hESC Registry Application Database

Detailed Listing for Request #: 2012-ACD-004
November 13, 2012

hESC Registry Application Search Results

Request #: 2012-ACD-004
Status: Pending

Review: ACD

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

Cell Lines: 1
Available: 0

Previous #:
2012-DRAFT-033

Email
Edit
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Switch to ADM

Organization: California Stem Cell, Inc.
Org Address: 18301 Von Karman Ave., Suite 130 Irvine, CA 92612
DUNS: 787412233 **Grant Number(s):**
Signing Official (SO): Kenneth Berger / (949) 201-9633 / ken@californiastemcell.com
Submitter of Request: / /
Submitter Comments: (None)

Line #1: CSC14
NIH Approval #:
Available: Other - Unknown at this time, but potentially available in the future.
Embryo from U.S.: Yes
Embryo Donated in Year(s): 2006
Provider Name: California Stem Cell, Inc.
Provider Phone: (949) 201-9633
Provider Email: ken@californiastemcell.com
Provider URL: www.californiastemcell.com
Provider Restrictions:

NIH Restrictions:

Additional Information:

Supporting Documents:
Document 1: (PDF - 11/09/2012) Cover Letter - Resubmission Request (Nov 2012)
Document 2: (PDF - 11/09/2012) Supporting New Evidentiary and Factual Information
Document 3: (PDF - 11/09/2012) Declaration of Antoine La, Embryology Lab Director, WCFC
Document 4: (PDF - 11/09/2012) Redacted Donor Consent Form For Embryo Donation
Document 5: (PDF - 11/09/2012) Study Protocol - Procedure for Procurement of Excess Embryos
Document 6: (PDF - 11/09/2012) Procedure for Presenting Informed Consent to Study Subjects
Document 7: (PDF - 11/09/2012) Cryopreservation Program Participation Agreement
Document 8: (PDF - 11/09/2012) Redacted Disposition of Frozen Embryos Contract
Document 9: (PDF - 11/09/2012) Blastocyst Derivation and Transfer to CSC Form
Document 10: (PDF - 11/09/2012) BioMed IRB Review and Approval

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Administrative Comments: (None)

Administrative Attachments: (None)

	Status History: **Draft:** 11/08/2012 **Pending:** 11/09/2012 **Emails Sent:** 11/09/2012-New_Applicaton_Email **Added By:** Commons\KENNETHBERGER **On:** 11/08/2012 | **Last Updated By:** Commons\KENNETHBERGER **On:** 11/09/2012 | **Record ID:** 129

Total Record Count = 1

Administration Page

Logout of NIH Form 2890 Admin Site

November 6, 2012

To: The Working Group of the ACD, NIH

From: Kenneth Berger, Ph.D., Director of Regulatory Affairs, California Stem Cell, Inc.

Subject: Resubmission Request for approval of the CSC14 stem cell line for use in NIH-funded research pursuant to Section II(B) of the NIH Guidelines for Human Stem Cell Research

California Stem Cell, Inc. ("CSC") respectfully resubmits its request for approval of the CSC14 stem cell line for use in NIH-funded research pursuant to Section II(B) of the NIH Guidelines for Human Stem Cell Research (the "NIH Guidelines"). 74 Fed. Reg. 32,170, at 32,175 (July 7, 2009). The CS14 cell line was previously reviewed by the Working Group for Human Embryonic Stem Cell Eligibility Review (the "Working Group"), which rendered a recommendation to the NIH Advisory Committee to the Director ("ACD") to disapprove the CSC14 cell line. The ACD met on June 15, 2012 and, based on the Working Group's recommendation, voted to recommend that the NIH Director deny CSC's request.

As explained in detail in New Document 2, "Supporting New Evidentiary and Factual Information," the Working Group's initial assessment of the CSC14 cell line was based on incomplete information from CSC and a possible misunderstanding of some of the material facts. In its resubmission, CSC has provided additional evidentiary information that fully addresses the concerns noted by the Working Group and ACD in their original reviews. Please see New Document 3, "Declaration of Antoine La, Embryology Lab Director, WCFC." CSC is also resubmitting the original evidentiary documents, see Documents 4-10.

New Documents

1. Cover Letter – Resubmission Request (Nov 2012)
2. Supporting New Evidentiary and Factual Information
3. Declaration of Antoine La, Embryology Lab Director, WCFC

Original Documents

4. Redacted Donor Consent Form For Embryo Donation
5. Study Protocol: Procedure for Procurement of Excess Embryos Following In-Vitro Fertilization Treatment to be used for the Derivation of New Embryonic Stem Cell Lines
6. Procedure for Presenting Informed Consent to Study Subjects
7. Cryopreservation Program Participation Agreement
8. Redacted Disposition of Frozen Embryos Contract
9. Blastocyst Derivation and Transfer to CSC Form
10. BioMed IRB Review and Approval

We thank you for your thoughtful consideration of our submission.

Respectfully submitted,

Kenneth L. Berger, PhD
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November 6, 2012

Supporting New Evidentiary and Factual Information

California Stem Cell, Inc. ("CSC") respectfully resubmits its request for approval of the CSC14 stem cell line for use in NIH-funded research pursuant to Section II(B) of the NIH Guidelines for Human Stem Cell Research (the "NIH Guidelines").[1] 74 Fed. Reg. 32,170, at 32,175 (July 7, 2009). The CS14 cell line was previously reviewed by the Working Group for Human Embryonic Stem Cell Eligibility Review (the "Working Group"), which rendered a recommendation to the NIH Advisory Committee to the Director ("ACD") to disapprove the CSC14 cell line.[2] The ACD met on June 15, 2012 and, based on the Working Group's recommendation, voted to recommend that the NIH Director deny CSC's request.

As explained in detail below, the Working Group's initial assessment of the CSC14 cell line was based on incomplete information from CSC and a possible misunderstanding of some of the material facts. In its resubmission, CSC has provided additional evidentiary information that fully addresses the concerns noted by the Working Group and ACD in their original reviews. For your convenience, we have restated the Working Group's major and minor concerns below, followed by CSC's response.[3]

I. **Major Concern -- Withdrawal Information**: "Insufficient documentation in the initial submission that the donors had been informed of their ability to withdraw consent up to the time that the embryos were used to derive stem cells. Postmeeting communications from CSCI provided no additional evidence that such language was in effect and had been distributed to the donors. Although the study protocol provides some information on this topic, there is no documentation that it was in place at the time of embryo derivation."

CSC Response:

We understand that the primary basis for the Working Group's recommendation to deny approval of the CSC14 cell line was an alleged failure of the donors to have been informed that he/she retained the right to withdraw their consent "until the embryo was actually used to derive embryonic stem cells or until information which could link the identity of the donor with the embryo was no longer retained." NIH Guidelines § II(A)(3)(d)(iii); 74 Fed. Reg. at 32,174.[4]

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[1] Stem cell lines that have received NIH approval for use in NIH-funded research are commonly referred to as being listed on the "NIH Registry." The term "approved" and "listed on the NIH Registry" are used throughout this document and are intended to be interchangeable.

[2] CSC's original submission was assigned number "2012-ACD-001."

[3] The "major" and "minor" concerns are taken from the Working Group's June 6, 2012 "Findings and Minutes of Discussions Regarding California Stem Cell, Inc. Submission 2012-ACD-001."

[4] The "withdrawal" aspect of informed consent is described in Section II(A) of the NIH Guidelines. However, CSC is requesting approval of its cell line under Section II(B). Therefore, while the Working Group is to "take into account the principles" of Section II(A) (including the withdrawal concept), it should not dogmatically apply those standards when reviewing the CSC14 cell line. To do so would be the equivalent of requiring full compliance with Section II(A) when conducting a Section II(B) review and would render Section II(B) superfluous, undermine the intent of the NIH Guidelines, and run counter to equity and fairness.

The donors of the embryo used to derive the CSC14 cell line were informed of their right to withdraw their consent. That information was conveyed verbally, rather than via the written informed consent document. We understand that this information was not considered by the Working Group in its initial review because CSC did not submit adequate information to demonstrate that the verbal right to withdraw information was actually conveyed. By this submission, we now provide direct evidence, in the form of a signed declaration from the embryologist who was responsible for implementing the protocol, that such information was routinely conveyed and was actually conveyed to the donors of the embryo used to derive the CSC14 cell line. *See* Declaration of A. La, dated August 11, 2012 (the "La Declaration") (Document 2).

