

## Guide to Submission

### Reprogenetics Submission #2010-ACD-006 (as of 22 April 2011)

Submission Coversheet .....	p. 1
IIB Assurance .....	p. 4
Reprogenetics Letter of Explanation .....	p. 5
Embryo Donation and Research Consent for RNJ7 (redacted) .....	p. 6
IVF Treatment Consent .....	p. 9
Modified Research Consent and Protocol (2004).....	p. 16
• Consent (NOT USED).....	p. 23
IRB Committee Approvals and Renewals (2002-2009).....	p. 28
• Approval of Consent and Protocol Modifications (2004) .....	p. 29
Materials included in Initial Working Group Review:	
• Embryo Donation and Research Consent - <i>Incorrect Version</i> ; used in initial review by WG .....	p. 38
• Research Protocol - <i>Incorrect Version</i> ; used in initial review by WG .....	p. 41
• Re-Consent: DONOR DID NOT SIGN/RETURN.....	p. 46
Correspondence and Other Information.....	p. 52

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## hESC Registry Application Database

Detailed Listing for Request #: 2010-ACD-006

April 22, 2011

## hESC Registry Application Search Results

<p><b>Request #:</b> 2010-ACD-006  <b>Status:</b> Pending</p> <p><b>Review:</b> ACD</p> <p><b>Assurance:</b> Yes (Section II(B))  <b>Certification:</b> Yes  <b>Authority:</b> Yes</p> <p><b>Cell Lines:</b> 1  <b>Available:</b> 0</p> <p><b>Previous #:</b>  2009-DRAFT-026  2009-ADM-008</p> <p><a href="#">Email</a>  <a href="#">Edit</a>  <a href="#">Delete</a>  <a href="#">Switch to ADM</a></p>	<p><b>Organization:</b> Reprogenetics, LLC  <b>Org Address:</b> 3 Regent Street, Suite 301 Livingston, NJ-07039  <b>DUNS:</b> 148120780      <b>Grant Number(s):</b>  <b>Signing Official (SO):</b> Santiago Munne / 9734365010 / <a href="mailto:munne@reprogenetics.com">munne@reprogenetics.com</a>  <b>Submitter of Request:</b> //   <b>Submitter Comments:</b> Please see Letter of Explanation attached.</p> <hr/> <p><b>Line #1:</b> RNJ7  <b>NIH Approval #:</b>  <b>Available:</b> Other - available for limited distribution  <b>Embryo from U.S.:</b> Yes  <b>Embryo Donated in Year(s):</b> 2008  <b>Provider Name:</b> Reprogenetics, LLC  <b>Provider Phone:</b> 9734365010  <b>Provider Email:</b> <a href="mailto:munne@reprogenetics.com">munne@reprogenetics.com</a>  <b>Provider URL:</b> <a href="http://www.reprogenetics.com/">http://www.reprogenetics.com/</a>  <b>Provider Restrictions:</b> Non-commercial and non-therapeutic use only. These restrictions may be lifted later.</p> <p><b>NIH Restrictions:</b></p> <p><b>Additional Information:</b></p> <hr/> <p><b>Supporting Documents:</b>  <b>Document 1:</b> (PDF - 12/14/2009) IVF Consent Form from Institute for Reproductive Medicine and Science at Saint Barnabas - Elements: 1  <b>Document 2:</b> (PDF - 12/14/2009) Original Research Protocol; IRB Approval; Research Consent Form - Elements: 1,2,3,4,5,6,7,8,9,10,11,13,15  <b>Document 3:</b> (PDF - 12/14/2009) Letter of Explanation of support documents - Elements: 16  <b>Document 4:</b> (PDF - 12/14/2009) Consent modification and IRB approval - Elements: 12,14,16  <b>Document 5:</b> (PDF - 12/14/2009) IRB approval letter to re-consent patients - Elements: 16  <b>Document 6:</b> (PDF - 12/15/2009) IRB letter of approval (uploaded by E. Gadbois) - Elements: 16</p> <hr/> <p><b>Administrative Comments:</b> Document 6/IRB letter of approval uploaded by E. Gadbois per request of submitter on Dec 15, 2009</p> <p>correspondence from 29 Jan 2010 uploaded by E. Gadbois</p> <p>additional correspondence uploaded by E. Gadbois</p> <p>SO IIB assurance uploaded by E. Gadbois</p>
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(2)

IIB staff analysis uploaded April 1 2010 by E. Gadbois

April 21 2010 Questions to Reprogenetics uploaded April 26 2010 by E. Gadbois

May 3 2010 correspondence uploaded by E. Gadbois

May 11 correspondence uploaded by E. Gadbois

May 17 2010 correspondence with submitter uploaded by E. Gadbois

June 14 2010 correspondence with submitter uploaded 15 Jun by D. Hannemann

Feb 17 submitter correspondence re: IRB approval history - uploaded by D. Hannemann 19 April 2011

IRB approval and renewal history - uploaded by D. Hannemann 19 April 2011

Feb 22 submitter correspondence re 2004 revised consent and protocol - uploaded by D. Hannemann 19 April 2011

2004 revised consent and protocol (sent by submitter on Feb 22) - uploaded by D. Hannemann 19 April 2011

Full Initial Consent (redacted) for RNJ7 sent by submitter on 22 Feb - uploaded by D. Hannemann 19 April 2011

Mar 15 submitter correspondence - uploaded by D. Hannemann 19 April 2011

Summary of hESC line characterization (Mar 15 email attachment) - uploaded by D. Hannemann 19 April 2011

Apr 13 submitter correspondence re: RNJ7 documentation - uploaded by D. Hannemann 19 April 2011

Apr 15 submitter confirmation of phone call summary - uploaded by D. Hannemann 19 April 2011

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**Administrative Attachments:**

- Document 1: (DOC - 01/29/2010) Jan 29 2010 response Munne
- Document 2: (PDF - 02/26/2010) further correspondence Feb 2
- Document 3: (DOC - 02/26/2010) attachment Feb 2 correspondence
- Document 4: (PDF - 03/12/2010) NIH senior staff email switch to ACD
- Document 5: (PDF - 03/23/2010) IIB assurance from SO
- Document 6: (DOC - 04/01/2010) IIB framework NIH staff analysis
- Document 7: (PDF - 04/26/2010) Questions to Reprogenetics 21 April 2010
- Document 8: (PDF - 05/04/2010) May 3 2010 email response
- Document 9: (DOC - 05/04/2010) May 3 2010 email attachment
- Document 10: (PDF - 05/13/2010) May 11 2010 email response
- Document 11: (PDF - 05/17/2010) May 17 2010 email from Reprogenetics

3

Document 12: (PDF - 06/15/2010) June 14 2010 email from submitter  
Document 13: (PDF - 02/01/2011) Jan 20 2011 email from Alikani  
Document 14: (PDF - 04/19/2011) 17 Feb Submitter email re: IRB history  
Document 15: (PDF - 04/19/2011) IRB approval and renewal letters  
Document 16: (PDF - 04/19/2011) 22 Feb Submitter email re: 2004 revised consent and protocol  
Document 17: (PDF - 04/19/2011) 2004 revised consent and protocol  
Document 18: (PDF - 04/19/2011) Full redacted donation consent for RNJ7  
Document 19: (PDF - 04/19/2011) Mar 15 submitter correspondence  
Document 20: (DOC - 04/19/2011) Summary of hESC line characterization (Mar 15 email attachment)  
Document 21: (PDF - 04/19/2011) Apr 13 submitter correspondence re: RNJ7 documentation  
Document 22: (PDF - 04/19/2011) Submitter confirmation of phone call

**Status History:**

**Draft:** 11/11/2009

**Pending:** 12/14/2009

**Emails Sent:** 12/14/2009-New\_Applicaton\_Email

**Previous ADM Request Number:** 2009-ADM-008

**Switched from ADM to ACD Date:** 03/12/2010

**Reason for Switch to ACD Review:**

NIH administrative review concludes that this submission is not approvable under Section IIA of the Guidelines but is eligible for review under Section IIB.

**Added By:** Commons\smunne1 **On:** 11/11/2009 | **Last Updated**

**By:** NIH\hannemannd **On:** 04/19/2011 | **Record ID:** 26

**Total Record Count = 1**

[Administration Page](#)

[Logout of NIH Form 2890 Admin Site](#)

**From:** [Santiago Munne](#)  
**To:** [Gadbois, Ellen \(NIH/OD\) \[E\]](#)  
**Cc:** [Mina Alikani](#)  
**Subject:** FW: RNJ7 NIH registration  
**Date:** Monday, March 22, 2010 2:43:39 PM

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Dear Dr. Gadbois,

Per your request of 12 march, 2010, I am sending you my assurance in accordance with Section IIB of the NIH stem cell research Guidelines, with respect to the following:

The embryo from which Reprogenetics' cell line RNJ7, currently under review by the NIH, was derived was donated prior to July 7, 2009; the embryo 1) was created using in vitro fertilization for reproductive purposes and it was to be discarded as a non-viable embryo according to predetermined criteria and with the full knowledge of the patient; and 2) was donated by individuals who sought reproductive treatment who gave voluntary written consent for the human embryo to be used for research purposes. Furthermore, the donor couple: (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 embryo after the donation for research.

If you require any other information regarding this cell line, please do not hesitate to contact me.

Santiago Munné, Ph.D.  
President  
Reprogenetics  
3 Regent Street, Suite 301  
Livingston, NJ-07039  
[munne@reprogenetics.com](mailto:munne@reprogenetics.com)  
Tel. 973-4365010  
Fax. 973-9921308  
[www.reprogenetics.com](http://www.reprogenetics.com)

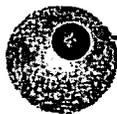
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This information has been disclosed to you from records whose confidentiality is protected by state law. State law prohibits you from making any further disclosure of such information without the specific written consent of the person to whom such information pertains, or as otherwise permitted by state law.

Letter of explanation of support documents submitted to the NIH hESC Registry by Reprogenetics, LLC, for **RNJ7** human embryonic stem cell line

1. The embryo utilized by Reprogenetics for derivation of **RNJ7** was donated by a patient undergoing infertility treatment at the Institute for Reproductive Medicine and Science (IRMS) at Saint Barnabas Medical Center (SBMC). Drs. Mina Alikani and Jacques Cohen who are listed as investigators on the original SBMC IRB-approved stem cell research protocol (which dates back to 2002) were employees of SBMC at the time, but later Drs. Cohen and Santiago Munné (another member of Dr. Cohen's team at IRMS) established Reprogenetics, LLC as an independent company while maintaining their research collaborations with IRMS & SBMC.
2. Element 3 of Section IIA of the guidelines specifies that all embryo disposition options available in the health care facility should have been explained to the embryo donors. **RNJ7** was derived from an embryo designated as "non-viable" as defined by specific laboratory criteria. Our IRB-approved consents and protocols specify that only non-viable embryos are being used for stem cell research. This designation would exclude such embryos from clinical use, i.e., transfer to a recipient uterus or cryopreservation. Non-viable embryos are normally discarded (as indicated in the consent form), therefore the consents contain no statement regarding any other embryo disposition options.
3. Elements 7, 12, and 14 of Section IIA of the guidelines are in reference to consents, and therapeutic and commercial use of cell lines. All embryo donations for stem cell research were by consent, obtained by IRMS at the time of donation. However, the original consent form did not allow for commercial or therapeutic use of the cell lines. We have therefore placed these specific (non-commercial/non-therapeutic) restrictions on the use of the cell lines.
4. With respect to #3 above, we have revised and amended the original consent form (2002) and have received IRB approval to contact the donors from whose embryos stem cell lines were derived, in order to request and obtain a new consent that discloses potential financial interest of the researchers and does not restrict commercial or therapeutic use of the cell lines (nor distribution to third parties). Once the new consents are obtained, we hope to be able to remove those restrictions from any approved lines on the registry. The relevant documents have been submitted.



6

**Stem-cell research using discarded non-viable embryos**

**A – You are invited to donate any “non-viable” embryos that may result from your current attempt at in-vitro fertilization. Participation will in no way affect the normal progress of your attempt at in vitro fertilization, including the possibility of later replacement of thawed embryos from this attempt, nor will it affect your chances of pregnancy, as the study of non-viable embryos would not commence until completion of each of the steps necessary to identify any individual embryo as non-viable.**

**B –The Gamete and Embryo Research Laboratory of the Institute for Reproductive Medicine and Science of Saint Barnabas Medical Center is engaged in studies aimed at developing new, more efficient ways of isolating and culturing embryonic stem cells. Stem-cells are cells that are not yet differentiated or changed into specialized cells such as muscle and blood cells. Embryos, even abnormal ones, can be used as a source of stem cells. Research on such embryonic stem cells is of fundamental importance for the progress of medicine, not least reproductive medicine, in the decades ahead. The reason is that stem cell research not only will allow a better understanding of the causes and mechanisms underlying a host of devastating diseases, but also offers a very real prospect of alleviating, even curing many of these diseases, among them Juvenile Diabetes and Muscular Dystrophy. Physicians and scientists at the Saint Barnabas Medical Center believe that the embryological research for which your non-viable embryos would be donated can play an important, even crucial role in the developments ahead.**

**Non-viable embryos are selected based on standard criteria used in our laboratory. Embryos are non-viable when eggs fertilize abnormally or fail to divide after fertilization. Others may divide too slowly or appear abnormal. Processes that are included in the evaluation of viability are fragmentation (the blebbing of cells) and the number of nuclei per cell. Fragments are not always considered detrimental, but certain types of fragmentation are known to cause demise of the embryo. Abnormal nuclei do not always cause failure of pregnancy, and the decision to consider such embryos abnormal is very much dependent on the ratio of abnormal cells and the type of abnormal nucleus. Criteria for evaluation are also stage-specific. In other cases embryos are considered non-viable because the embryo appears disorganized and several types of anomalies can be distinguished.**

**The non-viable embryos donated by you will be used in one or more of the following studies either before or after they are frozen:**

- The development of culture techniques that will allow scientists to isolate and grow stem-cells from a single or a few embryonic cells. These studies may involve using**

animal cells, including cells from animal embryos, for initial growth support. The animal cells would serve as "feeder cells", providing the right environment until the human cells can survive by themselves.

- Isolation and analysis of stem-cells from embryos discarded due to abnormal chromosome numbers.
- The development of improved methods for stem-cell storage. Thawed stem-cells would be tested for viability and characteristics as well as their ability to transform into other cell-types.
- The development of new methods for transforming stem-cells into other cell types.

Only your "non-viable" embryos, i.e. those that are unsuitable for replacement and would otherwise be discarded, are eligible for donation, and none of the experiments will give rise to normal embryos at any stage. However, the non-viable embryos donated by you may give rise to embryonic stem cells. These stem cells may be genetically normal or genetically abnormal depending, primarily, on whether the isolated cells from which they grew were genetically normal or abnormal to begin with. Both categories of stem cells are of fundamental scientific and biomedical interest.

The methods used in the studies include new processes of cell manipulation and culture of embryonic cells. Any non-viable embryos donated by you may thus be manipulated and cultured, in some instances for an extended period of time, 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 non-viable embryos, they could give rise to different cell types, such as pancreatic cells or neural cells. Frozen-thawed stem-cells and embryos will be subjected to the same research protocols as described above.

Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from, the non-viable embryos donated by you, will ever be used to impregnate another woman or to assist any individual or couple in any way to become pregnant. Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from the non-viable embryos donated by you, will ever be used for curing genetic or other disease, or for production of commercial stem-cell lines. Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from, the non-viable embryos donated by you, will ever be donated for use to other individuals, centers, or corporations.

D – Participation in these studies by donation of non-viable 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. It is also unlikely that you will receive any direct personal benefits from participation at this time; however, it is likely that, in the future, patients will benefit from the knowledge we will gain from these studies.

8

F – This consent form is being offered to all couples treated with IVF at Saint Barnabas Medical Center. Any information obtained during this study and identified with you will remain confidential. The Food and Drug Administration (FDA) and The Center for Disease Control (CDC) in association with the Society for Assisted Reproduction (SART) may inspect the records. There are no added costs related to your participation in this study. Your decision whether or not to participate will not prejudice your future relations with Saint Barnabas Medical Center and the treatment you now undergo in this institute. If you decide to participate, you are free to discontinue participation at any time. 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 have any questions regarding your rights as a research subject, please call the office of the IRB chairman, Dr. Goodman at (973) 322-5637. The principle investigator of this protocol is Dr. Steen Willadsen, who can be reached at 973-3226310. You may request a copy of this form.

G – I/We hereby attest that we have read the entire consent form, or that it has been read to us, so that we understand it completely. I/we further attest that any and all questions of mine/us regarding this form or this study have been answered to my/our complete satisfaction. We agree that stem-cells may be developed from our non-viable embryos.

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

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

Witnessed: name M. Braun, RN Signature [Handwritten Signature]

Date: 2/11/08

**Consent for In Vitro Fertilization/Assisted Reproduction**

I / we, \_\_\_\_\_ and \_\_\_\_\_, desire to participate in the Assisted Reproduction Program at The Institute for Reproductive Medicine and Science at Saint Barnabas, P.A. (IRMS). We understand that there are a number of steps to this procedure and that starting this process does not guarantee that we will complete the process, achieve pregnancy or delivery of a healthy child. One of our physicians has discussed with you the etiology of your condition, and alternative therapies, if any, that are available. We understand that the female partner will receive medication to induce the maturation of several eggs and during this period she will undergo a surgical procedure to retrieve her eggs. The steps may be performed by any of the following physicians: Margaret Garrisi, Serena Chen, Patricia Hughes, Natalie Cekleniak. The egg retrieval procedure will be done by needle aspiration, usually under ultrasound guidance or perhaps by laparoscopy. We understand that the eggs will be prepared and inseminated in marked dishes with a sample of the male partner's sperm after preparation, which removes the sperm from the seminal fluid. The embryos, which may result from fertilization, will be placed into the female partner's uterus by means of a small catheter, which passes through her cervix under ultrasound guidance. Following this transfer, blood hormone levels will be monitored in the female partner to make sure that there are adequate hormonal levels to support a developing pregnancy and then to determine if a pregnancy has resulted. We understand that each of these steps may fail and carries known risks as well as theoretical concerns as detailed in the following paragraphs.

**A - Ovulation induction**

We understand that a variety of medications are available for the induction of ovulation including clomiphene citrate (Clomid, Serophene), human menopausal gonadotropins (Pergonal,) pure follicle stimulating hormone (urofollitropin, FSH), human chorionic gonadotropin (hCG), recombinant FSH (Gonal-F or Follistim) and GnRH-agonists (leuprolide acetate, Lupron), and GnRH antagonists (Antagon, Cetrotide). We understand that some of these medications must be given by intra-muscular injection, which may cause bruising or discomfort at the injection site. These medications may cause the ovaries to become over stimulated, leading to a condition called ovarian hyper stimulation syndrome (OHSS). We understand that in its most severe form this condition might require hospitalization for intravenous fluids and monitoring until the syndrome resolves. Worldwide there have been rare reports of death following severe OHSS. We therefore understand the importance of maintaining close contact with the IVF team during the time that these medications are being used and for two weeks afterwards.

We understand that before the start of a cycle, the male partner will be asked to supply a semen sample for analysis by the andrology laboratory. He may be asked to take a specific antibiotic during the first part of the stimulation cycle to treat bacteria that may be present in order to increase chances for a successful fertilization. In certain cases, semen may also be frozen in advance to be certain of its availability at the time of egg retrieval.

**B - Monitoring protocol**

We understand that while receiving the medications listed above, the female partner will be closely monitored by the IVF team. We understand that this monitoring will include daily blood drawing, which can cause mild discomfort and bruising at the puncture site. We understand that ultrasound examination of the ovarian follicles and the uterus will be performed frequently. These examinations may at times be uncomfortable, but have no known risks of any kind. The female partner may also be asked to collect urine samples for further hormone analysis. We understand that if monitoring suggests a low probability for successful egg retrieval, that the stimulation cycle will be stopped and no egg retrieval will occur. We also understand that we may be given the option of starting the ovarian stimulation procedure again in a subsequent cycle.

**C - Egg retrieval**

We understand that, at a time determined by the IVF team, the female partner would be admitted to the egg retrieval procedure room and IVF laboratories at Saint Barnabas Medical Center. We understand that in the vast majority of cases, ultrasound directed needle puncture of the follicles will be done. Rarely, the retrieval may be done by laparoscopy under general anesthesia. We understand that the procedure involves the small risk of general anesthesia as well as injury to bowel, bladder, or blood vessels, which might require a large incision (laparotomy) to repair. We understand that a separate informed consent will be obtained for a laparoscopic retrieval if it becomes necessary. With either type of egg retrieval, we understand that in rare cases there could be bleeding from the site where the ovaries were punctured. This may require laparotomy (an incision in the abdomen) if the bleeding cannot be controlled through the laparoscope. The risks of the procedure are similar to the risks of laparoscopy, including general anesthesia.

We understand that we cannot be guaranteed that the number of eggs predicted prior to retrieval will indeed be recovered or that any of the eggs will be normal or ripe. Some follicles may not yield eggs and rarely none of the follicles will yield eggs. The egg retrieval involves equipment such as incubators, suction apparatuses and ultrasound machines that may fail because of technical malfunction. We also understand that once the eggs are isolated in the laboratory, that blood and abnormal nursing cells are removed from around the egg using dissection needles and that although unlikely, some or all of the eggs may be damaged in the process. Eggs may also be damaged because of shock due to differences in conditions.

Initial egg yield numbers are counted once and rapidly in order to place the eggs inside the incubators and stabilize conditions as soon as possible. Eggs themselves are not visualized during egg retrieval, but only the nursing cells surrounding the eggs. The normality of the eggs cannot be assessed at egg retrieval. The exact number of eggs is only determined later on at insemination or ICSI.

**D - Insemination, fertilization and embryo growth**

Once retrieved, the eggs will be incubated in a special solution (culture medium) and evaluated for timing of insemination by the embryology team of the IVF program. We understand that a sample of semen from the male partner, obtained by masturbation in a private collection room near the laboratory, will be evaluated, prepared, and used for insemination. Semen collection in this way can be unsuccessful and if there are any doubts, a sample can be prepared and frozen in advance for thawing at this time. However, in case of unexpected failure it is possible to obtain spermatozoa from a testicle using a minor operative procedure (testicular sperm retrieval). Separate consent is needed for this procedure.

The seminal fluid that surrounds the spermatozoa must be removed prior to insemination. Sperm processing involves high centrifugal force, washing with an artificial colloidal suspension called *Puresperm*<sup>TM</sup> or by swim-up. We understand that the consistency of highly viscous semen will be reduced by an enzyme. The prepared semen may be exposed to substances intended to promote sperm movement or materials intended to remove toxic substances. The zygotes or fertilized eggs are changed over into a culture solution. This solution may be changed every 48 hours or more frequently. Solutions may be specially tailored to embryonic stage. The embryos are checked at least once daily and their development is determined. Embryos will remain in the solution(s) for 48-120 hours and then transferred.

Should a pregnancy occur, we understand that no risk to the fetus is presently known to medical science arising from the materials and methods used in the preparation and handling of eggs, semen and embryos. We understand that not all eggs recovered can be fertilized, and that it is possible that none of the eggs may fertilize. We also understand that not all eggs may be ripe and that ripe eggs may be fertilized multiple times by sperm or even self-fertilize without the sperm participating. Zygotes and later stage embryos may develop abnormally at any time.

**E - Blastocyst culture, alternative culture and embryo transfer**

We understand that between three to four days after egg retrieval our embryos will be placed into the uterine cavity of the female partner. Alternatively you may be asked to consider having embryos transferred at the blastocyst stage five or six days after egg retrieval, using commercial culture solutions that support growth for a longer period. This protocol may be especially advantageous to couples who are at risk of multiple pregnancy, since the extended culture increases the opportunity for embryologists to select the highest quality embryos. A potential disadvantage is that some embryos may be more sensitive to prolonged presence in the laboratory with the result that cryopreservation and /or embryo transfer may not occur.

We know that some patients have embryos that develop slowly, or show different forms of microscopic anomalies such as fragmentation and multi-nucleation and may not become pregnant. This may be due to a sensitivity of the embryos to the standard culture conditions in the

laboratory. If this is a repeat attempt at assisted reproduction, we may be asked to have our eggs and zygotes cultured in a different culture medium in order to determine whether this sensitivity can be overcome. We realize that alternative culture is only effective in a proportion of the patients. The alternative culture may not have any benefit in our case, and we understand that pregnancy and success is not guaranteed.

For any embryo transfer, a thin catheter will be passed through the cervix and into the uterus so the embryo may be deposited there. We understand that this may involve some cramping and discomfort, and possibly a small amount of bleeding. Infection could be introduced at the time of the catheter insertion into the uterus, requiring antibiotic therapy. We understand there is not guarantee that any of the embryos thus transferred will result in a pregnancy.

We understand that the success of IVF can often relate directly with the number of embryos transferred to the uterus. We also understand that IVF significantly increases the risk for multiple gestation (more than one baby), and that this risk also correlates directly with either the number of embryos transferred, their development, the age of the female partner (or egg donor), the number of prior attempts and other unknown factors. We also understand that in rare cases, embryos may split in two or three, resulting in multiple fetuses; on occasion this can mean that there are more fetuses than embryos transferred. There are distinct obstetric risks to multiple gestations, the most serious of which are pre-term labor and the delivery of premature infants who require intensive care. It is the policy of this program to replace anywhere from one to six embryos in a given cycle all depending on availability and factors such as your age, cycle attempt and embryonic parameters. Any additional viable embryos may be cryopreserved (frozen) for possible replacement in a subsequent cycle. We understand that a separate consent for the cryopreservation must be completed if the embryos are to be cryopreserved.

**F - Post-transfer management**

We understand that, in conjunction with the transfer of embryos, the female partner may be given natural progesterone by intramuscular injection, vaginal suppository, or oral capsule in an attempt to increase the chances for successful implantation. Sometimes an additional hCG injection may be given instead of the progesterone. Should a pregnancy result, we understand that no harmful effects to the mother of the fetus are presently known to medical science from the use of this natural progesterone or hCG supplementation. During this period, we understand that various blood hormone levels may be evaluated.

**G - Disposition of unwanted or unsuitable cells, fluids, spermatozoa, eggs and embryos**

Bloods, blood products and cells as well as follicular and seminal fluids and cells contained therein obtained during follicular monitoring, egg or sperm retrieval, may be used for scientific observations. In the event that we have unused or unripe spermatozoa, these may be subjected to scientific observations or discarded without any further observations. Under no circumstances will these spermatozoa be used for fertilization purposes or donation to other individuals, couples, corporations or institutions. In the event that we have unripe, unfertilized or abnormally fertilized

eggs, these may be subjected to scientific observations or discarded without further studies. We understand that these eggs will never be used for fertilization purposes or donation to other individuals, couples, corporations or institutions and that further growth of them will be ceased immediately after the observation. We also understand that these eggs are unwanted and considered abnormal. Embryos that arrest after 1-6 days after egg retrieval, that are partially degenerate or for any other reasons considered unsuitable for embryo transfer or cryopreservation may be observed to determine cellular inclusions, genes, gene mutations, proteins and chromosomes. The studies use protocols that will cease the immediate growth of individual cells. We understand that these embryos or their cells will never be used for purposes other than those described and will never be offered to other individuals, couples, corporations or institutions. We also understand that these embryos or their cells are unwanted and considered abnormal.

A separate research consent form is being offered to you, by which you can grant permission for the use of your unwanted and unsuitable spermatozoa, eggs, embryos and their cells in research studies for the development of new reproductive technologies. This separate research protocol is being supervised by the Internal Review Board (IRB) of Saint Barnabas Medical Center, and you are not in any way required to give your permission. Your further and ongoing treatment at The Institute for Reproductive Medicine (IRMS) will not be affected if you do not wish to participate in that or any other IRB-reviewed protocol.

#### **H - Use of blood products**

We understand that maternal blood serum, derived from blood collected from the female partner shortly before egg collection will be prepared for culture with your eggs and embryos in order to promote growth. Sometimes we will not be able to use your serum. It has been shown in rare instances that maternal serum may inhibit embryos developing in-vitro. Human serum albumin, a commercially prepared blood product for clinical laboratory use, is added to the egg collection fluid, micromanipulation, and semen preparation fluids. Careful screening is done by the manufacturers to reduce the likelihood of transmission of infectious diseases such as HIV, Hepatitis B and C. To date there have been no documented cases of disease transmission linked to human serum albumin usage in our Center. We understand and accept the risk that use of these blood products could result in the transmission of HIV, Hepatitis and/or other viral or possibly as yet unknown non-viral diseases.

#### **I - Use of chemical substances, disposable items and mechanical devices during the procedures**

A large number of chemical substances (sugars, salts, enzymes, proteins), mechanical devices (incubator chambers, microscopes, air handling systems, filters, standard laboratory equipment) and disposable items (pipettes, petri dishes, flasks, microtools) are used during the laboratory procedures. There may be unknown risks associated with the use of any of these items that cause your procedure to fail, even though checks and quality control measures are performed on a regular basis. Thus far we do not know of any association between the use of these materials and anomalies of pregnancy and fetal development, but underlying unidentified problems may nevertheless exist. An enzyme made from cow testis called hyaluronidase is routinely used to

remove nursing cells from around the eggs, and there is a chance that this enzyme may inadvertently remove the zona pellucida (the layer surrounding eggs) and cause your procedure to fail. Another enzyme called chymotrypsin made from cow pancreas is used to reduce the viscosity of seminal fluid. This enzyme may also in very rare instances inadvertently remove the zona pellucida and also may cause your procedure to fail.

**J - Risks associated with procedures**

Based on current medical knowledge, we understand there does not appear to be a higher incidence of birth defects associated with IVF procedures. However, there is not at present sufficient statistical data available to definitively conclude that this is so. Therefore, we understand that IVF may impose risks to the fetus during development. We also understand that because more than one embryo or egg may be transferred, there may be a higher incidence of multiple births. An embryo may split when inside the uterus, forming monozygotic twins and there may be other associated anomalies. In certain cases, fetal reduction may be considered if more embryos implant that can be medically (or personally) deemed advisable to carry through a pregnancy. We also understand that ectopic or tubal pregnancies may occur in the procedure. These associated procedures can also produce increased financial and emotional burdens.

We understand and accept that the use of ovarian fertility drugs may be associated with an increased risk of ovarian diseases in later life, including cancer. We recognize that the exact risk, if any, has yet to be established and may not be known for many years.

