Lonza Walkersville, Inc.
8830 Biggs Ford Road
Walkersville, MD 21793 USA
www.lonza.com
Tel: (301) 898 7025
Fax: (301) 845 4024

Lonza

CERTIFICATE OF ANALYSIS
Provided for Research Purpose Only

Product Code: TC-1133 **Lot Number: 50-001-21, P20**

Product: Human CD34+ umbilical cord blood cell derived induced pluripotent stem cells (hiPSC) - Matched Research Grade hiPSC Working Cell Bank (WCB) **Manufacture Date: 20 May 2015**

TEST (Method)	SPECIFICATIONS Min.	Max.	Results
Fill Volume	***	***	1 mL
Sterility Test	***	***	Negative
Mycoplasma	***	***	Negative
CELL PERFORMANCE TESTING			
Stemness			
AP	***	***	Postive
IF (Oct3/4, SSEA-4, Nanog, TRA-1-81, TRA-1-60)	***	***	Positive
Flow Cytometry (SSEA-4, Tra-1-60, Tra-1-81)	Pass ≥ 70%	***	Pass
Pluripotency EB formation with IF for 3 germ layers (AFP, Tuj1, SMA)	***	***	Confirmed from Master Cell Bank
Residual plasmid Confirmation Vector clear by qPCR. Undetermined CT values resulted following 40 cycles of qPCR amplification with EBNA1-specific primers on 20-60 ng gDNA.	***	***	Confirmed from Master Cell Bank
Plating Efficiency	≥20 colonies in one 6-well	***	Pass
Identity Testing (STR Analysis)	***	***	Confirmed from Master Cell Bank
Karyotype	***	***	Normal

CELL PERFORMANCE TESTING IMAGES

Figure 1: TC-1133, lot 50-001-21, iPSC culture images before banking. (A) Passage 18, day 4 post-split; (B) Passage 19, day 4 post-split; (C) Passage 20, day 3 post-split.

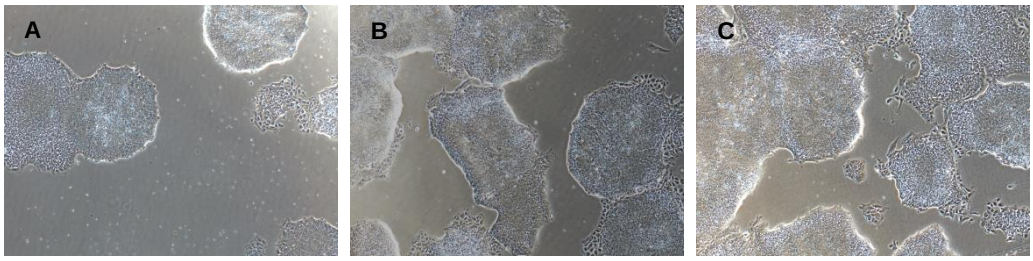

Figure 2: TC-1133, lot 50-001-21, P 20+2 (2nd passage after revival) hiPSCs are positive for SSEA4, OCT4, NANOG, TRA-1-60 and TRA-1-81. All the images were taken using 20×magnification.

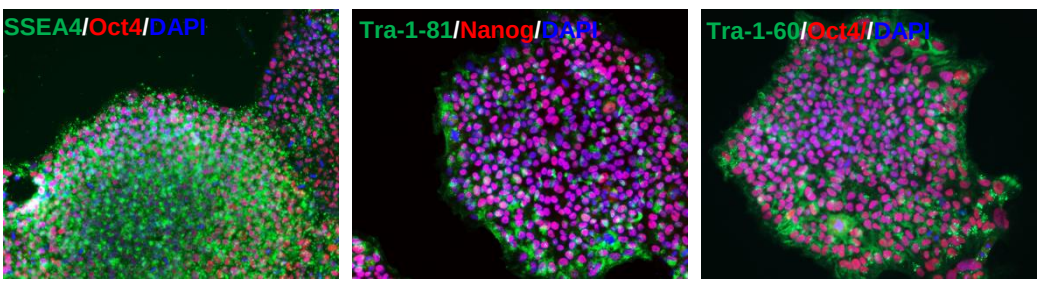

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Figure 3. Summary of flow cytometry results for TC-1133, 50-001-21, P20+2 (2nd passage after revival).

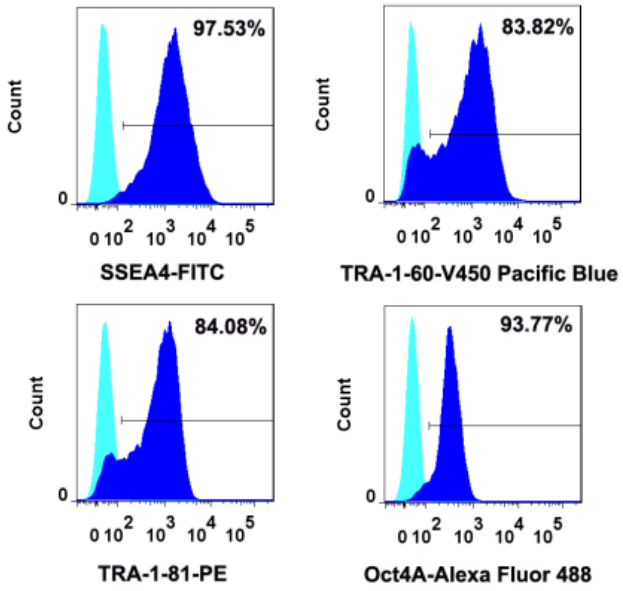

Figure 4: TC-1133, lot 50-001-21, P20+2 (2nd passage after revival) maintains normal karyotype, 46XY

