CRM Induced Pluripotent Stem (iPS) Cell Deposit Agreement

This deposit agreement together with the appendices ("Agreement") is effective as of the date of the last signature to the Agreement ("the Effective Date") and is by and between the _____, a not-for-profit organization ("REPOSITORY"), having its principal place of business at _____; and the NIH Center for Regenerative Medicine ("PROVIDER"), of the National Institutes of Health, an agency of the United States Federal Government (each a "Party," and collectively, the "Parties").

The Parties agree to the following terms and conditions and hereby enter into this Agreement:

1. **Definitions**. The terms listed in this Article will carry the meanings indicated throughout the AGREEMENT.

   1.1 COMMERCIAL PURPOSES: The use, sale, lease or license of a material for a fee in connection with any business or undertaking intended for profit.

   1.2 INDUCED PLURIPOTENT STEM CELL(S) ("iPS CELLS"): Cells (such as skin cells or lymphoblasts) "reprogrammed" to assume an embryonic stem cell-like state, by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells.

   1.3 IPS DISTRIBUTION MATERIAL TRANSFER AGREEMENT ("iPS DISTRIBUTION MTA"): The agreement found in Appendix C, including applicable addendums, for use with transfers of MATERIAL to REPOSITORY CUSTOMER.

   1.4 MATERIAL(S): ORIGINAL MATERIAL, PROGENY, and UNMODIFIED DERIVATIVES.

   1.5 MODIFIED DERIVATIVE(S): Substances that are not intact cells that REPOSITORY isolated or derived from NON-PLURIPOTENT MODIFICATIONS or PLURIPOTENT MODIFICATIONS and that are not UNMODIFIED DERIVATIVES.

   1.6 NON-PLURIPOTENT MODIFICATION(S): Cells that are created by the REPOSITORY from ORIGINAL MATERIAL, PROGENY or PLURIPOTENT MODIFICATIONS, but only if such cells are NOT capable of responding to extrinsically acting cues (such as growth factors, changing media conditions, and other similar cues) to differentiate into various cell types from each of the three embryonic germ layers (endoderm, ectoderm, mesoderm). For clarity, NON-PLURIPOTENT MODIFICATIONS may be multipotent, restricted progenitor cells, or may be terminally differentiated cells, but are NOT pluripotent. NON-PLURIPOTENT MODIFICATIONS may or may not have been genetically manipulated by the REPOSITORY in the manner described in the definition of PLURIPOTENT MODIFICATIONS.

1.7 ORIGINAL MATERIAL(S): The iPS CELLS deposited by the PROVIDER into the REPOSITORY, as described in Appendix A.

1.8 PLURIPOTENT MODIFICATION(S): iPS CELLS that are created by the REPOSITORY from ORIGINAL MATERIAL or PROGENY. PLURIPOTENT MODIFICATIONS differ from ORIGINAL MATERIAL and PROGENY as a result of a manipulation (genetic or otherwise) to the ORIGINAL MATERIAL or PROGENY performed by the REPOSITORY. Some examples of such genetic manipulations include: integration of a reporter gene, or correction of a genetic defect of the ORIGINAL MATERIAL. For clarity, PLURIPOTENT MODIFICATIONS are capable of self-renewal in culture and of responding to extrinsically acting cues (such as growth factors, changing media conditions, and other similar cues) to differentiate into various cell types from each of the three embryonic germ layers (endoderm, ectoderm, mesoderm).

1.9 PROGENY: Unmodified descendant iPS Cells from the ORIGINAL MATERIAL. Progeny retain the ability to self-replicate and the ability to differentiate into cell types from all three germ layers.

1.10 REPOSITORY CUSTOMER(S): Any person or entity that receives MATERIAL from REPOSITORY.

1.11 THIRD PARTY or THIRD PARTIES: Any person or entity that is not a PARTY to this AGREEMENT and is not a REPOSITORY CUSTOMER.