**K - Success rate and outcome**

We understand that failure to obtain a pregnancy may result from many reasons, including the following:

- Maturation of the egg(s) may not occur, or the time of the egg maturation may be misjudged, may not be predictable or may not take place in the monitored cycle.
- Pelvic adhesions may prevent access to the ovary with the follicles, thus causing the procedure to obtain the egg from the ovary to fail.
- The egg(s) obtained from the wife may be abnormal.
- Normal spermatozoa may not be available.
- Normal fertilization of the egg(s) by the sperm may not occur.
- Cleavage or growth of the embryo(s) may not occur at any day of development or the embryo(s) may not develop normally.
- The embryo(s) may become infected in the laboratory or an unforeseen laboratory accident may result in loss or damage to the eggs, sperm, or embryo(s).
- The embryo(s) may become contaminated by infection in the semen or bacteria from the vagina.
- Some embryos may not develop well in approved commercial culture medium despite standard testing.
- Implantation of the embryo(s) in the uterus after embryo transfer may not occur or an early pregnancy may be lost after an initial positive result

- Even if a pregnancy is established, we understand that delivery of a child may not occur due to miscarriage, ectopic pregnancy (outside the uterus), stillbirth, or other complications associated with pregnancy and delivery.
- There may be unknown side-effects from any of the procedures used resulting in abnormal pregnancy or abnormal fetal development

We understand that the members of the IVF team cannot guarantee that a pregnancy will result from this procedure. Even in normally fertile couples, the chance of pregnancy is approximately 25% in a given natural cycle. If no pregnancy occurs, we may be offered participation in future cycles when assessment by the IVF team reveals no contra-indications. We understand that the IVF team cannot guarantee the normality of any infant that results from this procedure.

We understand that we may at any time decide to withdraw from participation in this program without prejudice. Any information obtained during this procedure and identified with us will remain confidential and will be disclosed only with our permission. Any publication resulting from this procedure will not identify us individually. Representatives of The Food and Drug Administration (FDA), The Center for Disease Control (CDC) and The Department of Health of New Jersey may inspect the records.

We have been encouraged to ask questions and any that we have asked have been answered to our satisfaction. A member of the IVF team will answer future questions.

---

(Signature of patient) Date

---

(Signature of Partner, if not applicable write NA) Date

---

(Signature of Witness) Date

The Institute for Reproductive Medicine and Science at Saint Barnabas, is not owned by, and its physicians and other personnel are not employed by, Saint Barnabas Health Care System, Saint Barnabas Medical Center, or any of their affiliates.



The Institute for Reproductive Medicine  
and Science at Saint Barnabas

An affiliate of the Saint Barnabas Health Care System

August 18, 2004

Robert L. Goodman, MD  
Chairman, Institutional Review Board  
Saint Barnabas Medical Center  
Old Short Hills Road  
Livingston, NJ 07039

Dear Dr. Goodman:

I would like to submit the attached revised consent form entitled *Stem-cell research using discarded non-viable embryos* to the Institutional Review Board of Saint Barnabas Medical Center to be considered for expedited IRB review.

There have been some minor changes to the consent form, which have been highlighted. In reviewing the consent, it was also noticed that the telephone number for the IRB office has not been updated. I have highlighted this change as well.

With warmest regards,

Santiago Munné, Ph.D.

SM/laf  
Enclosure

Natalie A. Ceklentak, MD

Serena H. Chen, MD

Margaret G. Garrisi, MD

A Division of the Department of Obstetrics and Gynecology at Saint Barnabas Medical Center

94 Old Short Hills Road, East Wing - Suite 403, Livingston, NJ 07039 • voice: 973.322.8286 • fax: 973.322.8890 • website: www.sbivf.com

APPLICATION TO UNDERTAKE RESEARCH INVOLVING HUMAN SUBJECTS

Checklist

TITLE OF PROPOSED RESEARCH:

Stem-cell research using discarded non-viable embryos

INVESTIGATOR(S) AND DEPARTMENT(S):

Steen Willadsen, DVM, Jacques Cohen, Ph.D., Mina Alikani, M.Sc., Margaret Garrisi, M.D.,  
Santiago Munné, Ph.D. Institute for Reproductive Medicine and Science, Department of  
Gynecology and Obstetrics

THIS PROTOCOL IS TO BE CONSIDERED FOR

(check only one box)  EXEMPTION FROM REVIEW  
 EXPEDITED REVIEW  
 FULL IRB REVIEW

The proposed research will be carried out in cooperation with the following institution

Reprogenetics (if applicable)

Date of approval by cooperating institution's IRB \_\_\_\_\_

Human subjects would be involved in the proposed research as either:

None of the following

or including (Check all applicable boxes)

- |   |  |
|---|--|
| <input type="checkbox"/> Minors         | <input type="checkbox"/> Prisoner                      |
| <input type="checkbox"/> Fetuses        | <input type="checkbox"/> Mentally retarded             |
| <input type="checkbox"/> Abortuses      | <input type="checkbox"/> Mentally disabled             |
| <input type="checkbox"/> Pregnant women | <input type="checkbox"/> Non-English-speaking subjects |



APPLICATION TO UNDERTAKE RESEARCH INVOLVING HUMAN SUBJECTS

Part A (to be completed in typescript by all applicants)

1). Date 7/31/2004 2). IRB No. (leave blank)

3). Title of Project

Stem-cell research using discarded non-viable embryos

4). Responsible Investigator(s) Full Name(s) and Department(s)

Steen Willadsen, DVM, Jacques Cohen, Ph.D., Mina Alikani, M.Sc., Margaret Garrisi, M.D., Institute for Reproductive Medicine and Science of Saint Barnabas, Department of Gynecology and Obstetrics; Gamete and Embryo Research Laboratory at the Institute for Reproductive Medicine and Science of Saint Barnabas, Santiago Munné, Ph.D., Reprogenetics LLC

5). Personal Signature of Investigator(s)

Steen Willadsen

*Mina Alikani*

Mina Alikani

Santiago Munné

Jacques Cohen  
*Jacques Cohen*

Margaret Garrisi

*M. Garrisi, MD*

6). Personal Signature of Department Chairman

*Veronica Ravnika*

Veronica Ravnika, M.D.

7). Source of Funds for Study

Departmental

Number of Subjects to be Studied

1500

Dates of Study September 1, 2002 to August 31, 2005

Is this an multi-institutional study? X Yes        No

If yes, under what sponsorship? Institute for Reproductive Medicine and Science at Saint Barnabas, and Reprogenetics

- 8). Background of Proposed study (State briefly the reason for doing the study. What question(s) is it designed to answer and why is the question being asked? Include references to no more than three key literature citations, if appropriate.)

Abnormal gametes and embryos are an excellent source of material for studying anomalies that can occur during gametogenesis and embryogenesis. Discarded non-viable material resulting from in-vitro fertilization (IVF) can also be used to develop new technology applicable to the treatment of infertile patients (protocol #769). Protocol 769 was revised in February 2002 and allowed us to extend the study of non-viable embryos into the field of embryonic stem-cell research. We have developed several technologies that could almost certainly be used to make production of human embryonic stem-cells from embryos simpler and more efficient. The fact that these technologies primarily use non-viable embryos as the source of embryonic stem-cells is of particular relevance in the current funding climate which does not allow the use of viable human embryos for that purpose (Alikani and Willadsen; Reproductive Medicine Online; 5, 56-58, 2002). However, we have not yet developed stem-cell lines from such embryos. Here we propose to develop the technology further with the end-point of stem-cell formation. The isolation of chromosomally normal and abnormal stem-cell lines from non-viable embryos is important. For one thing it avoids the dilemma posed by the use of viable human embryos for stem-cell production, and may therefore allow government funding. The reason for making the present protocol separate from protocol 769 using non-viable embryos is the need for patients' permission to use discarded non-viable embryos for isolation of stem-cells. Inherent in this kind of research is the unpredictability of the duration of individual experiments, particularly since abnormal embryos and stem-cells can be frozen. The isolation and experimental culture of embryonic stem cells is considered to be of fundamental importance for the progress of medicine. Stem cell based research offers the prospect of cures to many devastating diseases such as Juvenile Diabetes, Muscular Dystrophy and Alzheimer's Disease.

The reason of the current update of this application is because of our long relationship with Dr. Munne, before an employee of Saint Barnabas, and now directing Reprogenetics, we want to expand the study to develop stem cells from chromosomally normal embryos detected from Preimplantation Genetic Diagnosis cycles.

- 9). Outline of Proposed Study (State briefly but precisely what is to be done. If the study is to be conducted according to a detailed protocol of a pharmaceutical company or outside agency, include a precis here and attach the full protocol as an appendix. If the study involves the use of a questionnaire or structured interview, attach the text of such instruments as an appendix. Note: IRB review focuses on the scientific merit and adequacy of experimental design as well as on issues of safety and protection of confidentiality).

Non-viable embryos donated by patients will be selected based on criteria used in our program. These are embryos that contain too few normal cells – often no normal cells at all – for the

formation of a viable/ normal conceptus. Non-viable embryos include those that have detrimental forms of fragmentation or multi-nucleation, or that stopped growing during serial observation. Other embryos may seem viable following preimplantation genetic diagnosis (PGD) (that is they divide) but are diagnosed as trisomic or monosomic. Yet other abnormal embryos are polyploid, haploid or chaotic mosaic.

The zona pellucida of the embryos will be removed, and individual mono-nucleate cells will be isolated. They will be grown together from cohorts of embryos in order to form pseudo-blastocysts (Alikani and Willadsen, 2002) or cultured individually with mouse or cow embryonic cells or embryos that have been manipulated to support the growth of human embryonic cells to develop into stem-cells. Animal and human cells will be immunologically or mechanically separated, but in some models the cells can be isolated by varying culture conditions. The stem-cell development will be studied by analyzing the expression of Oct-4, a gene that only is expressed in early embryos, and the inner cell mass and embryonic stem cells. Ploidy will be studied by fluorescence in-situ hybridization (FISH).

- 10) Subject (State the kind(s), ages, sex, and appropriate numbers of subjects to be studied. Indicate the criteria for the selection of the proposed kinds and number of subjects. If populations at special risk (cf. checklist) are to be studied, provide the reason(s) for their inclusion. Specify population groups to be excluded (e.g. pregnant women). Indicate composition of control groups.)

The investigations will be conducted in 500 patients annually. There are no risks to the couple and no specific groups will be excluded.

- 11). Drugs (Provide specific information on proposed dosage levels and schedules. Include both the generic and commercial name of each drug and summarize available information on efficacy and side effects. If none are to be administered, enter this statement: "No drugs will be given.")

No additional drugs are needed for the completion of the proposed studies other than those used for assisted reproduction procedures.

- 12). Blood Sampling (State the volume to be drawn on each occasion and the frequency of sampling from the same subject. If none is to be drawn, enter this statement: "No blood will be drawn.")

No blood will be drawn.

- 13). Tissue Sampling (State the type of tissue to be collected, volume (if applicable), and frequency of sampling from the same subject (if applicable). If no other tissues will be collected, enter this statement: "No other tissues will be collected.")

No extra tissues will be collected.

- 14). Radioactive Isotopes (Give the identity and dose of each isotope. If none are to be administered, enter this statement: "No radioactive isotopes will be given").

**No radioactive isotopes will be given.**

- 15). Safety (State in adequate detail any anticipated physical, mental, or emotional risk to the subjects of this research activity and the degree of likelihood that it may occur. If no such risk is anticipated, state why this is so).  
**There is no additional risk to the patients other than those involved with regular IVF.**
- 16). Confidentiality (Describe the adequate detail what measures will be taken to protect the confidentiality of the data to be obtained and the subject's rights to privacy).  
**Patient names, IDs, etc. will be kept strictly confidential. Files and databases will be locked or only made accessible to privileged investigators. Anonymous case reports will only be published after the patients grant permission.**
- 17). Informed Consent (State whether it is planned to obtain informed consent from each subject of the research activity. If informed consent will be obtained, complete the attached Part B. It is not planned to do so, provide in this space, thorough justification for its omission. Note: Federal regulations provide that written informed consent be obtained from each subject of a research activity, but this requirement may be waived by the IRB under specific circumstances (cf. attachment to Part B).  
**We will ask each couple to provide written consent after fully informing them in a private consultation. The IRB consent form is attached.**

# SAINT BARNABAS MEDICAL CENTER

An affiliate of the Saint Barnabas Health Care System

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

The Institute for Reproductive Medicine and Science  
At Saint Barnabas  
And  
Reprogenetics

## Stem-cell research using discarded non-viable embryos

A – You are invited to donate any “non-viable” embryos that may result from your current attempt at in-vitro fertilization. Participation will in no way affect the normal progress of your attempt at in vitro fertilization, including the possibility of later replacement of thawed embryos from this attempt, nor will it affect your chances of pregnancy, as the study of non-viable embryos would not commence until completion of each of the steps necessary to identify any individual embryo as non-viable.

B –The Gamete and Embryo Research Laboratory of the Institute for Reproductive Medicine and Science at Saint Barnabas and Reprogenetics are engaged in studies aimed at developing new, more efficient ways of isolating and culturing embryonic stem cells. Stem-cells are cells that are not yet differentiated or changed into specialized cells such as muscle and blood cells. Embryos, even abnormal ones, can be used as a source of stem cells. Research on such embryonic stem cells is of fundamental importance for the progress of medicine, not least reproductive medicine, in the decades ahead. The reason is that stem cell research not only will allow a better understanding of the causes and mechanisms underlying a host of devastating diseases, but also offers a very real prospect of alleviating, even curing many of these diseases, among them Juvenile Diabetes and Muscular Dystrophy. Physicians and scientists at the Institute for Reproductive Medicine and Science and Reprogenetics believe that the embryological research for which your non-viable embryos would be donated can play an important, even crucial role in the developments ahead.

Non-viable embryos are selected based on standard criteria used in our laboratory. Embryos are non-viable when eggs fertilize abnormally or fail to divide after fertilization. Others may divide too slowly or appear abnormal. Processes that are included in the evaluation of viability are fragmentation (the blebbing of cells) and the number of nuclei per cell. Fragments are not always considered detrimental, but certain types of fragmentation are known to cause demise of the embryo. Abnormal nuclei do not always cause failure of pregnancy, and the decision to consider such embryos abnormal is very much dependent on the ratio of abnormal cells and the type of abnormal nucleus. Criteria for evaluation are also stage-specific. In other cases embryos are considered non-viable because the embryo appears disorganized and several types of anomalies can be distinguished. Finally, embryos classified by Preimplantation Genetic Diagnosis (PGD) as being genetically abnormal were also considered non-viable.



The non-viable embryos donated by you will be used in one or more of the following studies either before or after they are frozen:

- The development of culture techniques that will allow scientists to isolate and grow stem-cells from a single or a few embryonic cells. These studies may involve using animal cells, including cells from animal embryos, for initial growth support. The animal cells would serve as "feeder cells", providing the right environment until the human cells can survive by themselves.
- Isolation and analysis of stem-cells from embryos discarded due to abnormal chromosome numbers.
- The development of improved methods for stem-cell storage. Thawed stem-cells would be tested for viability and characteristics as well as their ability to transform into other cell-types.
- The development of new methods for transforming stem-cells into other cell types.

