouse (if any) at the time the embryo was created.

Thus the embryos used under Licence 309709 were originally created by IVF procedures for IVF treatment in a clinic accredited by the Reproductive Technology Accreditation Committee of the Fertility Society of Australia and were subsequently declared to be excess to the reproductive needs of the couples for whom they had been created.

Section 24(1)(a) of the RIHE Act requires that:

> A licence is subject to the condition that before an excess ART embryo is used as authorised by the licence:
> (a) each responsible person in relation to the excess ART embryo must have given proper consent to that use: and
> (b) the licence holder must have reported in writing to the NHMRC Licensing Committee that such consent has been obtained, and any restrictions to which the consent is subject.

"Responsible person" is defined in section 8 of the RIHE Act.

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I confirm that the embryos used under Licence 309709, including the embryos which resulted in the MEL series of embryonic stem cell lines, were only used after proper consent had been obtained and the Licensing Committee had been notified of that fact.

The Licensing Committee has legislative responsibility for overseeing a monitoring process carried out by NHMRC inspectors I have appointed under the RIHE Act. The activities conducted under Licence 309709 have been inspected at least annually during the period of the licence. Inspections include audits of a representative number of individual embryos used under the licence to verify the existence of signed consent documents and a demonstrable link between the consent documents and recorded outcomes for the use of these embryos. I confirm that the inspections have not detected any non-compliance with these requirements.

Section 21 of the *Prohibition of Human Cloning for Reproduction Act 2002* makes it an offence with a penalty of 15 years imprisonment to conduct commercial trade in human eggs, human sperm or human embryos. Commercial trade includes offering or receiving of "valuable consideration" in connection with the use of gametes or embryos. The NHMRC inspectors have regularly provided information and advice on this matter to IVF clinics in Australia and the clinics are generally well aware of the prohibition. I have no reason to believe that there was any compensation or valuable consideration involved in the use of embryos under Licence 309709.

If you have any queries about this letter please contact Ms Melissa Crampton, Director of the Licensing Section on 02 6217 9424 or by e-mail (melissa.crampton@nhmrc.gov.au).

Yours sincerely,

Professor Jock Findlay AM
Chair
NHMRC Licensing Committee
15 November 2007

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***Research Involving Human Embryos Act 2002***

**Embryo Research Licensing Committee of the NHMRC**

# LICENCE

This licence is issued under s.21 of the *Research Involving Human Embryos Act 2002*. This licence authorises the use of excess ART embryos specified below, subject to the conditions specified in items 8 and 9 below.

| | | |
|---|---|---|
| 1. | Licence number: | 309709 |
| 2. | Licence holder: | Melbourne IVF Pty Ltd |
| 3. | Licence title: | A collaborative project between Melbourne IVF Pty Ltd and Stem Cell Sciences Pty Ltd to derive Human Embryonic Stem Cell Lines |
| 4. | Date of issue: | 11 June 2004 |
| 5. | Licence begins: | 11 June 2004 |
| 6. | Licence ends: | 11 June 2008 |
| 7. | Use of excess ART embryos authorised by the licence | Isolation of the inner cell mass from excess human ART embryos in order to establish ten embryonic stem cell lines under improved and defined culture conditions and to characterise those cell lines and study their growth and directed differentiation. |
| 8. | Standard conditions | All conditions that are specified in the document *Standard Conditions for Using Excess ART Embryos* as currently published on www.nhmrc.gov.au/embryo and as amended from time to time. |
| 9. | Special conditions: | All conditions that are specified in the *Special Conditions for Licence No. 309709.* |

The licence holder is reminded of the statutory provisions of the *Research Involving Human Embryos Act 2002* and the *Prohibition of Human Cloning Act 2002.*



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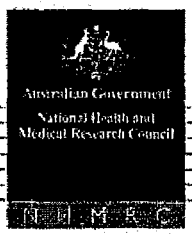


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**Embryo Research Licensing Committee of the NHMRC**

# Special Conditions for Licence No. 309709

| | | |
|---|---|---|
| 1. | Licence number: | 309709 |
| 2. | Licence holder: | Melbourne IVF Pty Ltd |
| 3. | Licence title: | A collaborative project between Melbourne IVF Pty Ltd and Stem Cell Sciences Pty Ltd to derive Human Embryonic Stem Cell Lines |

The conditions that are specified below are the special conditions that apply to this licence. The *Special Conditions* operate **in addition to** all conditions identified in the *Standard Conditions for Using Excess ART Embryos*. The *Special Conditions* prevail where there is an inconsistency between a special condition and a standard condition.

