

Guide to Submission

Hadassah Hebrew University Medical Center
Submission #2011-ACD-004

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hESC Registry Application Database
 Detailed Listing for Request #: 2011-ACD-004
 June 2, 2011

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hESC Registry Application Search Results

Request #: 2011-ACD-004
Status: Pending

Review: ACD

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

Cell Lines: 3
Available: 3

Previous #:
 2010-DRAFT-015
 2010-ADM-016

[Email](#)
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Organization: Hadassah Hebrew University Medical Center

Org Address: P.O. Box 12000 Jerusalem, Israel 91120

DUNS: 600063937 **Grant Number(s):**

Signing Official (SO): Hadas Lemberg / 011-972-2-677-7572 /

HadasL@hadassah.org.il

Submitter of Request: Benjamin E. Reubinoff / 011-972-507-874569 /

benjaminr@ekmd.huji.ac.il

Submitter Comments: There are additional supporting documents (such as "Information for the Donor") which have not been translated to English. If the attached documents are not enough to gain NIH approval, we can further translate such additional documentation and submit them.

Line #1: HAD-C 100

NIH Approval #:

Available: Yes

Embryo from U.S.: No

Embryo Donated in Year(s): 2006

Provider Name: Benjamin E. Reubinoff

Provider Phone: 011-972-507-874569

Provider Email: benjaminr@ekmd.huji.ac.il

Provider URL:

http://www.hadassah.org.il/English/Eng_SubNavBar/TheDoctors/ReubinoffBenjamin.htm

Provider Restrictions: Available for non-clinical research subject to an MTA that specifies the proposed research and includes a commitment to handle the stem cells ethically. Possible availability for clinical use subject to a review of the research proposal, ethical, and regulatory approvals.

NIH Restrictions:

Additional Information:

Line #2: HAD-C 102

NIH Approval #:

Available: Yes

Embryo from U.S.: No

Embryo Donated in Year(s): 2007

Provider Name: Benjamin E. Reubinoff

Provider Phone: 011-972-507-874569

Provider Email: benjaminr@ekmd.huji.ac.il

Provider URL:

http://www.hadassah.org.il/English/Eng_SubNavBar/TheDoctors/ReubinoffBenjamin.htm

Provider Restrictions: Available for non-clinical research subject to an MTA that specifies the proposed research and includes a commitment to handle the stem cells ethically. Possible availability for clinical use subject to a review of the research proposal, ethical, and regulatory approvals.

NIH Restrictions:

Additional Information:

Line #3: HAD-C 106

NIH Approval #:

Available: Yes

Embryo from U.S.: No

Embryo Donated in Year(s): 2008

2

Provider Name: Benjamin E. Reubinoff
Provider Phone: 011-972-507-874-569
Provider Email: benjaminr@ekmd.huji.ac.il
Provider URL:

http://www.hadassah.org.il/English/Eng_SubNavBar/TheDoctors/ReubinoffBenjamin.htm

Provider Restrictions: Available for non-clinical research subject to an MTA that specifies the proposed research and includes a commitment to handle the stem cells ethically. Possible availability for clinical use subject to a review of the research proposal, ethical, and regulatory approvals.

NIH Restrictions:

Additional Information:

Supporting Documents:

Document 1: (PDF - 12/30/2010) Letter from Signing Official - Elements: 16

Document 2: (DOC - 12/30/2010) Informed Consent Document (Translated) for hESC Clinical Trial - Elements: 1,2,3,4,5,9,10,11,12,13,14,15

Document 3: (DOC - 12/30/2010) Derivation of Clinical-Grade hESC Lines Protocol - English - Elements: 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15

Administrative Comments: SO certifications corrected by E. Gadbois 10 Jan 2011

22 Feb Submitter Response to NIH Questions - uploaded by DHannemann 22 Feb 2011

HADC104 was deleted at the request of the submitter on 1 March 2011--E. Gadbois

8 Mar NIH Email to submitter re:switch to WG review - by DHannemann 15 Mar 2011

NIH Staff IIB Analysis - by DHannemann 16 Mar 2011

Submission Compilation by NIH Staff (as of 17 Mar) - DHannemann 22 Mar 2011

Administrative Attachments:

Document 1: (PDF - 01/14/2011) Hadassah response Jan 13 2011

Document 2: (DOC - 02/22/2011) 22 Feb Submitter Response to NIH Questions

Document 3: (PDF - 03/15/2011) 8 Mar NIH email re: switch to WG review

Document 4: (DOC - 03/16/2011) NIH Staff IIB Analysis

Document 5: (PDF - 03/22/2011) Hadassah submission compilation (as of 17 Mar)

Document 6: (PDF - 03/29/2011) Hadassah IIB assurance

Document 7: (PDF - 05/23/2011) Hadassah May 22 2011 email

Document 8: (DOC - 05/23/2011) Hadassah May 22 2011 email attach

Status History:

Draft: 07/05/2010

Pending: 12/30/2010

Emails Sent: 12/14/2010-Six_Month_Reminder_1_Email -- 12/28/2010-Six_Month_Reminder_2_Email -- 12/30/2010-New_Application_Email

Previous ADM Request Number: 2010-ADM-016

Switched from ADM to ACD Date: 03/08/2011

Reason for Switch to ACD Review:

The administrative review group determined that the submission does not meet this Section IIA requirement: Element 8: Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.

Hadassah Medical Organization

Hadassah University Hospitals
Division of Research and Development

Dr. Hadas Lemberg
Deputy Director



27 March 2011

To: Ellen L. Gadbois ,Ph.D.
Office of Science Policy Analysis
National Institutes of Health

Re: New hESC Registry Application Request #2010-ADM-016

I hereby assure that the embryos from which the cell lines identified in item 6 of the form (HADC100, HADC102 and HADC106) was derived were donated prior to July 7, 2009, and the embryos: 1) were created using in vitro fertilization for reproductive purposes and no longer needed for this purpose; and 2) were donated by individuals who sought reproductive treatment ("donor(s)") who gave voluntary written consent for the human embryos to be used for research purposes.

Sincerely,

Dr. Hadas Lemberg
Deputy Director
R&D Division
Hadassah Medical Organization

CC: Dr. Arik Tzukert, Director R&D Division
Prof. Benjamin Reubinoff

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Jerusalem 91120, ISRAEL
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We, the undersigned:

First and last name (husband):	First and last name (wife):
I.D. No (husband):	I.D. No (wife):
Address:	Zip code:

- A. Hereby declare that we agree to participate in a clinical study, as specified in this document
- B. Hereby declare that we do not participate, at the time of signing this document, in any other clinical study, and that we are committed not to participate in any other clinical study during the whole period of this study.
- C. Hereby declare that it has been explained to us by:

Name of explaining investigator/deputy investigator:

1. that the senior investigators, **Prof Neri Laufer and Prof Benjamin Raubinoff** obtained from the Medical Institute Director an approval to conduct the clinical study involving human subjects, in its implication in the Public Health Regulations (medical experiments involving human subjects) – 1980 (hereafter the study):
2. that the senior investigator **Prof. Neri Laufer**, Head of Department of Gynecology, has¹ an affinity² to the study initiator, **Prof. Benjamin Raubinoff**,

¹ delete the unnecessary.