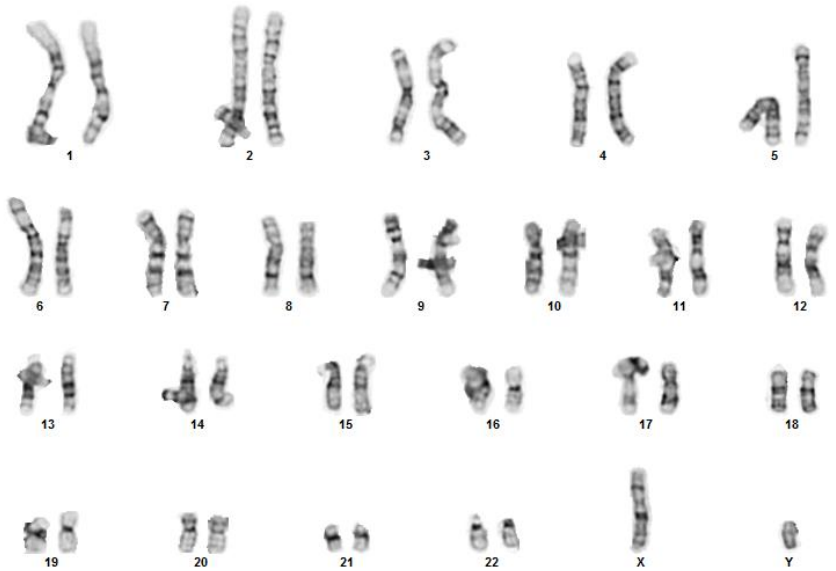

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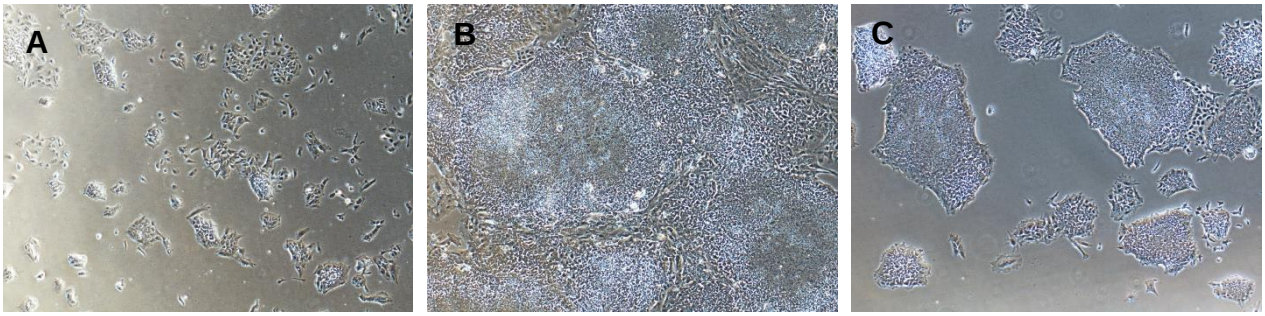
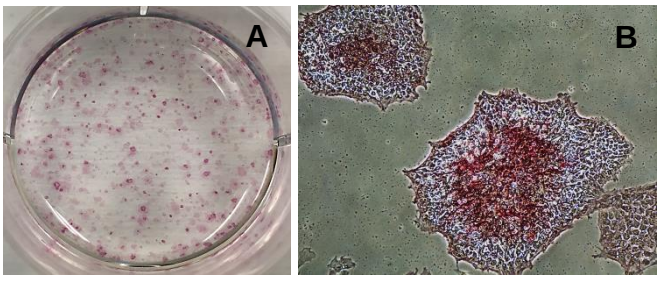
Figure 5: hiPSCs revived from the Matched Research Grade hiPSC Working Cell Bank (WCB) TC-1133, lot 50-001-21. ≥1x10^6 viable cells were frozen in 1 vial and thawed into 2 wells of six-well plate. (A) 1 day (P20+1) post revival from WCB (4X). (B) 4 days (P20+1) post revival from WCB (4X). The edge of the colonies may appear to be flat for the first couple passges, but the majority of the colonies should become compact once the culture reaches confluent. (C) Day 3 hiPSCs at P20+5 in L7™ hPSC culture system.



Important Note: The optimal split ratio ranges from 1:15 to 1:30 depned on the confluency when passaging in Lonza every-other-day feeding L7™ hPSC Medium (Cat No. FP-5007). Even though L7 hPSC Medium support every-other-day feeding, we strongly recommend feeding hiPSC daily when reviving hiPSC from the WCB. The hiPSC culture shown in Figure 5 has been fed daily for the first three passages and started every-other-day feeding from P20+4. Manual cleaning or selection was not performed during characterization process, however it is optional to adjust the quality of colonies.

Figure 6: hiPSC from the Matched Research Grade hiPSC WCB TC-1133, 50-001-21, P20+1, stains positive for alkaline phosphatase (AP). 1 vial of frozen cells were thawed into 4 wells of a 6 well-plate. (A) A representative well with AP positive colonies at day 5 post-revival. (B) AP positive colonies at 10 × magnification.



Lutheran Hospital
Institutional Review Board (IRB) Approval Form

IRB Name: Lutheran Hospital Institutional Review Board
IRB Address: 7950 W. Jefferson Blvd.
Fort Wayne, IN 46804
Principal Investigators: Nancy Dock, Ph.D.
Study Site(s): St. Joseph Hospital
700 Broadway
Fort Wayne, IN 46802

Lutheran Hospital of Indiana
7950 West Jefferson Blvd.
Fort Wayne, IN 46804

Protocol Title and Number: Umbilical cord recovery program for development of induced pluripotent stem cells for treatment of BPD. This is not a study but a Tissue collection service by Lonza for Cord or Umbilical blood to be utilized in research.

Date Reviewed by IRB: 01/15/14
The items below have been submitted for review:

- ☒ Proposal for Umbilical Cord for Clinical Application January, 2014
- ☒ Informed Consent For Umbilical Cord and Cord Blood Collection For Clinical Research Purposes
  IRB stamp or notation with approval date of 01/15/14
- ☒ HIPPA Authorization
- ☐ Other – specify:

Approval:

- ☐ Approval granted on _____
- ☒ Approval granted on 01/15/14 for all items above, for a period of 1 year or until 01/15/15.
- ☐ Conditional approval* granted on _____
- ☐ Not approved*

The IRB performing this review is duly constituted and operates in accordance and compliance with local and federal regulations and ICH guidelines

Shelly Scott		01/16/14
Printed Name (IRB Chair or designee)	Signature	Date of Signature

Exhibit A
Donor ID Number

UMBILICAL CORD BLOOD COLLECTION FOR CLINICAL RESEARCH PURPOSES INFORMED CONSENT

SPONSORS: Cell and Tissue Recovery Services, LLC (CTRS) and Lonza Walkersville, Inc. (Lonza) Walkersville, MD.

This consent form may contain words that you do not understand. Once you have read this form, you will be given an opportunity to ask questions you may have. Please ask the medical personnel or the on-site staff member to explain any words or information that you do not clearly understand.

THE PROGRAM

You are being asked to donate your baby's umbilical cord blood to CTRS. CTRS will be sending the donated umbilical blood to Lonza Walkersville, Inc. or "Lonza" to isolate a certain type of blood cell and turn it into so-called induced Pluripotent Stem Cells, abbreviated as "iPS" cells. **Normally the umbilical cord, cord blood and placenta are discarded by the hospital.**

iPS cells can be turned into many different types of cells, such as nerve, liver, and muscle cells and can be kept alive and stored in the laboratory for an indefinite period of time. iPS cells are different from embryonic stem cells. Researchers can learn a lot about various medical problems by studying iPS cells and may be able to use iPS cells generated from your baby's cells to make possible treatments either by testing new drugs or using the iPS cells to create cell replacement therapies.