## Number of embryos

| *Condition number* | *Condition* |
|---|---|
| 9101 | A maximum of 200 excess ART embryos may be removed from cryostorage and thawed in connection with this licence. |
| 9103 | The excess ART embryos must only be used to isolate the inner cell mass in order to establish ten embryonic stem cell lines under improved and defined culture conditions and to characterise those cell lines and study their growth and directed differentiation. |

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| 9104 | No excess ART embryos may be removed from cryostorage and thawed after Stem Cell Sciences Pty Ltd has established ten embryonic stem cell lines according to the following criteria:<br>• the ES cell line must possess a normal human diploid karyotype, and express immunologically defined markers and genes specific for embryonic stem cells;<br>• initial studies indicate that the cell line is immortal and pluripotent; and<br>• these lines must have been passaged ten times in culture and have been successfully cryopreserved on two occasions and shown to be free of contamination by adventitious agents. |

## Specified sites

| *Condition number* | *Condition* |
|---|---|
| 9201 | The use authorised by the licence must be conducted at the following site:<br><br>Melbourne IVF<br>320 Victoria Parade<br>EAST MELBOURNE VIC 3002 |
| 9202 | The licence holder must hold all records, including patient records, associated with the use authorised by the licence at the following sites:<br><br>Melbourne IVF<br>320 Victoria Parade<br>EAST MELBOURNE VIC 3002 |

## Persons authorised to use excess ART embryos

| *Condition number* | *Condition* |
|---|---|
| 9301 | The Principal Supervisor is that person identified in the letter dated 2 June 2004 (2004/026716, f.103) as an additional attachment to the application received on 8 October 2003 and lodged in accordance with s.20 of the *Research Involving Human Embryos Act 2002,* or as subsequently notified to and authorised by the Licensing Committee. The Principal Supervisor is responsible for supervision of the use of excess ART embryos as authorised by the licence. |
| 9302 | Stem Cell Sciences Pty Ltd is authorised to participate in the use of excess ART embryos under this licence. |

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| 9303 | The use of excess ART embryos under this licence may only be undertaken by those personnel of the licence holder identified in the letter dated 2 June 2004 (2004/026716, f.103) and those personnel of Stem Cell Sciences Pty Ltd identified in the letter dated 2 June 2004 (2004/026716, f.103) as an additional attachment to the application received on 8 October 2003 and lodged in accordance with s.20 of the *Research Involving Human Embryos Act 2002* or such other personnel subsequently notified to and authorised by the Licensing Committee. |

## Reporting

| | |
|---|---|
| 9401 | The licence holder must report progress on establishing embryonic stem cell lines in writing to the NHMRC Licensing Committee when the first 50 of the 200 excess ART embryos authorised in condition 9101 have been used. |
| 9402 | Stem Cell Sciences Pty Ltd must report to the licence holder in writing as soon as the ten embryonic stem cell lines have been established. |
| 9403 | The licence holder must report to the NHMRC Licensing Committee in writing as soon as the ten embryonic stem cell lines have been established – refer to conditions 9104 and 9402. |
| 9404 | In addition to the reports required by Standard Condition 3001, the licence holder is required to provide a further written report no later than 6 months following the expiry, revocation or surrender of the licence. This report must use the format specified in the document "Post-expiry report on embryonic stem cell lines established in accordance with a licence issued by the NHMRC Embryo Research Licensing Committee" as published and amended from time to time at the following website: http://www.nhmrc.gov.au/embryos/monitor/application/index.htm. |