² affinity – attachment of employment with salary, contractorship or any other way, or commercial or business attachment, or family or personal attachment, and any other attachment which may raise suspicion of conflict of interest or dependence, except for reimbursement or payment for participation in the committees according to procedure.

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who is employed in his department.

3. that the clinical study is conducted on the subject: **human embryonic stem cells – a potential infinite source of cells for transplantation.**
4. that we are free to choose not to participate in the clinical study, and that we are free to discontinue at any time our participation in the study, all this without affecting our rights to receive the regular treatment.
5. that it is guaranteed that our personal identity will be kept confidential by all those dealing with and involved in the study, and will not be made public in any publication, including scientific publications.
6. that the medical institute has arranged appropriate insurance for the participants in the study.
7. that if necessary, according to the doctor's decision, and subject to approval by the Institutional Helsinki Committee, we shall continue to receive the study preparation/device/accessory ¹ free of charge also after completion of the study, for a period not exceeding three years. During this period we shall continue to be under medical follow-up, if requested.
8. that we were assured the possibility to get answers to questions raised by us, and the possibility to consult another body (e.g. family doctor, relatives etc), in regard to taking the decision to participate in the clinical study and/or to continue our participation..
9. that in any problem related to the study we may call **Prof. Laufer at Tel:**

02-6776424

¹ delete the unnecessary.

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10. In case of completing a questionnaire – we are aware that we are allowed not to answer all the questions in the questionnaire or part of them.

11. We are aware that we are not allowed to participate in more than one study at the same time.

12. We are aware that after signing this document we shall receive a copy of this Informed Consent.

13. We are aware that in clinical studies involving women in their fertile years, in case of pregnancy during the clinical study, the woman will get consulting (by her doctor) concerning the fate of pregnancy, including the possibility of termination of pregnancy.

D. We hereby declare that we received detailed information on the clinical study, and particularly on the following details, which are further specified in this form in the paragraph “detailed information on the study”:

1) The purpose of the study is to produce stem cells from IVF embryos. The stem cells will be produced under the conditions and according to the guidelines which enable possible use of these cells in the future for transplantation in a variety of diseases, such as heart failure, diabetes, Parkinson’s disease, Alzheimer’s disease, spinal cord damage and others. The stem cells which will be produced will be also used for the advancement of basic scientific research and for the development of new drugs.

2) The study would use only donated fertilized eggs and embryos which have been frozen for 5 years or more and which are surplus, and not needed to be returned to the uterus for producing another pregnancy. The donation of frozen embryos will be possible only by free informed consent of both partners, i.e. the woman donating the

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eggs and the husband donating the sperms. A free informed consent of both partners (wife and husband) will also be required in the event that the sperm was donated to the couple by an anonymous donor. In case the embryo was produced by means of sperm from an anonymous donor donated to an unmarried woman, an informed consent of the donating woman only will be required. The donated embryos will be thawed and cultured until the stage of development of a blastocyst required for producing the stem cells (which occurs 5-7 days after fertilization). The embryos will not continue to exist after the production of the stem cells. In no case will the embryos be used for the fertilization of a woman.

3) The produced stem cells may be kept frozen and used for research and transplantations for years. The use of the stem cells in basic scientific and clinical research will be for the good of the public in accordance with the appropriate ethical rules for research in tissues from human origin, and subject to approval by the appropriate ethics committees and approval by the authorities regulating the production of drugs.

4) In order to advance the research in the field of stem cells and their use in transplantation, the embryonic stem cells produced will be supplied to researchers and doctors throughout the world, subject to their commitment to use these cells in basic research in accordance with the ethical rules appropriate for research with a tissue from human origin, and in transplantation, subject to approval by the appropriate ethics committees and by the authorities regulating the production of drugs. You will not be given any information and you will not be involved or influential in any way in regard to these transplantations.

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5) Since the target is to use the stem cells for transplantation in patients, you will undergo medical examinations similar to those of blood donors, including: an interview to find out about your personal and family medical history, as well as blood tests. Your blood samples will be kept frozen in case further tests will have to be done with your blood in the future. Further examinations will be performed only after receiving a detailed explanation on the type and significance of those examinations from an appropriate counselor (genetic counselor for genetic tests) and subject to your consent to this. The results of the blood tests will be given to you.

6) It is hereby clarified that the embryo donors will not receive any financial or other compensation for their contribution of embryos to the study. The study is not intended to bring results which would benefit the embryo donors directly from a medical or any other point of view. It is possible that the stem cells derived from the donated embryos, the cells developed from them or the results of the study performed with the stem cells would have a commercial potential. It is hereby clarified that in such an event the embryo donors will not benefit financially or in any other way.

Detailed information on the study

Production of lines of human embryonic stem cells – a potential source of cells for transplantation

1) Objectives of the study and introduction:

Many diseases are caused due to impaired function of cells or organs. In many cases it is impossible to sufficiently improve the impaired function by drugs or surgery, and the only way to cure the patient is by transplantation of cells or organs. The lack of organs, the difficulty in getting them and the restrictions related to rejection of the transplant

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limit the use of transplantation.

A scientific breakthrough which may solve, at least partially, the lack of tissues for transplantation, is the production of human embryonic stem cells. The stem cells are produced from surplus IVF embryos donated by couples who are not interested in continued use of these embryos for the treatment of infertility. The stem cells are produced from IVF embryos on the fifth or sixth day after fertilization. The embryo can no longer exist after the production of the stem cells.

The embryonic stem cells are characterized by their ability to multiply indefinitely, and also by their ability to be transformed into any type of human cell, such as cardiac cells, neurons, blood cells and others. Therefore, these cells may be used in the future as an indefinite source of cells for transplantation in a wide variety of diseases, such as cardiac failure, diabetes, Parkinson's disease, Alzheimer's disease, spinal cord damage and others. Moreover, these cells enable to carry out research on the early development in humans, which may contribute to the development of new drugs. The human embryonic stem cells can improve our understanding of various diseases, such as congenital defects, miscarriages and tumors. In addition, these cells can be used for checking the effectiveness and safety of new drugs.

Human embryonic stem cells have been successfully produced by us, as well as by few other groups of scientists throughout the world. The stem cells available today were produced for research purposes and it is unlikely that they are suitable for treatment of patients.

The purpose of this study is to produce new embryonic stem cells under the conditions

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and in accordance with the guidelines which will enable to use these cells for transplantation in the future. The new embryonic stem cells to be produced will be used also for the advancement of research and the development of drugs as specified above, in addition to their possible use for transplantation. The use of the stem cells will be strictly monitored for the good of the public and according to the accepted ethical rules.