In the future, researchers may study your baby's cells and/or the iPS cells derived from your baby's cells by looking at the DNA or genetic code in your baby's/iPS cells, altering some of that genetic code within the cells, testing in animals to study diseases and treatments, developing new drugs, and other processes not yet identified. All research conducted with your baby's/iPS cells must comply with all applicable laws and policies. The iPS cells made from your baby's cells will never be used to clone or to otherwise create an entire human being. iPS cells generated from your baby's cells may involve transplanting or testing with animals, but always will be performed within the laws and regulations for such research.

Medical research and society, as a whole, will benefit from sharing iPS cells and information among many researchers and institutions around the world. Your identity and the identity of your baby will be kept confidential by CTRS and Lonza.

If you choose to participate in the Program, your baby's umbilical cord blood will become the property of Lonza. Cells will be isolated from the umbilical cord blood, iPS cells will be made, and the iPS cells will be sent to the National Institutes of Health (NIH), commercial companies, and non-commercial organizations including universities and research institutes. iPS cells may be used for the development of cell therapies for the treatment of many diseases, may be used in clinical trials and may be eventually sold as patient treatments. Researchers will own the cells and the research results, may file patents or otherwise legally protect the development of products to be sold, and may financially benefit.

If you do not decide to donate your baby's umbilical cord blood, your medical treatment will not be affected in any way.

Continued on Next Page

Donor ID Number

THE COMPANIES

CTRS is a for-profit cell and tissue recovery agency specializing in the recovery of umbilical cord and will financially benefit by sending your baby's cord blood to Lonza.

Lonza Walkersville, Inc. (Lonza) is a life sciences company providing products and services worldwide to research organizations and companies performing research on cells. Lonza is a for-profit company that may benefit financially by providing iPS cells and/or cells generated from these iPS cells to researchers.

PROCEDURE

The delivery of your baby will not be changed in any way if the collection of the umbilical cord blood occurs. After delivery of the afterbirth (the placenta), it will be placed in a basin and moved to another room for the cord blood collection procedure. Your baby's cord blood will be taken from the umbilical cord and placed in a cord blood collection container and will be shipped to Lonza to separate out certain cell types and these will be used to make the iPS cells. The placenta and umbilical cord will be discarded by the Hospital.

If you decide to donate, there are several steps in the donation process.

Donors of human cord blood for cell therapies must be healthy. Your medical evaluation and blood testing will be used to determine that the therapies being developed from the donated umbilical cord blood are safe for persons who may receive the treatments made from the cells. All test results are kept confidential. Your health will be evaluated in the following ways:

1) You will be asked to complete a health questionnaire administered by a trained interviewer from CTRS.
2) Your hospital record will be reviewed by a physician.
3) One of your physicians will sign a form indicating that you and your baby's physical examinations are normal.
4) Approximately 27 ml (about 6 teaspoons) of blood will be collected from you by a medical professional during your hospital stay to make sure you do not have certain infections.

The blood samples from you will be tested by Lonza for certain infectious diseases, including the Human Immunodeficiency Virus (HIV, the virus that causes AIDS), Hepatitis B and C, syphilis (a venereal disease), cytomegalovirus, and some uncommon infections caused by viruses, including Human T-cell Lymphotropic Virus and West Nile Virus. CTRS will notify your physician or healthcare provider should the infectious disease results be medically important. However, CTRS or Lonza are not set up to do routine tracking, notifying, or counseling patients and cannot guarantee that you will be notified of the results once they have been provided to your health care provider. For this reason, if you are concerned about your risk of these diseases or conditions, you should speak to your doctor directly.

If your baby's cord blood cannot be used for making iPS cells, the cord blood will be discarded by Lonza.

RISKS/ BENEFITS

Donation of umbilical cord blood does not pose a risk to the mother or the baby. The collection procedure is performed on the placenta and umbilical cord in a room separate from your Labor and Delivery room.

During your hospital stay, your blood samples will be collected by inserting a needle into a vein in your arm. This procedure is unlikely to cause problems. However, there is a slight risk of fainting, local bleeding, pain, or development of a bruise or infection at the site of the needle puncture.

Continued on Next Page

Donor ID Number

There is no direct benefit to you; however your donation might lead to a better understanding of human health and result in the development of therapies for patients. If, in the future, researchers discover genetic information about your baby's cells you and your baby will not receive this information.

There is no cost to you or your insurance company for your participation. You will not be paid for this donation of cord blood. There will be no financial benefit to you, your baby, or your family, from the research results or from the sales of products.

Although CTRS and Lonza will take measures to keep your identity and the identity of your baby confidential, a possible risk of loss of confidential information does exist.

CONFIDENTIALITY

Your identity as a donor and the identity of your baby will be kept confidential and will not be available to researchers. Your signed Informed Consent Form and other forms will be maintained in locked files at CTRS and Lonza. Copies of these forms will be provided to Lonza to determine whether the cells obtained from your donation can be used for patient treatments. CTRS and Lonza will assign a unique identifier number to these forms and will not allow research companies or researchers to know your identity or the identity of your baby.

ALTERNATIVES

Your participation in this program is voluntary. Choosing not to participate in this program will not affect the medical care you receive.

If you donate your baby's umbilical cord blood to Lonza you will not have access to it for your own use.

Please note that there are other companies that, for a fee, will store cord blood for your baby's possible future medical use. Your doctor may have additional information about companies that store cord blood and can explain the potential benefits of doing so.

You are **not** giving up any legal claims, or legal rights, because of your participation in this research program. If you decide to withdraw your consent before the start of manufacture of iPS cells (within 2 weeks of your delivery date), the cells that you have donated will be destroyed. We will NOT be able to destroy iPS cells once they are created. The cells will not be retrievable after the iPS cells have been shared with other researchers.

PROTECTED HEALTH INFORMATION

By signing this informed consent, you agree to permit the staff of CTRS, physicians and health care providers who treat you and your baby (together, your "*Providers*") to use and disclose (release) health information about you and your baby as described below.

The health information that may be used and disclosed includes:

- Your age and ethnicity,
- Hospital records,
- Laboratory test results, and
- Information received by your *Providers* as part of the donation process.

Continued on Next Page
Donor ID Number

Your *Providers* may use the health information to evaluate whether you are a qualified donor. Lonza may use the information to evaluate whether you are a qualified (eligible) donor, to aid in the preparation of cells from the donated tissue, and to ensure that the cells may be used safely to develop and test a therapy for patients. Lonza may share this information about you with the research companies involved in developing and testing a therapy for patients, but will not share your identity or the identity of your baby. Records that identify you or your baby will not be released except as required by law.