## Other Conditions

| | |
|---|---|
| 9501 | Mouse feeder cells may only be used in the initial culture conditions for two of the ten intended stem cell lines. |
| 9502 | Stem Cell Sciences Pty Ltd must not unreasonably refuse to permit Inspectors appointed by the NHMRC Licensing Committee to access its premises for the purposes of ensuring compliance with special conditions 9103, 9104, 9401, 9402 and 9403. |
| 9503 | The *Standard Conditions For Using Excess ART Embryos*, which apply to the licence holder, also apply to Stem Cell Sciences Pty Ltd, except for conditions 2301, 3001, 4101, and 5001. |

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*Research Involving Human Embryos Act 2002*

**Embryo Research Licensing Committee of the NHMRC**

# Standard Conditions for Using Excess ART Embryos

This document specifies the standard conditions that apply to licences that are issued by the Embryo Research Licensing Committee of the NHMRC (the NHMRC Licensing Committee) under the *Research Involving Human Embryos Act 2002* and corresponding State laws for the use of excess ART embryos. The *Standard Conditions* apply to *every* licence unless the *Special Conditions* for a particular licence provide that a specific standard condition does not apply to that licence.

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ABN 88 601 010 284

## Current contact details

| *Condition number* | *Condition* |
|---|---|
| 1001 | The licence holder must give written notice to the NHMRC Licensing Committee Secretariat of a proposed change in the licence holder's telephone number, email address or postal address and must be able to receive calls, email or mail at that address and telephone number until the licence is varied to reflect the new address or telephone number. |
| 1002 | The licence holder must ensure that an email that is intended for the NHMRC Licensing Committee or the Committee Secretariat is sent to the Committee's email address: embryo.research@nhmrc.gov.au |
| 1003 | The licence holder must ensure that mail that is intended for the NHMRC Licensing Committee or the Committee Secretariat is sent to the Committee's postal address:<br><br>NHMRC Licensing Committee Secretariat<br>GPO Box 1421<br>CANBERRA ACT 2601 |
| 1004 | The licence holder must include the licence number in all correspondence directed to the NHMRC Licensing Committee or the Committee Secretariat. |

## Persons authorised to participate in the use of excess ART embryos

| *Condition number* | *Condition* |
|---|---|
| 2001 | The licence holder must ensure that each person who is identified in the licence conditions as a person who is authorised to participate in the use of excess ART embryos is at all times fully informed of the requirements of the *Research Involving Human Embryos Act 2002,* the *Prohibition of Human Cloning Act 2002*, any corresponding State law and the licence and its conditions. |
| 2101 | The licence holder must not permit a person to participate in the use of excess ART embryos unless the person is authorised to do so in the licence conditions. |

| *Condition number* | *Condition* |
|---|---|
| 2102 | If the licence holder becomes aware that a person who is not identified in the licence conditions has participated in the use authorised by the licence, the licence holder must within 3 days of having become so aware provide a written report to the NHMRC Licensing Committee.<br><br>A written report provided in accordance with this condition must include details on the following matters:<br><br>(a) The name of the person who participated in the use and a brief *curriculum vitae* for that person;<br><br>(b) The period during which the person participated in the use; and<br><br>(c) The circumstances that led to a person not identified in the licence conditions participating in the use authorised by the licence.<br><br>Where the licence holder is an individual, the licence holder is not required to give information that might tend to incriminate the individual or expose the individual to a penalty. |
| 2301 | The licence holder must give written notice to the NHMRC Licensing Committee within 7 days if a person who is identified in the licence conditions as a person who is authorised to participate in the use of excess ART embryos ceases to be involved in the use that is authorised by the licence. |