2) Methods

The study protocol and the explanation form in the framework of the application for donation of embryos were prepared according to the guidelines of the report of the consulting committee to the subject of bioethics of the National Israeli Academy of Sciences, and according to the ethical guidelines published by the American National Institute of Health (NIH) in 1999, in regard to the production of lines of human embryonic stem cells. The study protocol and the wording of the Informed Consent were approved by the Superior Helsinki Committee for Genetic Studies of the Israeli Ministry of Health.

- 1) The candidates for donation of embryos are couples or women whose egg was fertilized by the sperm of an anonymous donor.

Only the donation of fertilized eggs and surplus embryos which have been frozen for 5 years or more, and are not intended to be returned to the uterus for another pregnancy, will be accepted for the study. The donation of the frozen embryos will be only performed subject to free informed consent of the couple, i.e. the wife donating the eggs and the husband donating the sperm. Free informed consent by the couple (the husband and wife) will also be required in case the sperm was donated to the couple by an anonymous donor. In case the embryo was produced by the sperm of an anonymous donor donated to an unmarried woman, the informed consent will be requested only

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from the donating woman.

- 2) It is hereby clarified that it is your right to request the continued storage of the fertilized eggs up to an inclusive period of 10 years.
- 3) The embryos donated by you will be used only for the production of embryonic stem cells, in accordance with the protocols proven effective for this purpose. The production of stem cells is successful in part of the embryos and not in all of them.
- 4) It is hereby emphasized that the embryos donated by you will not be returned to the uterus of another woman.
- 5) The embryos donated by you will be thawed and cultured up to the stage of development of a blastocyst, which is necessary for the production of stem cells (which appears 5-7 days after fertilization), and not beyond that, and in no case more than 14 days from the day of fertilization. The embryos will not continue to exist after the production of the stem cells.
- 6) The research in embryos and in the stem cells produced from them will be conducted according to the ethical rules for research on tissues from human origin. The use of cells for transplantation will be conducted only subject to the approval by ethics committees and by the regulating medical authorities for the production of drugs.
- 7) The produced stem cells, as well as cells developed from them, may be kept frozen for years and used for research and treatment.
- 8) The purpose of this project is to advance the research in the field of human embryonic stem

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cells and their use in transplantation throughout the world. Embryonic stem cells produced in the framework of this study will be provided to researchers throughout the world, subject to their commitment that the research on stem cells will be conducted according to the rules of ethics appropriate to research in a tissue from human origin. The stem cells will be given for transplantation and clinical research throughout the world, only subject to approval by ethics committees and by authorities regulating the manufacture of drugs. The people receiving the lines of cells throughout the world will not give them to others without a clear approval in writing from the producers of these lines or their representative. The transfer of cells to others will be possible only subject to the conditions specified above in this paragraph.

- 9) You will not receive any information on the findings of this study or the results of tests conducted with the donated embryos or with the stem cells produced from them.
- 10) If stem cells will be produced from the embryos donated by you, the stem cells or cells developed from them may be used in a research related to transplantation in human beings, as well as in transplantation treatments in other human beings. You will not receive any information and you will not have any involvement or influence on these transplantations.
- 11) Any sign identifying the relation of the embryos to you will be removed before the production of the embryonic stem cells. In the course of the process of producing the cell lines and the research done with them there will be no sign identifying the cells with you.
- 12) The lines of cells produced from the embryos donated by you will receive a code name.

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The information identifying you with the code will be confidential and kept only in a safe at Hadassah hospital Ein-Karem. It is possible that a new disease which is unknown today will be discovered, which would make it necessary to apply to you for further details related to your medical history, or you may be asked to give blood for another test in order to exclude possible transmission of this disease to the transplanted patients. The probability that you will be approached is low. Such an approach will become possible and done only by approval of the Head of Gynecology at Hadassah Ein Karem. Since it would be possible to find you under the circumstances and subject to the process explained in this paragraph, according to the law of genetic information, the research in the samples donated by you is defined as a research with identified samples.

13) Since the target is to use the stem cells produced from the embryos donated by you for the treatment of patients, the U.S. medical authorities require that the donors (husband and wife) will undergo medical examinations similar to those of blood donors, including:

1) An interview to clarify personal and family medical history. The results of blood tests for infectious diseases which were done in the course of IVF treatment will be checked and documented.

Tests for blood type and infectious diseases including hepatitis A, B & C, rubella, herpes, pro-virus, HGV, TTV, Family SEN, CMV, as well as venereal diseases including gonorrhea, chlamydia and syphilis. Not necessarily all the above listed diseases will be checked.

2) In accordance with the U.S. medical authorities guidelines, your blood samples will be kept frozen in case it would be necessary to conduct further tests on your blood in the future. The probability of this happening is low, but it is possible that a new disease

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which is unknown today will be discovered in the future, such as an inherited or infectious disease, or that progress will be made in understanding the cause for a known disease. In such an event, it may be that in order to exclude with certainty the carrying of the disease by the stem cells and its possible transmission to transplanted patients, checking of the stem cells would not be sufficient, and it would be necessary to conduct further tests on your blood samples which are kept frozen. A further test on your blood samples in the future will be done only after approaching you again, and after you receive a detailed explanation on the type of test and its implication from an appropriate counselor (genetic counselor for genetic test) and subject to your consent to this. As said in paragraph 12, you may be approached only by approval of the Head of Gynecology at Hadassah Ein Karem.

3) You will receive the results of the blood tests.

3) The expected duration of time (treatment and follow-up):

One to two hours in which you will receive an explanation, have a medical interview, and blood will be drawn from you.

4) The expected benefit to the participant:

1) It is hereby clarified that you will not receive any financial or other benefit for your donation of embryos to the study.

2) It is hereby clarified that the study is not intended to bring results which would benefit you directly, medically or otherwise.

3) It is possible that the stem cells produced from the embryos donated by you, the cells developed from them or the results of the study performed on the stem cells, would have a commercial potential. It is hereby clarified that in such an event you will not

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have a financial or any other benefit.

5) Potential risks: There are no risks.

6) Potential discomfort: The discomfort involved in drawing blood from the vein.

7) Other relevant information:

Before you give your consent to the donation of embryos for this study, we wish to emphasize the following points:

1) Your agreement or disagreement to participate in the study and to donate the embryos would not have any implication or influence on the medical treatment you receive.

2) Ethical considerations supporting the production of human stem cells from surplus IVF embryos are:

A) The alternative to donation is to destroy these embryos or keep them frozen forever.

It is hereby clarified that the current regulations concerning IVF allow the destruction of frozen embryos after 5 years, unless a different instruction is given by the parents.