We believe that this declaration, coupled with the study protocol and policy documents describing the consenting process, provide adequate information for the Working Group to conclude that the guiding principles underlying the conveyance of the right to withdraw were met in this instance. We also note that ACD recently recommended the approval of several cell lines under Section II(B) for which the applicant (GENEA) did not convey the withdrawal right to donors in a manner that was fully compliant with Section II(A). Based on the Working Group's presentation at the June 15, 2012 ACD meeting, we understand that the approval recommendation for the GENEA cell lines was based on evidence that GENEA had policies in place at the time of the donation that called for the providing of the withdrawal information. Like GENEA, CSC has now provided clear and direct evidence that it had similar procedures and safeguards in place during the relevant time period. Equity and fairness demand that the same flexible standards that were applied to GENEA's application also be applied to CSC.

Additionally, the flexible standard applied to the GENEA cell lines, and that should be applied to the CSC14 cell line, is consistent with the underlying intent of the NIH Guidelines, as evidenced by the following excerpts from government documents (USA and UK):

Excerpt from Executive Order 13505 of March 9, 2009 "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells":

> "…The purpose of this order is to remove these limitations on scientific inquiry, to expand NIH support for the exploration of human stem cell research, and in so doing to enhance the contribution of America's scientists to important new discoveries and new therapies for the benefit of humankind…"

Excerpt from preamble to the NIH Guidelines:

> "… the NIH is also cognizant that in the more than a decade between the discovery of hESCs and today, many lines were derived consistent with ethical standards and/or guidelines developed by various states, countries, and other entities such as the International Society for Stem Cell Research (ISSCR) and the National Academy of Sciences (NAS). These various policies have many common features, rely on a consistent ethical base, and require an informed consent process, but they differ in details of implementation. For example, some require specific wording in a written informed consent document, while others do not. It is important to recognize that the principles of ethical research, e.g., voluntary informed consent to participation, have not varied in this time period, but the requirements for implementation and procedural safeguards employed to demonstrate compliance have evolved. In response to these concerns, the Guidelines state that applicant institutions

wishing to use hESCs derived from embryos donated prior to the effective date of the Guidelines may either comply with Section II (A) of the Guidelines or undergo review by a Working Group of the Advisory Committee to the Director (ACD). The ACD, which is a chartered Federal Advisory Committee Act (FACA) committee, will advise NIH on whether the core ethical principles and procedures used in the process for obtaining informed consent for the donation of the embryo were such that the cell line should be eligible for NIH funding. This Working Group will not undertake a *de novo* evaluation of ethical standards, but will consider the materials submitted in light of the principles and points to consider in the Guidelines, as well as 45 C.F.R. Part 46 Subpart A. Rather than 'grandfathering,' *ACD Working Group review will enable pre-existing hESCs derived in a responsible manner to be eligible for use in NIH funded research*." 74 Fed. Reg. at 32,172 (Italics added).

Excerpt from letter from the UK Steering Committee to the NIH commenting on the National Institutes of Health (NIH) draft Guidelines for Human Stem Cell Research (Lord Naren Patel of Dunkeld, Chairman of the UK Steering Committee for the Stem Cell Bank and for the Use of Stem Cell Lines, 25 May 2009.):

"The Steering Committee considers the requirements for consent of lines set out by NIH in the draft guidelines to be broadly appropriate for moving forward. However, in our view it is important that *modest flexibility is retained to ensure that the consenting requirements do not unnecessarily prevent the use of hESC lines that may have been consented at a time when there was not full awareness of the issues apparent today*." (Italics added)

II. **Major Concern -- IRB Approval:** "[There is a] 3-year gap between the date of embryo donation and IRB approval of the protocol. It is understood that CSCI is not officially required to have IRB approval because it does not receive HHS funds. Although no regulations were violated, the absence of IRB approval prior to the donation of sensitive materials presents more than just a regulation issue; the lack of an impartial review of the protocol presents an ethical problem. … The fact that CSCI did not obtain IRB approval of the protocol in advance is of significant concern. There is no such thing as retroactive IRB approval."

CSC Response:

CSC agrees with the Working Group that CSC was not required to obtain IRB approval of its protocol. In fact, IRB approval is not specifically required for approval of a cell line under Section II(A) of the NIH Guidelines. Additionally, we would agree with the Working Group's contention that there is no such thing as a "retroactive IRB approval" in those instances where prospective IRB approval is required. However, as the Working Group has correctly noted, prospective IRB approval was not required in this instance.

A retrospective IRB review is perfectly consistent with the Section II(B) guiding principles when the Working Group is reviewing situations where IRB approval was not required.[5] In fact, we

[5] CSC does not take a position on whether NIH could reasonably interpret Section II(A) of the Guidelines as requiring prospective IRB review and approval. In fact, CSC recognizes the inherent value to IRB review and currently voluntarily obtains prospective IRB reviews for its studies. However, as it relates to pre-2009 activities,

would submit that the concept of a retrospective IRB evaluation is clearly implied by the fact that NIH refused to require prospective IRB review and approval as a requirement for listing in the NIH Registry. *See* 74 Fed. Reg. at 32,171 ("The NIH concluded that employing the IRB review system for the donation of embryos … would preclude the establishment of an NIH registry of hESCs eligible for NIH funding, because there would be no NIH approval of particular hESCs."). Thus, the retrospective IRB review and approval of the CSC protocol was appropriate in this instance and it provides assurance that critical ethical criteria were met including proper informed consent and ensuring the general protection of patient welfare. After all, the responsibility of the Working Group is just that - a retrospective evaluation by a third party of the consenting process used to obtain CSC14.

III. **Minor Concern -- Allegedly Exculpatory Language:** The Working Group expressed a minor concern about potentially exculpatory (or contradictory) language within the "Commercial Developments" section of the informed consent form. The Working Group's primary concern with this matter is that the "cited language could add to the donors' confusion about their ability to withdraw the donation."

CSC Response:

To the extent that the language cited by the Working Group could be considered "exculpatory," any potentially adverse effect from the language was remedied by the withdrawal information that was verbally conveyed at the time of donation (as evidenced by the La Declaration). As a result, there is no reasonable basis to conclude that there was donor confusion about the ability to withdraw consent. The Working Group has acknowledged that the submitted protocol and process documents adequately discussed withdrawal procedures and CSC has submitted direct evidence that those documents were in place at the time of consent. Therefore, CSC has established that the withdrawal rights were clearly communicated to the donors in this instance.

IV. **Minor Concern – Alternatives to Research:** The Working Group raised a minor concern about the lack of alternatives to research donation contained in the consent form.

CSC Response:

Although the written informed consent did not explicitly address alternatives to research, the issue was adequately presented to donors in both oral and written forms. The study protocol and the invoice for cryopreservation services (included in amendments to the CRC original submission) provided donors with specific additional options to consider, such as donation of the embryo(s) to other couples for IVF treatment, donation of the embryo(s) for other research, or disposal. The Working Group previously acknowledged the adequacy of the language in these documents, but refused to consider them due to a lack of evidence that they were in use at the

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the unambiguous language of the NIH Guidelines permits the approval of cell lines that were derived without a prospective IRB review, provided that the guiding principles of the NIH Guidelines were met. As set forth in this resubmission, we believe the CSC14 cell line meets those standards.

relevant time period. The La Declaration conclusively proves that these documents were in effect at the time, thus fully responding to this concern.

V. **Minor Concern – Cryopreservation:** The Working Group expressed a minor concern related to language in the cryopreservation services invoice that, along with providing donors with information on possible alternatives, requested payment of a $500 fee for cryopreservation services. If the donor opted not to pay the fee or chose not to respond, the embryos would be considered abandoned and theoretically destroyed after 30 days. The Working Group was concerned that the 30-day period could be too brief for a couple to provide the money or to make a final decision about disposition.

CSC Response:

In response to a request for more information, CSC previously provided the Working Group with the Cryopreservation Program Participation Agreement (referenced in the invoice). This document states that if the agreement is terminated, the donors will receive a notice 90 days before the embryos are destroyed.

VI. **Minor Concern – Consent Language:** The Working Group expressed a minor concern about language in the consent form that disclosed Dr. Keirstead's possible ownership interest in CSC.

CSC Response:

With regard to the noted language in the informed consent, it was never CSC's intention to mislead, or be anything other than fully transparent, with all potential donors. While the drafting may have been somewhat less than artful, the disclosure was fully accurate and we believe beneficial to donors. Furthermore, the potential for this language to have resulted in confusion when the embryos used to derive the CSC14 cell line were donated, was greatly reduced by the transmission of vital information in the protocol and process documents that were in place at the time of consent.

VII. **Minor Concern – Contact Person for Withdrawal:** The Working Group noted that the informed consent form did not provide a name or contact information for individuals who decide to withdraw consent.