1.12 UNMODIFIED DERIVATIVES: Substances that are not intact cells that REPOSITORY either: (a) isolated or derived from ORIGINAL MATERIAL, PROGENY or other UNMODIFIED DERIVATIVES or (b) isolated or derived from NON-PLURIPOTENT MODIFICATIONS, PLURIPOTENT MODIFICATIONS or MODIFIED DERIVATIVES that are indistinguishable from substances that could have been isolated or derived from ORIGINAL MATERIAL, PROGENY or other UNMODIFIED DERIVATIVES.

2. <u>Deposit</u>.

2.1 PROVIDER agrees to deposit with REPOSITORY the amounts of ORIGINAL MATERIAL, as set forth in Appendix A, along with sufficient information, to the extent that it is available, concerning the culture and maintenance of the ORIGINAL MATERIAL and PROGENY.

2.2 Neither Personally Identifiable Information (PII) nor the key to coded PII will be given to the REPOSITORY by the PROVIDER.

2.3 REPOSITORY agrees not to contact or make any effort to identify individuals who are or may be the sources of human material from which the ORIGINAL MATERIAL was derived.

3. Distribution.

3.1 Subject to the terms and conditions of this Agreement, REPOSITORY agrees to store, replicate and maintain ORIGINAL MATERIAL and/or MATERIAL, as the case may be, in sufficient quantities to satisfy orders from REPOSITORY CUSTOMER.

3.2 REPOSITORY agrees to promote, market and distribute MATERIAL according to the terms and restrictions set forth in this Agreement, including Appendix B, and, if applicable, the terms and restrictions set forth in the iPS DISTRIBUTION MTA (Appendix C).

3.3 REPOSITORY may charge REPOSITORY CUSTOMER a reasonable fee for the maintenance and distribution of ORIGINAL MATERIAL and MATERIAL.

3.4 If distribution to a REPOSITORY CUSTOMER is for COMMERCIAL PURPOSES or if REPOSITORY CUSTOMER is a for-profit entity, then a license from NIH may be required, unless otherwise indicated in Appendix B. As such, REPOSITORY agrees to notify the REPOSITORY CUSTOMER that such a license may be required and agrees not to transfer the MATERIAL to REPOSITORY CUSTOMER until NIH notifies REPOSITORY that a license has been executed.

3.5 When distribution is to a REPOSITORY CUSTOMER that is a not-for-profit entity and is not for COMMERCIAL PURPOSES, REPOSITORY will execute with each such REPOSITORY CUSTOMER the iPS DISTRIBUTION MTA in Appendix C as a requirement for REPOSITORY CUSTOMER to receive the MATERIAL. Execution may be in electronic or printed format as determined by the REPOSITORY and REPOSITORY CUSTOMER. Any modifications to the iPS DISTRIBUTION MTA must be approved in writing by the PROVIDER prior to execution by REPOSITORY and REPOSITORY CUSTOMER.

3.6 REPOSITORY may not create NON-PLURIPOTENT MODIFCATIONS, PLURIPOTENT MODIFICATIONS, or MODIFIED DERIVATIVES from the MATERIALS.

3.7 In the event REPOSITORY discontinues distribution of MATERIAL, then thirty (30) days prior to discontinuation:

a. REPOSITORY will notify PROVIDER in writing of the discontinuation; and
b. REPOSITORY will provide PROVIDER with a minimum of two cryopreserved aliquots of the MATERIAL, unless otherwise declined by PROVIDER, and a written description of culture and maintenance procedures for the MATERIAL.

4. **Liability**.

4.1 PROVIDER represents that the ORIGINAL MATERIAL was derived from human samples collected under a protocol approved by its Institutional Review Board or equivalent body in accordance with federal guidelines for "Protection of Human Subjects" and satisfies all requirements and all applicable laws and regulations. A copy of the pertinent approval documentation from PROVIDER's Institutional Review Board or equivalent body will be provided to REPOSITORY by PROVIDER, upon REPOSITORY's request.

4.2 Each Party represents that it has the requisite power and authority to enter into this Agreement and to perform according to its terms, and that each Party's official signing this Agreement has authority to do so.

