Guide to Submission

Reprogenetics
Submission #2011-ACD-005

(1)

hESC Registry Application Database

Detailed Listing for Request #: 2011-ACD-005
June 10, 2011

hESC Registry Application Search Results

Request #: 2011-ACD-005
Status: Pending

Review: ACD

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

Cell Lines: 3
Available: 3

Previous #:
2011-DRAFT-004
2011-ADM-004

Email
Edit
Delete
Switch to ADM

Organization: Reprogenetics, LLC
Org Address: 3 Regent Street, Suite 301, Livingston, NJ 07039
DUNS: 148120780 **Grant Number(s):** n/a
Signing Official (SO): Santiago Munne / 9734365010 / munne@reprogenetics.com
Submitter of Request: Mina Alikani / 9733225043 / mina.alikani@embryos.net
Submitter Comments: The embryos from which RNJ18, 19, and 20 were derived were donated by the same patient during two treatment cycles. Becuse the two cycles took place within one year, the stem cell research consent given at the time of the first cycle was still considered valid.

Line #1: RNJ19
NIH Approval #:
Available: Yes
Embryo from U.S.: Yes
Embryo Donated in Year(s): 6/12/2009
Provider Name: Reprogenetics, LLC
Provider Phone: 9733225043
Provider Email: mina.alikani@embryos.net
Provider URL:
Provider Restrictions: No Restrictions

NIH Restrictions: NIH-funded research with this line is limited to research consistent with the following language from the informed consent document: "...characterization of stem cells from embryos discarded due to genetic defects or other abnormalities and the development of new methods for transforming stem cells into other cell types."

Additional Information: This cell line was derived from an embryo that definitively carried the maternal mutation for the disease, however, the status of the paternal mutation is unknown. The line could be either a compound heterozygote (positive for both the maternal and paternal mutations), or a simple heterozygote (positive for the maternal mutation and negative for the paternal mutation).

Line #2: RNJ20
NIH Approval #:
Available: Yes
Embryo from U.S.: Yes
Embryo Donated in Year(s): 6/12/2009
Provider Name: Reprogenetics, LLC
Provider Phone: 9733225043
Provider Email: mina.alikani@embryos.net
Provider URL:
Provider Restrictions: No Restrictions

NIH Restrictions: NIH-funded research with this line is limited to research consistent with the following language from the informed consent

(2)

document: "...characterization of stem cells from embryos discarded due to genetic defects or other abnormalities and the development of new methods for transforming stem cells into other cell types."

Additional Information: This cell line was derived from an embryo that definitively carried the maternal mutation for the disease, however, the status of the paternal mutation is unknown. The line could be either a compound heterozygote (positive for both the maternal and paternal mutations), or a simple heterozygote (positive for the maternal mutation and negative for the paternal mutation).

Line #3: RNJ18
NIH Approval #:
Available: Yes
Embryo from U.S.: Yes
Embryo Donated in Year(s): 2/25/2009
Provider Name: Reprogenetics, LLC
Provider Phone: 9733225043
Provider Email: mina.alikani@embryos.net
Provider URL:
Provider Restrictions: No Restrictions

NIH Restrictions: NIH-funded research with this line is limited to research consistent with the following language from the informed consent document: "...characterization of stem cells from embryos discarded due to genetic defects or other abnormalities and the development of new methods for transforming stem cells into other cell types."

Additional Information: This cell line was derived from an embryo that definitively carried the maternal mutation for the disease, however, the status of the paternal mutation is unknown. The line could be either a compound heterozygote (positive for both the maternal and paternal mutations), or a simple heterozygote (positive for the maternal mutation and negative for the paternal mutation).

Supporting Documents:
Document 1: (PDF - 01/26/2011) Consent form for donation of embryos - Elements: 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15
Document 2: (PDF - 01/26/2011) DO NOT READ (incorrect protocol #): WIRB study approval to collaborating IVF - Elements: 16
Document 3: (PDF - 01/26/2011) Certificate of approval for the study issued to Reprogenetics by WIRB - Elements: 16
Document 4: (PDF - 01/26/2011) Research protocol approved by WIRB - associated with the consent forms - Elements: 16
Document 5: (PDF - 01/28/2011) Redacted signed consent from donors of embryos for RNJ18, 19, and 20. - Elements: 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15
Document 6: (PDF - 01/28/2011) SO letter - Elements: 16

Administrative Comments: 28 Jan 2011 Submitter Email uploaded by DHannemann 28 Jan 2011

21 Mar 2011 Submitter Email uploaded by DHannemann 22 Mar 2011

21 Mar 2011 Submitter Responses to NIH Questions uploaded by

3

DHannemann 22 Mar 2011

WIRB Approval of Collaboration for IVF Clinic (correct protocol #) - uploaded by DHannemann 22 Mar 2011

WIRB Renewed Approval of Collaboration for Reprogenetics - uploaded by DHannemann 22 Mar 2011

Decision to move submission to ACD Working Group - uploaded by DHannemann 5 Apr 2011

IIB Assurance via email - uploaded by DHannemann 12 Apr 2011

15 Apr submitter response email - uploaded by DHannemann 20 Apr 2011

Notice of Study Closure (15 Apr email attachment) - uploaded by DHannemann 20 Apr 2011

Study Renewal for 2009 - 2010 - uploaded by DHannemann 20 Apr 2011

hESC Characterization Chart - uploaded by DHannemann 21 Apr 2011

Compilation of Submission as of 21 Apr - by DHannemann 21 Apr 2011

NIH restrictions and additional information about lines (per submitter) added by E. Gadbois on 10 June 2011

