Prize Announcement for New Fibrolamellar Carcinoma Cell Lines

Access to human fibrolamellar carcinoma (FLC) cell lines is important to accelerate research and treatment development against this lethal, rare cancer of adolescents and young adults. To address this critical need, the Fibrolamellar Cancer Foundation (FCF) seeks to create a collection of well-characterized FLC cell lines, each of which faithfully represents the biology of the tumor from which it was derived. To accelerate the accrual of a Fibrolamellar Cell Line Repository ("Collection") that will be available to the FLC research community, the FCF offers a $10,000 prize for each cell line that is approved by the FCF and deposited into the Collection as described below. This award is meant to encourage novel and creative approaches to establishing new cell lines and to enable broad access to these lines.

SUBMISSION PROCESS

Any investigator who has created a cell line derived from a human fibrolamellar carcinoma tumor is invited to submit the cell line for validation and inclusion in the Collection. Creators are encouraged to submit cell lines as soon as possible. To achieve standardization among the entire Collection, all validation experiments will be carried out in a laboratory designated by the FCF. Cell lines provided for validation will not be further distributed without the permission of the creator.

The process for submission of a cell line to the Collection is as follows:

1. Sign the accompanying Letter of Intent (Appendix A) indicating your acceptance of the terms and conditions outlined in this Prize Announcement and email it to **pcogswell@fibrofoundation.org**.
2. An FCF representative will contact you to coordinate transfer of the cell line to a designated lab for characterization and validation. If necessary, the FCF will help arrange a material transfer agreement between your institution and the designated laboratory governing the use of your cell line.
3. Cell lines must be tested for blood borne pathogens prior to receipt to establish correct Biosafety Level (BSL) handling and labeling. We recommend the Human Essential Clear Panel available from Charles River Laboratories.
4. Submit cell line(s) that have undergone at least 20 population doublings and any relevant data, tissue, or tissue derivatives to the designated repository. See Inclusion Criteria below for list of required materials and data.
5. Submit data generated on your cell line as proof of FLC characteristics.
6. Validation of the line will determine that the line is unique, human in origin, and has no mycoplasma contamination. Any data generated for the purpose of validating the cell line will be shared with you.
7. If the cell line has characteristics consistent with FLC and viability for research purposes, then it will be considered for inclusion in the Collection. You will be notified in writing by the FCF whether your cell line(s) were selected for inclusion in the Collection.
8. Once your cell line is selected for inclusion in the Collection, the next step will be for you or your institution to execute the FCF Fibrolamellar Cancer Cell Line Collection Material Deposit Agreement or another agreement approved in writing by the FCF to deposit your cell line our designated lab or central repository.
9. Upon finalizing the Deposit Agreement and depositing the cell line into the Collection, the FCF

will issue an award letter and payment form offering you an unrestricted prize for scientific and educational purposes in the amount of $10,000 for the cell line deposited into the Collection.

10. Once you complete and return the payment form, the FCF will mail a check to the "Fiscal Officer" address indicated on the payment form.

If you have questions about any aspect of this prize, please email **pcogswell@fibrofoundation.org**.

SUBMISSION REQUIREMENTS

For a cell line to be considered for inclusion in the Collection, the following must be submitted:

1. At least two frozen vials containing the cryopreserved cell line
2. A completely de-identified pathology report from the tumor of origin
3. A copy of the signed informed consent form authorizing collection of the tumor specimen from which the cell line was derived. The informed consent must allow for the use, storage, and distribution of the cell line for all research and development purposes and be clear that no profit from any commercial products derived from the cell line will be returned to the patient.
4. A description of cell line including
    a. initial tumor dissociation and culture method
    b. approximate number of passages
    c. time period over which cells were passaged
    d. any significant changes in phenotype or emergence of subpopulations during passage
    e. history of microbial contamination
5. Instructions for culturing the cell line including product information for media and any other reagents.
6. Information about the tumor from which the cell line was derived
    a. Anatomic location of the FLC
    b. Whether the tumor was primary, or recurrent
    c. Date tumor was resected or ascites fluid containing cancer cells was collected
    d. Indicate if a portion of the tumor or ascites fluid sample was also preserved.
7. Information about the patient from which the cell line was derived
    a. Demographics: gender, age at diagnosis, ethnicity
    b. Treatment history, including prior surgery, chemotherapy, immunotherapy, or radiation (if available)
    c. Patient outcome if known
    d. Is the patient alive or deceased?