## Reporting

| *Condition number* | *Condition* |
|---|---|
| 3001 | The licence holder must, during the currency of the licence, submit to the NHMRC Licensing Committee a written report not later than 30 days after each 31 March in respect of the six-month period ending on that 31 March and not later than 30 days after each 30 September in respect of the six-month period ending on that 30 September, in the format specified in the document "Report on the use of Excess ART embryos" as published and amended from time to time at the following website:<br>http://www.nhmrc.gov.au/embryos/monitor/application/index.htm<br>*or*<br>in an alternative format which has previously been approved in writing by the Chair of the NHMRC Licensing Committee.<br><br>The licence holder must also, not later than 30 days after the expiry, revocation or surrender of the licence, submit to the NHMRC Licensing Committee a written report in the format specified in the document "Final report on the use of excess ART embryos" as published and amended from time to time at the following website:<br>http://www.nhmrc.gov.au/embryos/monitor/application/index.htm<br>*or*<br>in an alternative format which has previously been approved in writing by the Chair of the NHMRC Licensing Committee. |

| *Condition number* | *Condition* |
|---|---|
| 3101 | If the licence holder becomes aware of any conduct undertaken in connection with the licence that breaches the *Research Involving Human Embryos Act 2002*, the *Prohibition of Human Cloning Act 2002*, or any corresponding State law, the licence holder must within 3 days of becoming so aware provide a written report to the NHMRC Licensing Committee.<br><br>A written report provided in accordance with this condition must include details on the following matters:<br><br>(a) The conduct that the licence holder believes constitutes a breach;<br><br>(b) The period during which this conduct took place; and<br><br>(c) The site at which this conduct took place.<br><br>Where the licence holder is an individual, the licence holder is not required to give information that might tend to incriminate the individual or expose the individual to a penalty. |
| 3102 | If the licence holder becomes aware of any conduct undertaken unintentionally in connection with the licence that, had it been undertaken intentionally, would breach the *Research Involving Human Embryos Act 2002,* the *Prohibition of Human Cloning Act 2002,* or any corresponding State law, the licence holder must within 3 days of becoming so aware provide a written report to the NHMRC Licensing Committee.<br><br>A written report provided in accordance with this condition must include details on the following matters:<br><br>(a) The conduct that the licence holder believes would constitute a breach if undertaken intentionally;<br><br>(b) The period during which this conduct took place; and<br><br>(c) The site at which this conduct took place.<br><br>Where the licence holder is an individual, the licence holder is not required to give information that might tend to incriminate the individual or expose the individual to a penalty. |
| 3103 | If the licence holder becomes aware of any conduct undertaken in connection with the licence that breaches a condition of the licence, the licence holder must within 3 days of becoming so aware provide a written report to the NHMRC Licensing Committee.<br><br>A written report provided in accordance with this condition must include details on the following matters:<br><br>(a) The conduct that the licence holder believes constitutes a breach;<br><br>(b) The period during which this conduct took place; and<br><br>(c) The site at which this conduct took place.<br><br>Where the licence holder is an individual, the licence holder is not required to give information that might tend to incriminate the individual or expose the individual to a penalty. |

| *Condition number* | *Condition* |
|---|---|
| 3104 | If the licence holder becomes aware that a person who is identified in the licence conditions has participated in the use of excess ART embryos authorised by the licence at a site that is not specified in the licence conditions, the licence holder must within 3 days of having become so aware provide a written report to the NHMRC Licensing Committee.<br><br>A written report provided in accordance with this condition must include details on the following matters:<br><br>(a) The site at which the use took place;<br><br>(b) The period during which the use took place at this site;<br><br>(c) The circumstances that led to the use at a site not specified in the licence conditions.<br><br>Where the licence holder is an individual, the licence holder is not required to give information that might tend to incriminate the individual or expose the individual to a penalty. |
| 3201 | The licence holder must immediately, by notice in writing, inform the NHMRC Licensing Committee of any investigation or prosecution by a Commonwealth, State or Territory agency that involves any matters that might reasonably be considered to affect the suitability of the licence holder to undertake the use of excess ART embryos authorised by the licence. |

## Monitoring

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| 3401 | The licence holder must implement and maintain processes that ensure that adequate records are made and stored to allow the conduct of the licensed use to be monitored for compliance with the requirements of the *Research Involving Human Embryos Act 2002* and the *Prohibition of Human Cloning Act 2002*, corresponding State law, the licence and the licence conditions. |
| 3501 | The licence holder must not unreasonably refuse to provide any additional information requested by the NHMRC Licensing Committee. The information must be in the form, if any, specified in the request. |
| 3601 | The licence holder must provide reasonable assistance and cooperation to the NHMRC Licensing Committee and its Inspectors in carrying out their powers, functions and duties under the *Research Involving Human Embryos Act 2002*, the *Prohibition of Human Cloning Act 2002*, and any corresponding State law. |