CTRS and Lonza also may disclose the information to representatives of government agencies, review boards, and other persons who watch over your safety and the safety of tissue donations. CTRS and Lonza will not otherwise use or provide any information that directly identifies you or your baby, except with your written permission or as required by law.

Your *Providers* may disclose the health information to:

- Representatives of CTRS.
- Representatives of Lonza Walkersville, Inc. ("Lonza"),
- Representatives of government agencies, review boards, and other persons who watch over the safety of tissue donations.
- Representatives of research organizations and companies and their Institutional Review Boards.

CTRS and Lonza will use the health information for record keeping and eligibility purposes only. Once your Providers communicate your health information and your child's health information to Lonza, the information may no longer be protected by federal privacy laws. However, Lonza and CTRS agree that they will not use or further communicate any health information that directly identifies you or your baby except as described in this Informed Consent Form.

If you have any questions regarding the donation of your umbilical cord blood, please contact:

Hospital Institutional Review Board
Telephone: 260-385-1143

Continued on Next Page

Donor ID Number

STATEMENT OF CONSENT

By signing below, you agree that you are participating voluntarily in this Program, that you have read and understand the above information, and that the Staff or your Doctor have clearly answered all of your questions about the umbilical cord blood donation for research and therapy purposes. You will be given a copy of this consent form for your records.

I authorize my *Providers* and my baby's *Providers* to use and disclose health information about myself and my baby as described in this Informed Consent.

Signature of Donor | Printed Name of Donor | Date

Address_____ City_____ State____ Zipcode_____

Signature of Person obtaining Consent and answering questions | Printed Name of Person obtaining Consent and answering questions | Date

Do not write below this line CTRS use

NINDS Human Cell and Data Repository
Material Transfer Agreement (Working Cell Bank)

This Materials Transfer Agreement (the "MTA") is made as of this _____, ___, 20__, (the "Effective Date") by and between **[NHCDR]**, with an office at **[PLEASE INSERT ADDRESS OF NHCDR]** ("Provider"), and **[PLEASE INSERT FULL LEGAL NAME OF PRINCIPAL INVESTIGATOR ("Principal Investigator"), REPRESENTING _____("Institution"),** with an office at **[PLEASE INSERT PI ADDRESS]**.

MISSION

The mission of the **NINDS Human Cell and Data Repository (NHCDR)** is to provide, develop, and manage cell and data research resources in order to advance discoveries into the causes and treatments of neurological diseases while concurrently protecting the rights of subjects providing human material resources.

PURCHASE PROCESS

This **Material Transfer Agreement (MTA)** must be executed by each investigator requesting **cell lines, DNA samples or other biological material (NINDS Materials)** from the NHCDR. Both the **recipient principal investigator (Principal Investigator)** and the institutional official who is authorized to make *legally binding* agreements for the **institution that employs the Principal Investigator (Institution)** must sign this MTA. Please note that the Institution will also be provided with appropriate certificate of assurance on cell lines to include karyotype information, pluripotency markers, mycoplasma testing, etc.

In addition to this MTA, the Principal Investigator must complete a **Statement of Research Intent (SRI)** (electronically for on-line orders or in hard copy for special requests for secondary distribution) describing the purpose of the research to be done using the NINDS Materials.

All fully executed MTAs will be kept on file at the NHCDR and considered applicable to subsequent purchases made by the Principal Investigator if at the same institution named in the originally signed MTA. If the NHCDR substantially revises this form in the future, the NHCDR reserves the right to require the Principal Investigator to execute the latest version of the MTA. A new SRI describing the intended research is required for all purchases.

HUMAN SUBJECTS ISSUES

Principal Investigator and Institution acknowledge that the conditions for use of the NINDS Materials are governed by the Rutgers University Institution Review Board **(IRB)** and must be in compliance with the Office of Human Research Protections (OHRP), Department of Health and Human Services (DHHS), regulations for the protection of human subjects found at 45 CFR Part 46. Under these regulations, research activities involving publicly available, existing specimens and data or research with existing specimens and data from which human subjects cannot be identified, either directly or through linked identifiers, may be exempt from the DHHS policy for protection of human research subjects (45 CFR §46.101(b)(4)). Recipient Principal Investigator and Institution remains subject to all state and local laws or regulations and institutional policies which may provide additional protections for human subjects.

When applicable to research described in the SRI, Principal Investigator should adhere to ethical standards established by the International Society for Stem Cell Research (ISSCR).

NHCDR will under no circumstances provide information that will allow identification of individual subjects. Further, the Principal Investigator agrees not to try to identify or contact the donor subject from whom the sample was derived.

HUMAN EXPERIMENTATION

Principal Investigator and Institution agree that the introduction of NINDS Materials or their derivatives (any cell product where NINDS Materials were used for creation or modification of the product) in human subjects, their administration to human subjects as part of clinical trials, or for diagnostic purposes involving human subjects, is strictly prohibited without the written consent of NINDS.

DETERMINATION OF OWNERSHIP

NINDS retains ownership of the NINDS Materials and any functional subunits thereof contained or incorporated in derivatives. Inventions and ownership of intellectual property resulting from the research will be determined by U.S. patent law.

COMMERCIAL USE

NINDS Materials were developed by Lonza under contract for the NIH. NINDS places no restriction on development of commercial products resulting from the knowledge gained from research using the NINDS Materials. However, iPS Academia Japan, Inc. ("iPS AJ") owns patents that may cover certain of the NINDS Materials, and can be contacted at http://ips-cell.net/e/license/policy.html to discuss obtaining a commercial license. NINDS Materials or material isolated from them, such as RNA, DNA, or protein, may not themselves be used in the manufacture of commercial products or sold or distributed as commercial products themselves. The NHCDR cannot provide a warranty or any assurances whatsoever relating to third-party property interests that may exist in the NINDS Materials. The attached Appendix A, "Notification to Recipient," is incorporated fully into this MTA as required by Lonza's license with iPS AJ and cannot be further modified. The Principal Investigator and the Institution will be responsible for adhering to the terms and conditions in Appendix A as well as those in the MTA. The terms and conditions attached hereto as Appendix A shall take precedence over any contrary or inconsistent terms and conditions appearing or referred to in this MTA.

RESEARCH USE

Principal Investigator and Institution understand that the NINDS Materials provided under this MTA are experimental and are for use in research, in teaching and as standards in clinical genetics laboratories. Principal Investigators using NINDS Materials as research standards or controls are responsible for complying with all applicable laws and regulations specific to that intended use, including any requirements for FDA approval.