Administrative Attachments:
Document 1: (PDF - 01/28/2011) 28 Jan Submitter Email
Document 2: (PDF - 03/22/2011) 21 Mar 2011 Submitter Email
Document 3: (DOC - 03/22/2011) 21 Mar 2011 Submitter Responses to NIH Questions
Document 4: (PDF - 03/22/2011) WIRB Approval of Collaboration for IVF Clinic
Document 5: (PDF - 03/22/2011) WIRB Renewed Approval of Collaboration for Reprogenetics
Document 6: (PDF - 04/05/2011) Decision to move submission to ACD Working Group
Document 7: (PDF - 04/12/2011) IIB Assurance email
Document 8: (PDF - 04/12/2011) Questions to Reprogenetics 8 April 2011
Document 9: (PDF - 04/20/2011) 15 Apr Submitter Response Email
Document 10: (PDF - 04/20/2011) Notice of Study Closure (15 Apr email attachment)
Document 11: (PDF - 04/20/2011) Study Renewal for 2009-2010
Document 12: (DOC - 04/21/2011) hESC Line Characterization Chart
Document 13: (PDF - 04/21/2011) Compilation of Submission (as of 21 Apr)

Status History:
Draft: 01/26/2011
Pending: 01/28/2011

Emails Sent: 01/28/2011-New_Applicaton_Email

IIB Assurance

(4)

From: Santiago Munne
To: HESCREGISTRY (NIH/OD); Mina Alikani
Subject: RE: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION
Date: Friday, April 08, 2011 4:29:23 PM

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[1].

Santiago Munné, Ph.D.
President
Reprogenetics
3 Regent Street, Suite 301
Livingston, NJ-07039
munne@reprogenetics.com
Tel. 973-4365010
Fax. 973-9921308
www.reprogenetics.com

From: HESCREGISTRY (NIH/OD) [mailto:hescregistry@mail.nih.gov]
Sent: Friday, April 08, 2011 4:22 PM
To: Mina Alikani; Santiago Munne
Cc: HESCREGISTRY (NIH/OD)
Subject: RE: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION

Dear Dr. Alikani and Dr. Munne,

Thank you for this information. 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. Could Dr. Munne please send an assurance under Section IIB of the Guidelines for the following provisions:

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[1].

Please also address the following issues that arose in the administrative review:

1) In your March 21, 2011 email regarding hESC lines RNJ18, 19, and 20, response 2b states that, ".... These donors had undergone PGD for a single gene defect ..." Please indicate whether the hESC lines RNJ18, 19 and 20 were found to have any known disease-specific mutations or other genetic abnormalities.

2) Also in your March 21, 2011 email, response 4 says that ... the consent form for the donations was signed on 02/24/2009." However, this date differs from the dates provided on the submission cover page:
   - RNJ18 (02/25/2009)
   - RNJ19 (06/12/2009)
   - RNJ20 (06/12/2009)

   Please clarify the dates that the embryo donation consent form was signed for each of these lines.

3) In addition, we note that the WIRB approval document for Dr. Weimer has an expiration date of 05/24/2009. Please provide the WIRB approval document in effect at the time of donation of the embryos from which RNJ19 and RNJ20 were derived.

[redacted]
ENTERED INTO WIRB EXCEL DATABASE
2-20-09 MAS

APPROVED
AS MODIFIED
Jun 13, 2008
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RESEARCH SUBJECT INFORMATION AND CONSENT FORM
Clinically Unusable Embryos

(5)

TITLE:	Human Embryonic Stem Cell Research Using Donated Human Embryos
PROTOCOL NO.:	None WIRB® Protocol #20041976
SPONSOR:	Reprogenetics, LLC Livingston, New Jersey United States
INVESTIGATOR:	Klaus Wiemer, Ph.D. Suite 220 12333 NE 130th Lane Kirkland, Washington 98034 United States
SITE(S):	Northwest Center for Reproductive Sciences, LLC Suite 220 12333 NE 130th Lane Kirkland, Washington 98034 United States
STUDY-RELATED PHONE NUMBER(S):	Klaus Wiemer, Ph.D. 425-284-4400

This consent form may contain words that you do not understand. Please ask the study Investigator or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

STUDY INFORMATION

Reprogenetics in collaboration with the in-vitro fertilization center (IVF center) is developing new, more efficient ways of isolating, characterizing, and freezing human embryonic stem cells, and generating new human embryonic stem cell lines.

Embryonic stem cells can be isolated from embryos around the fifth day of development. The embryo is destroyed in the process. These stem cells have the unique ability to continue to divide indefinitely and, under certain conditions, they can be turned into any kind of specialized

human cell, such as liver cells, heart cells, pancreatic cells, or nerve cells. For this reason, embryonic stem cells can be used to study, and possibly one day help treat, diseases or injuries that have caused patients' specialized cells to die or become damaged – diseases and injuries such as Parkinson's disease, heart disease, diabetes and spinal cord injury.

During the course of your current attempt at in-vitro fertilization (IVF) and/or IVF with pre-implantation genetic diagnosis (PGD), one or more of your embryos may be identified as unsuitable for transfer or cryopreservation based on chromosomal and/or other abnormalities. You are invited to provide any such embryos to this research project. Participation is completely voluntary and will in no way affect the normal progress of your attempt at IVF or IVF/PGD, including the possibility of later replacement of thawed embryos from this attempt, nor will it affect your chances of pregnancy. This research study will not begin until each of the steps necessary to identify any individual embryo as clinically unusable has been completed.

HOW EMBRYOS WILL BE USED

The clinically unusable embryos provided by you will be used in one or more of the following projects (rather than being discarded):

- The development of novel methods to isolate, characterize, and freeze embryonic stem cells.
- The development of culture techniques to grow many stem cells from one or a few embryonic cells.
- Isolation and characterization of stem cells from embryos discarded due to genetic defects or other abnormalities.
- The development of new methods for transforming stem cells into other cell types.