CSC Response:

As the Working Group has acknowledged, the document entitled "Process for Presenting Informed Consent to Study Subjects" contains information about who a donor should contact in order to withdraw the donor's consent. The Working Group previously refused to consider this document due to a lack of evidence that it was actually in use during the relevant time period.

As noted above, the La Declaration provides the requisite evidence to allow the Working Group to consider this document. Therefore, we believe this concern has been fully resolved.

* * * *

CSC respectfully submits that it has fully and adequately responded to all of the concerns that led the ACD to previously recommend the denial of the CSC14 cell line. The La Declaration provides clear, direct and convincing evidence that the protocol and procedures that called for the transmission of withdrawal information to all potential donors were in place and fully implemented when the embryo used to derive the CSC14 cell line was donated.

CSC14 is precisely the type of cell line that Section II(B) of the NIH Guidelines was intended to address. Although it may not have been collected using procedures that would be used today, CSC has established that the procedures that were employed ensured that the donors were fully informed of their rights and given a full opportunity to change their mind and withdraw their consent. As such, we respectfully submit that researchers receiving NIH funding should not be deprived access to this useful research tool.

WEST COAST FERTILITY CENTERS
Advanced Reproductive Technology and Microsurgery

David G. Diaz, M.D., FACOG *Medical Director*
Diplomate, American Board of Obstetrics and Gynecology
Reproductive Endocrinology and Infertility

August 11th, 2012

To Whom It May Concern:

In my position as embryologist and Director of the Embryology Laboratory at West Coast Fertility Centers (WCFC), I certify that in 2006, I, Antoine La, and the persons working in the Embryology Lab, were trained on the attached "Procedure for Presenting Informed Consent to Study Subjects" and on the attached " Procedure for Procurement of Excess Embryos Following In-Vitro Fertilization Treatment to be Used for the Derivation of New Embryonic Stem Cells." These documents were developed with the help of California Stem Cell, Inc. consultants to supplement the existing WCFC "Consent to Act as a Human Research Subject" form and were in place prior to the embryo donation for the derivation of CSC14. Additionally, I can certify that these procedures were followed and used for the consenting and procurement of the embryos for the derivation of the CSC14 stem cell line. Specifically, the donors were informed of their right to withdraw consent up to the time that the embryos were used to derive a cell line, and who to contact if withdrawal of consent was desired according to the above-mentioned procedures.

Sincerely,

Antoine La, TS, ELD, EMB
Embryology Laboratory Director
West Coast Fertility Centers
11160 Warner Ave Suite 411.
Fountain Valley, CA 92708
P: (714) 513-1399
F: (714) 513-1393

AUG 16 2006

WEST COAST FERTILITY CENTER
CONSENT TO ACT AS A HUMAN RESEARCH SUBJECT

Consent for Embryo Donation

CSC 14

Name of Donor(s): [redacted]

The purpose of this agreement is to obtain your written consent for the donation of excess or frozen embryo(s) that were produced for you as part of your infertility treatment with [redacted] M.D., Inc. dba West Coast Fertility Center ("WCFC") which was conducted in accordance with the terms and conditions of that Cryopreservation Program Participation Agreement dated 8/11/06 between you and WCFC.

Your agreement to donate your embryo(s) is completely voluntary. Your choice to donate or not to donate your embryo(s) will have no affect on the treatment you receive from WCFC. Because the election to donate your embryo(s) is strictly voluntary, before you sign this agreement and agree to donate your embryo(s), it is important that you read and discuss this agreement with someone at WCFC so that you understand and are comfortable with what will happen to your embryo(s) after they are donated. If, after reading this agreement and discussing the use of your embryo(s) with representatives of WCFC, you decide that you do want to make the donation, you will need to sign this agreement which will confirm your consent to allow your embryo(s) to be used for the purposes described below. Of course, before you sign this agreement and agree to donate your embryo(s) to research, you must first decide that they are no longer needed for your infertility treatment and that you would like them to be used in research.

PURPOSE/PROCEDURES

Your embryo(s) will be used under National Institutes of Health and National Academy of Sciences guidelines to develop human embryonic stem cells and human pluripotent stem cell lines. Stem cells are cells with the unique capacity to divide an unlimited number of times. A stem "cell line" means a group of cells that can live and divide outside of the body. A "pluripotent" stem cell line is a stem cell line that is capable of developing into a wide variety of cell types. The cells that will be used to derive the stem cell lines will be cells from either your cleavage stage embryo(s) or the inner cell mass of your embryo(s). The cells that will be used cannot develop into embryos nor can they be implanted into a woman's uterus.

The stem cells and stem cell lines that we hope to create from your embryo(s) will be used in research about human development, in transplantation research, in testing new pharmaceuticals and, if possible in the future, for therapeutic uses on humans.

The stem cells and stem cell lines derived from your embryo(s) may be frozen and kept for many years. It is contemplated that your embryo(s), and the stem cells and stem cell lines derived therefrom, will be used by the University of California, Irvine ("UCI") in research

being conducted by Dr. Hans S. Keirstead. However, depending on UCI's needs, some of your embryos, or the stem cells or stem cell lines derived from your embryos, may also be shared with, made available to, or transferred to other qualified researchers both in the for-profit and not-for-profit sectors. Your embryos, or the stem cells or stem cell lines derived from your embryos, may also be used by a for-profit entity other than WCFC in which Dr. [redacted] or Dr. Keirstead may have an ownership interest called California Stem Cell, Inc. ("CSCI") which is engaged in stem cell research.

COMMERCIAL DEVELOPMENT

Under federal law, if you do not sign this agreement, you would have the right to control the use of the stem cell lines derived from your embryo(s). However, by signing this agreement, you are giving up that right and authorizing the use of your embryo(s) for the research described in the PURPOSE/PROCEDURES section of this agreement. By signing this agreement, you also authorize WCFC, UCI, CSCI and others to use your embryo(s) and any stem cells or stem cell lines derived from your embryo(s) in any lawful way, including future research studies, transferring them to other for-profit or not-for-profit entities, or even destroying them should they no longer be required.

Samples obtained from your embryo(s) in this research may lead to discoveries that could be patented or licensed to for-profit or not-for-profit entities. You will receive no financial compensation should this occur. However, should WCFC, UCI or CSCI ever provide your embryo(s), stem cells or stem cell lines derived from your embryo(s) to a third party for any purpose, your privacy will be scrupulously protected and your identity will not be revealed. All of the protections described in the CONFIDENTIALITY section of this agreement will be followed. In addition to your anonymity being maintained, under no circumstances will you have any responsibility or liability for any use that may be made of your donated embryo(s).

RISKS

If you agree to donate your embryo(s), those embryo(s) will no longer be available for use in your infertility treatment program.

BENEFITS

Although there will be no direct medical benefit to you, it is the hope of the research scientists who will be using your embryo(s) that other people will benefit in the future through the research that is conducted on the stem cell lines derived from your embryo(s). The purpose of the research at UCI and CSCI is to advance scientific and medical knowledge.

[redacted]
Initial

COSTS AND COMPENSATION

You will not be compensated for the use of your embryo(s), nor will it cost you anything to donate your embryo(s). The decision to donate your embryo(s) will have no effect on the cost of your past or future IVF treatment with WCFC.

ALTERNATIVES TO DONATING YOUR EMBRYO(S)

If you choose not to donate your embryo(s), they will continue to be stored or otherwise handled according to the terms and conditions of the Cryopreservation Program Participation Agreement between you and WCFC.

FUTURE ACCESS TO INFORMATION

Once you donate your embryo(s), you will not be given information about what becomes of them or what is learned from working with the embryo(s) you donate or the cells or cell lines that are created from your embryo(s). Because of the anonymity of your donation, which is more particularly described in the CONFIDENTIALITY section, your donation is and must be made without restriction or direction as to the types of research which may be conducted or who may receive the cells or cell lines which may be derived from your embryo(s). However, as stated above, none of your embryos will be implanted into another woman's uterus or used to create a life.

CONFIDENTIALITY

If your embryo(s) are not already be in the possession of WCFC, the embryo(s) you donate will first be transferred to WCFC, which, in turn, will transfer them to UCI or CSCI. Before the embryo(s) are transferred from WCFC, the embryologist at WCFC will assign a randomly generated identification number to the embryo(s). Only this number will be transferred to UCI, CSCI or any other third party, and no patient specific or identifying data will be provided to any other person who might come into possession of or work with your embryo(s) or the cells or stem cell lines derived from your embryo(s). In other words, all of the information which identifies the embryo(s) as having been created by you (e.g., your name, address or other identifying information) will be protected by WCFC, and the only information that will ever leave WCFC about the identity of the embryo(s) will be the randomly generated identification number. Even if the research results in the publication of scientific papers or results in a therapy or patentable product, no information that identifies you or could link the embryo(s), stem cells or cell lines to you will be disseminated or made available.