## Use of Embryos

| *Condition number* | *Condition* |
|---|---|
| 4001 | The licence holder may not remove from cryostorage for the purpose of conducting the use authorised by the licence a greater number of excess ART embryos than the number specified in the special conditions of the licence. |

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| 4002 | If the licence holder is able to achieve the goals of the use authorised by the licence using fewer excess ART embryos than the total number stated in the special conditions of the licence, then the licence holder must not remove any further embryos from cryostorage for the use authorised by the licence. |
| 4101 | The licence holder must maintain a tracking system that uniquely identifies each excess ART embryo used in connection with the licence. The tracking system must link the unique identifier for each individual embryo to a specific licence and each 'responsible person'; 'responsible person' has the same meaning as in s.8 of the *Research Involving Human Embryos Act 2002*. |
| 4102 | The licence holder must record an outcome for each individual excess ART embryo removed from cryostorage, linking the outcome to the unique identifier for the embryo. |
| 4201 | As soon as the goals of the activity or project specified in Item 7 of this licence have been achieved or if the activity or project is discontinued for any reason, the licence holder must not use any further embryos even if proper consent has previously been obtained to use the embryos in the activity or project. The licence holder, as soon as practicable thereafter, must either:<br>(i) make arrangements to transfer these excess ART embryos to the clinic or unit that had responsibility for these prior to proper consent being obtained for the use specified in Item 7; or<br>(ii) obtain advice from the responsible persons who provided the proper consent and deal with these excess ART embryos in accordance with such advice. |

## Notification that Proper Consent has been obtained

| *Condition number* | *Condition* |
|---|---|
| 5001 | For the purposes of complying with s.24(1)(b) of the *Research Involving Human Embryos Act 2002*, the licence holder may report to the NHMRC Licensing Committee that 'proper consent' has been obtained either by providing a single written notification of consent in respect of all of the embryos authorised to be used, or by providing a series of written notifications in respect of groups of embryos at intervals during the period of licence. 'Proper consent' has the same meaning as in s.8 of the *Research Involving Human Embryos Act 2002*. |



# ASCC RESPONSE TO QUESTIONS RAISED BY NIH ADMINISTRATIVE REVIEW

The ASCC provides the following response to the series of questions raised by NIH. Further information or clarification can be provided if required.

1) **Please provide a copy of Document 5 as it was presented to the embryo donors for the lines MEL 1 – 4. We note the copy of Document 5 has a blank space behind "name of research project."**

   The consent form (Document 5), as provided in our submission, is identical to that also given to potential donors.

   Couples who indicated that they wish to donate their embryos to research, having done so by completing section 4 in the 'Consent to dispose or use excess embryos' consent form (Document 3), were then given plain language statements and consent forms for current research projects using human embryos. At that time, Melbourne IVF had two licensed research projects that involved the use of donated human embryos, one involving embryonic stem cell derivation and one involving the use of embryos for 'Development of testing procedures for unbalanced chromosome errors in human embryos' and the patients were offered the choice of which of those two projects they wished to donate their embryos towards.

   Therefore, it was important that the donors completed the "blank" sections of the consent form including stating their name, DOB, address, number of embryos frozen, and the name of research project they wished to participate in. The research project title is stated on the plain language statement (Document 4) and at the top of the specific consent form (Document 5).

2) **The Guidelines require that, "policies and/or procedures were in place at the health care facility where the embryos were donated that neither consenting nor refusing to donate embryos for research would affect the quality of care provided to potential donor(s)." Please address further how this element was met, including how the Australian licensing process is relevant.**

   Under Australian legislation, human embryos can only be used in licensed research projects where the embryos were originally created by assisted reproductive technology (ART) for use in treatment but have subsequently been shown to be in excess of the needs of the woman for whom it was created and her spouse (if any) at the time the embryos was created (see Document 2).