B) The withdrawal and growing of cells in a tissue culture from donated embryos does not mean disrespect to the human embryo in general, since diagnosis of embryos prior to their implantation in the uterus may be judged according to the same ethical criterion. Such pre-pregnancy diagnosis involves the selection of embryos and the destruction of other embryos. The pre-pregnancy method for detection of genetic diseases is accepted in the medical practice in Israel and in many other countries. In addition, other forms of research in human embryos are used today, such as studies intended to improve methods of embryo culture in the framework of IVF treatments. These studies involve

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the growing in test-tubes of fertilized eggs for about 6 days until they reach the blastocyst stage, in order to select, from the total number of embryos, those with the highest potential for implantation, and discard the rest.

8) Attachment of the company's explanatory pages to the patient:

Attached are, in addition, explanatory pages to the patient provided by the company:

yes/no? **No.**

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- E. We hereby declare that we gave our above consent out of our free will and that we understood all the above said. We also received a copy of the Informed Consent Form and the Information Sheet attached to this form (if available).
- F. By signing this Consent Form, we give our permission to the initiator of the clinical study, the Institutional Helsinki Committee and the Ministry of Health, free access to our medical records, in order to verify the clinical study methods and the clinical data. This access to our medical information will be done confidentially, in accordance with the laws and procedures of confidentiality.
- G. I hereby declare that I know and agree that the information related to my participation in the medical experiment will be submitted to my doctor at the Sick Fund in which I am insured. I am aware that according to the Arrangements Law, 2004, this information will not be used for any purpose, except for medical treatment and follow-up.

Names of participants in the clinical study	Signatures of participants in the study	Date
(husband) (wife)		

If necessary² :

Name of independent witness	Signature of witness	date	

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Investigator/Deputy Investigator declaration: The above consent was received by me, after I have explained to the participant in the clinical study all the above said, and I made sure that all my explanations were understood by him/her.

Name of explaining Investigator / Deputy Investigator:	Signature	Date
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² In case the participant in the study or his legal representative is not able to read this Informed Consent Form, an independent witness should be present during the explanation on the nature of the clinical study. After the participant or his legal representative gave his oral consent to participate in the study, the witness will sign the Consent Form and indicate the date of his signature.

**PROTOCOL FOR THE DERIVATION OF NEW HUMAN EMBRYONIC
STEM CELL LINES FROM SUPERNUMERARY IVF EMBRYOS**

(Translation from the Hebrew)

Background and Scientific Information of Research

Embryonic stem cells are pluripotent cells that are derived from the early stage embryo (the blastocyst stage). Embryonic stem cells are unique in their ability to multiply indefinitely in culture and have the ability to differentiate into virtually any cell of the body [1]. Because of these two features, human embryonic stem cells (hESCs) potentially have a wide variety of uses in medicine, pharmacology, and basic science. Human embryonic stem cells may be utilized as the source for cell transplantation in a wide range of diseases where there are missing cells or interference in the functioning of cells, such as in diabetes, Parkinson's disease, cardiac failure etc... Human embryonic stem cells can be used as a model of early human development and to allow the discovery of new genes, differentiation and regeneration factors of therapeutic importance. hESCs can be used in the development of new medicines, toxicology studies, or in the examination of the teratogenic potential of different materials.

Human embryonic stem cell lines were first derived by Thomson and his associates from supernumerary embryos donated by couples undergoing IVF treatment [2]. Our group was the second in the world to isolate human embryonic stem cells [3]. We derived six human embryonic stem cell lines, which are registered with the National Institute of Health and are eligible for American federal funding for research. We are widely distributing our cell lines to many researchers worldwide.

Our human embryonic stem cell lines were generated in a collaboration with researchers from the University of Monash in Australia and the National University of Singapore. The hESC lines generated in Singapore were derived from supernumerary IVF embryos donated by couples who no longer had use for their embryos for infertility treatment. The hESC lines were produced after the appropriate ethical approvals were obtained. Four of our lines were derived from frozen embryos that were, to the best of our knowledge, the only lines in the world generated according to the ethical guidelines released by the NIH in 1999 (Appendix 1).

Since the first descriptions of the derivation of human embryonic stem cell lines, many other groups of investigators around the world have produced hESC lines and today, 72 lines generated by various countries are on file with the NIH. Among these countries included the United States, Sweden, Israel (the Technion in Haifa), India, and Singapore. In light of the enormous therapeutic potential of hESCs, a growing number of scientists worldwide are employed today in their research and development which will eventually allow the exploitation the clinical potential of hESCs. It should be noted that Israel is a world leader in the area of research and development of human embryonic stem cells and researchers from Israel were involved in many of the published research on the subject [2, 3, 5, 6, 7, 17, 22].

The use of human embryonic stem cells for transplantation therapy may occur solely to the extent possible that the hESCs can be differentiated into cultures of

different types of cells that make up the human body (somatic cells). We were the first group to demonstrate somatic differentiation in vitro [3]. Our results, and the results of other groups show that human embryonic stem cells can differentiate in culture into nerve cells [3], blood cells [4], pancreatic cells that secrete insulin [5], heart muscle cells [6], and others [7].

One of the difficulties that restrict the use of human embryonic stem cells is the tendency of these cells to differentiate spontaneously into mixed cultures of many cell types. To exploit the remarkable potential of hES cells, improvement of currently used methods for culturing and manipulating the cells into pure populations of cells as well as controlling their differentiation is required. In the mouse model, methods have been developed that will direct the differentiation and selection of cells that allows the production of blood cells [8], insulin-secreting cells [9-10], nerve cells [11-14] and cardiac cells [15]. Moreover, the healing ability of these cells can be demonstrated after transplantation as models of diseases in animals [9, 16].

Recently it was shown that similar to mouse embryonic stem cells, pure populations of differentiated stem cells of one cell type can be obtained from hESCs [17, 18]. We have derived a method of producing almost pure populations of neural precursor cells from hESCs. These cells can multiply, differentiate in culture into different types of neurons and glia cells that make up the brain tissue of a human being [17]. After transplantation to the brain of newborn mice, the neural precursors responded to cues and signals of the developing brain migrated along established tracks and differentiated into neurons and glia cells that were dispersed the brain parenchyma [17]. Another group also reported similar results [18].

The research achievements in the field of human embryonic stem cells, as reviewed above, constitute a firm foundation for further developments that in the future may enable the exploitation of the enormous therapeutic potential of the hESCs. Considering the wide interest of the scientific and medical communities in this research field, rapid progress is expected, which will bring about preliminary attempts of clinical applications of hESCs.

The current hESC lines would not be suitable for clinical use as they were derived on mouse feeders which render these lines xenotransplantation products. Moreover, the hESC lines available for distribution were not derived using current Good Manufacturing Practice (cGMP) guidelines and lack the documentation necessary for use of these cells in transplantation therapy.