SHARED USE AND SECONDARY DISTRIBUTION

Secondary distribution, or the sharing of NINDS Materials with members of laboratories other than the Recipient Principal Investigator's, is not permitted except under certain clearly defined circumstances as described below and only with prior written authorization from the NHCDR. The Principal Investigator should read the restrictions under this section and Appendix A very carefully and contact the NHCDR Principal Investigator before distributing NINDS Materials or their derivatives. Any secondary distribution must include a copy of Appendix A, Notification to Recipient.

NINDS established an NINDS Repository Group consisting of program directors and staff with relevant scientific knowledge to review and authorize secondary distribution requests for NINDS Materials. Consistent with its mission to facilitate neuroscience research, the NHCDR and NINDS Repository Group will permit secondary distribution if such requests are supported under the mission of the NHCDR, if it can be established that protection of human subjects is ensured as necessary, if quality control of the NINDS Materials is ensured, and if an appropriate process for secondary distribution (as outlined in this MTA) is followed.

Permitted Uses as reviewed and approved by the NINDS Repository Group:

1. *Single-use, multi-investigator collaboration*. Two or more investigators initiate a collaborative project that requires the use by each laboratory of identical NINDS Materials. At the time the order is placed, Principal Investigator explains in the SRI that the NINDS Materials will be shared with specific, named collaborator(s) for a common research project. Secondary distribution to named collaborator(s) may be permitted when the SRI is identical for all the named collaborator(s). Each collaborating investigator must have a current, executed MTA on file with NINDS Repository.

2. *Multi-user core facility*. A core facility (for high-throughput screening, for example) obtains NINDS Materials for use by investigators within the facility to perform assays for use at that facility or for a consortium. The SRI should describe the ranges of studies that will be conducted using the NINDS Materials. In this situation, use of these materials in the core facility may be permitted if the NINDS Repository Review Group is assured that the use of the NINDS Materials is consistent with the research subject's informed consent. Since the NINDS Materials will be used in the same facility for multiple investigators, quality can be ensured.

3. *Distribution of samples for use as reference materials*. Principal Investigator may place an order for one or more NINDS Materials and describe in the SRI that the NINDS Materials will be distributed, either with or without modification, for use as a reference material. The SRI may not be able to specify which laboratories will receive NINDS Materials. The NINDS Repository Review Group will decide this type of request on a case-by-case basis with the advice of the NHCDR's Project Officer. Principal Investigator will be required to maintain records of where the NINDS Materials are sent. NINDS Materials must be distributed under a written agreement which includes: (i) a disclaimer of the NHCDR's responsibility regarding safety and quality; (ii) a requirement that the NINDS Materials be returned to the Principal Investigator or destroyed within a certain time frame or at the conclusion of the research; (iii) a restriction that the NINDS Materials or their derivatives are never transferred to a third party; and (iv) a notification that the NINDS Repository was the source of the materials.

4. *Development of a Unique Resource*. This permitted use involves the development of NINDS Materials into **substances comprising or containing an unmodified subunit of NINDS Materials (Unique Resource)**. Consistent with the NIH Research Tools Policy (64 FR 72,090), a Unique Resource encompasses a range of research tools, including but not limited to: subclones of unmodified cell lines, purified or fractionated subsets of the NINDS Materials, proteins expressed by DNA/RNA supplied by Principal Investigator, induced pluripotent cell lines, and monoclonal antibodies secreted by a hybridoma cell line. A Unique Resource is substantially different from the NINDS Materials. Simply modifying NINDS materials obtained from NHCDR through the introduction of a gene (e.g., hTERT or green fluorescent protein) would not qualify as creating a Unique Resource. The Principal Investigator's Institution may distribute the Unique Resource by using an appropriate agreement between the Institution and the **entity receiving the Unique Resource (Secondary Recipient)**. The transfer agreement for the Unique Resource must include:
   (i) a statement listing the identification number(s) of the NINDS Materials from which the Unique Resource was derived;
   (ii) a statement that the Secondary Recipient must acknowledge the NHCDR and the NINDS Materials identification number in any publications or presentations based on the utilization of the Unique Resource;
   (iii) a statement prohibiting the use of the unmodified Unique Resource for human experimentation or commercialization;
   (iv) a disclaimer that the Unique Resource has not undergone the standard quality control of the NHCDR; and

(v) a statement that the Unique Resource may not be used for commercial purposes except for internal research purposes.
(vi) A copy of Appendix A, Notification to Recipient.

In addition to the above statements (i) – (v), the transfer agreement for the Unique Resource must be consistent with NIH's Simple Letter Agreement for the Transfer of Materials or the UBMTA (Uniform Biological Material Transfer Agreement). Both of these agreements are found under the MTA section at: http://www.ott.nih.gov/forms-model-agreements#MTACTA

Institution is required to provide the NHCDR with the Unique Resource for distribution and protocols for its care, if appropriate, after an agreed upon embargo period.

Prohibited Uses:

1. *Multi-purpose use*. At some point after obtaining the NINDS Materials, Principal Investigator wishes to give a portion of the NINDS Materials or a culture derived from the NINDS Materials to another investigator who is working on a different project. In this case, secondary distribution of the NINDS Materials is prohibited because use of the NINDS Materials by the other investigator may not be consistent with the terms of this MTA and the Principal Investigator's SRI.

2. **The secondary distribution or sale of NINDS Materials for any purpose not specifically authorized above is PROHIBITED unless otherwise noted by NINDS Program staff**. If NINDS Materials are requested from Principal Investigator, he/she should direct the requester to the NHCDR.

DESTRUCTION AND FINAL REPORT

Unless instructed otherwise by NHCDR, Principal Investigator must destroy the NINDS Materials within five (5) years of receipt of the NINDS Materials or upon completion of research described under the SRI, whichever is shorter. Within six (6) months after destruction of the NINDS Materials, Principal Investigator must email NINDS@dls.rutgers.edu a final report including: (i) a brief summary of the research results or outcome of the project; (ii) a list of related publications or presentations; and (iii) a statement attesting destruction of the NINDS Materials. Principal Investigator should include his/her current contact information in the final report should follow up be required.

PUBLICATION

Principal Investigator must acknowledge the NHCDR and the NINDS Materials identification number in any publications or presentations based on research utilizing the NINDS Materials. Additionally, the following acknowledgement statement must be included in all publications, "*Generation of the GMP line LiPSC-GR1.1 was supported by the NIH Common Fund Regenerative Medicine Program, and reported in Stem Cell Reports. The NIH Common Fund and the National Center for Advancing Translational Sciences (NCATS) are joint stewards of the LiPSC-GR1.1 resource."*

BIOHAZARD

All cultured animal and human cells as well as other human biological have the potential for carrying viruses, latent viral genomes, and other infectious agents in a latent or inactive state. NINDS Materials should therefore NOT be treated as if they are free of contamination. NINDS Materials should always be handled carefully by trained persons under laboratory conditions which afford adequate biohazard containment following MINIMUM SAFETY GUIDELINES RECOMMENDED FOR WORKING WITH HUMAN CELL CULTURES. By

accepting the NINDS Materials, the undersigned assumes full responsibility for their safe and appropriate handling. Principal Investigator agrees to provide notice to the NHCDR of any containment or quality issues related to the NINDS Materials.