4.3 EXCEPT AS EXPRESSLY PROVIDED HEREIN, THE PARTIES MAKE NO EXPRESS OR IMPLIED WARRANTY AS TO ANY MATTER WHATSOEVER, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. THE PROVIDER MAKES NO REPRESENTATIONS THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT OR PROPRIETARY RIGHTS OF THIRD PARTIES. NO INDEMNIFICATION FOR ANY LOSS, CLAIM, OR LIABILITY IS INTENDED OR PROVIDED BY EITHER PARTY UNDER THIS AGREEMENT.

4.4 REPOSITORY agrees to comply with all applicable laws and regulations applicable to the making, maintenance, use, handling and distribution of MATERIAL.

5. **Term**.

5.1 The term for this Agreement shall begin on the Effective Date and continue until terminated pursuant to Section 5.2.

5.2 Either Party may terminate this Agreement with sixty (60) days written notice to the other Party.

5.3 In the event PROVIDER terminates this Agreement pursuant to Section 5.2, REPOSITORY shall immediately cease all manufacture, use and distribution of MATERIAL, and at PROVIDER's option, destroy or return all stocks of MATERIAL unless otherwise agreed to in writing. If PROVIDER opts to have REPOSITORY return stock of the MATERIAL, it agrees to pay the most recent cost per vial of MATERIAL listed in REPOSITORY's catalog.

6. **Relationship**. The relationship of the Parties is that of independent contractors and not agents of each other or joint venturers or partners. Each Party shall maintain sole and exclusive control over its personnel and operations.

7. **Amendments**. This Agreement may not be amended, superseded or waived except in writing and signed by the Parties. No term or provision contained herein shall be

deemed waived unless such waiver is in writing and signed by the Parties. If any provision of this Agreement is for any reason found to be unenforceable, the remainder of this Agreement will continue in full force and effect.

8. **Assignment**. Neither this Agreement nor any rights or obligations of any Party hereunder shall be assigned or otherwise transferred by either Party without the prior written consent of the other Party. The Parties acknowledge the applicability of 41 U.S.C. § 15, the Anti Assignment Act, to this Agreement. The Parties agree that the identity of the REPOSITORY is material to the performance of this Agreement and that the duties under this Agreement are nondelegable. Any attempted assignment or transfer will be void and of no force or effect.

9. **Governing Law**. This Agreement will be governed by U.S. federal law as applied by the Federal Courts in the District of Columbia.

10. **Entire Agreement**. This Agreement constitutes the entire agreement between the Parties with respect to the MATERIAL and supersedes all previous agreements or representations, whether written or oral, between the Parties relating to the same subject matter.

11. **Counterparts**. If this Agreement is executed in multiple counterparts, each counterpart original will have equal force and effect as the original. Furthermore, each photocopy or electronically transmitted copy of the Agreement shall have the same force and effect as the original.

12. **Survival**. The provisions of Articles 4, 5, 7 and 12 will survive the expiration or early termination of this Agreement.

SIGNATURES BEGIN ON THE NEXT PAGE

Each Party expressly certifies and affirms that the contents of any statements made herein are truthful and accurate to the best of knowledge and belief, and each official signing this Agreement on behalf of a Party further certifies and affirms that the official has the authority to do so.

FOR REPOSITORY:

Authorized Official:

_____ _____

[Name] Date
[Title]

Address:

FOR PROVIDER:

Authorized Official

_____ _____

[Name] Date
[Title]

Address:

Read and understand by the principal investigator:

_____ _____

[Name] Date
[Title]

Appendix A

Detailed Description of ORIGINAL MATERIAL [Article 1.7] PROVIDED TO REPOSITORY

(Attach info sheet for each iPS cell line.)