<u>The following items are requested but not required</u>

1. Several unstained slides from the tumor or cell sample from which the cell line was derived
2. A frozen and/or paraffin embedded tissue sample from the tumor of origin and/or nucleic acids derived from the tumor of origin
3. Normal tissue, peripheral blood mononuclear cells and/or non-tumor DNA from the patient from which the tumor was derived is strongly encouraged to discern somatic from inherited mutations
4. Any available data regarding phenotype (e.g., growth in soft agar or xenografts), genotype, copy number changes, gene expression, protein expression, or other validation experiments conducted on the purported FLC cell line.

INCLUSION CRITERIA

Cell lines can be propagated as cells attached to culture vessels or in three-dimensional culture. Stable "tumor organoids," potentially including a minority population of mesenchymal/tumor stromal cells in addition to cancer cells, will be accepted if they meet the inclusion criteria. Lines must retain characteristic features of FLC, including the DNAJB1-PRKACA fusion gene (for classic FLC), or other relevant markers such as loss of PRKAR1A, or genomic abnormalities consistent with "hepatocellular carcinoma with fibrolamellar- like features." A cell line may be initiated from a specimen taken directly from a patient or after propagation of tumor cells in a PDX model. Cell lines should be developed from independent specimens, usually from different patients. However, multiple cell lines derived from the same patient but grown from specimens obtained at different times (e.g., from a primary tumor and after a recurrence) or from different metastatic deposits will be considered. Each cell line will be evaluated for inclusion in the Collection based on the following criteria:

Criterion	Assay
All Required	

Confirmed FLC diagnosis of source tumor	• Histology
	  ○ Morphology
	  ○ Ideally, dually positive for cytokeratin 7 and CD68 by immunohistochemistry
	• Ideally, molecular and/or cytogenetic (e.g., break-apart FISH assay) analysis

Human species	Karyotype, human-specific PCR product, or hybridization to human oligonucleotide array
Rearranged genome	Karyotype, CGH, aCGH, or SNP array
Cell line retains DNAJB1-PRKACA gene fusion (typical FLC); or other molecular abnormalities consistent with FLC or HCC with FLC-like features	RNA sequencing, cytogenetic analysis, or DNA sequencing Confirmation of identity with molecular driver(s) of initial tumor, when available
Exhibits acceptable doubling rate	Doubling rate of 12 days or less
Cell line growth	At least 20 population doublings in culture [e.g., ca. 9 passages at 1:5 dilution]

PRIZE GUIDELINES AND EXPECTATIONS

In addition to satisfaction of the above scientific criteria, the FCF has the following guidelines and expectations for cell lines to be included in the Collection.

- Proper consent from the patient must have been obtained to allow for the use, storage, and distribution of the cell line for all research and development purposes. No profit from any commercial products derived from the cell line(s) shall be returned to the patient.
- Data generated in characterizing the cell line will be shared only with the creator and the FCF. This data will be kept confidential unless the creator waives this confidentiality. Upon inclusion in the Collection and acceptance of the prize, all properly deidentified data associated with the cell line provided to the FCF will be made public and distributed with the cell line.
- The FCF encourages creators to publish results of the research leading to the development and characterization of the new cell line(s), preferably in a peer-reviewed open access journal. Therefore, at the request of the creator, the FCF will embargo specific data generated in characterizing the cell line for up to six months to give the creator an opportunity to publish on the creation and characterization of the cell line.
- You or your institution must have entered into a Deposit Agreement with the FCF for purposes of depositing your cell line into the Collection.
- Upon acceptance of the prize, the FCF will be permitted to publicize the name of the institution and/or creator, and the amount of the prize.