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SIGNATURES

We, the undersigned, have read and understand this document and agree to adhere to the terms and conditions stated therein.

Name of Institution: _____

Name of Principal Investigator: _____

Signature of Principal Investigator: _____

Date: _____

Name of Institution Official who can make legal commitments on behalf of the Institution: _____

Title of Institution Official: _____

Signature of Institution Official: _____

Date: _____

The signed MTA and the SRI may be submitted to the NHCDR through the NHCDR online catalog

To contact the NHCDR
e-mail: NINDS@dls.rutgers.edu

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Appendix A

Notification to RECIPIENT

Definitions:

LONZA: Lonza Walkersville, Inc. and any of its affiliates.

CLIENT: The person or entity purchasing MATERIAL from LONZA.

RECIPIENT: CLIENT and/or any party receiving the MATERIAL or ALTERED CELLS either directly or indirectly from CLIENT.

MATERIAL: Pluripotent cells, derivatives of pluripotent cells, genetic modifications of pluripotent cells, partially-differentiated cells, and terminally-differentiated cells.

ALTERED CELLS: Changes made to the MATERIAL made only by a RECIPIENT.

COMMERCIAL PURPOSES: The sale, lease, license, or other transfer of MATERIAL or ALTERED CELLS to a for-profit organization. COMMERCIAL PURPOSES shall also include uses of MATERIAL or ALTERED CELLS by a for-profit organization, to perform contract research, to perform screening of compound libraries to produce or manufacture products for general sale, or to conduct research activities that result in any sale, lease, license, or transfer of MATERIAL or ALTERED CELLS. However, industrially sponsored academic research shall not be considered a use of MATERIAL or ALTERED CELLS for COMMERCIAL PURPOSES per se, unless any of the above conditions of this definition are met. NOR WILL SENDING THE MATERIAL OR ALTERED CELLS TO A FOR-PROFIT ORGANIZATION TO PERFORM SERVICES ON BEHALF OF THE RECIPIENT SUCH AS KARYOTYPING, HYBRIDIZATION, ARRAY AND GENOME ANALYSIS UNLESS THE ABOVE CONDITIONS ARE MET.

1. RECIPIENT shall have the right, without restriction, to distribute MATERIAL or ALTERED CELLS to academic organizations or to academic core laboratories for their internal non-commercial purpose only, which may include generation of data. RECIPIENT may also distribute MATERIAL or ALTERED CELLS to for-profit organizations under appropriate license from any third party(ies) required for such distribution.

2. RECIPIENT shall acknowledge that the MATERIAL and ALTERED CELLS is or may be the subject of an issued patent or pending patent application. Except as provided in this Notification, no express or implied licenses or other rights are provided to RECIPIENT under any patents, patent applications, trade secrets, licenses or other proprietary rights("INTELLECTUAL PROPERTY") of LONZA, or any third parties, including any altered forms of the MATERIAL made by LONZA. In particular, no express or implied licenses or other rights are provided to use the MATERIAL, or any related patents of LONZA, or any third parties, for COMMERCIAL PURPOSES.

3. If RECIPIENT desires to use or license the MATERIAL or ALTERED CELLS for COMMERCIAL PURPOSES, RECIPIENT agrees, in advance of such use, to negotiate in good faith with parties holding applicable intellectual property rights to establish the terms of a commercial license. It is understood by RECIPIENT that LONZA or any third party shall have no obligation to grant such a license to RECIPIENT, and may grant exclusive or non-exclusive commercial licenses to others, or sell or assign all or part of the rights in the MATERIAL or ALTERED CELLS to any third party(ies), subject to any pre-existing rights held by others and obligations to the Federal Government. For clarity, any terminally-differentiated cells made and sold by LONZA may be used by RECIPIENT for COMMERCIAL PURPOSES.

Nothing in this paragraph, however, shall prevent RECIPIENT from granting commercial licenses under RECIPIENT's intellectual property rights claiming ALTERED CELLS, or methods of their manufacture or their use.

4. Any MATERIAL and ALTERED CELLS delivered pursuant to this Notification is understood to be experimental in nature and may have hazardous properties. LONZA MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL ANDALTERED CELLS WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

5. Except to the extent prohibited by law, RECIPIENT assumes all liability for damages which may arise from its use, storage or disposal of the MATERIAL or ALTERED CELLS. LONZA will not be liable to RECIPIENT for any loss, claim or demand made by RECIPIENT, or made against RECIPIENT by any other party, due to or arising from the use of the MATERIAL or ALTERED CELLS by RECIPIENT, except to the extent permitted by law when caused by the gross negligence or willful misconduct of LONZA.

6. RECIPIENT agrees to use MATERIAL and ALTERED CELLS in compliance with all applicable statutes and regulations and agrees to notify RECIPIENT of same. For the removal of doubt, RECIPIENT shall not use MATERIAL and ALTERED CELLS for application and use for human/animal therapeutic, diagnostic and/or prophylactic purposes including but not limited to clinical applications, cell therapy, transplantation, and /or regenerative medicine without appropriate license.

7. RECIPIENT shall be required to convey a copy of this "Notification to RECIPIENT" to any person or party receiving MATERIAL or ALTERED CELLS from RECIPIENT.

8. LONZA has obtained its rights to manufacture the MATERIAL pursuant to a non-exclusive license agreement ("the AJ agreement") with iPS Academia Japan, Inc. ("AJ"). No rights, either express or implied, obtained by LONZA in the AJ agreement are provided to RECIPIENT to use the MATERIAL or ALTERED CELLS.

9. If RECIPIENT desires to use or license the MATERIAL or ALTERED CELLS for COMMERCIAL PURPOSES, RECIPIENT is not required to obtain further license or other rights from LONZA resulting from its manufacturing of the MATERIAL. Notwithstanding, the RECIPIENT is still required to meet the obligations of any other party (which may include AJ) provided for in this notification for use of the MATERIAL or ALTERED CELLS for COMMERCIAL PURPOSES.