[redacted]
Initial

SIGNATURE AND CONSENT

By signing this agreement, you are giving your permission for WCFC, UCI, CSCI and others to use and store the embryo(s) you donate in the manner and for the purposes set forth in the PURPOSE/PROCEDURES section of this agreement. In addition, by signing this agreement, you are specifically authorizing your embryo(s) to be used to create stem cells or stem cell lines and for those stem cells and stem cell line to be kept for as long as they remain useful and to used by and shared with other qualified researchers both in the for-profit and not-for-profit sector in research about human development, in transplantation research, in testing new pharmaceuticals and, perhaps one day for therapeutic uses on humans. By signing this agreement, you further understand that the stem cells or stem cell lines derived from your embryos may be used by CSCI, a for-profit entity in which Dr. [redacted] or Dr. Keirstead may have an ownership interest

DONOR

[redacted]

STUDY TITLE: PROCEDURE FOR PROCUREMENT OF EXCESS EMBRYOS FOLLOWING IN-VITRO FERTILIZATION TREATMENT TO BE USED FOR THE DERIVATION OF NEW EMBRYONIC STEM CELL LINES

Purpose of the study

The objective of this protocol is to develop human embryonic stem cells and human pluripotent stem cell lines to be used for cell transplantation research and therapy into humans using excess or frozen embryos already produced as part of infertility treatment.

To generate an embryonic stem cell line, the researchers may use embryos that were in excess or were considered unsuitable for in vitro fertilization donated by couples that have chosen to donate them as an alternative to continuing storage, donation to other infertile couples or discard. The cell lines that will be generated cannot develop into embryos nor can they be implanted into a woman's uterus.

Researchers will use either the day 2–3 (cleavage-stage) embryos or day 4-5 (blastocyst stage) embryos. When an embryo is used to generate stem cells, the embryo will be kept in culture until the blastocyst stage, which is essentially a five day old embryo that is made up of a hollow ball of cells containing an inner clump of 100 to 150 cells.

First, the outer layer of cells is removed. The inner clump of cells is allowed to grow and divide in the lab dish. These cells can continue dividing indefinitely, retaining the ability to form many different adult tissues which is why they are also called pluripotent cells. A stem cell line is a group of identical pluripotent stem cells that can be grown and multiplied in a lab dish.

The embryo(s) will not survive the stem cell derivation process, and will be handled respectfully, as is appropriate for all human tissue use in research.

Donation of embryos will be ancillary to the normal standard of care during the IVF procedures provided by Dr David G. Diaz, dba West Coast Fertility Center ("WCFC") and require no additional interventions or changes of the infertility treatment, such as additional surgical procedures or dose changes for the standard of care medications. The donors will be given the option to donate at the time the discussion about the fate of remaining excess embryos kept in storage at the clinic.

The stem cells will be derived and used following National Institutes of Health (NIH) and National Academy of Sciences (NAS) guidelines and may be used at some future time for research about human development, in transplantation research, in testing new pharmaceuticals and, if possible in the future, for the therapeutic uses on humans.

Background

Embryonic stem cells may provide new therapeutic options as well as insights into the mechanisms of many chronic diseases, such as Parkinson's, Alzheimer's, spinal cord injuries, and diabetes mellitus.

Currently, there are just a few human embryonic stem cell lines available for research and therapy development. However, new human embryonic stem cells lines are needed for the safe development of successful cell transplantation therapies.

Since the number of available human embryonic stem cells lines is limited, so is the genetic pool that they represent. New human embryonic cell lines would better represent the human diversity and will prove more useful for testing different lines generated from different donors for any application in order to find the line best suited for each therapeutic application.

Moreover, our scientists are planning to develop new embryonic stem cell lines from embryos that were shown to contain disease genes and were considered unsuitable for implantation. These are expected to be a powerful tool for understanding how devastating diseases develop and for discovering drugs to help treat these diseases.

Adult stem cells are an alternative stem cell source but since the adult stem cells are more restricted ability to expand and differentiate they may only be applied restrictively in limited applications.

Personnel

P. I.
As the principal investigator, Dr. Chris Airriess, PhD provides overall guidance for the project, and conducts a portion of the experiments outlined in this proposal. Other aspects of his role include planning of experimental details, supervising technical support and students, reviewing and analyzing data and writing and editing manuscripts.

Reproductive Center Staff
David Diaz, MD, FACOG: West Coast Reproductive Center. Dr. Diaz will use his expertise in embryo cryo-preservation and frozen embryo transfer to advise on technical aspects of research procedures that may increase the chance of obtaining new embryonic stem cell lines from frozen embryos.

Number of subjects

A total aggregate of 10 subjects will be enrolled for this study, representing approximately 5 couples donating excess frozen embryos or embryos that were considered unsuitable for in vitro fertilization.

The numbers were determined based on following published results in 2004, in “The New England Journal of Medicine”; title:“Derivation of Embryonic Stem-Cell Lines from Human

Blastocysts" by Douglas A. Melton, Ph.D. et al. where a total of 286 frozen and thawed cleaved embryos (6 to 12 cells each) were cultured to the blastocyst stage and 58 frozen and thawed blastocysts were allowed to re-expand in culture, 97 inner cell masses were isolated and 17 individual human embryonic stem-cell lines generated.

Gender of Subjects

The donors of embryos will be couples where both partners of the couple sign the consent form.

Age of Subjects

The characteristics of the proposed subject population for the embryo donation: healthy females between the ages of 21 and 40 and in good health and healthy males 18 years and older as determined during the IVF procedures.

Racial and Ethnic Origin

The racial distribution we aim for will be as follows: 2% African American, 0.8% American-Indian or Alaskan native, 16% Asian, 0.4% Native Hawaiian or other Pacific Islander, 78% White, and 2.8 % of other races.
The ethnic composition of the targeted donor population is 32% Latinos and 68% non-Hispanics.

Inclusion Criteria

1. All donors of embryos must provide valid informed consent.
2. Must have voluntarily received in-vitro fertilization procedures at West Coast Reproductive Center, which is a properly accredited fertilization center.
3. The donor must have excess embryos or embryos that were considered unsuitable for in vitro fertilization purposes.
4. Both parents must consent to donate.

Exclusion Criteria

1. Failure to meet the standards set for Inclusion Criteria
2. Positivity to sexually transmitted diseases (STD) panel
3. Women under 21 years old
4. Contraindications to pregnancy and ovarian stimulation;
5. At the time of decision to donate, indecision by one of the parents.

Vulnerable Subjects: N/A

Methods and Procedures

Consent timing

The potential subjects will only be approached if they have already undergone the IVF treatment or if the IVF procedures have been started. This way, no patients will decide to participate in the study solely to donate their embryos for research, but rather the option to donate for research will be part of the discussion the patient has with their treating doctor about the excess embryos resulted from the infertility treatment. The patients need to sign the Disposition of Embryos Form provided to them by their fertility clinic and choose to donate their frozen embryos for research. If they make this choice, they will be given a detailed consent form that they can keep until they are ready to make their decision, followed by signing the informed consent form.

Release procedures

The donated embryo(s) will first be stored at the West Coast Fertility Center, and then may be transferred to California Stem Cell, Inc ("CSCI") at least 30 days after consent forms are signed.

After the consent agreement is signed, the embryologist at the WCFC will release the donated embryo(s) to CSCI along with a randomly generated identification number that will be assigned to the embryo(s).

The following de-identified information (the names and the signatures blacked out) will accompany the donated embryo(s): the genetic information about the donated embryo(s), the date of the consent, the de-identified consent agreement and the results to infectious diseases tests done as part of the infertility treatment. The names of the donors, however, and any other information that may possibly identify the donor couple will be kept at WCFC.
Any information such as names, addresses, medical record numbers or other information that identifies the donors or could link the cells or cell lines derived from donated embryo(s) for will be protected, will not be published in scientific papers, and will not be made public if a cell therapy is developed during this research.

The donated embryo(s), the stem cells and stem cell lines derived there from, will primarily be used by CSCI, a for-profit entity that is engaged in stem cell research. However, some of the embryo(s), or the stem cells or the stem cell lines derived from donated embryos, may also be shared with, made available to, or transferred to other qualified researchers both in the for-profit and not-for-profit sectors.

Procedure aimed to procure embryos in an ethical manner:

The quality control will be conducted at the fertility center where the embryos were first obtained and may include donor testing for transmittable diseases.