Only your "non-viable" embryos, i.e. those that are unsuitable for replacement and would otherwise be discarded, are eligible for donation, and none of the experiments will give rise to normal embryos at any stage. However, the non-viable embryos donated by you may give rise to embryonic stem cells. These stem cells may be genetically normal or genetically abnormal depending, primarily, on whether the isolated cells from which they grew were genetically normal or abnormal to begin with. Both categories of stem cells are of fundamental scientific and biomedical interest.

The methods used in the studies include new processes of cell manipulation and culture of embryonic cells. Any non-viable embryos donated by you may thus be manipulated and cultured, in some instances for an extended period of time, 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 non-viable embryos, they could give rise to different cell types, such as pancreatic cells or neural cells. Frozen-thawed stem-cells and embryos will be subjected to the same research protocols as described above.

Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from, the non-viable embryos donated by you, will ever be used to impregnate another woman or to assist any individual or couple in any way to become pregnant. Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from the non-viable embryos donated by you, will ever be used for curing genetic or other disease, or for production of commercial stem-cell lines. Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from, the non-viable embryos donated by you, will ever be donated for use to other individuals, centers, or corporations.

**D** – Participation in these studies by donation of non-viable 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. It is also unlikely that you will receive any direct personal benefits from participation at this time; however, it is likely that, in the future, patients will benefit from the knowledge we will gain from these studies.

**F** – This consent form is being offered to all couples treated with IVF at Saint Barnabas Medical Center. Any information obtained during this study and identified with you will remain confidential. The Food and Drug Administration (FDA) and The Center for Disease Control (CDC) in association with the Society for Assisted Reproduction (SART) may inspect the records. There are no added costs related to your participation in this study. Your decision whether or not to participate will not prejudice your future relations with Saint Barnabas Medical Center and the treatment you now undergo in this institute. If you decide to participate, you are free to discontinue participation at any time. 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 have any questions regarding your rights as a research subject, please call the office of the IRB chairman, Dr. Goodman at (973) 322-5548. The principle investigators of this protocol are Dr. Steen Willadsen and Santiago Munne, who can be reached at 973-3226236, respectively. You may request a copy of this form.

**G** – I/We hereby attest that we have read the entire consent form, or that it has been read to us, so that we understand it completely. I/we further attest that any and all questions of mine/us regarding this form or this study have been answered to my/our complete satisfaction. We agree that stem-cells may be developed from our non-viable embryos.

Signed: name female partner \_\_\_\_\_ Signature \_\_\_\_\_

Signed: name male partner \_\_\_\_\_ Signature \_\_\_\_\_

Witnessed: name \_\_\_\_\_ Signature \_\_\_\_\_

Date: \_\_\_\_\_

26

SAINT BARNABAS MEDICAL CENTER  
AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION FOR RESEARCH  
(HIPAA 45 CFR PART 164)

Patient Name: \_\_\_\_\_ Patient MRN: \_\_\_\_\_

Protocol IRB #/Protocol: Stem-Cell Research using discarded non-viable embryos

The purpose of this research is as follows: To develop chromosomally normal stem cells from chromosomally abnormal and unviable embryos diagnosed as such by PGD.

*A representative of Saint Barnabas Medical Center or principal investigator must answer these questions completely before providing this authorization form to you. PLEASE DO NOT SIGN A BLANK FORM. You or your personal representative should read the descriptions below before signing this form.*

This document specifically relates to the uses and disclosures of your "protected health information" or "PHI" as referred to in the federal law. For study purposes, your PHI may include records of your blood samples, physical examinations, test results, medical history and any other data collected or reviewed during the course of the study.

By signing this authorization, you are agreeing that your physicians and other health care providers may provide Saint Barnabas Medical Center and the investigators with the PHI they request for purposes of the study. You also are agreeing that Saint Barnabas Medical Center and the investigators may, for purposes of the study, use your PHI collected or created as part of the study and share this information with the parties described below. Additionally, you are agreeing that, during the study, you may not have access to the PHI obtained or created as part of this study, although you will have access to this information once the study is finished.

This information may be shared, with the individuals and/or organization described on this form, these parties may not be required to protect the privacy of your information by law. It is your right to refuse to sign this authorization form. If you do not sign this form, you will not be able to participate in the research study. You will not receive the research treatment that was described to you. Your health care outside the study will not be affected. The payment for your health care or your health care benefits will not be affected.

If you sign this authorization form, you will have the right to withdraw it at any time. To withdraw, the authorization will prohibit further use or disclosure of your health information. If the hospital has already used your health information approved by your authorization or needs the information to fulfill an obligation or analyze the data, the use or disclosure can not be stopped. This authorization form will not expire unless you withdraw it. If you want to withdraw this authorization, please write to Robert Goodman, MD, IRB Chairman, 94 Old Short Hills Road, Livingston, New Jersey 07039

**I. Who will have access to and/or use your health information?**

The following individuals and/or organization(s) may have access to use, disclose or receive my identifiable health information. They may only share the information to the individuals/parties indicated on this list. This information must be shared with you, the research subject and/or your personal representative, as required by law.

- Every research site for this study, including Saint Barnabas Medical Center and the research support staff (for example, research study assistant) at each study location: Reprogenetics, LLC (West Orange, NJ) .
- Every health care personnel who provides services to you in connection with this study.
- Any laboratories, other individuals/organizations that analyze your health information in connection with this study.
- The following research sponsors: Reprogenetics, LLC (West Orange, NJ) .
- The National Cancer Institute and/or the National Institute of Health.
- The United States Food and Drug Administration, or other governmental surveillance organization.
- The members and staff of the hospital's Institutional Review Board and Privacy Board.
- Principal Investigator and Co-Principal Investigation(s) : Santiago Munné, PhD, Mercedes Garcia Bermudez, PhD, Pere Colls, PhD.
- Members of the Research Team including the participating investigators, research assistants, clinical nurses, and clerical support staff.
- Employees of the Contract Research Organization (CRO):
- Others (as described below):

Patient Initial: \_\_\_\_\_

Version Date: April 14, 2003

**II. What information will be used or disclosed?**

The boxes checked below should provide you with a description of the information to be used or disclosed in the research.

- Your entire research record
- Any part of your medical records held by the hospital
- The following information: The genetic diagnosis of your oocytes, embryos or PGD procedure, if stem cells were obtained from those embryos and the characteristics of those stem cells, female age.

**SPECIFIC UNDERSTANDINGS**

**III. Research Participant or Research Participant's Representative Must Read and Initial the Following:**

1. I understand that my participation in the research discussed by this authorization is conditioned upon my signing of this research authorization. Initials \_\_\_\_\_

**For Clinical Trials:**

2. I understand that, despite any statements made in other places in this authorization, while the clinical trial is ongoing, Investigator or Hospital may refuse to permit me access to individually identifiable health information obtained in the course of the clinical trial. I also understand that I will be granted access to this health information following the completion of the clinical trial. Initials \_\_\_\_\_

**SIGNATURE**

\_\_\_\_\_  
Signature of Subject or Personal Representative Date

\_\_\_\_\_  
Print Name of Subject or Personal Representative

\_\_\_\_\_  
Description of Personal Representative's Authority

**Expiration Date:**

- None
- End of Research 3/30/2006
- Date: \_\_\_\_\_

**CONTACT INFORMATION**

*The contact information of the subject or personal representative who signed this form should be filled in below.*

**Address:** \_\_\_\_\_ **Telephone:** \_\_\_\_\_ (daytime)  
 \_\_\_\_\_ (evening)

**THE SUBJECT OR HIS OR HER PERSONAL REPRESENTATIVE MUST BE PROVIDED WITH A COPY OF THIS FORM AFTER IT HAS BEEN SIGNED.**

# SAINT BARNABAS MEDICAL CENTER

An affiliate of the Saint Barnabas Health Care System

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

September 24, 2002

Jacques Cohen, Ph.D.  
Saint Barnabas Medical Center  
Institute For Reproductive Medicine & Science  
101 Old Short Hills Road, Suite 501  
West Orange, NJ. 07052

RE: IRB Study # 02-33

Dear Dr. Cohen:

**Meeting Date:** 8/20/2002

**At:** Saint Barnabas Med Ct

**Protocol Title:**

STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS

To advise you that the above referenced Study has been presented to the Institutional Review Board identified above, and the following action taken subject to the conditions and explanation provided below.

**Internal #:** New Appl

**Expiration Date:** 8/19/2003

**On Agenda For:** Initial Submission

**Reason 1:**

**Description** Date Received- 7/31/2002

**IRB ACTION:** Approved

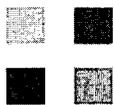
**Action** Protocol (dated 8/26/02) and consent form (dated 8/23/02) approved

**Explanation:** IRB regulations require submission of an annual report and prompt notification of untoward events. At the completion of your study a final report should be submitted.

Sincerely,

Robert L. Goodman, M.D.  
Chairman, IRB



 **SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

RONALD J. DEL MAURO  
 Chairman  
 Board of Trustees

November 02, 2004

Jacques Cohen, Ph.D.  
 Saint Barnabas Medical Center  
 Institute For Reproductive Medicine & Science  
 101 Old Short Hills Road, Suite 501  
 West Orange, NJ. 07052

RE: IRB Study # 02-33                      At: Saint Barnabas Med Ct

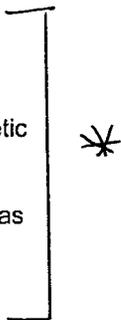
Dear Dr. Cohen:

**Protocol Title:**  
 STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS

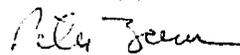
This letter is to acknowledge the receipt of the information identified below.

**Expiration Date:**      8/19/2003  
**Our Internal #:**        1072  
**Type of Change:**      Consent Modification                      Approved  
**Expedited ?:**              
**Date of Change:**        11/2/2004  
**Date Received:**        11/2/2004  
**On Meeting Date:**      11/16/2004

**Description:**      Revised informed consent form dated 8/18/04  
                              - Addition of Reprogenetics  
                              - Update of contact information for investigators and IRB  
                              - Addition of sentence "Finally, embryos classified by Preimplantation Genetic  
                              Diagnosis (PGD) as being genetically abnormal were also considered non-  
                              viable."  
                              Updated IRB application - Dr. Múnee previously employed by Saint Barnabas  
                              is now the Director of Reprogenetics



Respectfully yours,

  
 N. Peter Zauber, M.D.  
 Co-Chairman, IRB



**SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

Friday, November 19, 2004

Jacques Cohen, Ph.D.  
Saint Barnabas Medical Center  
Institute For Reproductive Medicine & Science  
101 Old Short Hills Road, Suite 501  
West Orange, NJ. 07052

RE: IRB Study # 02-33

Dear Dr. Cohen:

**Meeting Date:** 11/16/2004                      **At:** Saint Barnabas Med Ct

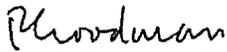
**Protocol Title:**  
STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS

To advise you that the above referenced Study has been presented to the Institutional Review Board identified above, and the following action taken subject to the conditions and explanation provided below.

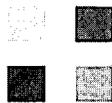
**Internal #:** 1090  
**Expiration Date:** 11/15/2005  
**On Agenda For:** Renewal  
**Reason 1:** Progress Report                      **Reason 2:**  
**Description:** HIPAA Tool #1  
**IRB ACTION:** **Approved**  
**Action** Please make HIPAA Tool #1 available to all patients you are planning to enroll.  
**Explanation:**

IRB regulations require submission of an annual report as long as patients are enrolled in the study and prompt notification of untoward events. At the completion of your study a final annual report should be submitted.

Sincerely,

  
Robert L. Goodman, M.D.  
Chairman, IRB



 **SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

RONALD J. DEL MAURO  
 Chairman  
 Board of Trustees

January 18, 2006

Jacques Cohen, Ph.D.  
 Saint Barnabas Medical Center  
 Institute For Reproductive Medicine & Science  
 101 Old Short Hills Road, Suite 501  
 West Orange, NJ. 07052

RE: IRB Study # 02-33

Dear Dr. Cohen:

**Meeting Date:** 1/17/2006                      **At:** Saint Barnabas Med Ct

**Protocol Title:**  
 STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS

To advise you that the above referenced Study has been presented to the Institutional Review Board identified above, and the following action taken subject to the conditions and explanation provided below.

**Internal #:** 1660  
**Expiration Date:** 1/16/2007  
**On Agenda For:** Renewal  
**Reason 1:** Progress Report                      **Reason 2:**  
**Description:**  
**IRB ACTION:** **Approved**  
**Action** IRB regulations require submission of an annual report and prompt notification of  
**Explanation:** untoward events. At the completion of your study a final report should be submitted.

Sincerely,

  
 Robert L. Goodman, M.D.  
 Chairman, IRB



**SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

February 21, 2007

Jacques Cohen Ph.D.  
Saint Barnabas Medical Center  
Institute For Reproductive Medicine & Science  
101 Old Short Hills Road, Suite 501  
West Orange NJ 07052

**RE: IRB Study # 02-33**

Dear Dr. Cohen:

**Meeting Date:** 2/20/2007

**At:** Saint Barnabas Med Ct

**Protocol Title:**

STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS

This is to advise you that the above referenced Study has been presented to the Institutional Review Board, and the following action taken subject to the conditions and explanation provided below.

**Internal #:** 2201

**Expiration Date:** 2/19/2008

**On Agenda For:** Renewal

**Reason 1:** Progress Report

**Reason 2:**

**Description:** Revised informed consent form dated 1/25/07 - updates Principal Investigator's current contact information

**IRB ACTION:** **Approved**

**Condition 1:**

**Action**

**Explanation:** IRB regulations require submission of an annual report and prompt notification of untoward events. At the completion of your study a final report should be submitted.

Sincerely,



Robert L. Goodman, M.D.  
Chairman, IRB



**SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

April 9, 2009

Jacques Cohen Ph.D.  
Saint Barnabas Medical Center  
Institute For Reproductive Medicine & Science  
101 Old Short Hills Road, Suite 501  
West Orange NJ 07052

Dear Dr. Cohen:

This letter is to acknowledge the receipt of the information identified below.

**Our Study # 02-33**

**Protocol Title: STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS**

**Expiration Date:** 3/17/2009  
**Our Internal #:** 3229  
**Type of Change:** Consent Modification                      Pre Meeting Action: Approved  
**Expedited ?:** Yes  
**Date of Change:** 4/9/2009  
**Date Received:** 4/9/2009  
**On Meeting Date:** 4/21/2009

**Description:**

Revised informed consent form dated 3/13/09

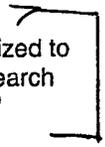
Page 2, paragraph 3, has been deleted -"Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from the non-viable embryos donated by you, will ever be used for curing genetic or other disease, or for production of commercial stem-cell lines." The reasons for this are obvious. Stem-cell lines once obtained are rare commodities and clinically important. They can not be shared with universities or other institutions by the self-imposed limitations of this paragraph. This paragraph has been replaced with Section E which was verbatim obtained from guidelines provided by NIH regarding this topic.

Section E states "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."



Respectfully yours,

N. Peter Zauber, M.D.  
Co-Chairman, IRB

**SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

April 21, 2009

Jacques Cohen Ph.D.  
Saint Barnabas Medical Center  
Institute For Reproductive Medicine & Science  
101 Old Short Hills Road, Suite 501  
West Orange NJ 07052

**RE: IRB Study # 02-33**

Dear Dr. Cohen:

**Meeting Date:** 4/21/2009

**At:** Saint Barnabas Med Ct

**Protocol Title:**

**STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS**

This is to advise you that the above referenced Study has been presented to the Institutional Review Board, and the following action taken subject to the conditions and explanation provided below.