None of the clinically unusable embryos will be used to produce a baby or a pregnancy. The embryos provided by you may give rise to embryonic stem cells that may be stored for many years. These stem cells may be genetically normal or genetically abnormal. Both categories of stem cells are of fundamental scientific and biomedical interest.

The methods used in these studies include new processes of cell manipulation and culture of embryonic cells. Any clinically unusable embryos provided by you may thus be manipulated and cultured, or may be stored, in a frozen state, for later studies. These possibilities also apply to any embryonic stem cells isolated. If embryonic stem cells are obtained from your clinically unusable embryos, they could give rise to different cell types, such as pancreatic cells or neural cells. Frozen-thawed stem cells may be used in research as described above.

The clinically unusable embryos provided by you, or any cells isolated from, or developed from those embryos, will not ever be used to impregnate another woman or to assist any individual or couple in any way to become pregnant.

RISKS

Participation in these studies by providing clinically unusable embryos will cause no additional physical discomfort whatsoever during the conduct of your procedure, nor will your chances of becoming pregnant be affected in any way.

BENEFITS

You will not receive any direct personal benefits from participation at this time; however, it is possible that future patients will benefit from the knowledge gained from these studies.

COSTS

There are no added costs related to your participation in this study.

ALTERNATIVES

This is not a treatment study. Your alternative is to decline to participate in this study.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study Investigator must get your authorization (permission) to use or give out any health information that might identify you.

What information may be used and given to others?
If you choose to be in this study, the study Investigator will get personal information about you. This may include information that might identify you and information about your health.

Who may use and give out information about you?
Information about your health may be used and given to others by the study Investigator and collaborators. They might see the research information during and after the study.

Who might get this information?
Your information may be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor.

Information about you and your health which might identify you may be given to:

- The U.S. Food and Drug Administration (FDA) , Washington, D.C.
- Department of Health and Human Services (DHHS) agencies, Washington, D.C.
- Governmental agencies in other countries
- The Center for Disease Control (CDC)
- Society for Assisted Reproduction (SART)
- The Western Institutional Review Board® (WIRB®)

Why would this information be used and/or given to others?
Information about you and your health that might identify you may be given to others to carry out the research study. Personnel/consultants associated with the Sponsor may use this information to evaluate the results of the study.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by WIRB®. WIRB is a group of people who perform independent review of research as required by regulations.

What if I decide not to give permission to use and give out my health information?
By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to participate in this research by providing your clinically unusable embryos.

May I withdraw or revoke (cancel) my permission to use and give out my health information?
This permission will be good until December 31, 2050.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study Investigator. If you withdraw your permission, you will not be able to participate in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

(9)

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AS MODIFIED
Jun 13, 2008
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VOLUNTARY PARTICIPATION/WITHDRAWAL

Your decision whether or not to participate will not change your future relations with the Northwest Center for Reproductive Sciences, LLC and the treatment you now have in this IVF center. Your participation is voluntary and your refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to participate, you are free to discontinue participation at any time before the embryos are used in the study. However, once the embryos are destroyed in the stem cell collection process or any of the related methods, you will not be able to change your mind or request that any of the collected stem cells be removed from this research project.

Your participation in this study may be stopped at any time by the study investigator or the sponsor without your consent for any of the following reasons:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan;
- or for any other reason.

DISCLOSURE OF RESEARCHERS' POTENTIAL FINANCIAL INTERESTS

In addition to their scientific interests in this research project, the individuals conducting this stem cell study might profit financially from the research. There may be current or potential financial benefits to the researchers, the participating institution(s), and other research institutions or researchers arising from discoveries made through this research project and the stem cells collected from your embryos.

If you are undergoing fertility treatment, it is important that your doctor informs you of any personal benefits s/he may gain by your agreement to provide embryos for this project.

The person who has been authorized to provide you with information may also have a personal vested interest in this research project. Please feel free to ask your doctor if you have any questions about this.

QUESTIONS

If you have any questions concerning this study, contact the study Investigator, Klaus Wiemer, Ph.D., who can be reached at 206-262-1101.

If you have questions about your rights as a research subject, you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789.

WIRB is a group of people who perform independent review of research.

(10)

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Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to participate in this study, you will receive a copy of this signed and dated consent form.

SOURCE OF FUNDING

Funding for this research study will be provided by Reprogenetics. Reprogenetics may receive governmental or non-governmental grants for this project.

CONSENT

I/We have read the entire consent form, or it has been read to us. All questions regarding this consent form or this study have been answered to my/our satisfaction. I/We agree that stem cells may be developed from my/our clinically unusable embryos which would otherwise have been discarded.

I/we authorize the use and disclosure of my/our health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I/we have not waived any of the legal rights which I/we otherwise would have as a subject in a research study.

Signed: name female partner [redacted] Signature [redacted]

Signed: name male partner [redacted] Signature [redacted]

Witnessed: name [redacted] Signature [redacted]

Person Conducting Informed Consent Discussion: name Shanita Miller Signature [redacted]

Date: 2/24/09

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AS MODIFIED
Jun 13, 2008
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---------- **Use the following only if applicable** ----------

If this consent form is read to the subject(s) because the subject(s) are unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject(s). The subject(s) freely consented to participate in the research study.

Impartial Witness: name_____ Signature_____

Date:_____

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

(12)

Revised Research Protocol (WIRB 20041976)

Date: 02/15/2008

Title: Human Embryonic Stem Cell Research Using Donated Human Embryos

Sponsor: Reprogenetics, LLC. Principal Investigator: Santiago Munné, Ph.D.

Background of reason for research:

The inner cell mass of the human blastocyst contains cells that are pluripotent. When they are isolated from surrounding trophectoderm and placed under the right conditions in vitro, they are able to differentiate into all cell types in the adult body. These human embryonic stem cells (hESCs) can be propagated indefinitely and used as a source of cells and tissues for transplantation, to assist in developing and testing new drugs, and to study disease and its progression. The main source of hESCs currently is surplus frozen human embryos donated by patients undergoing in vitro fertilization (IVF) for infertility treatment.