For this type of donation, the following procedures will be followed:

a. The clinic's personnel will inform the couple about the options available for their excess or unsuitable for transfer embryos such as freeze for future use, discard embryos, donation to other couples, or donation of embryos for research;
b. If the couple chooses the option to donate, they will be informed of the details of this research protocol by the full consent form which will be handed to or mailed to the couple.
c. The informed consent session will then be scheduled and will be conducted by a WCFC representative. The consent session will take place in person.
d. 30 days after the date the consent is signed, the material will be transferred from the clinic to CSCI
e. If the couple decides to withdraw from the study within the 30 day waiting period, the frozen material will be returned in the couple's possession and will not be transported to CSCI.

No Fertility Center employees who have objections to stem cell research will be required to provide information about donation or participate in the consenting of subjects for embryo donation.

All the donated embryos including the ones found by Pre-Implantation Genetic Diagnosis (PGD) to be genetically aberrant will be used to generate stem cell lines (genetically aberrant lines may be useful research tools). The only exclusion criterion from the derivation procedure is the viability of the blastocyst; the procedures for stem cell derivation will be performed only on live blastocysts.

In order to prevent any misguidance for generating excess embryos, the fertility specialist (physician) will not be involved in the process of obtaining the informed consent and will not be compensated for any material transferred to CSCI.

For the transportation of donated frozen embryos, the vials (straws) containing the frozen biological material will be packed and transported to CSCI in biosafety recipient vessels, immersed in liquid nitrogen. At CSCI the samples will be transferred into appropriate liquid nitrogen storage vessels.

At CSCI, the frozen material in LN2 (liquid nitrogen) can be kept indefinitely. The thawed blastocysts will be kept intact in culture for a maximum of 12 days, or the formation of a primitive streak begins, whichever is earlier. After thawing, the culture dishes will be labeled with the blastocyst code and an expiration date which represents the current date plus 14 days minus the number of days which the embryo was kept in culture prior to thawing.

Whether a human embryonic stem cell line is derived from a genetically normal or aberrant blastocyst (diagnosed at the time of PGD), the line will be preserved and stored in the CSCI cryofacility and the genetical status noted in the log.

The donors will be informed of the characteristics of donated embryos, as part of their clinical care, at the fertility clinic at the time of PGD. The donors will not be informed of any defects caused by later manipulations associated with derivation of hESC lines; as such lines would be immediately discarded.

No cash or any kind of compensation will be provided for donating blastocysts for research purposes.

Data Management and Monitoring

The confidential data, subject to HIPAA, will be stored at the fertility center. CSCI PI will keep a copy of the consent form from each donor and a registry of the material transferred to CSCI, using the encoding system described in the Confidentiality section. Detailed data (parameters, media compositions, factors, concentrations etc.) about each derivation will be written in Laboratory Notebooks and systematized in electronic databases. The results will be communicated in tables, graphs or pictures, where applicable. All data will be de-identified to maintain the confidentiality and privacy of donors.

Data Storage and Confidentiality

Donated embryo(s) will first be stored at the WCFC, and then may be transferred to CSCI 30 days after the date the consent agreement was signed, the embryologist at the fertility center will release the donated embryo(s) to California Stem Cell Inc. along with a randomly generated identification number that will be assigned to the embryo(s).

The following de-identified information (the names and the signatures blacked out) will accompany the donated embryo(s): the genetic information about the donated embryo(s), the date of the consent, the de-identified consent agreement and the results to infectious diseases tests done as part of the infertility treatment. The donor's name, however, and any other information that may possibly identify the donor couple will be kept at the Fertility Center.

Any information such as the name, address, medical record number or other information that identifies the donor or could link the cells or cell lines to the identity of the donor will be protected, will not be published in scientific papers, and will not be made public if a cell therapy is developed during this research.

Regulatory entities such as the Food and Drug Administration (FDA) may have access to the de-identified research records such as the consent agreement, testing results, and research data. The donor's identity will not be voluntarily released or disclosed to these entities without the donor's separate consent, except as specifically required by law in situations such as the need to track the cells back to the donor when a cell transplantation therapy is available.

Information learned in this research (research data) may be used by the research team or made available to other investigators. The researchers plan to maintain the research data indefinitely.

Risk/Benefit Assessment

This study will advance scientific and medical knowledge. The subject will not be given information about what is learned from working with the cells that are donated or the cells or cell lines created.

At some point in the future, embryos the subject donates will be used for basic science experimentation and may be used for human transplantation research. The donation must be made without restriction or direction as to what types of research may be conducted or who may receive cells which may be derived.

Risks

The embryo(s) will no longer be available for use in the infertility program as they will be used to create human embryonic stem cell lines for research. The embryo(s) will not survive the cell line derivation process and they will not be capable of developing into a fetus.

Protection against Risks

There are no unforeseeable risks associated with these study procedures. For this reason, the consent document describes the foreseeable risks to allow the donor to make an informed decision.

The potential for breach of confidentiality will be prevented by the following procedures: all information that will or might possibly identify the donor of the embryo(s) is contained in the original consent with names and signatures. Access to this document will be restricted to the researcher that the donor discussed the consent with and the clinic personnel involved in the donation process.

The CSC investigator and other researchers will only have access to a coded consent, coded embryo(s), and the de-identified disease information found by PGD if available.

Potential Benefits to the donor
The donors will not directly benefit from participation in this research study at this time.

Potential Benefits to Others or Society
People may benefit in the future through what is learned from the research. At some point in the future, cells from the embryo(s) or materials(s) donated will be used to advance scientific and medical knowledge in human development, testing new pharmaceuticals, and human transplantation as a therapy.

Alternatives to Participation

The alternatives to embryo donation, at the donor's direction and if medically appropriate, are as follows: donation of the embryo(s) to other couples for IVF treatment, donation of the embryo(s) for other research, continued storage for future implantation, or disposal.

Recruitment for embryo donation

The option of participating in this study is presented to the potential donors by the fertility center personnel after PGD (in the case of embryo(s) showing genetic disorders and are not destined for implantation) or after a successful fertilization (if the couple decides to discard the excess frozen embryos). The option of donating can be presented in person or by phone if the couple gives permission to be contacted as such. If the couple is interested, they will receive a detailed consent form that outlines the purpose of this research, the eligibility criteria, the risks, and all other elements necessary for the informed consent process.

Couples that completed the in vitro fertilization process and are facing the decision of donation of the embryo(s) to other persons for IVF treatment, donation of the embryo(s) for other research, continued storage for future implantation, or disposal may contact the research team if they wish to donate for the research.

There will be no recruitment before the fertilization begins as those patients are not eligible to participate in the study. The study team will not advertise the option to donate for this research protocol at any public places or media. However, the researchers may be contacted by couples that are looking for alternatives to discarding their stored excess frozen embryo(s).

The following types of embryos may be donated by the couples participating in this study:

1. If the embryo(s) is unsuitable for future transfers:
    - embryo(s) with PGD showing genetical disorders
    - poor quality embryos when the couple decides to use better grade embryos for implantation

2. Embryo(s) suitable for future transfers:
    - normal, good quality excess embryos
    - sex selection after PGD

Process of Consent

The subject is presented with the options, and then the consent document is read and discussed, to ensure that the process provides ample opportunity for the investigator and the subject to exchange information and ask questions. The informed consent process includes giving potential subjects adequate information concerning the study through the informed

consent document and answers to the subject's questions, providing adequate opportunity for the subject to consider all options presented in the Disposition of Embryos Form, ensuring that the subject has comprehended this information, obtaining the subject's voluntary agreement to participate after the consent document is comprehensively presented and, continuing to provide information as the subject or situation requires.

The subject has the option to take the consent home if they need more time to make the decision.

During the consent process, the couple donating embryos will be given the option to consent separately in order to avoid undue influence upon one another.

No cash or any kind of payments will be provided for donating blastocysts for this research protocol. All donors will be provided a copy of the informed consent form to keep.

By signing the consent form the donor is allowing the researchers to use the donated embryo(s) and any stem cell lines derived for research described in the consent form. Through the signature, the donor is authorizing California Stem Cell Inc. to use the donated embryo(s) and any stem cell lines derived from the donated material in any lawful way, including future studies, transfer to other for-profit or nonprofit entities, and even to destroy them if they are no longer required.

The frozen embryo(s) will not be moved or transferred to CSCI until 30 days after the consent is signed.

The cryopreserved donated material may be frozen for an undefined period of time.

Consent withdrawal

To withdraw consent, the subjects can either write to Dr. David Diaz at West Coast Reproductive Center, 11160 Warner Ave., Suite 411, Fountain Valley, CA 92708 or call WCFC (24/7) at (714) 513-1319 (calling for withdrawal is put in place to avoid delays caused by pauses in mailing during weekends or holidays).