   Furthermore, to grant a licence for the use of human embryos in research in Australia, the NHMRC Licensing Committee must be satisfied that appropriate protocols are in place so that 'proper consent' is obtained.

The consent process must address a number of key issues, summarized in NHMRC Embryo Research Licensing Committee Information Kit Appendix 6, and described in relevant guidelines and/or legislation including:

| Specific requirement | Relevant Australian legislation or guidelines |
|---|---|
| Consent of responsible persons must be voluntary and not subject to any coercion, inducement or influence, including financial | National Statement 2007 2.2.1, 2.2.9 & 2.2.10 ART Guidelines 2007 15.5 (Noting offence provisions in the *Prohibition of Human Cloning for Reproduction Act 2002* s.21 regarding commercial trade in human embryos) |
| The process for obtaining consent for involvement in the research is clearly separated form clinical care | ART Guidelines 2007 9.10, 15.5 |
| Research using human embryos should be conducted at a location that separates the woman's clinical care from the research | National Statement 2007 3.6.5 |

As stated in Document 2, the NHMRC Licensing Committee was satisfied that policies and procedures were in place that satisfied 'proper consent'.

In addition, Document 4 (P2 Para 4) explicitly states that "Withdrawal of consent by the donating couple at any time prior to the use of the embryos will not affect the donating couple's current or future treatment at Melbourne IVF".

3) **The Guidelines require that, "Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize hESCs in research. The attending physician responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize hESCs should not have been the same person unless separation was not practicable." Please provide the name of the "Principal Supervisor" as described in condition #9301 of the Embryo Research License No. 309709. Also please address whether the treating physician(s) responsible for reproductive clinical care was/were involved in the research.**

The Principal Supervisor was Dr David Edgar, Scientific Director of Melbourne IVF (remains the current Scientific Director).

As described in Document 1, there was a deliberate segregation of duties between the clinic, Melbourne IVF and the authorized participant, Stem Cell Sciences Pty Ltd. Melbourne IVF had the responsibility to obtain proper consent from the patient, oversee the retrieval and thawing of the embryos, whilst Stem Cell Sciences were responsible for deriving and characterizing the human embryonic stem cell lines (which occurred at their laboratory following initial isolation of the inner cell mass). This

segregation ensured a natural firebreak between donors and the research deriving and using the stem cell line.

The original treating physician was not directly involved in obtaining consent from the patient, in the thawing and use of the embryos or any research involving the human embryonic stem cell lines once derived. As the donors had completed their IVF treatment, as demonstrated by their declaration that the embryos were in excess of their requirements in consent forms, their reproductive clinical care could not be affected due to their participation or refusal to participate in the project.

4) **The Guidelines require that during the consent process, donor(s) were informed "that the donation was made without any restriction or direction regarding the individuals(s) who may received medical benefit from the use of the hESCs, such as who may be the recipients of the cell transplants." Were donors informed of this provision? If not, please explain why not.**

The MEL series of cell lines were derived for research use only. Clinical use was not contemplated. Licence 309709 allowed excess ART embryos to be used for the isolation of the inner cell mass "in order to establish ten embryonic stem cell lines under improved and defined culture conditions and to characterize those cell lines and study their growth and directed differentiation".

Both the specific consent form (Document 5) states that the embryonic stem cell lines derived in the project will be used for research projects (second dot point - "We understand that Embryonic Stem (ES) cell lines will be created in this project and that the cells and cell lines will be used for basic stem cell research").

Clinical use is not contemplated and as such the issue of restriction or direction was not specifically addressed. However, both the plain language statement (Document 4) and the specific consent form state that the donation is altruistic, which implies the donor can not redirect or restrict the future use of any stem cell line derived in the project.

In addition, Document 5 (P2 Para 1) states that once lines are established and disseminated "we cannot retrieve or withdraw our consent" which has the practical impact of removing the donors' right to place any further restriction or direction on the use of the lines created.

5) **Please confirm whether there are any restrictions on research use of these cell lines. Were any clinical uses envisioned?**

There are no restrictions on the use of the MEL cell lines provided appropriate ethical approval is obtained for the proposed research use.