Reprogenetics is engaged in generating new embryonic stem cell lines from different categories of human embryos as well as developing new, more efficient ways to characterize and cryopreserve human embryonic stem cells.

Scientists at Reprogenetics have shown that embryos classified by embryologists as clinically unusable, i.e., unsuitable for transfer to the patient or cryopreservation for future thaw and transfer to the patient, and embryos classified after Preimplantation Genetic diagnosis (PGD) as abnormal are potential sources of stem cells. Others have shown that potentially normal frozen-thawed embryos are also a potent source of stem cells.

Objective(s) of research:

The primary objectives of this research are to 1) derive genetically normal human embryonic stem cell lines from morphologically and/or genetically abnormal embryos; 2) derive genetically abnormal human embryonic stem cell lines from genetically abnormal embryos; and 3) derive genetically normal human embryonic stem cell lines from morphologically normal frozen-thawed human embryos. Further objectives of the research are to develop safe and efficient cryopreservation protocols for long-term preservation and storage of human embryonic stem cells and to develop fast and reliable methods for identification and characterization of human embryonic stem cells.

The embryos to be used for the research are donated by patients undergoing infertility treatment at in vitro fertilization clinics which are clients of Reprogenetics.

Background of investigational article (if appropriate), including known risks/discomforts (may be in Investigator's Brochure):

There will be no extra discomfort to the patient; the research is conducted on in vitro generated embryos donated by patients for research.

FDA status of drug/biologic/device [approved, investigational, IDE#, 510(k), NSR, etc.]:
None.

Results from previous, related research.
The attached publication describes background experiments conducted at Saint Barnabas Medical center; the protocols were previously approved by the Internal Review Board of Saint Barnabas Medical center. The research proposed here is to be done with a number of other private IVF clinics many of which do not have their own Internal Review Boards.

Description of research design, including a discussion of the appropriateness of the methods.
We have proposed two methods to produce normal stem cell lines from abnormal embryos. These methods are described in detail in Alikani and Munné (Stem Cell Reviews, 2005; attached). Some chromosomally abnormal embryos will give rise to abnormal stem cells only; these are also of great scientific and clinical interest and may be used as models for studying genetic diseases or developing therapeutic strategies. Protocols for derivation of human embryonic stem cells have been published by others and will be followed without substantial modification during our studies.

Number of subjects and distribution (if applicable)
The efficiency of deriving stem cell lines from both abnormal and potentially normal embryos remains low, although we and others are actively investigating more efficient derivation and expansion methods. Our aim is to derive at least one cell line from each commonly occuring chromosome abnormality, as well as 100 normal stem cell lines. That is about 150 stem cell lines, or up to 3000 embryos assuming an efficiency rate of 5%, although this efficiency rate should improve over time and when potentially normal embryos are used. The number of embryos donated by patients varies greatly so it is difficult to accurately estimate the number of patients needed to donate embryos.

Inclusion and Exclusion Criteria (Age [if limited], Gender [if limited, reasons for limitations]
There will be no exclusions based on race, age, or sex.

Informed consent or surrogate consent [don't address surrogate, assume none]
Proposed revisions to WIRB consent form are attached.

Schedule or flow chart of study visits/procedures
WIRB approved consent forms will be sent to IVF centers participating in the research. The IVF centers will send embryos donated for research to Reprogenetics either in a fresh state, via portable incubators sent to the clinic by Reprogenetics or the donated embryos may be frozen by the clinics, and sent to Reprogenetics in a liquid nitrogen shipper at a later time. Once at Reprogenetics, the donated embryos are processed according to established protocols for derivation and expansion of embryonic stem cell lines and further studies.

Potentially normal frozen embryos that are no longer wanted by patients, following their explicit consent, will be sent to Reprogenetics in liquid nitrogen shippers either by the IVF center or the storage facility where they are stored.

Stem cell lines will be validated, characterized, sub-cloned, and frozen for future use by Reprogenetics or other researchers or companies.

Serious Adverse Event (SAE) management
Participation in these studies will cause no SAE for the patients donating the embryos.

Provisions for protecting subject privacy.
Patient name, social security number, or other identifying information will not be shared with any other entity outside Reprogenetics. The cell lines will be identified with sequential numbers which are not related to the donor patient's identification and will not identify the donor. Our written and electronic records where patient names and embryo numbers are recorded are secured as is done routinely for all client patients of Reprogenetics during clinical preimplantation genetic diagnosis.

Information for subjects: payment for participation, compensation for injury, extra costs to subjects resulting from participation, extra costs to third-party payers because of a subject's participation.
There will not be any payment for participating in the study; no injuries are expected. There are no extra costs for participating. However, there will be significant cost for the IVF centers for collecting, freezing, and shipping the material to Reprogenetics. Reprogenetics will reimburse such costs to the clinics.

Consent form: submitted, or request for WIRB to write (fee)
A revised consent form is attached.

Statistics (how will data be analyzed - is the sample size sufficient to be statistically significant?)
Data will be kept in spreadsheets and stored electronically. Extensive statistical analyses are not required at this time.

WIRB®

(360) 252-2500
1-800-562-4789
FAX: (360) 252-2498

Western Institutional Review Board ®

Western International Review Board®

3535 SEVENTH AVENUE, SW, OLYMPIA, WA 98502-5010
P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Santiago Munne Ph.D.
Suite 301
3 Regent Street
Livingston, New Jersey 07039

BOARD ACTION DATE: 4/22/2008
PANEL: 4
STUDY APPROVAL EXPIRES: 2/10/2009
STUDY NUM: 1064001
WIRB PRO NUM: 20041976
INVEST NUM: 111507
WO NUM: 1-487119-1
CONTINUING REVIEW: Annually
SITE STATUS REPORTING: Quarterly

SPONSOR: Reprogenetics, LLC
PROTOCOL NUM: None
AMD. PRO. NUM:
TITLE:
Human Embryonic Stem Cell Research Using Donated Human Embryos

APPROVAL INCLUDES:

Consent Form - Clinically Unusable Embryos [S1]
Consent Form - Frozen Embryos [S0]

WIRB APPROVAL IS GRANTED SUBJECT TO:

RE-CONSENTING INSTRUCTIONS: All subjects who will be enrolled in the future for this study must sign the most current WIRB-approved consent form(s).