Appendix B

Additional Terms and Conditions
for REPOSITORY's Use of MATERIALS
[Article 3.2]

Original Material	**Distribution Restrictions** *(check all applicable boxes)*	**Modification Restrictions** *(check all applicable boxes)*	**Source** (Include Protocol #, if applicable)	**Comments**
	□ No restrictions □ for nonprofit research, or government research use only For-profit entity permitted: □ internal research use only □ Commercial Purposes □ **NIH license required**	Non-Pluripotent Modifications □ Prohibited Pluripotent Modifications □ Prohibited		

Appendix C:

iPS DISTRIBUTION MATERIAL TRANSFER AGREEMENT
For use by REPOSITORY to Transfer CRM iPS CELLS to REPOSITORY CUSTOMERS
[Articles1.1.3, 3.5]

I. Parties:

1. PROVIDER: Center for Regenerative Medicine, National Institutes of Health, Bethesda, MD (NIH/CRM), a trans-NIH initiative administratively housed within the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)/NIH.

2. REPOSITORY: _____

3. REPOSITORY CUSTOMER: _____

4. REPOSITORY CUSTOMER SCIENTIST: _____

II. Definitions:

1. COMMERCIAL PURPOSES: The use, sale, lease or license of a material for fee in connection with any business or undertaking intended for profit.

2. INDUCED PLURIPOTENT STEM CELLS ("iPS CELLS"): Adult cells (such as skin cells or lymphoblasts) "reprogrammed" to assume an embryonic stem cell-like state, by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells.

3. MATERIAL(S): ORIGINAL MATERIAL, PROGENY, and UNMODIFIED DERIVATIVES.

4. MODIFIED DERIVATIVES: Substances that are not intact cells that REPOSITORY CUSTOMER isolated or derived from NON-PLURIPOTENT MODIFICATIONS or PLURIPOTENT MODIFICATIONS and that are not UNMODIFIED DERIVATIVES.

5. NON-PLURIPOTENT MODIFICATIONS: Cells that are created by the REPOSITORY CUSTOMER from ORIGINAL MATERIAL, PROGENY or PLURIPOTENT MODIFICATIONS, but only if such cells are NOT capable of responding to extrinsically acting cues (such as growth factors, changing media conditions, and other similar cues) to differentiate into various cell types from each of the three embryonic germ layers (endoderm, ectoderm, mesoderm). For clarity, NON-PLURIPOTENT MODIFICATIONS may be multipotent, restricted progenitor cells, or may be terminally differentiated cells, but are NOT pluripotent.

NON-PLURIPOTENT MODIFICATIONS may or may not have been genetically manipulated by the REPOSITORY CUSTOMER in the manner described in the definition of PLURIPOTENT MODIFICATIONS.

ORIGINAL MATERIAL(S): The iPS CELLS provided by the REPOSITORY to the REPOSITORY CUSTOMER, as described in Appendix ONE.

6. PLURIPOTENT MODIFICATIONS: iPS CELLS that are created by the REPOSITORY CUSTOMER from ORIGINAL MATERIAL or PROGENY. PLURIPOTENT MODIFICATIONS differ from ORIGINAL MATERIAL and PROGENY as a result of a manipulation (genetic or otherwise) to the ORIGINAL MATERIAL or PROGENY performed by the REPOSITORY CUSTOMER. Some examples of such genetic manipulations include: integration of a reporter gene, or correction of a genetic defect of the ORIGINAL MATERIAL. For clarity, PLURIPOTENT MODIFICATIONS are capable of self-renewal in culture and of responding to extrinsically acting cues (such as growth factors, changing media conditions, and other similar cues) to differentiate into various cell types from each of the three embryonic germ layers (endoderm, ectoderm, mesoderm).

7. PROGENY: Unmodified descendant iPS Cells from the ORIGINAL MATERIAL. Progeny retain the ability to self-replicate and the ability to differentiate into cell types from all three germ layers.

8. THIRD PARTY or THIRD PARTIES: Any person or entity that is not a PARTY to this AGREEMENT and is not a REPOSITORY CUSTOMER.