TERMS AND CONDITIONS OF PRIZE

1. AWARDS PROCESS

   The decision to include a cell line in the Collection and to award a $10,000 prize to the cell line's creator will be made by the FCF Board of Directors based on the recommendation of expert advisors, the availability of funding, and other pertinent factors. The FCF will consider the genetic and biological characteristics of the cell line, as well as accompanying data regarding the tumor from which the cell line was derived. Investigators will be notified in writing by the FCF whether cell line(s) are selected or not for inclusion in the Collection. Upon validation, selection for inclusion in the Collection, execution of the Deposit Agreement and deposit of the cell line with the FCF designated repository, the FCF will issue an award letter and payment form offering an unrestricted prize for scientific and educational application in the amount of $10,000 for the cell line deposited into the Collection.

2. ACCEPTANCE OF AWARD

   A grantee indicates acceptance of an award and will become bound by the terms and conditions attached to the award notification letter by signing the award notification letter and depositing funds disbursed by the FCF. Each prize will be awarded on the terms and conditions outlined herein.

3. DISBURSEMENT POLICY

   This prize is made to reward the creator of an FLC cell line for contributing that cell line to the FCF Cell Line Collection. The prize is made as an unrestricted award to the creator's institution to be used at

the sole discretion of the creator for scientific and educational application. Payment to the creator's institution will be made by check unless otherwise requested by an authorized institutional official. Checks will be mailed to the "Fiscal Officer" address indicated on the payment form.

4. LIABILITY

Upon acceptance of this award, the creator and the creator's institution will indemnify and hold harmless the FCF, its Board, officers, agents, advisors and constituents from any claim, judgment, award, damage, settlement, liability, negligence, or malpractice arising from research or investigation activities related to this award.

Appendix A

Intent to Submit Cell Lines for Inclusion in Fibrolamellar Cancer Foundation Cell Line Collection

I have read and agree to the terms and conditions of the Fibrolamellar Cancer Foundation Repository ("Collection") set forth in the Prize Announcement and intend to submit the cell line(s) named as follows to be considered for inclusion in this Collection:

[insert names of cell line(s)]_____

I will make these cell line(s) available to the FCF for the purposes of characterization and validation. I understand that data generated on my cell line(s) will be shared with me and with the FCF to serve as a basis for the decision whether to accept my cell line(s) for inclusion in the Collection. I understand that inclusion in the Collection is not guaranteed and is determined by the FCF Board of Directors based on the characterization of the cell line, the availability of funding, and other pertinent factors.

If my cell line(s) are selected for inclusion in the Collection, then, as a condition to my receipt of any corresponding award from the FCF, I will deposit my cell line(s) with the designated repository under Deposit Agreement approved by the FCF to use, store and distribute this cell line(s) for all research and development purposes.

Name _____

Job Title _____

Organization _____

Address _____

_____

Investigator's Full Name (typed)

_____ _____

Signature **Date**

Appendix B

LETTER OF AGREEMENT FOR THE TRANSFER OF MATERIALS

("Agreement")

PARTIES

Provider: _____	Recipient: The Fibrolamellar Cancer Foundation
Address: _____	Address: 20 Horseneck Lane
_____	Greenwich, CT 06830

Provider Investigator: _____

Provider and Recipient are hereinafter referred to individually as the "Party" and collectively as the "Parties".

RECITALS

WHEREAS, Provider Investigator has created a new [specify type of biological materials] (the "Materials");

WHEREAS, Recipient [has extended an award to Provider Investigator for the creation of the Materials and] will, on behalf of the Provider and Provider Investigator, [deposit the Materials with an Authorized Distributor for distribution]/[distribute the Materials] to the scientific community; and [*select appropriate bracketed text and delete other bracketed text*]

WHEREAS, the Parties now intend to enter into this Agreement to set forth the terms and conditions that will govern this arrangement;

NOW THEREFORE, in consideration of the mutual promises and covenants contained in this Agreement, the Parties agree to be bound by the Terms and Conditions as they appear below.

TERMS AND CONDITIONS

1. The Materials are the property of Provider and are made available as a service to the research community.

2. Materials shall include any unmodified derivative and unmodified progeny of the Materials, as well as any biological materials (including, without limitation: cells, tissues, fluids, etc.) which contain or incorporate the Materials and are derived directly from the Materials or its unmodified progeny. The Materials shall not include other substances created or developed through use of the Materials.