The purpose of the proposed project is to develop new lines of human embryonic stem cells that will be suitable for use in the clinic. Production of these new lines will be done in coordination with the guidelines of regulatory authorities in Israel (Ministry of Health) and the United States (FDA) while ensuring strict quality control, including documentation, and the prevention of contact with animal components in the process. Derivation of hESC lines will be performed with a variety of embryos of various HLA types which will allow a better fit between the type of the donor hESC line and the recipient in future transplantations, enabling a reduction in immune HLA rejection response [21]. Beyond the importance of the production of the lines for potential clinical applications, derivation of new hESC lines has also significant scientific

importance. Additional lines will expand the numbers of existing lines available for research and allow comparison between lines of diverse genetic backgrounds. In addition, the lines will be used for the development of medicines. The lines will be used strictly for the benefit for the public good and according to acceptable ethical practices.

Rationale of the Research

Cell therapy is an innovative treatment that can treat millions of patients. For instance, worldwide, there are over 120 million diabetics and more than 16 million patients with neurodegenerative disorders and the therapeutic potential of cell therapy has been demonstrated in both conditions [19, 20]. A major limitation in the treatment by transplanted cells is the difficulty in obtaining large numbers of human cells to transplant in millions of patients. Potentially, this limitation can be overcome by using hESCs that can undergo unlimited proliferation and multiplication and can differentiate to any cell type of the body.

Research results reported today in the field of human embryonic research are promising and constitute the basis that will enable future use of hESCs in transplantation therapy. However, there are still obstacles that need to be overcome before clinical trials involving the transplantation of hESCs can be performed. While it is difficult to estimate how long it will take before research involving human embryonic stem cells will arrive at clinical trials, because of the considerable worldwide research that is in effect, quick progress in this area of technology is expected.

Because existing lines of hESCs are not suitable for use in clinical trials, in this project, we will develop new lines of human embryonic stem cells suitable for use in future transplantation. The process of deriving these new lines will take time and it is necessary to start the process in time so that these lines will be available when the research in this area will arrive at the stage of clinical trials.

The derivation of new lines is important for two additional reasons: Additional lines of cells will increase the variety and genetic diversity available in existing stem cell lines, and will advance research of phenomena that will be expressed differently in the various lines. If there were available a wide array of human embryonic stem cell lines of differing HLA types, they could be used in the future to more precisely match the tissue types of the donated cells to the recipient, potentially minimizing the expected immune rejection after transplantation [21]

An ideal infrastructure for the development of new cell lines for use in transplantation therapy currently exists at Hadassah. The institution contains a large on-site IVF department, a laboratory highly experienced in derivation, culture, characterization [3], and cryopreservation [22] of human embryonic stem cells, and a GMP facility that is appropriate to meet the requirements of the FDA for the development of cells for transplantation in which the new lines will be derived.

Israel is considered in the world today one of the leading countries in the area of human embryonic stem cell research. The lines that we have derived by us will be used in many research laboratories worldwide. The development of the new lines of

cells will enable us in the future to be the source of such cells for clinical trials in the world and will place Israel in the first line of countries that will allow the medical community to use human embryonic stem cells for transplantation.

Protocol and Details of the Experiment

DONATION OF CRYOPRESERVED EMBRYOS:

Derivation of the new hESC lines will be performed only with supernumerary IVF embryos that were cryopreserved from couples or women who used anonymous sperm donation in their IVF treatments in Israel. The recruitment of embryo donors will adhere to the following conditions:

1. Donation of the cryopreserved embryos will be performed under full and voluntary informed consent of both husband and wife where the wife donates an oocyte and the husband donates the sperm. Informed consent from both husband and wife will be required even if the sperm was donated by an anonymous donor. In the case where sperm was donated by an anonymous donor to an unmarried woman, only the woman will be required to sign the informed consent. The process of informed consent by the donors will be performed under full voluntary consent that preserves the human dignity of the donors.
2. The first approach to the donors whose consent is requested will be performed by an individual not on the research team and not by a physician who treated the donors for reproductive purposes. This individual will be a member of the IVF department in which the donor couple was treated. Before their first visit, the donor couple will receive oral information regarding the research, about its nature and meaning, and will be given time to read the informed consent document and clarify with the team any points that may require clarification. Only after the donors' questions and issues have been dealt with will the donor couple or single donor mother who is interested in donating sign the informed consent.
3. Potential donors will only be couples who have undergone IVF or women who have used anonymous sperm donation for IVF and have successfully completed their fertility treatments and have achieved a pregnancy that has resulted in a birth and have supernumerary embryos cryopreserved for longer than 5 years.
4. Donation of supernumerary embryos will be possible only if the embryo donor couples or women who have used anonymous sperm donation and have undergone IVF, have completed their family building, and have no interest in thawing the embryos for the establishment of pregnancy. It is preferred that the donors would express a desire to destroy the cryopreserved fertilized oocytes. It will be clarified to the donors that it is their right to request the continuation of storage of these fertilized oocytes for a total of 10 years.
5. There will not be an overlap and there will be separation between the medical team that provided IVF medical care to the potential donors and will obtain

the donation (headed by Professor Laufer) and the team that will develop the cell lines and will deal with research and development of the hESCs (headed by Professor Reubinoff).

6. In no way will the donors be financially or otherwise compensated for their embryo donation to the research.
7. The following points will be clarified to the couple, which are also included in the informed consent form:
 - A. All donated embryos will be utilized specifically for the derivation of human embryonic stem cell lines according to the protocols that have proven to be effective for this purpose. Successful derivation of stem cells is possible from only a portion of the embryos and not from all.
 - B. The embryos will be thawed and cultured to the blastocyst stage that is required for the derivation of stem cells (day 5-7 after fertilization). The embryos will not be cultured beyond this stage and in no case beyond 14 days from the day of fertilization.
 - C. The human embryonic stem cells will be handled ethically and respectfully, as is appropriate for all human tissue used in research. The use of cells for transplantation will take place only with the approval of ethical committees and approval of pharmaceutical regulatory authorities.
 - D. All identifiers linking the embryos to the donors will be removed prior to the derivation of the human embryonic stem cells. During the derivation process and research with the cell lines, there will not be any sign that identifies the cells with the embryo donors.
 - E. The derived cell lines will receive a code name. Information that identifies the cell line with the donors will be confidential and will be maintained in a safe at Hadassah Ein Kerem. If in the future, in the case that a disease that is unknown to date will be discovered, the donors may be approached to obtain more medical information or additional blood tests. The donor couple will only be approached with the approval of the Head of Gynecology at Hadassah Ein Kerem and only if there will be the possibility of preventing the transmission of disease to the transplant patients. Since the donors may be approached under the circumstances and according to the procedures described above, in accordance with the rule regarding genetic information, the research, with the donation of such samples, will be defined as research samples with identifiable samples.
 - F. Subject to the FDA guidelines, the donors will undergo a medical screening similar to that for blood donors:
 - a. An interview to clarify personal and familial medical histories. Results of the blood tests for infectious diseases performed during IVF treatment will be checked and recorded. Blood typing and infectious diseases, including viruses that infect the liver like Hepatitis A, B and

C, rubella, herpes, parvovirus, HGV, TTV, SEN family, CMV, and sexually transmitted diseases that may include gonorrhea, Chlamydia and syphilis. Not necessarily all the diseases listed above will be tested for.