**Internal #:** 3224

**Expiration Date:** 4/20/2010

**On Agenda For:** Renewal

**Reason 1:** Progress Report

**Reason 2:**

**Description:**

**IRB ACTION:** Approved

**Condition 1:**

**Action**

**Explanation:** IRB regulations require submission of an annual report and prompt notification of untoward events. At the completion of your study a final report should be submitted.

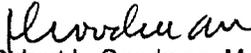
PLEASE NOTE: The Saint Barnabas Medical Center IRB Policy #29 states under Investigator Responsibilities, Item #9, "On-Site adverse events and unanticipated outcomes will be reported to the IRB by the Principal Investigator within seventy-two hours of the investigator becoming aware that there has been an on-site adverse event."

EXPIRATION DATE: 4/20/10: A REQUEST FOR RENEWAL MUST BE SUBMITTED TO THE IRB OFFICE AT LEAST 30 DAYS PRIOR TO THE



ABOVE EXPIRATION DATE. AN ANNUAL REPORT FORM IS ENCLOSED.

Sincerely,

  
Robert L. Goodman, M.D.  
Chairman, IRB

37

 **SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

RONALD J. DEL MAURO  
 Chairman  
 Board of Trustees

October 8, 2009

Jacques Cohen Ph.D.  
 Saint Barnabas Medical Center  
 Institute For Reproductive Medicine & Science  
 101 Old Short Hills Road, Suite 501  
 West Orange NJ 07052

Dear Dr. Cohen:

This letter is to acknowledge the receipt of the information identified below.

**Our Study # 02-33**

**Protocol Title: STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS**

**Expiration Date:** 4/20/2010  
**Our Internal #:** 3445  
**Type of Change:** (Other)                      Pre Meeting Action: Acknowledged  
**Expedited ?:** No  
**Date of Change:** 10/8/2009  
**Date Received:** 10/8/2009  
**On Meeting Date:** 10/20/2009  
**Description:**

Receipt of notification (letter dated September 15, 2009) that the investigator will re-consent patients with revised informed consent form dated 3/13/09. The revised consent form was reviewed and granted expedited approval on April 9, 2009.

]\*

Respectfully yours,

  
 Robert L. Goodman, M.D.  
 Chairman, IRB



■ **SAINT BARNABAS**  
■ **MEDICAL CENTER**

*An affiliate of the Saint Barnabas Health Care System*

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

The Institute for Reproductive Medicine and Science  
Of Saint Barnabas Medical Center

**Stem-cell research using discarded and abnormal embryos**

**A** – You are invited to donate any “non-viable” embryos that may result from your current attempt at in-vitro fertilization. Participation will in no way affect the normal progress of your attempt at in vitro fertilization, including the possibility of later replacement of thawed embryos from this attempt, nor will it affect your chances of pregnancy, as the study of non-viable embryos would not commence until completion of each of the steps necessary to identify any individual embryo as non-viable.

**B** –The Gamete and Embryo Research Laboratory of the Institute for Reproductive Medicine and Science of Saint Barnabas Medical Center is engaged in studies aimed at developing new, more efficient ways of isolating and culturing embryonic stem cells. Stem-cells are cells that are not yet differentiated or changed into specialized cells such as muscle and blood cells. Embryos, even abnormal ones, can be used as a source of stem cells. Research on such embryonic stem cells is of fundamental importance for the progress of medicine, not least reproductive medicine, in the decades ahead. The reason is that stem cell research not only will allow a better understanding of the causes and mechanisms underlying a host of devastating diseases, but also offers a very real prospect of alleviating, even curing many of these diseases, among them Juvenile Diabetes and Muscular Dystrophy. Physicians and scientists at the Saint Barnabas Medical Center believe that the embryological research for which your non-viable embryos would be donated can play an important, even crucial role in the developments ahead.

The non-viable embryos donated by you will be used in one or more of the following studies:

- The development of culture techniques that will allow scientists to isolate and grow stem-cells from a single or a few embryonic cells. These studies may involve using animal cells, including cells from animal embryos, for initial growth support. The animal cells would serve as “feeder cells”, providing the right environment until the human cells can survive by themselves.
- Isolation and analysis of stem-cells from embryos discarded due to abnormal chromosome numbers.
- The development of improved methods for stem-cell storage.
- The development of new methods for transforming stem-cells into other cell types.



Only your "non-viable" embryos, i.e. those that are unsuitable for replacement and would otherwise be discarded, are eligible for donation, and none of the experiments will give rise to normal embryos at any stage. However, the non-viable embryos donated by you may give rise to embryonic stem cells. These stem cells may be genetically normal or genetically abnormal depending, primarily, on whether the isolated cells from which they grew were genetically normal or abnormal to begin with. Both categories of stem cells are of fundamental scientific and biomedical interest.

The methods used in the studies include new processes of cell manipulation and culture of embryonic cells. Any non-viable embryos donated by you may thus be manipulated and cultured, in some instances for an extended period of time, 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 non-viable embryos, they could give rise to different cell types, such as pancreatic cells or neural cells.

Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from, the non-viable embryos donated by you, will ever be used to impregnate another woman or to assist any individual or couple in any way to become pregnant. Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from the non-viable embryos donated by you, will ever be used for curing genetic or other disease, or for production of commercial stem-cell lines. Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from, the non-viable embryos donated by you, will ever be donated for use to other individuals, centers, or corporations.

**D** – Participation in these studies by donation of non-viable 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. It is also unlikely that you will receive any direct personal benefits from participation at this time; however, it is likely that, in the future, patients will benefit from the knowledge we will gain from these studies.

**F** – This consent form is being offered to all couples treated with IVF at Saint Barnabas Medical Center. Any information obtained during this study and identified with you will remain confidential. The Food and Drug Administration (FDA) and The Center for Disease Control (CDC) in association with the Society for Assisted Reproduction (SART) may inspect the records. There are no added costs related to your participation in this study. Your decision whether or not to participate will not prejudice your future relations with Saint Barnabas Medical Center and the treatment you now undergo in this institute. If you decide to participate, you are free to discontinue participation at any time. 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 have any questions regarding your rights as a research subject, please call the office of the IRB chairman, Dr. Goodman at (973) 322-5637. The principle investigator of this protocol is Dr. Steen Willadsen, who can be reached at 973-3226310. You may request a copy of this form.

**G** – I/We hereby attest that we have read the entire consent form, or that it has been read to us, so that we understand it completely. I/we further attest that any and all questions of mine/us regarding this form or this study have been answered to my/our complete satisfaction. We agree that stem-cells may be developed from our non-viable embryos.

Signed: name female partner \_\_\_\_\_ Signature \_\_\_\_\_

Signed: name male partner \_\_\_\_\_ Signature \_\_\_\_\_

Witnessed: name \_\_\_\_\_ Signature \_\_\_\_\_

Date: \_\_\_\_\_

APPLICATION TO UNDERTAKE RESEARCH INVOLVING HUMAN SUBJECTS

Checklist

TITLE OF PROPOSED RESEARCH:

Stem-cell research using discarded non-viable embryos

INVESTIGATOR(S) AND DEPARTMENT(S):

Steen Willadsen, DVM, Jacques Cohen, Ph.D., Mina Alikani, M.Sc., Margaret Garrisi, M.D.,  
David Sable, M.D. Institute for Reproductive Medicine and Science, Department of Gynecology  
and Obstetrics

THIS PROTOCOL IS TO BE CONSIDERED FOR

(check only one box)

- EXEMPTION FROM REVIEW
- EXPEDITED REVIEW
- FULL IRB REVIEW

The proposed research will be carried out in cooperation with the following institution  
\_\_\_\_\_ (if applicable)

Date of approval by cooperating institution's IRB \_\_\_\_\_

Human subjects would be involved in the proposed research as either:

None of the following

or including (Check all applicable boxes)

- Minors
- Fetuses
- Abortuses
- Pregnant women
- Prisoner
- Mentally retarded
- Mentally disabled
- Non-English-speaking subjects



Abnormal gametes and embryos are an excellent source of material for studying anomalies that can occur during gametogenesis and embryogenesis. Discarded non-viable material resulting from in-vitro fertilization (IVF) can also be used to develop new technology applicable to the treatment of infertile patients (protocol #769). Protocol 769 was revised in February 2002 and allowed us to extend the study of non-viable embryos into the field of embryonic stem-cell research. We have developed several technologies that could almost certainly be used to make production of human embryonic stem-cells from embryos simpler and more efficient. The fact that these technologies primarily use non-viable embryos as the source of embryonic stem-cells is of particular relevance in the current funding climate which does not allow the use of viable human embryos for that purpose (Alikani and Willadsen; Reproductive Medicine Online; 5, 56-58, 2002). However, we have not yet developed stem-cell lines from such embryos. Here we propose to develop the technology further with the end-point of stem-cell formation. The isolation of chromosomally normal and abnormal stem-cell lines from non-viable embryos is important. For one thing it avoids the dilemma posed by the use of viable human embryos for stem-cell production, and may therefore allow government funding. The reason for making the present protocol separate from protocol 769 using non-viable embryos is the need for patients' permission to use discarded non-viable embryos for isolation of stem-cells. Inherent in this kind of research is the unpredictability of the duration of individual experiments, particularly since abnormal embryos and stem-cells can be frozen. The isolation and experimental culture of embryonic stem cells is considered to be of fundamental importance for the progress of medicine. Stem cell based research offers the prospect of cures to many devastating diseases such as Juvenile Diabetes, Muscular Dystrophy and Alzheimer's Disease.

- 9). Outline of Proposed Study (State briefly but precisely what is to be done. If the study is to be conducted according to a detailed protocol of a pharmaceutical company or outside agency, include a precis here and attach the full protocol as an appendix. If the study involves the use of a questionnaire or structured interview, attach the text of such instruments as an appendix. Note: IRB review focuses on the scientific merit and adequacy of experimental design as well as on issues of safety and protection of confidentiality).

Non-viable embryos donated by patients will be selected based on criteria used in our program. These are embryos that contain too few normal cells – often no normal cells at all – for the formation of a viable/ normal conceptus. Non-viable embryos include those that have detrimental forms of fragmentation or multi-nucleation, or that stopped growing during serial observation. Other embryos may seem viable following preimplantation genetic diagnosis (PGD) (that is they divide) but are diagnosed as trisomic or monosomic. Yet other abnormal embryos are polyploid, haploid or chaotic mosaic.

The zona pellucida of the embryos will be removed, and individual mono-nucleate cells will be isolated. They will be grown together from cohorts of embryos in order to form pseudo-blastocysts (Alikani and Willadsen, 2002) or cultured individually with mouse or cow embryonic cells or embryos that have been manipulated to support the growth of human

embryonic cells to develop into stem-cells. Animal and human cells will be immunologically or mechanically separated, but in some models the cells can be isolated by varying culture conditions. The stem-cell development will be studied by analyzing the expression of Oct-4, a gene that only is expressed in early embryos, and the inner cell mass and embryonic stem cells. Ploidy will be studied by fluorescence in-situ hybridization (FISH).

- 10) Subject (State the kind(s), ages, sex, and appropriate numbers of subjects to be studied. Indicate the criteria for the selection of the proposed kinds and number of subjects. If populations at special risk (cf. checklist) are to be studied, provide the reason(s) for their inclusion. Specify population groups to be excluded (e.g. pregnant women). Indicate composition of control groups.)

**The investigations will be conducted in 500 patients annually. There are no risks to the couple and no specific groups will be excluded.**

- 11). Drugs (Provide specific information on proposed dosage levels and schedules. Include both the generic and commercial name of each drug and summarize available information on efficacy and side effects. If none are to be administered, enter this statement: "No drugs will be given.")

**No additional drugs are needed for the completion of the proposed studies other than those used for assisted reproduction procedures.**

- 12). Blood Sampling (State the volume to be drawn on each occasion and the frequency of sampling from the same subject. If none is to be drawn, enter this statement: "No blood will be drawn.")

**No blood will be drawn.**

- 13). Tissue Sampling (State the type of tissue to be collected, volume (if applicable), and frequency of sampling from the same subject (if applicable). If no other tissues will be collected, enter this statement: "No other tissues will be collected.")

**No extra tissues will be collected.**

- 14). Radioactive Isotopes (Give the identity and dose of each isotope. If none are to be administered, enter this statement: "No radioactive isotopes will be given").

**No radioactive isotopes will be given.**

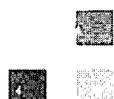
- 15). Safety (State in adequate detail any anticipated physical, mental, or emotional risk to the subjects of this research activity and the degree of likelihood that it may occur. If no such risk is anticipated, state why this is so).

**There is no additional risk to the patients other than those involved with regular IVF.**

- 16). Confidentiality (Describe the adequate detail what measures will be taken to protect the confidentiality of the data to be obtained and the subject's rights to privacy).

**Patient names, IDs, etc. will be kept strictly confidential. Files and databases will be locked or only made accessible to privileged investigators. Anonymous case reports will only be published after the patients grant permission.**

- 17). Informed Consent (State whether it is planned to obtain informed consent from each subject of the research activity. If informed consent will be obtained, complete the attached Part B. It is not planned to do so, provide in this space, thorough justification for its omission. Note: Federal regulations provide that written informed consent be obtained from each subject of a research activity, but this requirement may be waived by the IRB under specific circumstances (cf. attachment to Part B). **We will ask each couple to provide written consent after fully informing them in a private consultation. The IRB consent form is attached.**

 **SAINT BARNABAS**  
**HEALTH CARE SYSTEM**  
*Saint Barnabas Medical Center*

(46)

RONALD J. DEL MAURO  
Chairman  
Board of Trustees

April 9, 2009

Jacques Cohen Ph.D.  
Saint Barnabas Medical Center  
Institute For Reproductive Medicine & Science  
101 Old Short Hills Road, Suite 501  
West Orange NJ 07052

Dear Dr. Cohen:

This letter is to acknowledge the receipt of the information identified below.

**Our Study # 02-33**

**Protocol Title: STEM CELL RESEARCH USING DISCARDED NON-VIABLE EMBRYOS**

**Expiration Date:** 3/17/2009  
**Our Internal #:** 3229  
**Type of Change:** Consent Modification                      **Pre Meeting Action:** Approved  
**Expedited ?:** Yes  
**Date of Change:** 4/9/2009  
**Date Received:** 4/9/2009  
**On Meeting Date:** 4/21/2009

**Description:**

Revised informed consent form dated 3/13/09

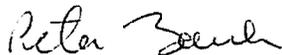
Page 2, paragraph 3, has been deleted -"Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from the non-viable embryos donated by you, will ever be used for curing genetic or other disease, or for production of commercial stem-cell lines." The reasons for this are obvious. Stem-cell lines once obtained are rare commodities and clinically important. They can not be shared with universities or other institutions by the self-imposed limitations of this paragraph. This paragraph has been replaced with Section E which was verbatim obtained from guidelines provided by NIH regarding this topic.

Section E states "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."