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Full AAHRPP Accreditation

Theodore D. Schultz, J.D., Chairman

4/24/2008
(Date)

This document electronically reviewed and approved by Orive, Otto on 4/24/2008 7:22:29 AM PST. For more information call Client Services at 1-360-252-2500

WIRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:

- Reprogenetics, LLC, Suite 301, 3 Regent Street, Livingston, New Jersey 07039

If the PI has an obligation to use another IRB for any site listed above and has not submitted a written statement from the other IRB acknowledging WIRB's review of this research, please contact WIRB's Client Services department.

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate.

    a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.

    b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB.

    c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

3. Obtain pre-approval from WIRB for any planned deviations that could adversely affect the safety or welfare of subjects, or the integrity of the research data and any changes in the research activity. The only exception is when changes are necessary to eliminate apparent immediate hazards to subjects. Immediately report to WIRB any such emergency changes implemented.

4. Promptly report to WIRB any new information that may adversely affect the safety of the subjects or the conduct of the trial.

    a. Report to WIRB all adverse events that are unanticipated and possibly related, within 10 days of the investigator becoming aware of them.

    b. Promptly report to WIRB other unanticipated problems involving risks to human subjects or others. These events do not readily fit the formal definition of Adverse Event, but could impact human subject safety and/or rights. Examples include theft of a computer containing private identifiable subject information, or study staff getting ill from inhaling a study agent.

    c. Provide reports to WIRB concerning the progress of the research, when requested.

5. Report to WIRB any unplanned protocol variance that could adversely affect the safety or welfare of subjects, or the integrity of the research data, within 10 days of becoming aware of the variance. Other unplanned variances may be recorded on a log and submitted with continuing review reports.

Federal regulations require that WIRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WIRB. These reports must be returned even though your study may not have started.

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Contact	**Company Name**
Santiago Munne Ph.D.	Reprogenetics, LLC

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1-800-562-4789
FAX: (360) 252-2498

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Western International Review Board®

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P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Klaus Wiemer Ph.D.
Suite 220
12333 NE 130th Lane
Kirkland, Washington 98034

BOARD ACTION DATE: 6/13/2008
PANEL: 4
STUDY APPROVAL EXPIRES: 5/24/2009
STUDY NUM: 1067751
WIRB PRO NUM: 20041976
INVEST NUM: 114800
WO NUM: 1-496813-1
CONTINUING REVIEW: Annually
SITE STATUS REPORTING: Quarterly

SPONSOR: Reprogenetics, LLC
PROTOCOL NUM: None
AMD. PRO. NUM:
TITLE:
Human Embryonic Stem Cell Research Using Donated Human Embryos

APPROVAL INCLUDES:
Revised Protocol (02-15-2008)
Consent Form - Clinically Unusable Embryos [S1]
Consent Form - Frozen Embryos [S0]

WIRB APPROVAL IS GRANTED SUBJECT TO:
RE-CONSENTING INSTRUCTIONS: All subjects who will be enrolled in the future for this study must sign the most current WIRB-approved consent form(s).

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Full AAHRPP Accreditation

Theodore D. Schultz, J.D., Chairman

6/23/2008
(Date)

This document electronically reviewed and approved by Reese, Owen on 6/23/2008 7:42:02 AM PST. For more information call Client Services at 1-360-252-2500

WIRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:

- The Northwest Center for Reproductive Sciences, LLC, 12040 Northeast 128th Street, Kirkland, Washington 98034

If the PI has an obligation to use another IRB for any site listed above and has not submitted a written statement from the other IRB acknowledging WIRB's review of this research, please contact WIRB's Client Services department.

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate.

    a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.

    b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB.

    c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

3. Obtain pre-approval from WIRB for any planned deviations that could adversely affect the safety or welfare of subjects, or the integrity of the research data and any changes in the research activity. The only exception is when changes are necessary to eliminate apparent immediate hazards to subjects. Immediately report to WIRB any such emergency changes implemented.

4. Promptly report to WIRB any new information that may adversely affect the safety of the subjects or the conduct of the trial.

    a. Report to WIRB all adverse events that are unanticipated and possibly related, within 10 days of the investigator becoming aware of them.

    b. Promptly report to WIRB other unanticipated problems involving risks to human subjects or others. These events do not readily fit the formal definition of Adverse Event, but could impact human subject safety and/or rights. Examples include theft of a computer containing private identifiable subject information, or study staff getting ill from inhaling a study agent.

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Klaus Wiemer Ph.D.	Northwest Center for Reproductive Sciences, LLC

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P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Santiago Munne Ph.D.
Suite 301
3 Regent Street
Livingston, New Jersey 07039

BOARD ACTION DATE: 2/5/2009
PANEL: 4
STUDY APPROVAL EXPIRES: 2/10/2010
STUDY NUM: 1064001
WIRB PRO NUM: 20041976
INVEST NUM: 111507
WO NUM: 1-530407-1
CONTINUING REVIEW: Annually
SITE STATUS REPORTING: Quarterly

SPONSOR: Reprogenetics, LLC
PROTOCOL NUM: None
AMD. PRO. NUM:
TITLE:
Human Embryonic Stem Cell Research Using Donated Human Embryos

APPROVAL INCLUDES:
Study and Investigator for an additional continuing review period. This approval expires on the date noted above.