- b. According to the United States medical authorities, blood samples of the donors will be retained frozen in the event that additional tests of the blood samples may need to be performed in the future. The likelihood of this happening is low, but perhaps in the future, new diseases currently unknown may be discovered, for example, infectious or hereditary disorders, or progress into the cause of some disease will become known. In this case, that in order to rule out with certainty that the human embryonic stem cells may be possible carriers of the disease and may possibly transfer it to patients transplanted with the cells, and it may not be possible to positively test the stem cells lines, then the reserved blood samples from the donors will be tested. Further testing of the reserved blood samples in the future will only be performed after the donors will receive full explanations about the nature and cause of the tests and the meaning of the results (from genetic counselors for genetic testing), subject to their consent. As stated in section E, the donors will be approached only after approval by the Chairman of Gynecology in Hadassah Ein Kerem Hospital is obtained.
 - c. The donors will receive the results of the blood tests.
- G. It will be declared to the donors that the donated embryos will not be returned to the uterus of another woman.
 - H. No information will be sent to the donor couple about the research or the tests that will be performed on the embryos that will be donated or the stem cells that will be derived from them.
 - I. The stem cells that will be derived and the cells that will be developed from them may be kept frozen and used in research and treatment for many years.
 - J. In the case where stem cells are derived from donated embryos, the stem cells or cells developed from them may be used in research related to transplantation in humans or in transplantation therapy in humans. It is clarified that no information will be sent to the donors and that they will have no involvement or influence on any of these transplants.
 - K. The study does not intend to bring results that will directly medically benefit donors or in any other manner.
 - L. The embryonic stem cells that will be derived from the donated embryos, the cells that will be developed from them or the results of research that will be performed on them may have a potential

commercial value. It will be clarified that in such a case, the donors will not benefit either financially or otherwise.

- M. The goal of the project is to advance research in human embryonic stem cells and their use in transplantation worldwide. The stem cells that will be derived in the research will be delivered to other researchers and utilized worldwide subject to the consent of the recipients to handle the stem cells ethically and respectfully, as is ethically appropriate for all human tissue used in research. The embryonic stem cells will be used in transplantation and clinical research around the world only under the approval of ethical committees and subject to the guidelines of pharmaceutical regulatory authorities. The Helsinki Committee for Genetic Experiments of the Israel Ministry of Health will receive a report on contracts to deliver the cells with reference to all aspects of such contracts.

Recipient of the stem cells around the world will not deliver the cells to an additional party without written approval from the primary providers who developed the cell lines or their representatives. Transfer of the cells to others will be allowed only subject to the conditions listed above, in this section.

- N. Ethical considerations regarding research with IVF embryos are as follows:
1. Consideration of the alternatives: an ethical consideration for the donation of frozen embryos which are not candidates for their return to the uterus for reproductive purposes is the alternative of their destruction or preservation forever in the cryopreserved state. It should be clarified for the couple that current regulations involving IVF allow the destruction of frozen embryos after five years, unless otherwise directed by the parents of the embryos.
 2. Moral consistency: another ethical consideration is that the removal of cells from a donated embryo and growth of cells in culture does not harm the respect paid to the embryo in general; this is because the same ethical standard is used in relation to the diagnosis of embryos before their implantation in the uterus. Preimplantation Genetic Diagnosis (PGD) involves choosing embryos and destroying others. The pre-implantation genetic diagnosis method for identifying genetic diseases is a common medical practice in Israel and many other countries. In addition, human embryos are used in various studies such as research to improve culture methods in the course of IVF treatments. Such studies involve the growth of fertilized oocytes in vitro for 6 days until the development of the blastocyst in order to choose, from all the embryos, those with the highest potential to implant, and to discard the rest.

The research goal is to develop a pool of new lines of human embryonic stem cells with a wide range of HLA types that will be suitable for future clinical

use. Recruitment of embryos will continue until this goal is met. The estimated number of fertilized oocytes that will be necessary to accomplish this goal will be around 200. The approach to the embryo and fertilized oocyte donors will mainly be in the first year of the research. Thawing of the embryos and derivation of the stem cells will mainly begin during the second year of the research. Based on our experience and on the experience of others, it will be possible to derive stem cells from about 44% of human blastocysts with good morphological quality and developed ICMs (11/25, [2, 3, unpublished data]). Since the proposed research will use a slightly different system suitable for the derivation and culturing of cells for use in transplantation, the efficiency (rates) may be slightly lower.

With the existing culture conditions in the IVF unit at Hadassah, 30% of thawed embryos are expected to develop into good quality blastocysts. Therefore, we expect to receive about 65 blastocysts, which are expected to generate about 20 stem cell lines.

Thawing and Culturing of the Embryos to the Blastocyst Stage:

Included in the study are embryos from couples who are not carriers of the infectious diseases listed above. Thawing of the embryos will be performed according to our standard protocol [23]. After their thawing, the embryos will be referred to only by a code and any identifiers linking the embryos to the donors will be removed. The identities of the donors will remain confidential, as described above. The embryos will be cultured until the blastocyst stage and not further, according to our standard protocol [24]. The length of culturing (including the period of time before cryopreservation) from fertilization until the blastocyst stage is about a week and in no case will it exceed 14 days.

Blastocysts with a developed ICM and a normal morphology will be selected to continue the derivation process and the remaining embryos will be discarded. The process of thawing and culturing will be held under strict quality control and documented in accordance with and in coordination with medical regulatory authorities in the country (Ministry of Health) and in the US (FDA).

Derivation, Characterization, Cryopreservation of Human Embryonic Stem Cell Lines

The process of derivation, culture, and preservation of the frozen reservoir of new cell lines will be performed under strict quality control (using cGMPs) and documentation, which will allow the use of the cells in transplantation.

Derivation, culture, and cryopreservation will be performed in accordance with a protocol that we developed, whose effectiveness was proven [3, 22]. The protocol will be adjusted for cell production system requirements for use in clinical trials. Therefore, we will use reagents that are appropriate for the culture of cells intended for transplantation and with feeder cells of a human origin. Our preliminary research results indicate that human embryonic stem

cells can be derived and cultured on feeder layers of human origin and there is no need for mouse feeder layers.

The new cell lines will undergo characterization similar to the characterization of the cell lines that we derived in the past [3] to prove that we have indeed derived human embryonic stem cells.

HLA classification will be determined for each line.

The new cell lines will undergo screening for infectious diseases subject to the guidelines of the medical regulatory authorities of drugs in the country (Ministry of Health) and in the United States (FDA). A stock of cells will be frozen for future use.