In respect of clinical use, as address in response to Q4 above, this was not envisaged. The agreement between ASCC and SCS to establish the lines only allowed for distribution and use of the lines for research purposes, although this could be by commercial or not-for-profit entities. Practically, the lines were not established and maintained under "GMP" conditions and are not suitable for clinical purposes.

6) **Please detail whether hESC lines MEL-1, MEL-2, MEL-3 or MEL-4 have any known disease-specific mutations or genetic abnormalities. This does not affect the review to determine eligibility under the Guidelines but if the lines are listed on the Registry, inclusion of such information is helpful for NIH grantees.**

All four MEL lines were shown to have a normal karyotype with no known disease-specific mutation or genetic abnormalities.

(32)

**From:** Megan Munsie
**To:** HESCREGISTRY (NIH/OD)
**Cc:** David Collins
**Subject:** RE: New hESC Registry Application Request #2011-ADM-008
**Date:** Tuesday, July 12, 2011 7:59:41 PM

Dear Dr Hannemann,

Thank you for your email advising us on the next stage of the review process.

We would be very happy for "Not for clinical use" to be indicated in the "Provider Restrictions" field, if the cell lines are approved for inclusion on the NIH Registry.

In relation to the statements in the specific Consent Form and the Plain Language Statement, the statement that "no commercial gains will result from the derivation of the ES lines" was included to address potential concerns from the donors that the **derivation** may have been a commercial arrangement given the involvement of the then biotechnology company, Stem Cell Sciences Pty Ltd. In this instance, the statement was in relation to the parties involved in the derivation. We wanted to make it very clear that this project was an altruistic undertaking by all parties with the sole objective to use our collective expertise to create and share a valuable resource.

The other statement sought to address potential concern in relation to the **use** of the cell lines derived in the project. Given that the intent was to share the cell lines widely with other parties, including companies, it was thought advisable to include a statement that made it clear that donors should not expect any financial benefit from discoveries made through the use of these lines. By making this a clear statement in the consent, it allowed the donors the opportunity to decline to be involved if they found such terms unacceptable.

Whilst these comments may appear contradictory, there was substantial consideration around commercial issues, and in particular donor expectations, at the time. As one of the first approved projects in Australia under the legislation that governs the use of human embryos in research, our consent and plain language statements attracted substantial scrutiny from the National Health and Medical Research Council's Embryo Research Licensing Committee and our local ethics committee.

We are happy to provide additional information or clarification as required.

Kind regards,
Megan

**Megan Munsie PhD**
**Australian Stem Cell Centre**
**☎ 61 3 92711111 ✆ 0417585621**

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**From:** HESCREGISTRY (NIH/OD) [mailto:hescregistry@mail.nih.gov]
**Sent:** Wed 7/13/2011 12:22 AM
**To:** David Collins; Megan Munsie
**Cc:** HESCREGISTRY (NIH/OD)
**Subject:** RE: New hESC Registry Application Request #2011-ADM-008

Dear Mr. Collins and Dr. Munsie,

Thank you for your response. The Advisory Committee to the Director's Working Group for Human Stem Cell Eligibility Review has begun review of this submission and the following questions have arisen.

In your 2 May 2011 response to the fifth question from us, you explain that the lines are not suitable for clinical purposes. If the cell lines are approved for inclusion on the NIH Registry, we suggest that we indicate "Not for clinical use" in the "Provider Restrictions" field.

We also note that the Melbourne IVF Consent For the Use of Embryos For the Derivation of Embryonic Stem Cell Lines and the Plain Language Statement both state that "no commercial gains will result from the derivation of ES lines" but then inform the donors that they have no claim now or in the future on any financial benefits that may be generated from the use of these cell lines. Can you explain further what was meant by these statements? Presumably commercial companies could profit from non-clinical research uses of these lines.