3. THE MATERIALS ARE NOT FOR USE IN HUMAN SUBJECTS OR FOR DIAGNOSTICS PURPOSES.

4. Recipient may further distribute the Materials either (a) under an agreement substantially in the form of the Simple Letter of Agreement for the Transfer of Materials attached as Exhibit A (the "Distribution MTA") or (b) for further distribution through an Authorized Distributor. In any Distribution MTA, Provider will be designated as the "INSTITUTION", and Recipient will include the following citation for reference in Paragraph 5 of the Distribution MTA:

   [*identify citation reference for specific materials*]

   The following entities are designated by the Parties as Authorized Distributors:

   [*identify authorized distributors, if any, such as ATCC or Jackson Labs*]

5. The Material is experimental in nature and must be used with prudence and appropriate caution, since not all of its characteristics are known. THE MATERIAL IS PROVIDED WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED.

6. The Recipient agrees to use the Material in compliance with all applicable statutes and regulations.

7. Recipient assumes all liability for damages, which may arise from Recipient's negligence. Provider (including, but not limited to, its directors, trustees, officers, employees, students, and agents, as applicable) will not be liable to Recipient for any loss, claim or demand made by any other party, due to or arising from Recipient's negligence except to the extent permitted by law when caused by the gross negligence or willful misconduct of Provider.

8. This Agreement shall be governed by the laws of the State of Connecticut, without reference to its choice of law rules. The Parties may not assign or otherwise transfer this Agreement or any rights or obligations under this Agreement, whether by operation of law or otherwise. Any such attempted assignment will be null and void. This Agreement constitutes the entire agreement between the Provider and the Recipient with respect to the Materials and supersedes all previous agreements and representations. This Agreement will remain in full force and effect for as long as the Recipient, any Authorized Distributor, or any recipient under any Distribution Agreement holds any Materials. This Agreement may be executed in two or more counterparts, each of which shall be deemed to be an original as against any Party whose signature appears thereon, but all of which together shall constitute but one and the same instrument. This Agreement may not be amended or modified except by a writing executed by authorized representatives of both Parties.

WHEREFORE, the Parties have caused this Agreement to be executed by their respective duly authorized representatives as of the date of the last signature hereto ("Effective Date").

FIBROLAMELLAR CANCER FOUNDATION	[INSTITUTION NAME]
_____	_____
Authorized Signature	Authorized Signature
Name:	Name:
Title:	Title:
Date:	Date:

Exhibit A

Simple Letter Agreement for the Transfer of Materials

In response to RECIPIENT'S request for the MATERIAL (defined below), the Fibrolamellar Cancer Foundation (FCF) asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the MATERIAL:

1. MATERIAL means: [*specify biological materials to be transferred*].

   The above MATERIAL is the property of the:

   [*specify name and address of providing institution*] ("INSTITUTION")

   and is made available through an agreement with the FCF as a service to the research community for the purpose of scientific research and collaborations.

   MATERIAL shall include any unmodified derivative and unmodified progeny of the MATERIAL, as well as any biological materials (including, without limitation: cells, tissues, fluids, etc.) which contain or incorporate the MATERIAL and are derived directly from the MATERIAL or its unmodified progeny. The MATERIAL shall not include other substances created or developed through the use of the MATERIAL, and RECIPIENT shall retain all rights in such other substances.

2. THIS MATERIAL IS NOT FOR USE IN HUMAN SUBJECTS OR FOR DIAGNOSTICS PURPOSES.

3. The MATERIAL will be used for teaching or research purposes only.

4. The MATERIAL will not be further distributed to others by the RECIPIENT. The RECIPIENT shall refer any request for the MATERIAL to the FCF.