Use of the New Stem Cell Lines

The new lines will serve as a reservoir base from which to develop cells for transplantation. For each future transplantation experiment, a separate application shall be submitted to the Helsinki Committee and use of the cells for transplantation will take place only with ethical approval and approval of the medical regulatory authorities of drugs.

Stem cells will be given to researchers and physicians around the world who display suitable research proposals and subject to appropriate ethical approvals.

The new human embryonic stem cells will also be used in basic scientific research. These studies will be conducted in accordance with the ordinary rules pertinent to research with human cells.

Health Information for Which We will Follow up Retrospectively

Retrospective medical monitoring of the donor couple will include only ensuring that they are not infected with HIV viruses, with liver viruses such as Hepatitis A, B & C, rubella, herpes, parvovirus, CMV, FAMILY SEN, TTV, HGV, and sexually transmitted diseases such as gonorrhea, Chlamydia, and syphilis. The donors were not necessarily tested for all the diseases mentioned above during IVF treatment in which the excess embryos were frozen.

Medical Safety

Couples donating their embryos will not be exposed to any medical danger.

Ethics

Preparation of this application for approval to produce new lines of human embryonic stem cells is based on the Law of Protection of Genetic Information, the Prohibition of Genetic Intervention, Public Health Regulations (IVF) 1987, and recommendations from two sources:



1. The Report from the Bioethics Committee of the Israel Academy of Sciences on the use of embryonic stem cells in medical research (Appendix 2). The Committee recommended allowing contribution of "surplus" embryos (not necessary for reproductive purposes) for the production of human embryonic stem cells for medical research subject to exceptions which we adopted.
2. Ethical guidelines published by the NIH in 1999 in connection with the production of lines of human embryonic stem cells which will be approved for use in research with US government funding (Appendix 1).

In conjunction with the guidelines and recommendations of these sources, the following ethical considerations guided our request:

1. The goal in the donation of the embryos to research is to derive new human embryonic stem cell lines that will be suitable for use in clinical medical research. The derivation of the new lines is to benefit medical research, mankind and humanity.
2. The creation of embryos for research purposes is not ethical. Therefore, the production of cell lines will be performed only with surplus frozen embryos (for 5 years or more) generated in the first place to implant in the woman to fertilize her but are no longer needed for reproductive purposes. To ensure that the embryos are not needed for reproductive purposes, the donation of embryos will only be accepted by couples who have completed their family-building, and the alternative to donating embryos to research is to either discard them or to hold them (cryopreserved) unused forever.
3. Situations where the donation of embryos will have an effect on the medical treatment of the couple must be prevented. Therefore, donor couples will only be approached for donation only after their reproductive medical treatment has been completed, and in this manner a complete separation between fertility treatment and donation of the embryos will be accomplished.
4. Donation of the embryos will be performed under full voluntary informed consent of the couple with an emphasis on preserving the dignity and autonomy of the donors.
5. To ensure the autonomy of the couple in the decision to donate, there will not be an overlap between the medical staff responsible for the IVF treatment or the medical team that will obtain the donation from the couples and the staff responsible for the research and who will derive the stem cell lines and will deal with research and development.
6. Purchase or sale of embryos is not ethical and therefore the donors will not receive payment, financial benefits or otherwise for the contribution of the embryos and the medical staff that will obtain the

donation from the couples will not directly receive financial payment or otherwise for obtaining the embryo donation.

7. The identity of the donors will remain confidential. Before the beginning of the derivation of the stem cell, any signs identifying the embryo with the donor couple will be removed. During the derivation process and research into the cell lines, there will not be any sign that identifies the cells with the embryo donors.
8. The stem cell lines that will be developed will receive a code name. Information that identifies the cell line with the donors will be kept secret and confidential and will only remain in a safe at Hadassah Ein Kerem Hospital. In the future, in case a disease which is not known today is revealed, the couple may be contacted for additional medical information or further blood tests. Contact with the couple will be performed only after approval by the Director of the Department of Gynecology, Hadassah Ein Kerem Hospital but only if such contact would be essential for the removal of possible transmission of diseases to transplanted individuals.
9. Growth of the embryos in the laboratory will be only up to the blastocyst stage, which is necessary to derive stem cells, and in any case, not beyond 14 days.
10. The only use of the donated embryos would be in the derivation of lines of human embryonic stem cells.
11. Like other medical developments, it is possible that the research and development of the human embryonic stem cells will be supported by commercial entities. In the case that the stem cell lines or the research into them has commercial value, embryo donors will not enjoy any financial gain.
12. Donation of the embryos will be without any limits by the donors, with regard to the individuals that can or can not benefit from receiving transplantation of cells derived from the stem cells.

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From: benjamin_reubinoff
To: HESCREGISTRY (NIH/OD); hadasl@hadassah.org.il
Cc: Shelly Jannenbaum
Subject: RE: New hESC Registry Application Request #2010-ADM-016
Date: Thursday, January 13, 2011 9:53:22 AM

Dear Diane Hannemannhe

Thanks for your email.

The protocol and embryo donation consent documents that we submitted are the versions that were in effect during the time of the embryo donation for these hESC lines.

Best regards

]*

Prof. Benjamin Reubinoff, M.D., Ph.D.

Director of the Hadassah Human Embryonic Stem Cell Research Center
Sidney Swartz Chair in Human Embryonic Stem Cell Research

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(HESCREGISTRY (NIH/OD :ענתק לידיעה:
RE: New hESC Registry Application Request #2010-ADM-016 :נושא]

Dear Dr. Lemberg and Dr. Reubinoff,

Thank you for your recent submission. As NIH begins review of this submission, please tell us if the protocol and embryo donation consent documents you submitted are the versions that were in effect during the time of the embryo donation for these hESC lines.

Sincerely,

Diane Hannemann

Diane E. Hannemann, Ph.D.
Office of Science Policy Analysis
Office of the Director
National Institutes of Health
voice: 301.594.0064
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WHEN NECESSARY

From: HESCREGISTRY (NIH/OD)
Sent: Thursday, December 30, 2010 4:37 AM
To: Hadasl@hadassah.org.il; benjaminr@ekmd.huji.ac.il
Subject: New hESC Registry Application Request #2010-ADM-016

To: Hadas Lemberg (Signing Official)
Benjamin E. Reubinoff (Submitter)

This is to confirm that the hESC Registry Application request, as detailed below, has just been submitted and is pending NIH Administrative review. You can expect to hear back from us about the status of your application soon.

While pending review, the name of the stem cell line (Question 6) will appear on the public NIH Human Embryonic Stem Cell Registry for Submitted hESC Lines Pending Review.

After review, your organization name, name of the stem cell line(s) and the method of NIH review (Administrative Review or review by the Working Group of the Advisory Committee to the Director) will be posted on the Web page of hESC Lines Reviewed for NIH Funding Eligibility.