9. UNMODIFIED DERIVATIVES: Substances that are not intact cells that REPOSITORY CUSTOMER either: (a) isolated or derived from ORIGINAL MATERIAL, PROGENY or other UNMODIFIED DERIVATIVES or (b) isolated or derived from NON-PLURIPOTENT MODIFICATIONS, PLURIPOTENT MODIFICATIONS or MODIFIED DERIVATIVES that are indistinguishable from substances that could have been isolated or derived from ORIGINAL MATERIAL, PROGENY or other UNMODIFIED DERIVATIVES.

III. Terms and Conditions of this Agreement:

1. The REPOSITORY CUSTOMER agrees that the MATERIAL:

   (a) will not be used in human subjects, in clinical trials, or for diagnostic purposes involving human subjects without the written consent of the PROVIDER;

   (b) will be used only in compliance with applicable laws and regulations;

   (c) will, in the case of entities receiving funding from agencies of the United States to conduct human stem cell research, be used only in compliance with applicable National Institutes of Health Guidelines on Human Stem Cell Research: http://stemcells.nih.gov/policy;

(d) will not be used in research in which the MATERIALS are introduced into non-human primate blastocysts;

(e) will not be used in research involving the breeding of animals where the introduction the MATERIALS may contribute to the germ line; and

(f) is subject to the additional terms and conditions in the appendices attached hereto.

2. The REPOSITORY CUSTOMER acknowledges that the MATERIAL may be the subject of a patent application or covered by patent rights in one or more countries. Except as provided in this Agreement, no express or implied licenses or other rights are provided to use the MATERIAL, NON-PLURIPOTENT MODIFICATIONS, PLURIPOTENT MODIFICATIONS, MODIFIED DERIVATIVES or any related patents for COMMERCIAL PURPOSES.

3. No ownership rights to the MATERIAL, including any MATERIAL contained or incorporated in NON-PLURIPOTENT MODIFICATIONS, PLURIPOTENT MODIFICATIONS or MODIFIED DERIVATIVES are conveyed to the REPOSITORY CUSTOMER under this Agreement.

4. Exclusive of any third-party rights that may exist, the REPOSITORY CUSTOMER retains ownership of: (a) NON-PLURIPOTENT MODIFICATIONS and (b) those substances created through the use of the MATERIAL, NON-PLURIPOTENT MODIFICATIONS or PLURIPOTENT MODIFICATIONS, but which are not PROGENY or UNMODIFIED DERIVATIVES.

5. Unless restricted by Appendix TWO or Appendix THREE, The REPOSITORY CUSTOMER may transfer MATERIAL to other nonprofit or governmental parties if permission from the REPOSITORY is first obtained, or in the event that the REPOSITORY no longer maintains or sells MATERIAL, permission of the PROVIDER.

6. REPOSITORY CUSTOMER shall have the right to nonexclusively distribute:

   (a) NON-PLURIPOTENT MODIFICATIONS or PLURIPOTENT MODIFICATIONS subject to Appendix TWO and Appendix THREE restrictions, if any, and the following term:

      i. In the event that REPOSITORY CUSTOMER enters into negotiations to provide or license PLURIPOTENT MODIFICATIONS to a THIRD PARTY for COMMERCIAL PURPOSES, then REPOSITORY CUSTOMER will notify that THIRD PARTY of PROVIDER's ownership of MATERIALS that are contained or incorporated within the PLURIPOTENT MODIFICATIONS. It is recognized by the REPOSITORY CUSTOMER that such COMMERCIAL PURPOSES may require a

license from PROVIDER, who has no obligation to grant a license to any ownership interest in MATERIAL incorporated in the PLURIPOTENT MODIFICATIONS.

(b) MODIFIED DERIVATIVES subject to Appendix TWO and Appendix THREE restrictions, if any, and the following terms:

i. REPOSITORY CUSTOMER will transfer such substances, and sufficient rights to use them, to other academic and governmental research institutions for internal research purposes at nominal cost, and will implement arrangements to effect such transfers.