Best regards,
Diane Hannemann

*Diane E. Hannemann, Ph.D.*
*Office of Science Policy Analysis*
*National Institutes of Health*
*tel: 301-594-0064*
*fax: 301-402-0280*

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**From:** David Collins [mailto:David.Collins@stemcellcentre.edu.au]
**Sent:** Thursday, June 16, 2011 3:41 PM
**To:** HESCREGISTRY (NIH/OD)
**Cc:** Megan Munsie
**Subject:** RE: New hESC Registry Application Request #2011-ADM-008

Dear Ms Gadbois

Thank you for your and apologies for the delay in responding. Unfortunately both Dr Munsie and I are at a stem cell conference in Toronto this week hence the tardy response.

We would like our submission considered by the Advisory Committee to the Director, NIH under the Section IIB criteria. I can also confirm that the requirements set out in your earlier e-mail were complied with.

Specifically I hereby assure that the embryo from which the cell line(s) identified in item 6 of the form was derived was donated prior to July 7, 2009, and the embryo:
1) was created using in vitro fertilization for reproductive purposes and was no longer needed for this purpose; and
2) was donated by individuals who sought reproductive treatment ("donor(s)") who gave voluntary written consent for the human embryo to be used for research purposes.

We will be back in the office next week and at that point we can provide you with any further information needed and these assurance in writing.

Thank you once again for your assistance in this submission and please do not hesitate to contact me if there is any further information required ahead of the ACD's working group meeting.

Kind regards, David Collins

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**From:** HESCREGISTRY (NIH/OD) [mailto:hescregistry@mail.nih.gov]
**Sent:** Fri 17/06/2011 1:31 AM
**To:** David Collins; Megan Munsie
**Cc:** HESCREGISTRY (NIH/OD)
**Subject:** RE: New hESC Registry Application Request #2011-ADM-008

Mr. Collins and Ms. Munsie,

If you are willing to have this submission considered by the Advisory Committee to the Director, NIH, under the Section IIB criteria, it would be great if you could let us know in the next few days so we can put it on the agenda for the ACD's working group, which meets later this month. Just so you know, this submission is very similar to a submission from the University of New South Wales for Endeavour-2, which was reviewed by the ACD and is now listed on the NIH Registry.

Please let us know if you have any questions regarding this request.

Sincerely,
Ellen Gadbois

*Ellen L. Gadbois, Ph.D.*
*Office of Science Policy Analysis*
*Bldg 1 Room 218D*
*National Institutes of Health*
*voice: 301-594-2567*
*fax: 301-402-0280*

(34)

Australian Stem Cell Centre

25 October 2011

Dr Ellen L. Gadbois
Office of Science Policy Analysis
National Institutes of Health
Bldg 1 Room 218D

Dear Dr Gadbois,

**Notification of change in signing official for MEL lines registration**

Thank you for your email advising us that the Working Group for Human Stem Cell Eligibility Review has finished its analysis of our application to register MEL-1 and MEL-2 lines on the NIH Human Embryonic Stem Cell Registry.

I am writing to advise that the Australian Stem Cell Centre will cease its operations in the coming months and ownership and responsibility for distribution of the MEL lines has now been transferred to Stem Cells Ltd, a not-for-profit company operating within the University of Queensland. The new Signing Official has been confirmed to me by Stem Cells Limited as being Victoria Turner of the Australian Institute for Bioengineering and Nanotechnology at the University of Queensland (details provided below). Victoria has been informed of developments and provided with correspondence and documents associated with our application.

With respect to distribution, MEL-1 and MEL-2 will continue to be available through Millipore and through Victoria Turner at the University of Queensland (details provided below).

**Ms. Victoria Turner**
Manager - Stem Cell Facility
Australian Institute for Bioengineering & Nanotechnology (AIBN)
Building 75 - Cnr of College and Cooper Road
The University of Queensland
Brisbane
QLD 4072
Australia

T: +61 7 3346 3472
F: +61 7 3346 3886973
E: v.turner@uq.edu.au

Please contact me if there are any further steps needed to transfer this application to Stem Cells Limited or if you require any additional information or clarification on the ownership of the MEL lines and their distribution following ASCC's closure. Thank you again for your assistance in progressing our application to register these lines.

Yours sincerely

Mr David Collins
Chief Executive Officer