WIRB APPROVAL IS GRANTED SUBJECT TO:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Full AAHRPP Accreditation

Theodore D. Schultz, J.D., Chairman

2/5/2009
(Date)

This document electronically reviewed and approved by Reese, Owen on 2/5/2009 6:50:27 PM PST. For more information call Client Services at 1-360-252-2500

WIRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:

- Reprogenetics, LLC, Suite 301, 3 Regent Street, Livingston, New Jersey 07039

If the PI has an obligation to use another IRB for any site listed above and has not submitted a written statement from the other IRB acknowledging WIRB's review of this research, please contact WIRB's Client Services department.

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6. Ensure that prior to performing study-related duties each member of the research study team has had training in the protection of human subjects appropriate to the processes required in the approved protocol.

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Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Klaus Wiemer Ph.D.
Suite 220
12333 NE 130th Lane
Kirkland, Washington 98034

BOARD ACTION DATE: 4/30/2009
PANEL: 4
STUDY APPROVAL EXPIRES: 5/24/2010
STUDY NUM: 1067751
WIRB PRO NUM: 20041976
INVEST NUM: 114800
WO NUM: 1-548324-1
CONTINUING REVIEW: Annually
SITE STATUS REPORTING: Quarterly

SPONSOR: Reprogenetics, LLC
PROTOCOL NUM: None
AMD. PRO. NUM:
TITLE:
Human Embryonic Stem Cell Research Using Donated Human Embryos

APPROVAL INCLUDES:
Study and Investigator for an additional continuing review period. This approval expires on the date noted above.

WIRB APPROVAL IS GRANTED SUBJECT TO:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
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Full AAHRPP Accreditation

Robert A Taylor DO for
Theodore D. Schultz, J.D., Chairman

5/5/2009
(Date)

This document electronically reviewed and approved by Taylor, Robert on 5/5/2009 6:44:14 AM PST. For more information call Client Services at 1-360-252-2500

WIRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:

- The Northwest Center for Reproductive Sciences, LLC, 12040 Northeast 128th Street, Kirkland, Washington 98034

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Santiago Munne Ph.D.	Reprogenetics, LLC
Klaus Wiemer Ph.D.	Northwest Center for Reproductive Sciences, LLC

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(360) 252-2500 I 1-800-562-4789 I FAX (360) 252-2498

Sasha Sadowy
Suite 301
3 Regent Street
Livingston, New Jersey 07039

January 8, 2010

SUBJECT: CONFIRMATION OF CLOSURE AND CONCLUSION OF IRB OVERSIGHT

Principal Investigator: Klaus Wiemer Ph.D.
Sponsor: Reprogenetics, LLC
Sponsor Pr. No.: None

WIRB Study No.: 1095220
WIRB Pr. No.: 20060680

Western Institutional Review Board (WIRB) acknowledges receipt of a study closure notification for the above-referenced study. Accordingly, WIRB has closed the above-referenced study effective January 8, 2010. WIRB oversight of the investigator's conduct of this protocol has ended.

WIRB closes studies when it receives notification of all of the following (Study Closure form is available at www.wirb.com).

1. All subjects have finished their final visits and follow-up,
2. The sponsor or the sponsor representative has indicated the study is closed at the site, and
3. If the study was conducted under a Federalwide Assurance (FWA), all data analysis at the site is completed.

Sites must have active on-going IRB approval in order to enroll subjects, perform any study interventions, collect/report new data, and/or, if under an FWA, analyze identified data at the site.

Please note, sites that have only completed enrollment (i.e., closed to accrual) cannot be closed if data relating to subjects is still being collected.

If you believe that this study closure was requested in error, please contact us immediately to avoid a substantial gap in IRB oversight for the above-referenced research at Klaus Wiemer Ph.D.'s site.

cc : Klaus Wiemer Ph.D., Northwest Center for Reproductive Sciences, LLC
WIRB Study File

(24)

From: Mina Alikani [mailto:mina.alikani@embryos.net]
Sent: Friday, January 28, 2011 12:46 PM
To: Gadbois, Ellen (NIH/OD) [E]
Cc: Santiago Munne
Subject: Additional cell lines submitted

Dear Dr. Gadbois,

I have just completed submission of five additional cell lines on behalf of Reprogenetics for administrative review. I would like to add the following:

First, cell lines RNJ11 and RNJ12 were derived from donations by IRMS patients (like RNJ7) but these donor patients agreed with and signed a new consent form that we believe fulfills the requirements of section IIA. I submitted the redacted signed reconsent forms but only included the signature page. I am attaching the full consent here in case that is a problem.

Secondly, cell lines RNJ18-20 are from a donation made by a patient undergoing treatment in a collaborating IVF center, Northwest Center for Reproductive Sciences, in Kirkland, Washington. The collaboration was acknowledged and approved through WIRB and all the supporting paperwork was submitted. This submission should also fulfill section IIA requirements. *

As before, if there are any questions or concerns regarding these submissions, please do not hesitate to contact me.

Best wishes,

Mina Alikani, Ph.D.

15 March 2011 - Email Attachment

(25)

Table 1. Summary of Characteristics of new hES Cell Lines Derived by Reprogenetics.