5. The RECIPIENT agrees to acknowledge the INSTITUTION and the FCF, and cite the appropriate reference as indicated below in any publications reporting use of the MATERIAL.

   a. [*identify citation reference for specific materials*]

6. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE FIBROLAMELLAR CANCER FOUNDATION AND THE INSTITUTION MAKE NO REPRESENTATIONS AND EXTEND 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 WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. IN NO EVENT WILL THE FCF OR THE INSTITUTION BE LIABLE FOR ANY INDIRECT, SPECIAL, INCIDENTAL, PUNITIVE

OR CONSEQUENTIAL DAMAGES OF ANY KIND IN CONNECTION WITH OR ARISING OUT OF THIS AGREEMENT, THE MATERIAL OR ANY RELATED INFORMATION (WHETHER IN CONTRACT, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE), EVEN IF THE FCF OR THE INSTITUTION HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. IN NO EVENT WILL THE FCF'S CUMULATIVE LIABILITY EXCEED ANY FEES PAID BY THE RECIPIENT UNDER PARAGRAPH 9 BELOW, EXCEPT IN THE EVENT OF THE FCF'S GROSS NEGLIGENCE, WILLFUL MISCONDUCT OR FRAUD.

7. Indemnity.

If the RECIPIENT is a Federal or State non-profit organization that is prohibited by law from entering into the indemnification obligation set forth in the subsequent paragraph:

The RECIPIENT assumes all liability for any and all claims, losses, expenses and damages (including reasonable attorney's fees) arising out of or relating to the RECIPIENT's or RECIPIENT SCIENTIST's use, receipt, handling, storage, transfer, disposal and other activities relating to the MATERIAL, provided that the RECIPIENT's liability shall be limited to the extent that any such claim arises out of the Fibrolamellar Cancer Foundation's gross negligence, willful misconduct or fraud, and provided further that if the RECIPIENT is the U.S. federal government or a state institution or a foreign equivalent organization, the RECIPIENT assumes such liability only to the extent permitted under the Federal Tort Claims Act, 28 U.S.C. §§ 2671 et seq. or under equivalent applicable state or foreign law.

If the RECIPIENT is a for-profit organization or a private non-profit organization:

The RECIPIENT agrees to indemnify and hold harmless the FCF and the INSTITUTION against all claims, losses, expenses and damages (including reasonable attorney's fees) arising out of or relating to the RECIPIENT's or RECIPIENT SCIENTIST's use, receipt, handling, storage, transfer, disposal and other activities relating to the MATERIAL, provided that the RECIPIENT's liability shall be limited to the extent that any such claim arises out of the Fibrolamellar Cancer Foundation's gross negligence, willful misconduct or fraud. All non-monetary settlements will be subject to the Fibrolamellar Cancer Foundation's and the INSTITUTION's consent.

8. The RECIPIENT and RECIPIENT SCIENTIST agree to use the MATERIAL in compliance with all applicable statutes and regulations.

9. The MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested, the amount will be indicated here:

10. This Agreement shall be governed by the laws of the State of Connecticut, without reference to its choice of law rules. The RECIPIENT and RECIPIENT SCIENTIST may not assign or otherwise transfer this Agreement or any rights or obligations under this Agreement, whether by operation of law or otherwise. Any such attempted assignment will be null and void.

11. This Agreement constitutes the entire agreement between the FCF and the RECIPIENT and RECIPIENT SCIENTIST with respect to the MATERIAL and supersedes all previous agreements and representations. In the event of any breach of this Agreement by the RECIPIENT or RECIPIENT SCIENTIST, all rights granted hereunder by the FCF shall

immediately terminate and the RECIPIENT and RECIPIENT SCIENTIST shall destroy all unused MATERIAL.

12. The FCF, RECIPIENT and RECIPIENT SCIENTIST must sign both copies of this letter and return one signed copy to the FCF. The FCF will then notify the INSTITUTION and send the MATERIAL to the RECIPIENT.

PROVIDER INFORMATION and AUTHORIZED SIGNATURE

The Fibrolamellar Cancer Foundation
Address: 20 Horseneck Lane
Greenwich, CT 06830

Name of Authorized Official: _____
Title of Authorized Official: _____

_____ _____
Signature of Authorized Official Date

RECIPIENT INFORMATION and AUTHORIZED SIGNATURE

Recipient Scientist:
Recipient Organization:
Address line 1:
Address line 2:
Telephone #:
Name of Authorized Official: _____
Title of Authorized Official: _____

_____ _____
Signature of Authorized Official Date

Certification of Recipient Scientist: I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

_____ _____
Recipient Signature Date