Subject/Representative Comprehension

The consent is written in easy to understand lay language and it starts with the glossary of terms for easy comprehension of the procedures described.

Research donation forms

The donation of embryos will use the following forms that will be made available to the couple:

1. Disposition of Embryos Form

2. Informed consent form which provides detailed information about this research study according to the required elements of informed consent in 21 CFR Part 50 and records the donor's signature.

Costs to the Subject

Donation of embryo(s) created during the subject's fertility treatment involves no extra cost to the subject. The only costs for the donors of embryos are those that have been part of standard IVF medical care.

Payment for Participation/Compensation

No cash or any kind of compensation will be provided for donating embryos for this study protocol. The embryo donors may be reimbursed for the permissible incidental costs, such as the cost of storing of frozen material.

The cost of storage of donated embryos from the time of signing the informed consent to the time the donated material will be transferred to CSCI will be covered by the study funds and not by the subject (normally the patient pays for storing frozen oocytes or embryos at the fertility center).

Procedure for Presenting Informed Consent to Study Subjects

Patients at West Coast Fertility will only be approached regarding this study if they have already undergone IVF or IVF procedures have already been started. This ensures that no patients will take part in the study solely to create embryos for the purposes of research. This study will be discussed with the patient only as part of the discussion for the dispostion of embryos that are excess or unused following completion of IVF procedures. If patients decide that they would like to donate their excess embryos to research, they must first sign a "Disposition of Embryos Form" provided by West Coast Fertility Center indicating that they would indeed like to donate their excess embryos to research. If they choose to donate to this research study, they will be given a detailed consent form that they can keep and review until they are ready to make their decision.

The subject will be presented with the options, and then the consent document will be read and discussed, to ensure that the process provides ample opportunity for the individual conducting informed consent and the subject to exchange information and ask questions. The informed consent process includes giving potential subjects adequate information concerning the study through the informed consent document and answers to the subject's questions, providing adequate opportunity for the subject to consider all options presented in the Disposition of Embryos Form, ensuring that the subject has comprehended this information, obtaining the subject's voluntary agreement to participate after the consent document is comprehensively presented and, continuing to provide information as the subject or situation requires.

The subject has the option to take the consent home if they need more time to make the decision.

During the consent process, the couple donating embryos will be given the option to consent separately in order to avoid undue influence upon one another.

No cash or any kind of payments will be provided for donating blastocysts for this research protocol. All donors will be provided a copy of the informed consent form to keep.

By signing the consent form the donor is allowing the researchers to use the donated embryo(s) and any stem cell lines derived for research described in the consent form. Through the signature, the donor is authorizing California Stem Cell Inc. to use the donated embryo(s) and any stem cell lines derived from the donated material in any lawful way, including future studies, transfer to other for-profit or nonprofit entities, and even to destroy them if they are no longer required.

The frozen embryo(s) will not be moved or transferred to CSCI until 30 days after the consent form is signed.

Consent withdrawal

To withdraw consent, the subjects can either write to Dr. David Diaz at West Coast Reproductive Center, 11160 Warner Ave., Suite 411, Fountain Valley, CA 92708 or call WCFC (24/7) at (714) 513-1319 (calling for withdrawal is put in place to avoid delays caused by pauses in mailing during weekends or holidays).

CRYOPRESERVATION PROGRAM PARTICIPATION AGREEMENT

This Cryopreservation Program Participation Agreement and Informed Consent ("Agreement") is made on _____ among David G. Diaz M.D., Inc. dba West Coast Fertility Centers ("WCFC"), and _____ ("Patient") and _____ ("Partner").

RECITALS

A. Patient and Partner are attempting to achieve a pregnancy by means of WCFC's Assisted Reproductive Program.

B. To assist some of its patients in achieving a pregnancy, WCFC offers a Cryopreservation Program ("Cryo Program") to qualified patients. Cryopreservation (freezing) is a clinical procedure at WCFC that is designed to initiate a successful pregnancy after thawing cryopreserved human embryos or eggs. Participation in this clinical procedure is voluntary and if Patient and Partner elect not to participate, their decision will not affect their relations with WCFC in any manner, except that Patient and Partner will no longer have those embryos or eggs available for our use in either WCFC'S or anyone else's infertility treatment program.

C. With knowledge that their participation is voluntary, Patient and Partner desire to enroll in WCFC's Cyro Program on the terms and conditions set forth below.

AGREEMENT

1. <u>Patient's and Partner's Representations</u>. Patient and Partner represent to WCFC that they have consulted with, or have had the opportunity to consult with, such advisors as were necessary to enable them to decide to participate in the Cryo Program.

2. **Sperm and Egg Contributions.** Partner agrees to provide his sperm, and Patient agrees to provide her oocytes (eggs) to WCFC to be used in the Cryo Program. (If donated sperm or eggs are to be used, a separate form must be signed concurrently with this Agreement.)

3. **Cryopreserved Material.** WCFC will use its best efforts to achieve fertilization of one or more of Patient's eggs. If more eggs are retrieved and/or fertilized than are presently desirable for transfer into Patient, the embryos or unfertilized eggs (as applicable) which are not being currently transferred will be cryopreserved (frozen) by WCFC in order to preserve them for later transfer into Patient. (In cryopreserved form these embryos and eggs will be referred to as "Cryopreserved Material"). Patient and Partner acknowledge that the Cryopreserved Material has no capacity to produce human life until an egg or embryo has been thawed and properly transferred into the Patient. Patient and Partner also acknowledge that the process of thawing an egg, producing an embryo and transferring the embryo into the Patient is not achievable in all instances, and that the process may not work for Patient and Partner, despite the best efforts of WCFC.

4. **Use of the Cryopreserved Material.** WCFC will maintain, utilize or dispose of the Cryopreserved Material in the following manner:

a. So long as both Patient and Partner remain in the Cryo Program, the Cryopreserved Material will be stored exclusively for the benefit of Patient and Partner and used, after consultation with Patient and Partner, to assist Patient in achieving a pregnancy.

b. Upon termination of Patient's and Partner's participation in the Cryo Program (as defined in Section 5, below), unless otherwise provided for in this Agreement, all of Patient's and Partner's interest in the Cryopreserved Material will pass to WCFC, at which time

WCFC will destroy the Cryopreserved Material following standard medical laboratory procedures for elimination of bio-hazardous material. If this Agreement terminates for any of the reasons set forth in paragraphs 5(c)iii, 5(c)iv or 5(c)vii, WCFC will give Patient and Partner 90 days prior written notice (as provided in Section 12) before destroying the Cryopreserved Material.

c. In the event a dispute arises between Patient and Partner, or between Patient, Partner and WCFC, with respect to the Cryopreserved Material, WCFC will maintain the Cryopreserved Material in its frozen state at Patient's and Partner's expense, until a final court order is entered telling WCFC what to do with the Cryopreserved Material.

5. <u>Payment/Term/Termination</u>.

a. During the term of this Agreement (defined below), Patient and Partner shall pay to WCFC the following professional fees for the cryopreservation (freezing) of their embryos or eggs:

i. $700 for the preparation of the Cryopreserved Material and storage of the Cryopreserved Material for two years after the initial freezing; and

ii. $600 for the one year extended term storage fee if Patient and Partner extend the term of this Agreement under paragraph 5(b), below.

b. The term of this Agreement shall be two years from the date that Patient's Cryopreserved Material first becomes available for use in the Cryo Program. At the end of the two year term, Patient and Partner must either transport their Cryopreserved Material to a long-

term storage facility other than WCFC or execute a written agreement extending the term of this Agreement for one additional year. Ninety days prior to the termination of this Agreement, WCFC will give Patient and Partner notice of the termination date of the Agreement and their options under this Agreement.

c. This Agreement may be terminated by either Patient and Partner or WCFC upon the happening of any of the following events:

i. Patient and Partner advise WCFC in writing that they want to end their participation in the Cryo Program and terminate this Agreement. Patient's and Partner's signatures must be notarized.

ii. A final court order: (1) orders the termination of Patients and Partners participation in the Cryo Program; (2) directs WCFC to deliver to Patient, Partner or some third party all, but not less than all, of the Cryopreserved Material; or (3) directs WCFC to destroy all, but not less than all, of the Cryopreserved Material

iii. This Agreement reaches the end of its two year term and it is not extended in writing.

iv. In the opinion of WCF's medical director, Patient's physical condition changes such as to render her incapable of receiving a transfer or of carrying a pregnancy to term.

v. If either Patient or Partner die, unless they have initialed aparagraph in Section 16(a), below, authorizing the survivor to remain in the Cryo Program.

vi. If both Patient and Partner die, unless the legal representative of the last-to-die's estate notifies WCFC in writing within 90 days of the date of the last-to-die's death what use to make of the Cryopreserved Material or unless Patient and Partner have initialed a paragraph in Section 16(b), below, and then in accordance with the provisions of the selected paragraph in Section 16(b).

vii. If Patient and Partner fail to pay WCFC in accordance with the provisions of paragraph 5(a), above.

d. If Patient and Partner elect to extend the term of this Agreement, the extended term shall be for one additional year. At the end of this one year extended term, Patient and Partner must arrange for the storage of their Cryopreserved Material at a long term storage facility and arrange for the transport of the Cryopreserved Material in accordance with the provisions of Section 6, below. If Patient and Partner do not arrange for the storage and transport of their Cryopreserved Material at the end of the extended term, then WCFC shall destroy the Cryopreserved Material following standard medical laboratory procedures for elimination of bio-hazardous material. Ninety days prior to the termination of the extended term of this Agreement, WCFC will give Patient and Partner notice of the termination date of the Agreement and their two options under this paragraph—storage at another facility or destruction of the Cryopreserved Material. Under no circumstances shall the term of this Agreement extend beyond three years.