Title: Instruction for Use – NIH – LiPSC GR1.1 - Matched Research Grade hiPSC Working Cell Bank (WCB); P/N: TC-1133, Lot No. 50-001-21	**Doc.No.:**	**Page:** 1 of 6
	Edition: 25Feb 2016	**FINAL**

Materials:

Cat No.	**Description**	**Size**	**Store Condition**
CTM-5058	L7 hPSC Basal Medium	500 ml	2-8°C, protected from light
CTM-5059	L7 hPSC Medium Supplement (100X)	5 ml	-20°C to -80°C, protected from light
FP-5020	L7™ hPSC Matrix	1 mg	-20°C to -80°C
FP-5013	L7™ hPSC Passaging Solution	100 mL	room temperature

Product description:

- Two cryovials of matched research grade working cell bank of TC-1133, Lot No.50-001-21, Passage 20

Instruction:

1. Upon receiving the cells, immediately transfer the vials to vapor phase or liquid nitrogen for proper storage.
2. Store the provided materials properly as described in the table.

3. Prior to thawing the TC-1133, lot 50-001-21- matched research grade hiPSC Working Cell Bank (WCB), prepare L7™ hPSC Matrix Stock Solution in cell culture grade water as described in the **"L7™ hPSC Matrix Technical Information & Instructions".** The stocking solution (1 mg/ml) aliquots can be stored at -20°C to -80°C for up to three months. Avoid repeated freeze-thaw cycles.

4. On the day before reviving the TC-1133, lot 50-001-21- Matched Research Grade hiPSC WCB, thaw an aliquot of the L7™ hPSC Matrix Stock Solution at room temperature. Dilute the L7™ hPSC Matrix Stock Solution with DPBS **with calcium and magnesium** (Lonza Catalog No. 17-513F, or equivalent) to create 10 µg/ml working solution. (i.e. add 60 µl of 1 mg/ml L7™ hPSC Matrix Stock Solution to 6 ml of DPBS to coat 1 six-well plate, 1 ml per well).
5. Incubate the coated six- well plate in a 37°C, 5% CO2 humidified incubator. Though the plate can be ready to use after 1 hour incubation for expansion or passaging, **we recommend incubating the plate overnight for the best thawing efficiency**.
6. Preparing complete L7 hPSC medium as described below:
   a) Thaw the L7 hPSC Medium Supplement (100X) (CTM-5059) at room temperature or overnight at 2-8°C, protected from light.
   b) Add the completely thawed 5ml L7™ hPSC Medium Supplement to 500 ml basal medium (CTM-5058) to make complete L7™ hPSC Medium. Mix well before use. The L7™ hPSC medium is light sensitive. **Store the complete L7™ hPSC medium protected from light at 2°-8°C when not in use. NOTE: This complete medium is Lonza daily feeding medium and requires changing the medium every day.**
   c) After adding the supplement to the basal medium, the completed medium can be used up to two weeks. **Do not freeze the complete medium.**
7. Thawing TC-1133, lot 50-001-21- Matched Research Grade hiPSC WCB.
   a. Prior to thawing the cryovial of cells, warm up the completed L7 hPSC medium to room temperature protected from light.
   b. Quickly thaw the cryovial in a 37°C water bath, being careful not to submerge the entire vial. Wipe the cryovial with 70% ethanol and transfer it to BSC when there is only a small crystal ice remaining.
   c. Gently transfer the thawed cell suspension to a 15 ml sterile conical tube using a 1ml serological pipet. Slowly add 9 ml of the complete L7™ hPSC Medium to the tube.
   d. Centrifuge at 200 x g for 5 minutes at room temperature.

e. Carefully discard the supernatant and resuspend the pellet in 10 ml of pre-warmed complete L7™ hPSC Medium. Gently pipet up and down 2-3 times to mix the cells. **Avoid excessive pipetting.**

f. Remove the L7 Matrix Solution from the 6-well plate, immediately dispense 2.5 ml cells into each well of the six-well plate (1 vial to 4 wells of six-well plate). **Do not let the coated well dry out before adding cells to the wells.**

g. Gently rock the plate to evenly distribute the cells and return to the 37°C, 5% CO2, humidified incubator.

h. Change the growth medium the day after seeding and check cell attachment and morphology. Some debris will be present after 24 hours post-thaw. Distinct colonies with defined borders should be visible starting from day 2-3. At first passage after thaw, some spontaneous differentiation (~5-15%) could be observed in the culture depending on the utilized cell culture system.

i. Passage the cells once the cells reaches 70-90% confluent following instruction provided in "L7**™ hPSC Passaging Solution Technical Information & Instructions**". It usually takes 5-7 days for the cell to be ready for passaging. At some rare cases, if the attachment was extremely low and the culture couldn't reach 70-90% confluency after 7 days, you may passage the cells based on the size of the colonies and the differentiation level. The split ratio will also need to be adjusted accordingly.

j. We recommend passaging the cells at 1:8-1:15 split ratio if the culture reaches confluency of 70-90% when using L7™ hPSC medium (CTM-5058 and CTM-5059). In general, the split ratio for passaging / plating the cells depends on the choice of cell culture system.

Important Highlights

TC-1133, lot 50-001-21- Matched Research Grade hiPSC Working Cell Bank (WCB) (named LiPSC GR1.1 in recent GMP manuscript publication - (1)) has been successfully revived in L7™ hPSC culture system, Essential 8™ Medium (Life Technologies) and mTeSR™ 1 Medium (STEMCELL Technologies) (see Supplumentary Data below). Cell morphology may look slightly different depending on which cell culture system has been chosen. We recommend reviving the cells in the provided materials and cell culture system. After 2 passages, the cells can be transferred to other cell culture system if needed. **The optimized thawing ratio is 1 vial to 2-4 wells of six-well plate.**

Note: L7™ hPSC medium (CTM-5058 and CTM-5059) has been used to manufacture TC-1133, lot 50-001-21 master cell bank. The matched research garde WCB has been generated and characterized using L7™ hPSC medium (Lonza Cat No: FP-5007), which is a Xeno-free, Every-other-day feeding medium. Please find attached the detailed information for the Every-Other-Day medium in "**L7™ hPSC BulletKit™ Medium Technical Information & Instructions**". There is no need for adaptation when switching medium from **daily feeding** L7™ hPSC Medium (CTM-5058 and CTM 5059) to **every-other-day feeding** L7™ hPSC medium (FP-5007) and vice versa. The cells perform similarly in either medium.