Embryo Source	IVF Clinic	IVF Clinic	IVF Clinic	IVF Clinic	IVF Clinic	IVF Clinic
Category	**Fresh**	**Fresh**	**Fresh**	**Fresh**	**Fresh**	**Fresh**
Status	Discarded	Discarded	Discarded	Discarded	Discarded	Discarded
PGD	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Cell Line Characteristics						
Highest Passage #	50	45	48	25	24	21
Human Feeder Cells	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Karyotype/FISH	Normal (46,XY)	Normal (46, XX)	Normal (46, XY)	FISH (XX)	FISH (XX)	FISH (XX)
Stem Cell Markers:						
SSEA-1	-	-	-	-	-	-
SSEA-4	+	+	+	+	+	+
TRA 1-60	N/A	N/A	N/A	N/A	N/A	N/A
TRA 1-81	+	+	+	+	+	+
Oct-4	+	+	+	+	+	+
Nestin	-	-	-	-	-	-
Sox2	+	+	+	+	+	+
Straws Cryopreserved	**37**	**27**	**9**	**17**	**18**	**19**

Table 2. Summary of Characteristics of New hES Cell Lines Derived by Reprogenetics.

Human Embryonic Stem Cell Lines Derived by Reprogenetics, LLC						
Cell Line Code	**RNJ13**	**RNJ14**	**RNJ15**	**RNJ16**	**RNJ17**	**RNJ18**
Embryo						
Source	IVF Clinic	IVF Clinic	IVF Clinic	IVF Clinic	IVF Clinic	IVF Clinic
Category	Fresh	Fresh	Fresh	Fresh	Fresh	Fresh
Status	Discarded	Discarded	Discarded	Discarded	Discarded	Discarded
PGD	N/A	N/A	Monosomy 20 Trisomy 22 (XY)	Trisomy 15, 22 (XX)	Complex Abnormal (XXX)	Single Gene Defect
Cell Line Characteristics						
Highest Passage #	19	21	15	18	8	16
Human Feeder Cells	Yes	Yes	Yes	Yes	Yes	Yes
FISH/PCR	FISH Normal (XX)	FISH Normal (XY)	FISH Normal (XY)	Trisomy 22 (XX)	FISH Normal (XX)	SGD Nephrotic Syndrome
Stem Cell Markers:						
SSEA-1	-	-	-	-	N/A	-
SSEA-4	+	+	+	+	N/A	+
TRA 1-60	N/A	N/A	N/A	N/A	N/A	N/A
TRA 1-81	+	+	+	+	N/A	+
Oct-4	+	+	+	+	N/A	+
Nestin	-	-	-	-	N/A	-
Sox2	+	+	+	+	N/A	+
Straws Cryopreserved	19	18	7	10	2	17

Submitter Response Email

(27)

Monday, March 21, 2011
From Reprogenetics, LLC
Re: Cell Lines RNJ18, 19, 20
Presented by Mina Alikani, Ph.D.

Response to questions forwarded to Reprogenetics on 11 February 2011:

1. Can you please confirm that we have the correct version of the protocol and the embryo donation consent form (i.e. those versions that were in effect at the time of donation of these embryos)?

Yes, you do have the correct version of the protocol and the embryo donation consent form. This protocol was sent to WIRB on 3 February 2008 and it was approved in April of that year. The protocol remains valid until closure of the study or until further revisions are submitted. The consent form associated with the protocol was approved in June of 2008 and it would be valid until study closure. Annual reports of course are required in order to keep the study open and those have been submitted as required.

2. a. Please explain Dr. Wiemer's role: he is listed as an investigator on the consent form, but Dr. Munne is listed as the principal investigator on the protocol.

Dr. Wiemer was the Director of the IVF Laboratory at Northwest Center for Reproductive Sciences (NWCRS), LLC, at the time of this donation. This center is among the IVF centers that are approved by the WIRB as research collaborators of Reprogenetics. Thus even though Dr. Munne remains the principle investigator and the sponsor of the research, the collaborating center has a designated person (in this case, Dr. Wiemer) who acts as a coordinator, i.e., submits required data to WIRB for annual study renewal, and coordinates shipment of clinically unusable embryos.

b. Please explain whether any members of the research team were involved in reproductive treatment of the embryo donors.

No. Dr. Wiemer was the laboratory Director but he played no role in the research, except for coordinating shipment of abnormal embryos, nor did he benefit from the research. However, these donors had undergone PGD for a single gene defect and sample biopsied blastomeres of their embryos were sent to Reprogenetics for analysis. NWCRS was a client of Reprogenetics at the time of this donation. Dr. Wiemer is no longer working at NWCRS.

c. Please clarify where the lines were derived (Reprogenetics is listed as the sponsor on the protocol, but the Northwest Center for Reproductive Sciences is listed as the site on the consent form).

The lines were derived at Reprogenetics, LLC. The patients underwent IVF treatment at the Northwest Center for Reproductive Sciences. The SITE refers to the site where the

embryos were generated. The consent specifies that the study is conducted by Reprogenetics (in collaboration with the IVF center).

3. Please confirm that the cell lines were derived from blastocyst-stage embryos. Note that the Guidelines define hESCs as "cells that are derived from the inner cell mass of blastocyst stage human embryos."

Yes. The lines were derived from isolated inner cell masses of blastocysts. The general methods have been described in one published paper (Moore et al., 2010).

4. We note that the embryo donation dates all occurred during a time period during which neither of the Western IRB study approvals provided were in effect: please address that issue.

With sincere apologies for this confusion, two documents were sent to you by error:
1) The Certificate of Approval for Reprogenetics was not the most recent (this is renewed annually) and
2) The Certificate of approval for Northwest Center for Reproductive Sciences refers to the wrong protocol number. Please note that the WIRB protocol number for this study is 20041976. The correct certificate is attached along with this document.

For further clarification, we are including the table below. WIRB study approvals were in effect at the time of donation of these embryos. Please note that the consent form for the donations was signed on 02/24/2009. The date of the general IVF consent form is not known at this time but we can request that information, along with a redacted copy of that consent – if necessary by contacting the physicians at NWCRS.

	Protocol Revision Approval	Consent Form Approval	Certificate of Approval (Reprogenetics)	Certificate of Approval (NWCRS)
Date issued	02/15/2008	06/13/2008	04/22/2008	06/13/2008
Valid until			02/10/2010	05/24/2009

5. Please specify how the following requirement from the NIH Guidelines is met: "During the consent process, donor(s) were informed of the following:… 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."