6. <u>Transport of Cryopreserved Material</u>. Patient and Partner acknowledge that WCFC, for medical reasons, recommends against the transporting of the Cryopreserved Material

for any purpose. Therefore, to the extent that it becomes necessary for the Cryopreserved Material to be transported from WCFC to any third party, Patient and Partner jointly and severally: (i) assume all risk and expense associated with the transport of the Cryopreserved Material; (ii) agree to indemnify and, if necessary, defend WCFC from all liability, costs and expenses (including any attorney fees incurred by WCFC) associated with any transport of the Cryopreserved Material; (iii) pay WCFC a laboratory transport fee in addition to WCFC's other costs and expenses; and (iv) comply with such other conditions as WCFC may in its reasonable discretion impose in order to effectuate the safe transport of the Cryopreserved Material.

7. <u>WCFC's Right to Discontinue the Program</u>. WCFC presently intends to operate its Cryo Program indefinately. However, WCFC reserves the right to discontinue for any reason the operation of the Cryo Program following not less than 90 days written notice to Patient and Partner. If within 90 days following notice that the Cryo Program will be terminated, Patient and Partner instruct WCFC with respect to the disposition of the Cryopreserved Material, WCFC will follow those instructions at the sole expense of Patient and Partner. If Patient or Partner do not instruct WCFC what to do with the Cryopreserved Material within 90 days after notice is given, WCFC will destroy the Cryopreserved Material following standard medical laboratory procedures for destruction of bio-hazardous material.

8. <u>No Assurances.</u> Patient and Partner acknowledge that the procedures involved in harvesting and fertilizing eggs and creating and implanting embryos are risky and may not lead to Patient achieving a pregnancy. Patient and Partner want to participate in the Cryo Program with full knowledge that there is no guarantee that a pregnancy will occur.

9. <u>Frozen Embryos Involve Risks.</u> Although laboratories worldwide now have the

ability to cryopreserve human embryos and to establish pregnancy after transfer, this does not mean that cryopreservation eliminates the normal risk of obstetric complications or fetal abnormalities, but rather that cryopreservation does not appear to create an increased risk, although the possibility of a presently unforeseen risk cannot be completely eliminated. However, while cryoperservation may not increase the risk of fetal abnormalities, it does decrease the likelihood that pregnancy will be achieved because the pregnancy rate for embryo transfers is lower with cryopreserved embryos than with newly created "fresh" embryos.

10. No Liability for Mechanical Failure. Patient and Partner understand that mechanical support system equipment failure can occur. Patient and Partner therefore acknowledge and agree that neither WCFC, nor its officers, directors, employees, or agents are liable for any destruction, damage, or improper freezing, maintenance, storage, withdrawal, thawing, or delivery caused by or resulting from any malfunction of the storage tank or laboratory instruments used to cryopreserve and maintain the Cryopreserved Material, any utility failure, strike, cessation of services or other labor disturbance, any war, act of a public enemy or other disturbance, any fire, wind, earthquake, water, or any other acts of nature, or the failure of any other laboratory which may have possession of the Cryopreserved Material. Patient and Partner specifically waive their right to sue WCFC, its officers, directors, agents or employees, in the event the embryos or eggs are lost or destroyed because of equipment failures or acts beyond the control of WCFC, either as enumerated above or otherwise.

11. No Insurance or Other Compensation. Patient and Partner understand and agree that WCFC neither has nor provides insurance coverage to compensate Patient or Partner if the embryos or eggs are harmed in any way by the cryopreservation procedure described in this

Agreement. Additionally, WCFC does provide any compensation or free medical care to Patient or Partner if the embryos or eggs are harmed in any way by the cryopreservation procedure described in this Agreement.

12. Notices. All notices required under this Agreement shall be given by certified mail, return receipt requested with a copy by regular mail postage prepaid to Patient and Partner at the address following their signature on this Agreement and to WCFC at 11160 Warner Avenue, Suite 411, Fountain Valley, CA 92708. Notice will be deemed given 3 days after the certified and regular letters are mailed with sufficient postage, whether the certified mail is signed for or not. Either party may change their mailing address by notifying the other in accordance with this section. It is the responsibility of the patient and partner to notify WCFC in writing anytime there is a change of address.

13. Further Consents. Each time Patient and Partner desire to use any of the Cryopreserved Material, both Patient and Partner must sign a written consent instructing WCFC what use to make of the material.

14. Attorney Fees. In any action or proceeding arising out of this Agreement, the prevailing party shall recover reasonable attorney fees.

15. Arbitration and Jurisdiction.

a. Any dispute arising out of this Agreement which is not resolved within 30 days after written notice, shall be first submitted to mediation before a retired judge affiliated with JAMS or Judicate West to be agreed upon by the Parties. If the mediation does not successfully resolve the dispute, the dispute shall be submitted to binding arbitration in Orange County, California in accordance with California Code of Civil Procedure § 1281, *et seq.*, before a retired

judge affiliated with JAMS or Judicate West to be agreed upon by the Parties. If the Parties cannot agree upon an mediator or arbitrator within ten days after any party requests mediation or arbitration, then the matter shall be submitted to JAMS and JAMS will select the mediator or arbitrator. The arbitrator who is selected/appointed shall have final and binding authority to make any necessary rulings, orders and awards. Any award rendered by such arbitration shall be final and binding on the Parties and judgment confirming the award may be entered thereon in the Orange County Superior Court. The parties agree that the provisions of California law applicable to health care providers shall apply to all disputes within the ambit of this agreement, including, without limitation, Code of Civil Procedure sections 340.5 and 667.7 and Civil Code sections 3333.1 and 3333.2. Any party may bring before the arbitrator a motion for summary judgment or summary adjudication in accordance with the Code of Civil Procedure section 437 (c) and the arbitrator shall have the authority to make rulings or render an award in the same manner and under the same circumstances that a sitting judge would have the authority to grant a motion a motion for summary adjudication or summary judgment. Discovery shall be conducted pursuant to Code of Civil Procedure section 1283.5. The prevailing party in any such dispute shall be entitled to recover attorney fees.

b. The Parties agree to submit to the jurisdiction of the Orange County Superior Court in any action arising out of this Agreement. Patient and Partner also understand and agree that they are waiving their right to a trial by a jury of their peers.