Supplumentary Data

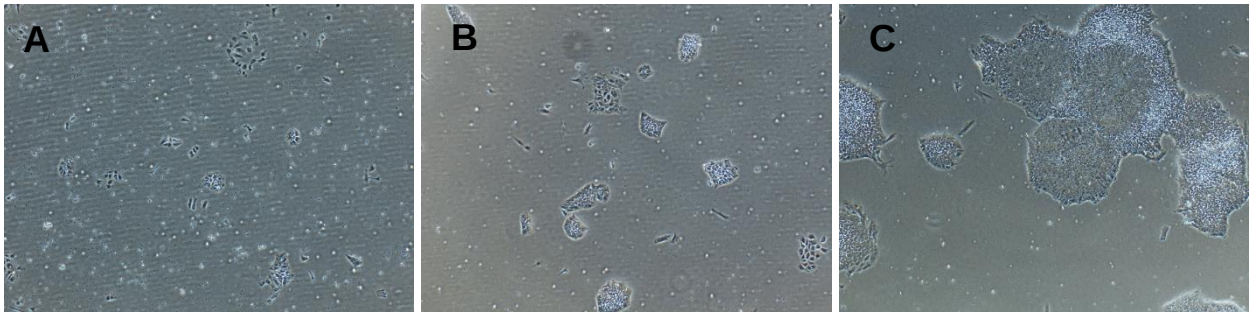

Figure 1: hiPSCs revived from the Matched Research Grade hiPSC Working Cell Bank (WCB) TC-1133, lot 50-001-21 in L7™ hPSC Medium (CTM-5058 and CTM-5059) on L7™ hPSC Matrix (FP-5020). Cells from 1 vial of the WCB were thawed into 4 wells of six-well plate. (A) 1 day (P20+1) post revival from the WCB (4X). (B) 3 days (P20+1) post revival from the WCB (4X). (C) 5 days (P20+1) post revival from the WCB (4X). The colonies should become compact at day 3-5.

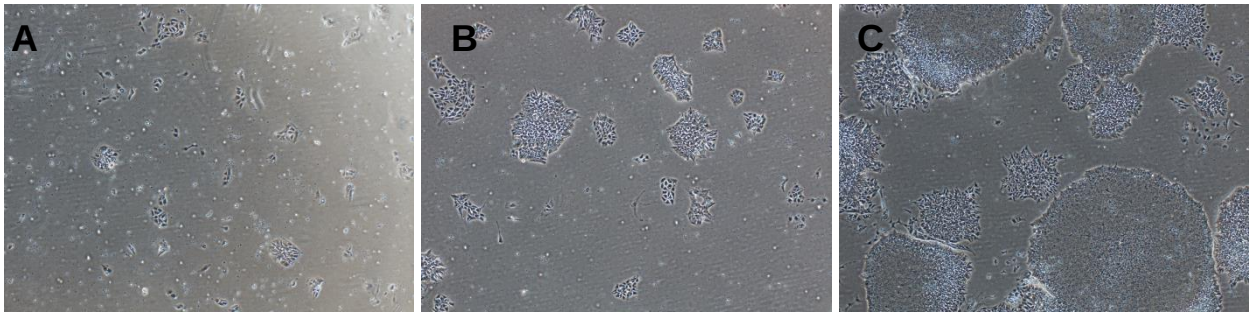

Figure 2: hiPSCs revived from the Matched Research Grade hiPSC Working Cell Bank (WCB) TC-1133, lot 50-001-21 in Essential 8™ culture system. Cells from 1 vial of WCB were thawed into 4 wells of six-well plate in Essential 8™ Medium. (A) 1 day (P20+1) post revival from WCB (4X). (B) 3 days (P20+1) post revival from WCB (4X). (C) 5 days (P20+1) post revival from WCB (4X). The colonies should become compact at day 3-5.

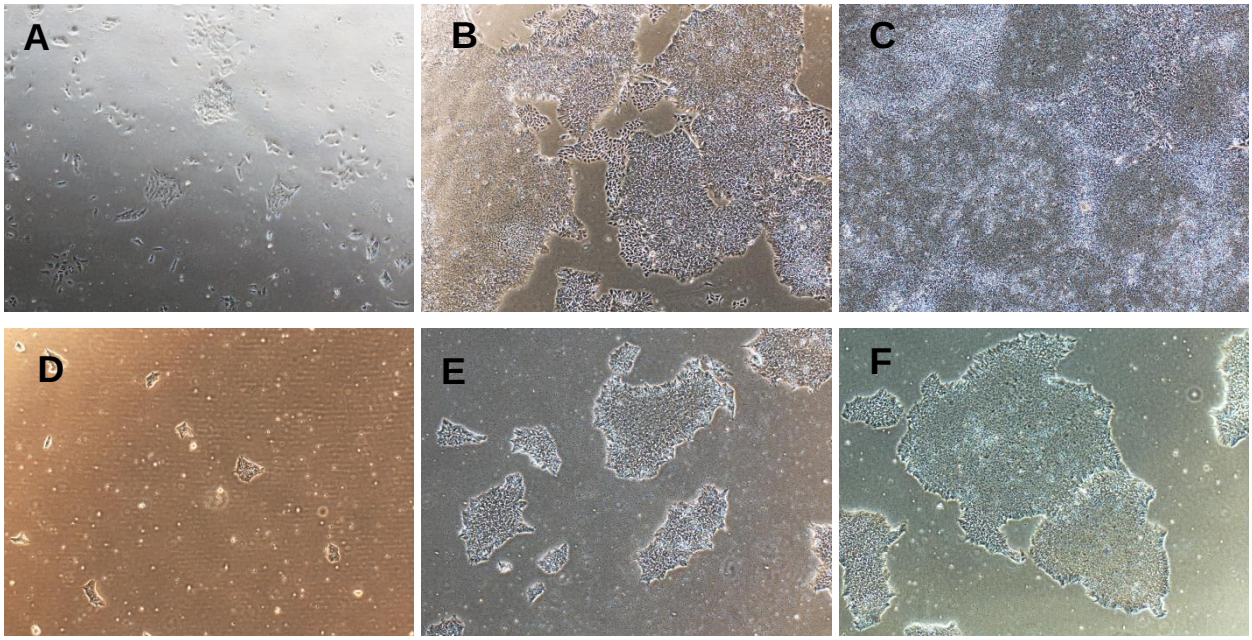

Figure 3: hiPSCs revived from the Matched Research Grade hiPSC Working Cell Bank (WCB) TC-1133, lot 50-001-21 in mTeSR™ 1. Cells from 1 vial of WCB were thawed into 2 wells of six-well plate in mTeSR™ 1 hPSC medium (A) 1 day (P20+1) post revival from WCB (4X). (B) 4 days (P20+1) post revival from WCB (4X). (C) 5 days (P20+1) post revival from WCB (4X). (D) 1 day (P20+2) after 1st passaging at 1:10 split ratio (4X). (E) 3 days (P20+2) after 1st passaging at 1:10 split ratio (4X). (F) 5 days (P20+2) after 1st passaging at 1:10 split ratio (4X).

Reference:

1. Baghbaderani, B A, Tian, X, Neo, B Het al. cGMP-Manufactured Human Induced Pluripotent Stem Cells Are Available for Pre-clinical and Clinical Applications. Stem cell reports. 2015;5(4):647-59. Epub 2015/09/29.