Under the section DISCLOSURE OF RESEARCHERS' POTENTIAL FINANCIAL INTERESTS on page 5 of the consent form, it is stated,

"In addition to their scientific interests in this research project, the individuals conducting this stem cell study might profit financially from the research. There may be

current or potential financial benefits to the researchers, the participating institution(s), and other research institutions or researchers arising from discoveries made through this research project and the stem cells collected from your embryos.

If you are undergoing fertility treatment, it is important that your doctor informs you of any personal benefits s/he may gain by your agreement to provide embryos for this project.

The person who has been authorized to provide you with information may also have a personal vested interest in this research project. Please feel free to ask your doctor if you have any questions about this."

Under the section, BENEFITS on page 3 of the consent form, it is stated,
"You will not receive any direct personal benefits from participation at this time; however, it is possible that future patients will benefit from the knowledge gained from these studies."

These paragraphs were directly taken from the ISSCR sample consent form for embryo donation.

6. Please specify how the following requirement from the NIH Guidelines is met: "During the consent process, donor(s) were informed of the following:... Whether information that could identify the donor(s) would be available to researchers." .... So did in fact Reprogenetics have information identifying donors, and if so, were embryo donors informed of this?

Reprogenetics clinical team was aware of the patient's name since PGD for this case was performed by Reprogenetics. Reprogenetics was also aware of the development history of the embryos but Reprogenetics does not send any patient identifying information to any other entities. As it is the policy of our group, researchers must see a signed research consent using any embryos in research. The embryo donors were informed about this in the consent, as it specifies, on page 3, under the section, "Who might get this information?"

"Your information may be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor."

(30)

From: Mina Alikani
To: HESCREGISTRY (NIH/OD)
Cc: Santiago Munne
Subject: Re: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION
Date: Friday, April 15, 2011 4:28:20 PM

Thank you, Dr. Gadbois. As I noted, it is my understanding that the donor couple was aware that their initial consent was still valid and that this was confirmed verbally with them. I will be contacting WIRB regarding additional paperwork.

Best wishes,

Mina Alikani, Ph.D.

On 4/15/11 3:36 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:

Dr. Alikani,

Thank you for this information. For our records, I'm noting that you told us today that the donors verbally confirmed for Dr. Wiemer that they still wished to donate embryos in the second treatment cycle. We also look forward to whatever information you can provide on the status of WIRB approval after 5/24/2009.

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

From: Mina Alikani [mailto:mina.alikani@embryos.net]
Sent: Friday, April 15, 2011 1:42 PM
To: HESCREGISTRY (NIH/OD); Santiago Munne
Subject: Re: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION

Dear Dr. Gadbois,

Please see our answers below.

Best wishes,

Mina Alikani, Ph.D.

On 4/8/11 10:22 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:
Dear Dr. Alikani and Dr. Munne,

Thank you for this information. 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. Could Dr. Munne please send an assurance under Section IIB of the Guidelines for the following provisions:

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[1] <#_ftn1> .

Sent by Dr. Munne.

Please also address the following issues that arose in the administrative review:

1) In your March 21, 2011 email regarding hESC lines RNJ18, 19, and 20, response 2b states that, ".... These donors had undergone

PGD for a single gene defect ..." Please indicate whether the hESC lines RNJ18, 19 and 20 were found to have any known disease-specific mutations or other genetic abnormalities.

Yes. All three lines have been confirmed to have the genetic mutation for which PGD was performed; the mutation causes congenital nephrotic syndrome. *

2) Also in your March 21, 2011 email, response 4 says that ... the consent form for the donations was signed on 02/24/2009." However, this date differs from the dates provided on the submission cover page:

- RNJ18 (02/25/2009)
- RNJ19 (06/12/2009)
- RNJ20 (06/12/2009)

Please clarify the dates that the embryo donation consent form was signed for each of these lines.

A WIRB consent form was signed by the donor couple on 02/24/2009 which remained valid for one year; they underwent two treatment cycles. Following the first cycle, their abnormal embryos were donated and one cell line was established (RNJ18) and following the second cycle, their abnormal embryos were again donated and two cell lines were established (RNJ19 & 20). I believe that the dates referenced above are the dates the abnormal embryos were received by Reprogenetics but I need to confirm this information.

3) In addition, we note that the WIRB approval document for Dr. Weimer has an expiration date of 05/24/2009. Please provide the WIRB approval document in effect at the time of donation of the embryos from which RNJ19 and RNJ20 were derived.

I believe the certificate we sent is the last one we have available. This study was closed on 8 January, 2010 after a study closure report was submitted to the WIRB by Dr. Wiemer on 12/31/09. The study closure confirmation sent by WIRB is enclosed.

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

From: Mina Alikani [mailto:mina.alikani@embryos.net]
Sent: Monday, March 21, 2011 3:33 PM
To: HESCREGISTRY (NIH/OD)
Cc: Santiago Munne
Subject: Re: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION

Dear Diane,

This is in reference to cell lines RNJ 18, 19, and 20. Attached, please find a letter listing our responses to the questions that were forwarded to us on 2/11/11 (Dr. Gadbois' original e-mail also attached). In addition, two updated certificates of approval – one for Reprogenetics and another for NWCRS – which were omitted by error in the original submission are also attached.

I hope this addresses all the issues discussed in your recent e-mails but if I have missed anything or if other questions or concerns should arise, please do not hesitate to contact me.

Sincerely,

Mina

Mina Alikani, Ph.D.

On 3/17/11 12:20 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:
Dear Dr. Alikani,

Thank you for this additional information. We look forward to also receiving responses to the other emails (3) I sent on 3/15/2010. To help us with our records, please send us separate responses for each of these emails.