Respectfully yours,



N. Peter Zauber, M.D.  
Co-Chairman, IRB

# Re-consent Information

48



March 31, 2009

Robert L. Goodman, M.D.  
Chairman, IRB  
Saint Barnabas Medical Center  
Livingston, NJ 07039

Dear Dr. Goodman:

I hope this letter finds you well. We would like to update the consent form for our protocol 02-33 entitled "Stem-cell research using discarded non-viable embryos".

In the consent form (page 2, paragraph 3), we have eliminated the paragraph "Neither the non-viable embryos donated by your, nor any cells isolated from, or developing from the non-viable embryos donated by you, will ever be used for curing genetic or other disease, or for production of commercial stem-cell lines". The reasons for this are obvious. Stem-cell lines once obtained are rare commodities and clinically important. They can not be shared with universities or other institutions by the self-imposed limitations of this paragraph. We have therefore deleted it and replaced it with section E which was verbatim obtained from guidelines provided by NIH regarding this topic. Some of these cell lines are clinically important and should be shared for research. We have obtained a number of nice lines from this research and there is interest from other institutes to share the material.

Please feel free to contact me if you have any questions or concerns. I can be reached at 973.436.5011.

Sincerely,

A handwritten signature in black ink, appearing to read "Jacques Cohen".

Jacques Cohen, Ph.D.

JC/laf

LEADERS IN SCIENCE partner in care

Enclosure

SERENA H CHEN MD • MARGARET GRAF GARRISI MD • NATALIE A CEKLENIAC MD

DONOR DID NOT SIGN / RETURN

(49)



**Stem-cell research using discarded non-viable embryos**

**A** – You are invited to donate any “non-viable” embryos that may result from your current attempt at in-vitro fertilization. Participation will in no way affect the normal progress of your attempt at in vitro fertilization, including the possibility of later replacement of thawed embryos from this attempt, nor will it affect your chances of pregnancy, as the study of non-viable embryos would not commence until completion of each of the steps necessary to identify any individual embryo as non-viable.

**B** –The Gamete and Embryo Research Laboratory of the Institute for Reproductive Medicine and Science at Saint Barnabas and Reprogenetics are engaged in studies aimed at developing new, more efficient ways of isolating and culturing embryonic stem cells. Stem-cells are cells that are not yet differentiated or changed into specialized cells such as muscle and blood cells. Embryos, even abnormal ones, can be used as a source of stem cells. Research on such embryonic stem cells is of fundamental importance for the progress of medicine, not least reproductive medicine, in the decades ahead. The reason is that stem cell research not only will allow a better understanding of the causes and mechanisms underlying a host of devastating diseases, but also offers a very real prospect of alleviating, even curing many of these diseases, among them Juvenile Diabetes and Muscular Dystrophy. Physicians and scientists at the Saint Barnabas Medical Center believe that the embryological research for which your non-viable embryos would be donated can play an important, even crucial role in the developments ahead.

Non-viable embryos are selected based on standard criteria used in our laboratory. Embryos are non-viable when eggs fertilize abnormally or fail to divide after fertilization. Others may divide too slowly or appear abnormal. Processes that are included in the evaluation of viability are fragmentation (the blebbing of cells) and the number of nuclei per cell. Fragments are not always considered detrimental, but certain types of fragmentation are known to cause demise of the embryo. Abnormal nuclei do not always cause failure of pregnancy, and the decision to consider such embryos abnormal is very much dependent on the ratio of abnormal cells and the type of abnormal nucleus. Criteria for evaluation are also stage-specific. In other cases embryos are considered non-viable because the embryo appears disorganized and several types of anomalies can be distinguished.

The non-viable embryos donated by you will be used in one or more of the following studies either before or after they are frozen:

- The development of culture techniques that will allow scientists to isolate and grow stem-cells from a single or a few embryonic cells. These studies may involve using animal cells, including cells from animal embryos, for initial growth support. The animal cells would serve as “feeder cells”, providing the right environment until the human cells can survive by themselves.

LEADERS IN SCIENCE partners in care

SERENA H CHEN MD • MARGARET GRAF GARRISI MD • NATALIE A CEKLENIAK MD

94 Old Short Hills Road, Suite 403E, Livingston, NJ 07039 T 973.322-8286 F 973.322.8890

609 Washington Street, Hoboken, NJ 07030 T 201.963.7640

W www.sbivf.com

- Isolation and analysis of stem-cells from embryos discarded due to abnormal chromosome numbers.
- The development of improved methods for stem-cell storage. Thawed stem-cells would be tested for viability and characteristics as well as their ability to transform into other cell-types.
- The development of new methods for transforming stem-cells into other cell types.

Only your "non-viable" embryos, i.e. those that are unsuitable for replacement and would otherwise be discarded, are eligible for donation, and none of the experiments will give rise to normal embryos at any stage. However, the non-viable embryos donated by you may give rise to embryonic stem cells. These stem cells may be genetically normal or genetically abnormal depending, primarily, on whether the isolated cells from which they grew were genetically normal or abnormal to begin with. Both categories of stem cells are of fundamental scientific and biomedical interest.

The methods used in the studies include new processes of cell manipulation and culture of embryonic cells. Any non-viable embryos donated by you may thus be manipulated and cultured, in some instances for an extended period of time, 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 non-viable embryos, they could give rise to different cell types, such as pancreatic cells or neural cells. Frozen-thawed stem-cells and embryos will be subjected to the same research protocols as described above.

**D** – Participation in these studies by donation of non-viable 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. It is also unlikely that you will receive any direct personal benefits from participation at this time; however, it is likely that, in the future, patients will benefit from the knowledge we will gain from these studies.

**E** – *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.

**F** – This consent form is being offered to all couples treated with IVF at Saint Barnabas Medical Center. Any information obtained during this study and identified with you will remain confidential. The Food and Drug Administration (FDA) and The Center for Disease Control

(5)

(CDC) in association with the Society for Assisted Reproduction (SART) may inspect the records. There are no added costs related to your participation in this study. Your decision whether or not to participate will not prejudice your future relations with Saint Barnabas Medical Center and the treatment you now undergo in this institute. If you decide to participate, you are free to discontinue participation at any time. 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 have any questions regarding your rights as a research subject, please call the office of the IRB chairman, Dr. Goodman at (973) 322-5637. The principle investigator of this protocol is Dr. G. John Garrisi, who can be reached at 973-322-8286. You may request a copy of this form.

G – I/We hereby attest that we have read the entire consent form, or that it has been read to us, so that we understand it completely. I/we further attest that any and all questions of mine/us regarding this form or this study have been answered to my/our complete satisfaction. We agree that stem-cells may be developed from our non-viable embryos.

Signed: name female partner \_\_\_\_\_ Signature \_\_\_\_\_

Signed: name male partner \_\_\_\_\_ Signature \_\_\_\_\_

Witnessed: name \_\_\_\_\_ Signature \_\_\_\_\_

Date: \_\_\_\_\_

(52)

**Hannemann, Diane (NIH/OD) [E]**

---

**From:** Santiago Munne [munne@reprogenetics.com]  
**Sent:** Friday, January 29, 2010 10:17 AM  
**To:** HESCREGISTRY (NIH/NIDCD)  
**Cc:** Mina Alikani  
**Subject:** FW: New hESC Registry Application Request #2009-ADM-008  
**Attachments:** Request #2009-ADM-008\_RESPONSE TO QUESTIONS.DOC

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Dear Dr. Gadbois,

Attached please find a document answering your questions. ] see pp. 53-54

Best wishes,

Santiago Munné, Ph.D.  
President  
Reprogenetics  
3 Regent Street, Suite 301  
Livingston, NJ-07039  
[munne@reprogenetics.com](mailto:munne@reprogenetics.com)  
Tel. 973-4365010  
Fax. 973-9921308  
[www.reprogenetics.com](http://www.reprogenetics.com)

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This information has been disclosed to you from records whose confidentiality is protected by state law. State law prohibits you from making any further disclosure of such information without the specific written consent of the person to whom such information pertains, or as otherwise permitted by state law.

---

**From:** HESCREGISTRY (NIH/NIDCD) [mailto:hescregistry@mail.nih.gov]  
**Sent:** Thursday, January 28, 2010 2:33 PM  
**To:** Santiago Munne  
**Cc:** HESCREGISTRY (NIH/NIDCD)  
**Subject:** RE: New hESC Registry Application Request #2009-ADM-008

Thank you for your submission. The NIH Administrative Review team has several questions about the submission. Please reply to this email and attach any relevant documents and we will update your submission.

1. Please confirm that RNJ7 was derived from the inner cell mass of a blastocyst stage human embryo (as required under the definition of hESCs in the Guidelines.)

**(SUPPORTING INFORMATION FROM SUBMITTER IN JANUARY 29, 2010 EMAIL):**

RE: New hESC Registry Application Request #2009-ADM-008  
RESPONSE TO QUESTIONS

1. Please confirm that RNJ7 was derived from the inner cell mass of a blastocyst stage human embryo (as required under the definition of hESCs in the Guidelines.)

- Yes. RNJ7 was derived from the inner cell mass of a human blastocyst. ] \*

2. We note that the letter of explanation indicates that the donor of the embryo from which RNJ7 was derived was "a patient." Please confirm that the individuals(s) who sought reproductive treatment gave voluntary written consent for donation of the embryo. For example, if it was a couple who sought treatment, whether both partners (even if one was not a gamete donor) gave consent for donation of the embryo.

- Yes. The couples under treatment for infertility gave voluntary written consent for embryo donation. This includes both the female and the male partner whose gametes were used to generate the embryos for reproductive purposes. ] \*

3. Please address further how the following element of the Guidelines is met: "Element 4. No payments, cash or in kind, were offered for the donated embryos."

- Element 4 of the Guidelines is met in Paragraph D, on page 2 of the stem cell research consent form (DOCUMENT 2) in which it is stated:

your chances of becoming pregnant be affected in any way. It is also unlikely that you will receive any direct personal benefits from participation at this time; however, it is likely that, in the future, patients will benefit from the knowledge we will gain from these studies. ] \*

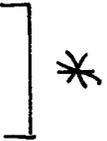
4. Please address further how the following element of the Guidelines is met: "Element 6. Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize hESCs in research. The attending physician 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." In particular, please clarify which individual was the treating physician for the donor of the embryo from which RNJ7 was derived and which individuals were investigators.

- Element 6 of the Guidelines is met since the treating physician was Dr. Margaret Garrisi (along with Drs. Natalie Cekleniak and Serena Chen) of the Institute for Reproductive Medicine and Science at Saint Barnabas Medical Center (NJ); the researchers are at Reprogenetics, LLC (NJ) and have no role whatsoever in the consenting process or the IVF treatment process. ] \*

5. Please address further how the following element of the Guidelines is met: "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."

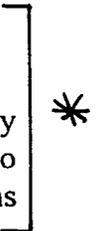
- Element 7 of the Guidelines is met as we have a copy of the actual consent the patients signed before commencing their treatment cycle, for donation of their non-viable embryos at the completion of their treatment cycle. This process is standard practice at IRMS.



6. Please address further how the following element of the Guidelines is met: "Element 8. Donor(s) should have been informed that they retained the right to withdraw consent until the embryos were actually used to derive embryonic stem cells or until information that could identify the donor(s) was no longer retained by the researchers, if applicable."

- Element 8 of the Guidelines is met in Paragraph F on page 2 of the stem cell research consent (DOCUMENT 2). It states:

institute. If you decide to participate, you are free to discontinue participation at any time. 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 have any questions

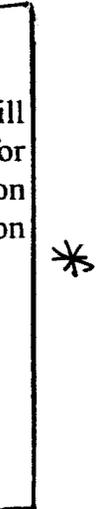


7. Please address further how the following element of the Guidelines is met: "Element 15. Whether information that could identify the donor(s) would be available to researchers."

- Element 15 of the guideline is met in Paragraph F of the stem cell research consent form (DOCUMENT 2) which states that:

Medical Center. Any information obtained during this study and identified with you will remain confidential. The Food and Drug Administration (FDA) and The Center for Disease Control (CDC) in association with the Society for Assisted Reproduction (SART) may inspect the records. There are no added costs related to your participation

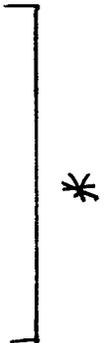
- This guarantees confidentiality except in the case of specific agencies/organizations which may be involved in oversight. Of course, in order to accept the donations, Reprogenetics is given access to the identity of the donors so we can confirm that proper consents have been obtained from the donor and get detailed information on the donated embryo/s. No other entity will have access to any identifying information (except for cell line number) and Reprogenetics will in due course de-identify the cell lines it banks.



8. Please confirm which version of the consent form was used for the donation of the embryo from which RNJ7 was derived.

The patients have signed two consent forms: general IVF consent (DOCUMENT 1) and stem cell research consent (DOCUMENT 2).

We have stated (DOCUMENT 3) that the donors will be asked by the treating physicians at IRMS whether they are willing to sign a newer version of the consent form. The donors of RNJ7 have not yet been contacted. If and when they decide to sign the new consent, we will make a submission to the NIH Registry in order to remove the present restrictions on the use of this particular cell line.



**From:** Santiago Munne  
**To:** HESCREGISTRY (NIH/NIDCD)  
**Cc:** Mina Alikani  
**Subject:** RE: New hESC Registry Application Request #2009-ADM-008  
**Date:** Tuesday, February 02, 2010 11:18:33 AM  
**Attachments:** Request #2009-ADM-008 2nd RESPONSE TO QUESTIONS Final.doc

Dear Dr. Gadbois,

Please find attached our response to your questions.

] see pp. 56-57

Best wishes,

Santiago Munné, Ph.D.  
President  
Reprogenetics  
3 Regent Street, Suite 301  
Livingston, NJ-07039  
[munne@reprogenetics.com](mailto:munne@reprogenetics.com)  
Tel. 973-4365010  
Fax. 973-9921308  
[www.reprogenetics.com](http://www.reprogenetics.com)

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**From:** HESCREGISTRY (NIH/NIDCD) [mailto:[hescregistry@mail.nih.gov](mailto:hescregistry@mail.nih.gov)]  
**Sent:** Friday, January 29, 2010 1:55 PM  
**To:** Santiago Munne  
**Cc:** Mina Alikani; HESCREGISTRY (NIH/NIDCD)  
**Subject:** RE: New hESC Registry Application Request #2009-ADM-008

Dr. Munne,

Thank you for the additional information you have provided. I would like to clarify several points of your response:

1. Please provide further clarification regarding the roles of the treating physicians and the research deriving and/or proposing to utilize hESCs at the time of the donation of the embryo, and how the first sentence of Element 6 is met ("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").

In particular, we note that the original research protocol (document 2) states that Dr. Garrisi was an investigator at the Institute for Reproductive Medicine and Science. Please describe Dr. Garrisi's role in the research.

We also note that Dr. Cohen was listed as an investigator at the Institute for Reproductive Medicine and Science on the 2002 protocol, although it is our understanding from the Reprogenetics website that Reprogenetics, LLC was founded in 2000 by Dr. Cohen and Dr. Munne. Please describe further Dr. Cohen's and Dr. Munne's roles with regards to treatment and/or research at the time of the donation of the embryo.

2. Please also clarify whether the donors were informed whether information that could identify them would be available specifically to the researchers.

Thank you again.