16. **Future Disposition**. Should something unexpected happen to Patient or Partner, Patient and Partner would like WCFC to process the Cryopreserved Material in accordance with their instructions set forth in this Section 16. (Please choose one option each from paragraphs a,

b and c, below. Both partners must agree upon and initial the choice for it to be effective.)

a. If either Patient or Partner should die, the Cryopreserved Material should be:

i. _____/_____ Destroyed according to WCFC's policy for destruction of
Patient/Partner

bio-hazardous material.

ii. _____/_____ Given to Partner or Patient, whichever remains alive.
Patient/Partner

iii. _____/_____ Donated to the University of California, Irvine or to
Patient/Partner

California Stem Cell, Inc. to be used to create stem cells or stem cell lines which will be used by qualified researchers in both the for-profit and not-for-profit sectors in research about human development, in testing new pharmaceuticals and, perhaps one day for therapeutic uses in humans. (This choice requires you to also sign an agreement entitled "West Coast Fertility Center Consent to Act a Human Research Subject" which will be provided to you.)

b. If both Patient and Partner die, the Cryopreserved Material should be:

i. _____/_____ Destroyed according to WCFC's policy for destruction of
Patient/Partner

bio-hazardous material.

ii. _____/_____ Donated to another infertile couple.
Patient/Partner

iii. _____/_____ Donated to the University of California, Irvine or to
Patient/Partner

California Stem Cell, Inc to be used to create stem cells or stem cell lines

which will be used by qualified researchers in both the for-profit and not-for-profit sectors in research about human development, in testing new pharmaceuticals and, perhaps one day for therapeutic uses in humans (This choice requires you to also sign an agreement entitled "West Coast Fertility Center Consent to Act a Human Research Subject" which will be provided to you.)

c. If Patient and Partner are divorced the Cryopreserved Material should be:

i. _____/_____ Destroyed according to WCFC's policy for destruction of
Patient/Partner

bio-hazardous material.

ii. _____/_____ Given to: _____
Patient/Partner

(must be either Patient or Partner)

17. **Entire Agreement.** Except for the instructions given to WCFC in the Disposition of Extra Eggs/Embryos agreement that Patient and Partner have signed with WCFC, Patient and Partner acknowledge and agree that all of their rights and duties and all of WCFC's rights and duties concerning the Cryopreserved Material are set forth in this Agreement and that there are no understandings or agreements concerning the Cryopreserved Material except as expressly set forth in this Agreement. Patient and Partner expressly represent to WCFC that they are not relying on any oral representations of WCFC, or any staff member of WCFC, concerning the Cryopreserved Material that are not set forth in this Agreement.

18. **Receipt of Agreement**. Patient and Partner acknowledge that they have received a signed copy of this Agreement and that this Agreement forms a binding contract among Patient and Partner and WCFC.

Dated: _____

_____
Patient Signature

_____
(Print Name)

_____
(Address for Notice Purposes)

_____
Partner Signature

_____
(Print Name)

_____
(Address for Notice Purposes)

Dated: _____

_____
W.C.F.C. Representative Signature

_____
(Print Name)

WEST COAST FERTILITY CENTERS
Advanced Reproductive Technology and Microsurgery

[redacted] *Medical Director*
Diplomate, American Board of Obstetrics and Gynecology
Reproductive Endocrinology and Infertility

JUL 3 1 2006

Date: [redacted]

Dear [redacted]

Fees for: [redacted]

RE: DISPOSITION OF FROZEN EMBRYOS / OOCYTES.

The contract pertaining to the storage of your frozen material in our Laboratory has expired. You must select one of the options below and return this form within two weeks.

1. Continue storage of frozen embryos/oocytes for an **oneyear fee of $500**.

PATIENT SIGNATURE **SPOUSE/PARTNER SIGNATURE**

2. Discard the embryos/oocytes according to the Center's policy.

PATIENT SIGNATURE **SPOUSE/PARTNER SIGNATURE**

3. Donate your frozen embryos/oocytes to another infertile couple.

PATIENT SIGNATURE **SPOUSE/PARTNER SIGNATURE**

4. Donate your frozen embryos/oocytes to West Coast Fertility Centers for research. You will receive a more detailed research consent.

[redacted]

If you wish to continue storage, please enclose payment for $500. If after 30 days from this notice West Coast Fertility Centers has not received any contact from you, we will consider your participation in the Cryopreservation Program terminated and the embryos will be considered abandoned under the terms of our Cryopreservation Program Participation Agreement. If you have any questions, please contact [redacted] in our Laboratory: (714) 513-1399 x 120.

Please return this letter with your decision to:

West Coast Fertility Centers
11160 Warner Ave Suite 411
Fountain Valley, CA 92708

[redacted], M.D., Medical Director
West Coast Fertility Centers

Human Stem Cell Line Registry

CSCI Code: **hCSC 14**	Line established: YES ☒ NO ☐
Derived by: Gabriel Nistor	Date transferred to CSCI: 10/30/06

Blastocyst information

Provenience	IVF Clinic name:	West Coast Fertility Centers						
	Source:	Frozen ☒ Fresh ☐						
	Status:	Surplus ☐ Discarded ☒						
	Embryologist:	Antoine La						
Fertilization	Date: 09/16/05	Grading:	Day 1	Day 2	Day 3	Day 4	Day 5	PGD/gender
Method: IVF ☐ ICSI ☒			2 PN	4C	8C			N/A
Freezing	Date: 09/19/05	Stage: Day 3				Location: WCFC		
Thawing	Date: 10/27/06	Operator: A.L./G.N.				Location: WCFC		

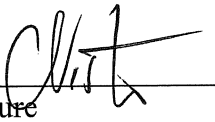
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Grading and development	7/8						

Procedures

Derivation	Hatching	Date: 10/30/06 Location: WC FC
		Spontaneous ☐ Assisted ☐ Dissected ☒
	Plating	Date: 10/30/06 Location: WC FC
	Substrate	Matrigel
	Feeders	Mouse ☐ Human ☐ CM ☐ Defined ☒
	Date when first colony observed:	11/13/06

Attached Documents

☒ Copy of Consent	☐ Media formulation	☒ Pictures
☐ In Vitro Characterization	☐ Contamination testing	☐ .
☐ Karyotype	☐ In Vivo Characterization	☐ .
☐ DNA Fingerprint	☐ Frozen Stock Availability	☐ .

Name	Signature	Date
Gabriel Nistor		11/15/06

Name Signature Date

BioMed·IRB

IRB Meeting Date: November 11, 2009 **Expiration Date:** November 11, 2010

BIOMED IRB INITIAL APPROVAL NOTIFICATION

Study Title: PROCEDURE FOR PROCUREMENT OF EXCESS EMBRYOS FOLLOWING IN-VITRO FERTILIZATION TREATMENT TO BE USED FOR THE DERIVATION OF NEW EMBRYONIC STEM CELL LINES

Sponsor: California Stem Cell, Inc.

Protocol Number: CSC-0902

Protocol Date: November 5, 2009

Principal Investigator: Chris N. Airriess, PhD

Approved Facilities: West Coast Fertility Centers
11160 Warner Ave., Suite 411
Fountain Valley, CA 92708

BioMed IRB has approved the above referenced study as having satisfied the criteria for research on November 11, 2009. Chris N. Airriess, PhD, as Principal Investigator was approved for the above referenced study at the November 11, 2009 meeting. The designated facilities were approved for this study at the November 11, 2009 meeting. The IRB has granted approval for research to be conducted only to those sites that are listed under the entitled "**Approved Facilities**" section of this letter.

The IRB committee has determined that the risk assessment for this study is Minimal.

It was the determination of the IRB Committee that, in this instance, an Informed Consent document is not necessary.

The IRB has determined that continual review of this study will occur Annually.

Approximately thirty days before November 11, 2010, you will be required to complete a Continuing Review Report Form. Continuing review is the responsibility of the Principal Investigator. If you do not receive this form, please contact the IRB office immediately. The Continuing Review Report Form must be received by the due date to allow ample time for ongoing review before the study's expiration date.

IRB approval is granted conditional on your adherence to the following requirements:

- The information submitted to the IRB is true and correct.
- Research will be conducted in accordance with the approved protocol.
- All materials used to recruit study subjects must be pre-approved by the IRB.
- Additional safeguards will be followed when vulnerable subjects, such as children or minors, are participants in the study.

The investigator agrees to report the following information to the IRB:

- Serious Adverse Events occurring at your site should be reported within ten (10) calendar days from the date of discovery by the investigator.
- Serious Adverse Events (IND Safety Reports) occurring at other sites should be reported no later than thirty (30) days from the date of discovery.
- Any changes in the research activity (i.e. changes in study staff, facility etc.) should be reported promptly. In addition, the investigator will not make any changes in the research without the IRB's approval, except when necessary to eliminate apparent immediate hazards to study subjects.
- Any other unanticipated problems involving risks to study subjects.
- Any other unanticipated problems involving risks to the intergrity of the data for this study.

BioMed IRB is comprised of a diverse group of individuals in accordance with the Federal Regulations and the International Conference on Harmonization guidance for Good Clinical Practice. BioMed IRB follows written procedures for performing review, documenting meeting minutes, disclosure of member conflict of interest prior to deliberation or voting, as well as the retention of all records containing research materials as required by the Code of Federal Regulations (21CFR parts 50 and 56; and 45 CFR part 46).

On behalf of the BioMed IRB, I certify that the information contained in this letter is true and correct as verified by the minutes and records of the BioMed IRB.

Please keep a copy of the application material, as well as a copy of this letter, in your files for future reference. Should you have questions or concerns, please do not hesitate to contact this office.

Sincerely,

Authorized Signature

Study Manager
Title

Cecilia Barrena
Printed Name

November 11, 2009
Date

CC: Rania Nasis, MD, MBA, California Stem Cell, Inc.