If the cell line is approved for inclusion on the NIH Registry, information entered into Questions 6-9 will be posted on the NIH Human Embryonic Stem Cell Registry for hESC Lines Eligible for NIH Funding.

1) Please explain whether researchers outside of Hadassah Hebrew University Medical Center with whom the stem cell lines are shared in the future would be required to undergo any particular review process (by Hadassah Hebrew University Medical Center or another institution) for their own use of these cell lines or for further distribution of the cell lines. We note on page 9 of the protocol, under "Use of the New Stem Cell Lines," the reference to review by the Helsinki Committee for future transplantation experiments and to "appropriate ethical approvals" for use by researchers and physicians around the world. We also note similar language in the first paragraph on page 9 of the informed consent form.

In response to your question and in line with our ethical approval please specify in the registry in the field of "Available for distribution" the following:

"Available for non-clinical research subject to an MTA that specifies the proposed research and includes a commitment to handle the stem cells ethically.

Possible availability for clinical use subject to a review of the research proposal, ethical and regulatory approvals."

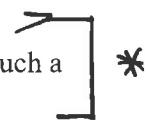
2) Please confirm whether there are any known disease-specific or genetic mutations in these lines. Such information is not related to the review under the Guidelines, but rather is information that is helpful for NIH grantees to see if the lines are approved and listed on the Registry. No known disease-specific or genetic mutations are associated with these lines.

4) Please confirm that voluntary written consent was obtained from all individuals who sought reproductive treatment. In particular we are wondering if a couple composed of two women would have been eligible embryo donors under the protocol, and if so, whether both members of such couples provided voluntary written consent for embryo donation. (Please note we are not asking about consent by third-party gamete donors, which is not required under the NIH Guidelines.) All individuals who sought reproductive treatment gave voluntary written consent to donate their supernumerary embryos to the research. We did not have any donor couples composed of two women. Theoretically, a couple composed of two women would have been eligible as

unpublished
data

*

embryo donors under our protocol, and in such a case both members of such a couple would have had to provide voluntary written consent.



5) We note that embryo donation to another couple for reproductive uses is not listed as an option for use of remaining embryos. Please confirm whether or not this was an option at the IVF clinic, and if it was an option, how the embryo donors were informed of that possibility. Embryo donation to another couple for reproductive purposes is not an option for use of remaining embryos in Israel.

6) Please provide further detail on the timing of when consent was obtained for donation of the embryos relative to the fertility treatment. If there were several stages to obtaining consent, please describe those.

Only donors with supernumerary embryos frozen over 5 years and who had completed their family building were approached for the donation.

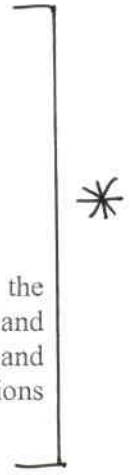
With regard to the process of obtaining the consent, at the first approach to the donors, they received oral information regarding the research, about its nature and meaning. They were then given time to read the informed consent document and clarify with the team any questions that they had. Only after the donors' questions and issues were dealt with, the donors signed the informed consent.

7) Element 8 of the NIH Guidelines requires that "Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable." Please specifically address how this element was met.

At clause 4 (page 2) of our informed consent it is specified that the donors declare that it was explained to them that, "We are free to choose not to participate in the clinical study, and that we are free to discontinue at any time our participation in the study".

At page 8 clause 5 it is specified to the donors that "The embryos will not continue to exist after the production of the stem cells."

Given the above we think that it was clear to the donors that they could withdraw their consent to donate the embryos until the production of the stem cells.



NIH Working Group Questions and Answers

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New hESC Registry Application Request #2010-ADM-016

1) Please address what confidentiality provisions are in place for the medical information collected about the embryo donors, including the blood test results.

The medical information collected about the embryo donors, including the blood/swab test results, is recorded in the CRFs, whose access is limited only to the Clinical Trial Coordinator.

Once the donors have signed the informed consent documents, all documentation associated with the donors are marked with a code; the code is locked in a safe whose access is limited only to the Clinical Trial Coordinator. No documentation is marked with the identity of the donors. The CRFs are filed in a locked storage facility; admittance to the storage is restricted only to the Clinical Trial Coordinator.

The CRFs were reviewed by the CRA when monitoring is performed. During monitoring, the Clinical Trial Coordinator presented the CRFs to the CRA and reviewed the documents with him.

2) Who has access to the records of blood test results?

The Clinical Trial Coordinator has access to the records of the blood test results. The Clinical Trial Coordinator presented to the PI the blood and swab results for reviewing according to Good Clinical Practice.

These results, marked with a code and without any identifying information, were also made available for review to the monitoring CRA, when monitoring was performed.

3) Are blood test results communicated privately with one spouse and not available to the other?

The blood test results were routinely sent together. In a single case where the blood tests suggested an active venereal disease, the spouse was notified individually by phone and according to this donor request the results were not sent by mail.

4) How long are the records with the embryo donor's medical information retained?

The records with the embryo donor's medical information (CRFs) will be maintained for 15 years after the conclusion of the use of the stem cell lines, which shall be specified in the Hadassah hESC Center's MTA.

5) Are the confidentiality provisions for the medical information explained to the embryo donors?

Yes, the confidentiality provisions for the medical information were explained to the embryo donors.

6) Were all donors of the embryos from which HAD-C 100, 102, and 106 were derived given embryo donation consent materials written in a language with which they were comfortable?

The informed consent documents were written in Hebrew. The donors of the embryos of HAD-C 100, 102 and 106 were all Hebrew-speakers and therefore were comfortable with the Hebrew language. The consent material was not written in scientific language but was written with the lay person in mind, and therefore was comprehensible and clear.

7) Page 1, Section B of the embryo donation consent states that the donors, "Hereby declare that we do not participate, at the time of signing this document, in any other clinical study, and that we are committed not to participate in any other clinical study during the whole period of this study ".The Working Group notes that testing could be done at any point in the future on the donor blood samples, so it is not clear when the study would actually conclude. Please address when you consider this study to conclude and how you would apply the prohibition in the context of another study:

The study period is defined as the time from signing the informed consent, until the donors complete the process of undergoing physical examination, blood/swab sampling, and are interviewed by the staff. In general, the entire process was performed within one to two hours' time, as stated in our informed consent document (page 11, section #3). Since our study is a non-interventive clinical trial, the donors are not restricted from participating in another study beyond this period.

With regard to additional serum testing in the future, as stated in the informed consent, this is highly unlikely, and can occur only after the donors sign an additional consent document and only after permission to approach the donors is obtained by the Chairman of Obstetrics and Gynecology of Hadassah (page 11, section #13(2)). Given all the above considerations, we do not consider this unlikely situation as an extension of the study period particularly when taking into consideration that the donors need to sign a consent to the additional blood tests. We therefore limit and define the study period as above.

In summary, the donors are free to participate in any additional clinical studies once the initial study period is concluded.