**(SUPPORTING INFORMATION FROM SUBMITTER IN FEBRUARY 2, 2010 EMAIL):**

Sunday, January 31, 2010  
RE: New hESC Registry Application Request #2009-ADM-008  
SECOND RESPONSE TO QUESTIONS

1. Please provide further clarification regarding the roles of the treating physicians and the research deriving and/or proposing to utilize hESCs at the time of the donation of the embryo, and how the first sentence of Element 6 is met ("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").

In particular, we note that the original research protocol (document 2) states that Dr. Garrisi was an investigator at the Institute for Reproductive Medicine and Science. Please describe Dr. Garrisi's role in the research.

- Dr. Margaret Garrisi did not have a role in the research in 2002 or in 2008, when the embryo in question was donated. It is the internal policy of IRMS to have representation from the clinical team on all research protocols initiated by the scientific team and submitted to the IRB of Saint Barnabas Medical Center. This ensures that all parties are aware of and agree with the proposed research projects. Therefore, both Drs. Garrisi (Clinical Director since 2004) and Sable (Clinical Director in 2002) were listed on the protocol as investigators.
- The consenting process at IRMS does not involve the physicians unless patients are being recruited for a clinical trial in which case the physicians must explain all dimensions of the trial to the patient. Ordinarily, patients have their initial intake with an attending physician during which their history and physical are discussed and a treatment plan is devised and agreed upon. All consents including research consents are later presented to patients by the nurses; patients are asked whether they are interested in participation. Patients who are interested sign the consents and those who are not simply do not sign the consents.

We also note that Dr. Cohen was listed as an investigator at the Institute for Reproductive Medicine and Science on the 2002 protocol, although it is our understanding from the Reprogenetics website that Reprogenetics, LLC was founded in 2000 by Dr. Cohen and Dr. Munne. Please describe further Dr. Cohen's and Dr. Munne's roles with regards to treatment and/or research at the time of the donation of the embryo.

- Dr. Cohen was the Scientific Director at IRMS in 2002 and had both clinical and research laboratory duties there. He left his clinical laboratory position at Saint Barnabas in 2004, but he has maintained a working relationship with IRMS (through Tyho-Galileo Research Laboratories) as an off-site Scientific Director. He has a role in maintaining the embryology database and overseeing some aspects of the research program at IRMS. Dr. Munné was in charge of preimplantation genetics at IRMS in 2002. Between the years 2000 and 2004, Reprogenetics operated within IRMS and performed PGD testing for IRMS patients as well as patients from other centers. Currently, Reprogenetics continues to perform PGD testing for IRMS. However, neither Dr. Cohen nor Dr. Munné

has any role in the management or clinical care of IRMS patients. They also do not have a role in patient recruitment for research.

] \*

2. Please also clarify whether the donors were informed whether information that could identify them would be available specifically to the researchers.

- This is not explicitly stated in the consent form. However, IRMS patients are made aware, for instance through the IRMS website (<http://www.sbivf.com/science.html>), that both Dr. Munné and Dr. Cohen are involved in some research projects at IRMS. That this specific team (but no others) has access to patient information is also implied by the statement in the consent form indicating that the patients can withdraw from the studies at any time, meaning that embryos are not immediately de-identified upon donation. Furthermore, immediate de-identification would mean that the system of checks and balances for consent verification prior to embryo use in research would have to be abandoned. At the same time, all parties rely on this system to avoid errors in the use of gametes and embryos in research. As stated earlier, Reprogenetics does not provide any patient identifying information to other researchers that may use the cell lines.

] \*

**From:** [Mina Alikani](#)  
**To:** [HESCREGISTRY \(NIH/NIDCD\)](#)  
**Cc:** [Santiago Munne](#)  
**Subject:** Re: New hESC Registry Application Request #2009-ADM-008  
**Date:** Monday, May 03, 2010 12:13:49 PM  
**Attachments:** [Responses to questions\\_RNJ7\\_May2010.doc](#)

---

Dear Dr. Gadbois,

Please see our responses to all forwarded questions in the attached document. As detailed in the document, the first and last questions await a response from IRMS. As soon as we have those, we will forward them to you.

see pp. 59-62

Best wishes,

Mina Alikani, Ph.D.

On 5/3/10 10:59 AM, "HESCREGISTRY (NIH/NIDCD)" <[hescregistry@mail.nih.gov](mailto:hescregistry@mail.nih.gov)> wrote:

Hello again Dr. Alikani and Dr. Munne,

The Working Group has added two questions to its earlier query. Can you respond to these questions as well as the previous set below? I apologize for any confusion and appreciate your ongoing efforts to provide additional information to NIH.

- 1) Can you please explain whether Saint Barnabas Medical Center and the Institute for Reproductive Medicine and Science have any financial interests in Reprogenetics?
- 2) Can the Institute for Reproductive Medicine and Science confirm that no payments (or other types of inducements) were made for the donation of embryos for research?

Thank you again and please let me know if you have any questions about 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*

**From:** Mina Alikani [<mailto:mina.alikani@embryos.net>]  
**Sent:** Tuesday, April 27, 2010 12:01 PM  
**To:** HESCREGISTRY (NIH/NIDCD)  
**Subject:** Re: New hESC Registry Application Request #2009-ADM-008

Responses to questions forwarded by Dr. Gadbois on 4/21/2010 and 5/3/10 regarding RNJ7:

1. If the reconsenting has taken place: can you provide a copy of the revised consent form with the signature (redacted) of the patient whose embryo was used to create line RNJ7? Alternatively, could you send a letter attesting that the signee has personally seen the signature of the donor on the 2009 revised consent form?

We will forward this as soon as it becomes available. It is our understanding that the patient has not yet returned the signed document.

] \*

2. When did you and Dr. Cohen found Reprogenetics?

Reprogenetics was founded in the year 2001.

] \*

Why was the fact of commercialization not disclosed explicitly in the 2009 re-consent?

The 2009 consent was modeled after the sample consent form published by the International Society for Stem Cell Research (ISSCR). Therefore, a paragraph identical to that in the ISSCR model consent was inserted in the 2009 consent form stating explicitly the potential financial interest in the cell lines – which necessarily implies commercialization of cell lines.

] \*

3. Please confirm that Dr. Garrisi and the treating MD for the IVF patient who donated the embryo for RNJ7 have no financial interest in Reprogenetics.

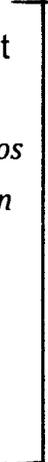
Neither Dr. Garrisi (the treating physician for the IVF patient who donated the embryo for RNJ7) nor any of the other IRMS physicians, staff members, or embryologists have any financial interest in Reprogenetics.

] \*

4. Why did the 2009 re-consent form not contain specific language stating

that the hESC line might be used for allogenic transplantation?

The question of therapeutic use was addressed by removal of a statement in the original consent form which stipulated, "*Neither the non-viable embryos donated by you, nor any cells isolated from, or developing from the non-viable embryos donated by you, will ever be used for curing genetic or other disease, or for production of commercial stem-cell lines.*" There was no deliberate decision *not to* mention allogenic transplantation. It is of course the most unlikely eventuality since we never claimed that these cells were produced under GMP conditions or that they meet all existing/potential FDA requirements for tissue transplantation.



5. Did any of the embryology staff who made decisions as to which embryos were suitable for reproductive purposes have any financial interest in Reprogenetics or have they been co-authors on any abstracts or publications resulting from this hESC research?

None of the embryologists on the staff at IRMS have any financial interest in Reprogenetics or have been co-authors on abstracts or publications that have resulted from this hESC research. Nonetheless, we would argue that inclusion of embryologists on abstracts to acknowledge their contributions, if any, to studies involving stem cells would be both ethical and legitimate.



When they determined whether specific embryos were suitable for reproductive purposes, were they blinded as to whether the IVF patient had agreed to donate unsuitable embryos for research?

It is the internal policy of IRMS, as it is of most IVF laboratories that engage in research on human embryos, to confirm that patients have given written informed consent to embryo research. This confirmation is done on the day before oocyte retrieval and noted on the patient's embryology record. The confirmation is of paramount importance if errors are to be avoided. As such, it is not possible, nor proper, to blind the embryologists with respect to consents. The criteria for embryo selection for transfer and



cryopreservation are well established in written protocols of the laboratory and have been in use at IRMS since 1995. Of course, as discoveries are made, these criteria are modified, amended, and revised – as they should be. The embryologists are trained to make embryo selection decisions with two primary objectives: 1) selecting the best quality embryo(s) for transfer to the patient’s uterus during the current treatment cycle and 2) selecting good to fair quality embryos for cryopreservation for use in a future cycle, with the informed written consent of the patient and when applicable. The ultimate goal of the embryo selection procedure is to establish a healthy pregnancy. Embryos judged as poor quality, i.e., those with multiple morphological, developmental, and/or chromosomal abnormalities, are discarded according to protocol if the patient has not consented to research or moved to a special incubator dedicated to research embryos. This process has been in place since 1995.



\*

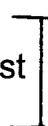
6. Please confirm with regards to the donating couple of RNJ7 that both members of the couple gave consent for donation of the embryo, even if one of the members of the couple was not a gamete donor. (Your response on January 29, 2010 was slightly unclear on this point.) The NIH Guidelines do not require consent from third-party gamete donors, but they do require consent from the individual(s) who sought reproductive treatment.



\*

Written consent for stem cell research was signed by both the female and male partner of the couple who donated the embryo from which RNJ7 was established. This is standard practice at IRMS.

7. Can you please explain whether Saint Barnabas Medical Center and the Institute for Reproductive Medicine and Science have any financial interests in Reprogenetics?



\*

Neither Saint Barnabas Medical Center nor IRMS has any financial interest in Reprogenetics.

8. Can the Institute for Reproductive Medicine and Science confirm that no payments (or other types of inducements) were made for the donation of embryos for research?

(b2)

The consent forms signed by donating patients specifically state that the patient does not receive any benefits from donation of embryos. Accordingly, there is absolutely no payment or any other type of inducements for the donation of embryos for any type of research, including stem cell research. We will request that the clinical Director at IRMS make this statement personally and we will forward her e-mail to Dr. Gadbois.



**From:** [Mina Alikani](#)  
**To:** [Gadbois, Ellen \(NIH/OD\) \[E\]](#)  
**Cc:** [Santiago Munne](#)  
**Subject:** FW: embryos donated for research  
**Date:** Tuesday, May 11, 2010 8:01:35 PM

---

Dear Dr. Gadbois,

Per your recent request, Dr. Garrisi has written on behalf of IRMS to confirm that embryo donations to research are not compensated in any way by IRMS. Her e-mail is below.

] \*

The second outstanding matter – that of the new consent from the donors of the embryo from which RNJ7 was established - remains unresolved. Dr. Garrisi has informed us that although the patients have received the new consent form, they have not yet returned a signed copy to IRMS. As such, we will continue to impose the original limitations of no therapeutic use and no commercial use on this particular cell line. If the patients should return the new consent, we will forward a redacted copy to you.

] \*

Best wishes,

Mina Alikani, Ph.D.

----- Forwarded Message

**From:** Margaret Garrisi <[MGarrisi@sbivf.com](mailto:MGarrisi@sbivf.com)>  
**Date:** Tue, 11 May 2010 18:04:18 -0400  
**To:** Mina Alikani <[mina.alikani@embryos.net](mailto:mina.alikani@embryos.net)>  
**Subject:** embryos donated for research

Dear Dr. Mina Alikani,

At the Institute for Reproductive Medicine and Science at Saint Barnabas, no payments or other inducements are or have been made to patients who donate embryos for research.

] \*

Sincerely,  
Margaret Graf Garrisi, MD  
Medical Director of Assisted Reproduction  
Institute for Reproductive Medicine and Science at Saint Barnabas

----- End of Forwarded Message

**From:** [Mina Alikani](#)  
**To:** HESCREGISTRY (NIH/NIDCD)  
**Subject:** Re: embryos donated for research  
**Date:** Monday, May 17, 2010 2:07:31 PM

---

Dear Dr. Gadbois,

Thank you for your e-mail. We will inform the NIH of the patient's decision as soon as we are informed by IRMS. Further, we would like RNJ7 to be considered but with the previously stipulated restrictions.

] \*

Lastly, there are other cell lines which we plan to submit for which we do have new consents. We gave priority to RNJ7 because of existing non-commercial research interests and the fact that it has been well characterized.

Best wishes,

Mina Alikani, Ph.D.

On 5/17/10 1:57 PM, "HESCREGISTRY (NIH/NIDCD)" <[hescregistry@mail.nih.gov](mailto:hescregistry@mail.nih.gov)> wrote:

Hello Dr. Alikani,

Thank you again for the additional information. Please do let us know if the donors sign the new consent form (or if they ultimately decline to do so).

Can you confirm that you would like NIH to make a determination on eligibility of the line for listing on the NIH Registry even if the donor has not signed the new consent form?

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:** Tuesday, May 11, 2010 8:02 PM

**From:** [Mina Alikani](#)  
**To:** [HESCREGISTRY \(NIH/NIDCD\)](#)  
**Cc:** [Santiago Munne](#)  
**Subject:** Re: embryos donated for research  
**Date:** Monday, June 14, 2010 11:37:12 AM  
**Importance:** High

---

Dear Dr. Gadbois,

My apologies for the delayed response to your e-mail.

We were not involved in the conversations between the doctors and their patients, therefore we do not have direct knowledge of the content of those discussions. However, on 01/05/10, Dr. Chen requested a written description of the changes which she could forward to her patients as a follow-up to their telephone conversations. I sent Dr. Chen the following description on 01/05/10 :

*Regarding the new version of the consent for stem cell research using discarded non-viable embryos: The new consents **remove three restrictions** from the original consent and allow the following:*

- 1) *Therapeutic use of the cell lines (but at this time therapeutic use is not intended).*
- 2) *Commercial use of the cell lines.*
- 3) *Donation/transfer of the cell lines to other entities.*

*In addition, a statement has been added declaring potential financial interest of the researchers in the cell lines. These changes are partly in order to comply with new NIH guidelines and partly to allow wider usage of the stem cell lines including those already derived.*

I later sent (02/01/10) this description to Dr. Garrisi since she had (mis)understood that the financial interests of the patients were at issue.

Please let us know if this sufficiently addresses the Working Group's concern.

Best wishes,

Mina Alikani, Ph.D.

On 6/2/10 11:50 AM, "HESCREGISTRY (NIH/NIDCD)" <[hescregistry@mail.nih.gov](mailto:hescregistry@mail.nih.gov)> wrote:

Hello Dr. Munne and Dr. Alikani,

The ACD stem cell working group has asked if you could provide the documentation (or information that was conveyed orally) that was sent to the

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66

**From:** Mina Alikani  
**To:** HESCREGISTRY (NIH/OD)  
**Cc:** Santiago Munne  
**Subject:** Re: New hESC Registry Application Request #2011-ADM-004  
**Date:** Thursday, February 17, 2011 4:14:35 PM  
**Attachments:** 02-33 approval and renewal letters.pdf

Dear Dr. Gadbois,

Attached, please find all the documentation related to the protocol in question. You will note that this IRB-approved protocol (02-33) was in place and valid at the time of these donations. It was renewed and reapproved on a yearly basis, as we are required to submit a report to the IRB and state whether we wished to continue the study.

See  
pp. 28-37

Please let me know if this answers the WG's concerns.

Best wishes,

Mina Alikani, Ph.D.