7. There is no restriction on REPOSITORY CUSTOMER's development of commercial products resulting from the knowledge gained from research using the MATERIAL, MODIFIED DERIVATIVES, NON-PLURIPOTENT MODIFICATIONS or PLURIPOTENT MODIFICATIONS.

8. The REPOSITORY CUSTOMER is free to file patent application(s) claiming inventions made by the REPOSITORY CUSTOMER through the use of the MATERIAL but agrees to notify the PROVIDER upon filing a patent application claiming MATERIALS, NON-PLURIPOTENT MODIFICATIONS, PLURIPOTENT MODIFICATIONS, MODIFIED DERIVATIVES or method(s) of manufacture or use(s) of the MATERIAL.

9. REPOSITORY CUSTOMER AND REPOSITORY CUSTOMER SCIENTIST agree not to attempt to identify or contact the donor subject from whom the ORIGINAL MATERIAL was or may have been derived.

10. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties and its use may require acquisition of rights from THIRD PARTIES. The REPOSITORY and PROVIDER MAKE NO REPRESENTATIONS AND EXTEND NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF THE MATERIAL, ITS SOURCE, MERCHANTABILITY, TRANSFER OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

11. **For U.S. State Institutions**: The REPOSITORY CUSTOMER agrees to be responsible for any claims, costs, damages or expenses resulting from any injury (including death) damage, or loss that may arise solely from its use of the MATERIAL and to hold harmless and indemnify the PROVIDER, REPOSITORY and THIRD PARTIES to the extent permitted by law.

12. **For all other Institutions:** Except to the extent prohibited by law and except for U.S. Government agencies (which may not agree to an indemnification obligation), the REPOSITORY CUSTOMER hereby agrees to hold harmless and indemnify the REPOSITORY and PROVIDER against any claim arising from the REPOSITORY

CUSTOMER's receipt, storage, disposition and/or use of the MATERIAL, and any claim that the REPOSITORY CUSTOMER's use of the MATERIAL violates any intellectual property or other rights of a THIRD PARTY, or violates any provision of local, national or international law, except to the extent permitted by law when caused by the gross negligence or willful misconduct of the REPOSITORY and PROVIDER.

13. This Agreement shall not be interpreted to prevent or delay publication of research findings resulting from the use of the MATERIAL. The REPOSITORY CUSTOMER SCIENTIST agrees to provide appropriate acknowledgement of the source of the MATERIAL in all publications.

14. In all oral presentations or written publications concerning the use of MATERIAL, REPOSITORY CUSTOMER will acknowledge PROVIDER's contribution of ORIGINAL MATERIAL unless requested otherwise by PROVIDER.

15. Additional terms, if any, are in Appendix THREE.

SIGNATURES BEGIN ON THE NEXT PAGE

REPOSITORY CUSTOMER expressly certifies and affirms that the contents of any statements made herein are truthful and accurate to the best knowledge and belief, and the official signing this Agreement on behalf of REPOSITORY CUSTOMER further certifies and affirms that he or she has the authority to do so.

Authorized Official:

_____ _____

[Name] Date
[Title]
[Institution]

Address:

I have read and understand the terms of this agreement.

_____ _____

[Repository Customer Scientist name] Date
[Title]

Appendix ONE

Detailed Description of ORIGINAL MATERIAL PROVIDED TO REPOSITORY CUSTOMER
[Article I.4]

(Attach info sheet for each iPS cell line.)

Appendix TWO

Additional Terms and Conditions for REPOSITORY CUSTOMER's Use of MATERIALS
[Article III.5]

Original Material	**Distribution Restrictions** *(check all applicable boxes)*	**Modification Restrictions** *(check all applicable boxes)*	**Source** (Include Protocol #, if applicable)	**Comments**
	□ No restrictions □ for nonprofit research, or government research use only For-profit entity permitted: □ internal research use only □ Commercial Purposes □ **NIH license required**	Non-Pluripotent Modifications □ Prohibited Pluripotent Modifications □ Prohibited		

Appendix THREE

Article 11 Additional Terms

(default is “none”)