On 2/16/11 12:50 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:

Thank you. To go back to the protocol: the protocol you submitted with RNJ7 is attached, so can you check whether this is the correct protocol for RNJ11 and 12? The protocol was approved for use from September 1, 2002-August 31, 2005. We note that RNJ11 and 12 came from embryos donated in 2008 (as did RNJ7), so please confirm we have the protocol that was in effect during the donations of all of those embryos.

Sincerely,  
Ellen Gadbois

**From:** Mina Alikani [mailto:mina.alikani@embryos.net]  
**Sent:** Tuesday, February 15, 2011 2:16 PM  
**To:** HESCREGISTRY (NIH/OD)  
**Subject:** Re: New hESC Registry Application Request #2011-ADM-004

Yes. That is correct, Dr. Gadbois. Thank you.  
Best wishes,

Mina Alikani, Ph.D.

On 2/15/11 1:09 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:

Thank you Dr. Alikani. Can you also confirm whether the new consent document signed by the donors of the embryos from which RNJ11 and RNJ12 were derived are identical to the re-consent document that was included in the RNJ7 submission (but not signed by those donors)?

Sincerely,  
Ellen Gadbois

**From:** Mina Alikani [mailto:mina.alikani@embryos.net]  
**Sent:** Monday, February 14, 2011 2:34 PM  
**To:** HESCREGISTRY (NIH/OD)  
**Subject:** Re: New hESC Registry Application Request #2011-ADM-004

Yes – thank you, Dr. Gadbois. It is the same protocol we submitted with RNJ7 but I will resend it as soon as I have a minute to look in my files!

Best,  
Mina

On 2/14/11 2:22 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:

Certainly. Please don't forget the other request (attached) regarding the two submissions that have been moved to the ACD Working Group for review—we need to have the protocol that was in effect at the time of donation of those embryos. It may be the same version as the protocol you submitted with your first submission, but we don't assume anything.

67

**From:** Mina Alikani  
**To:** HESCREGISTRY (NIH/OD)  
**Subject:** Re: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION  
**Date:** Tuesday, February 22, 2011 11:28:41 AM  
**Attachments:** Stem Cell Research 2004 consent revision[1].pdf  
**Importance:** High

Dear Dr. Gadbois,

I have now looked into the question regarding the IRB letter of 2 November, 2004 further and obtained more documents that clarify the situation a little more. I have concluded that while a revision to the consent and the protocol went through the IRB on 2 November, 2004, as you will note in the attached document, the IRMS clinical staff who normally oversees the consenting process did not put this latest version of the consent into use in 2004. Instead, they continued to use, by error, an earlier version of the consent – i.e., the version that was signed by the donors of RNJ7, 11, and 12.

\*  
SEE  
pp. 16-27

Again, I do apologize for the confusion this has caused. There are many entities and individuals involved here, including the IRMS clinical staff, IRB staff, and one staff person at Reprogenetics who overlooks the submission of protocols to the IRB, renewals, reports, etc. This arrangement is evidently error-prone. I think the fact that the 2004 version of the consent did not go into circulation at IRMS is simply a reflection of the latter.

Best wishes,

Mina Alikani, Ph.D.

On 2/18/11 3:13 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:

Dr. Alikani and Dr. Munne,

Please know that NIH appreciates the importance of hESC research and we appreciate the considerable work involved in gathering information on lines. This process is also under considerably scrutiny and we need to make sure that decisions are made based on the correct documents and information.

Sincerely,  
Ellen Gadbois

**From:** Mina Alikani [mailto:mina.alikani@embryos.net]  
**Sent:** Friday, February 18, 2011 2:00 PM  
**To:** HESCREGISTRY (NIH/OD); Santiago Munne  
**Subject:** Re: New hESC Registry Application Request #2011-ADM-004

Dear Dr. Gadbois,

Thank you for your e-mail. I will make every effort to clarify everything for you within the timeframe you have specified. I hope the WG understands that reconstructing a paper-trail going back 8 years can be challenging and create confusion, particularly when more than one entity is involved and organizational changes have taken place during that period, as was the case for Reprogenetics.

Moreover, speaking on my own behalf, I have gotten the impression that this process assumes us to be "guilty until proven innocent," so I feel compelled to say that for the past twenty years, thanks to a well-informed and generous infertility patient population and their decisions to donate human embryos to research solely on the basis of altruism, we have conducted some crucial research in the field of assisted reproduction - research that has been of fundamental importance to improving outcomes for all infertility patients and research that the NIH has refused to fund for political reasons. All of this work has been done in the most responsible manner we thought possible, with utmost respect for the patients and their rights, and cognizant of the special status of the human preimplantation embryo. Our work in the area of human embryonic stem cells has not been any different. I believe that the paperwork we have submitted so far attests to that even if some aspects are unclear. But it is my distinct impression that the NIH is actively searching for improprieties here. This is disheartening.

Best wishes,

Mina Alikani, Ph.D.

On 2/18/11 12:03 PM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:  
Hello Dr. Alikani and Dr. Munne,

Thank you for your recent email. I am sorry to keep asking, but I need to be sure we have the correct paperwork corresponding to these lines, and I am confused on the following points:

68

**From:** Mina Alikani  
**To:** HESCREGISTRY (NIH/OD)  
**Subject:** Re: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION  
**Date:** Tuesday, March 15, 2011 2:02:48 PM  
**Attachments:** hESC\_Lines\_Reprogenetics2011.doc  
**Importance:** High

Dear Dr. Hannemann,

Thank you for your e-mail. In response to your question, RNJ7, 11, and 12 were not derived from PGD embryos and as far as we know, they do not contain genetic mutations. - though they have not been specifically tested for such abnormalities.

For further clarification, I have enclosed here a table that lists our cell lines, their origin, and the extent of characterization done for each. I hope this will be helpful.

The wording in the highlighted question 8 of the application to which you refer is actually puzzling to me – I have the distinct impression that the word “normal” should have actually been “abnormal”. At the time this revision was made, I was not involved directly in this project. The project really started back in 2002 with a series of hypothetical aims and goals and evolved to what it is today with more specific goals – each stage of this evolution having been managed by different team members. I have offered this previously to Dr. Gadbois as a way of explaining some confusions and uncertainties. At the same time, I have and will continue to emphasize that our work has never crossed any ethical boundaries and we have and continue to adhere to basic principles of ethical research conduct.

SEE  
pp. 69-70  
\*

Best wishes,

Mina Alikani, Ph.D.

On 3/15/11 10:50 AM, "HESCREGISTRY (NIH/OD)" <hescregistry@mail.nih.gov> wrote:

Dear Dr. Alikani,

Thank you for the additional information. Looking at the 2004 application (attached), we note that item 8 states, "... we want to expand the study to develop stem cell from chromosomally normal embryos detected from Pre-implantation Genetic Diagnosis cycles."

Please let us know whether any the cell lines in review (RNJ7, RNJ11, or RNJ12) was derived from embryos that were tested by PGD and if any of the lines contain genetic mutations.

We will also be sending 3 follow-up emails to confirm documentation on each of the cell lines. Please respond to each email separately to help us with our records. Again, thank you for your on-going efforts to answer our questions.

Sincerely,  
Diane Hannemann

*Diane E. Hannemann, Ph.D.  
Office of Science Policy Analysis  
National Institutes of Health  
tel: 301-594-2567  
fax: 301-402-0280*

**From:** Mina Alikani [mailto:mina.alikani@embryos.net]  
**Sent:** Tuesday, February 22, 2011 11:27 AM  
**To:** HESCREGISTRY (NIH/OD)  
**Subject:** Re: New hESC Registry Application Request #2011-ADM-004 FURTHER CLARIFICATION  
**Importance:** High

Dear Dr. Gadbois,

I have now looked into the question regarding the IRB letter of 2 November, 2004 further and obtained more documents that clarify the situation a little more. I have concluded that while a revision to the consent and the protocol went through the IRB on 2 November, 2004, as you will note in the attached document, the IRMS clinical staff who normally oversees the consenting process did not put this latest version of the consent into use in 2004. Instead, they continued to use, by error, an earlier version of the consent – i.e., the version that was signed by the donors of RNJ7, 11, and 12.

Again, I do apologize for the confusion this has caused. There are many entities and individuals involved here, including the IRMS clinical staff, IRB staff, and one staff person at Reprogenetics who overlooks the submission of protocols to the IRB, renewals, reports, etc. This arrangement is evidently error-prone. I think the fact that the 2004 version of the consent did not go into circulation at IRMS

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

<b>Human Embryonic Stem Cell Lines Derived by Reprogenetics, LLC</b>						
<b>Cell line Code</b>	<b>RNJ7</b>	<b>RNJ8</b>	<b>RNJ9</b>	<b>RNJ10</b>	<b>RNJ11</b>	<b>RNJ12</b>
<b>Embryo</b>						
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
<b>Cell Line Characteristics</b>						
Highest Passage #		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)
<b>Stem Cell Markers:</b>						
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
<b>Embryo</b>						
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
<b>Cell Line Characteristics</b>						
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
<b>Stem Cell Markers:</b>						
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

**From:** [Mina Alikani](#)  
**To:** [HESCREGISTRY \(NIH/OD\)](#)  
**Cc:** [Santiago Munne](#)  
**Subject:** Re: RNJ7 - hESC Registry Application #2010-ACD-006  
**Date:** Wednesday, April 13, 2011 12:28:39 PM

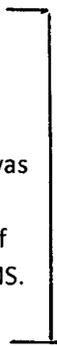
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Dear Dr. Hannemann:

Regarding your questions:

As indicated on the last page of the full redacted consent for RNJ7, the date indicated on the consent signed by the patient is 8/23/2002. Thus the answer to your first question is YES.

The documentation attached to the IRB letter dated 2 November 2004 shows that a paragraph was added to question number 8 of the application/protocol. The paragraph is highlighted in the document. The IRB had approved the protocol revisions submitted on that date (and in August of 2004) but the consent form associated with those revisions was never put into circulation by IRMS. Thus the answer to your second question is No.



I hope this clarifies the issues of concern. However, if you wish to discuss this matter over the telephone, please let me know if this Friday, 15 April, or the following Monday would be a possibility.

Sincerely,

Mina Alikani, Ph.D.

On 3/25/11 1:19 PM, "HESCREGISTRY (NIH/OD)" <[hescregistry@mail.nih.gov](mailto:hescregistry@mail.nih.gov)> wrote:

Dear Dr. Alikani,

Thanks so much for your recent responses. Before the working group can review these materials, we still need to confirm which versions of the protocol and donation consent forms were used for each hESC line (RNJ7, RNJ11, and RNJ12). We ask this as some of the materials originally submitted to NIH were later replaced by you. For example, the version of the donation consent for RNJ7 first submitted was a version dated 06/29/02, and later replaced with a version dated 8/23/2002. To help simplify our request, I've outlined what we have in our records and ask that you confirm if we have cited the correct information.

Also, please be sure to include Dr. Munne on your emails to NIH as he is the Signing Official for these submissions and all materials for review need to come through him. As stated in the "Certification" section of the submission application, Dr. Munne has agreed that:

“By submitting this request, I certify that the statements and Assurance herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001).”

Please confirm the version of the indicated documentation that was used for RNJ7, as listed below:

RNJ7

· Embryo Donation Consent, version dated 8/23/2002:

- Yes
- No
- If no, please clarify which version used.

· Protocol version used at the time of embryo donation was the version dated 6/30/2002:

- Yes
- No
- If no, please clarify which version was used.

From the information NIH has received from you, we understand that the protocol dated 6/23/2002 was modified and approved by the IRB in 2004, but that this modified version of the protocol was not implemented by the clinic when the embryos were donated for the derivation of RNJ7. As such, please confirm above if the protocol actually used in relation to RNJ7 was the version dated 6/30/2002.

We will send you two separate emails for confirmation of the materials for RNJ11 and RNJ12, respectively. To assist us with our records, please respond to each email separately and confirm that Dr. Munne concurs with the response.

Please let us know if you have questions. If it would be helpful to discuss by phone, we are happy to do so.

Sincerely,  
Diane Hannemann

**From:** Mina Alikani [<mailto:mina.alikani@embryos.net>]  
**Sent:** Friday, March 18, 2011 12:40 PM  
**To:** HESCREGISTRY (NIH/OD)  
**Subject:** Re: RNJ7 - hESC Registry Application #2010-ACD-006

Dear Dr. Hannemann,

Please see my responses in red below.

Best wishes,

Mina Alikani, Ph.D.

On 3/15/11 10:57 AM, "HESCREGISTRY (NIH/OD)" <[hescregistry@mail.nih.gov](mailto:hescregistry@mail.nih.gov)> wrote:  
Dear Dr. Alikani,

We're writing to confirm documentation for RNJ7.

- 1) CONSENT - For cell line RNJ7, please confirm that the embryo donation consent version 8/23/2002 was used (attached), not the embryo donation consent version 6/29/2002 sent to NIH in the original RNJ7 submission.

As indicated on the signed document, the version is 8/23/2002; the original document sent to the NIH, as I recall, was an unsigned general version and may have had a different date associated with it; I have not compared the two documents to see whether there are differences.

\*

- 2) PROTOCOL:

- a. For RNJ7, please confirm which protocol version was followed. Attached please find the IRB application, dated 06/30/2002, which was sent to NIH with the original RNJ7 submission.

The original protocol was approved in 2002; it was modified and reapproved in 2004, but we discovered much later that the consent associated with the revised protocol was not circulated at the time (hence the discrepancy in RNJ 7 documents). The original protocol did not explicitly state the standard method of hESC isolation, although this was the only means by which the cell lines were derived. For that reason, we have amended the protocol during the 2011 annual review through an amendment and a letter to the IRB that state that ALL cell lines derived by and currently banked at Reprogenetics were derived through either whole blastocyst culture or isolation and culture of the ICM of the blastocyst. This amendment is attached.

\*

b. For RNJ7, please confirm that the protocol used was IRB-approved.

]\*

Please see 'a' above.

Sincerely,  
Diane Hannemann

*Diane E. Hannemann, Ph.D.  
Office of Science Policy Analysis  
National Institutes of Health  
tel: 301-594-2567  
fax: 301-402-0280*

**From:** Mina Alikani  
**To:** HESCREGISTRY (NIH/OD)  
**Cc:** Santiago Munne  
**Subject:** Re: summary of conversation regarding RNJ7, 11, 12--please confirm  
**Date:** Friday, April 15, 2011 3:51:50 PM

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Dear Dr. Gadbois:

I confirm this summary of our earlier telephone conversation. Thank you. ]

Best wishes,

Mina Alikani, Ph.D.

On 4/15/11 3:31 PM, "HESCREGISTRY (NIH/OD)" <[hescregistry@mail.nih.gov](mailto:hescregistry@mail.nih.gov)> wrote:

Hello Dr. Alikani,

Per our conversation today, we understand that the materials behind the attached November 2, 2004 letter from Dr. Zauber (IRB application with protocol, item 1 date 7/31/2004, and embryo donation consent version 8/18/2004) were reviewed and approved by the IRB, but the embryo donation consent version 8/18/2004 was not used. The IRB application included a new statement (in item 8) expanding the study to develop stem cells from embryos on which pre-implantation genetic diagnosis (PGD) had been performed. However, RNJ7, 11, and 12 were not derived from embryos which underwent PGD testing. ]

\*

We are also confirming per our conversation that donors of the embryo from which RNJ12 was derived signed the 3/13/2009 version of the embryo donation re-consent form.

Please confirm this information for our records.

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*