

Prize Announcement for Fibrolamellar Carcinoma PDX Models

Access to patient-derived xenograft (PDX) models of fibrolamellar carcinoma (FLC) represents an important need to accelerate research and treatment development against this lethal, rare cancer of adolescents and young adults. PDX tumor lines derive from grafts of a human patient's cancer cells into immunodeficient mice, and are propagated from mouse to mouse. The Fibrolamellar Cancer Foundation (FCF) seeks to create a collection of at least ten well-characterized FLC PDX models, each of which faithfully represents the biology of an independent starting human tumor. PDX models from tumors diagnosed as "hepatocellular carcinoma with fibrolamellar-like features" are also of potential interest. The Foundation has partnered with South Texas Accelerated Research Therapeutics (XenoSTART) to create a FLC Patient-Derived Xenograft (PDX) Repository ("Collection"). Towards this end, the FCF will offer a \$10,000 prize for each validated PDX model that is approved by the FCF and deposited into the Collection at XenoSTART.

SUBMISSION PROCESS

Any investigator who has created a PDX model derived from a human FLC tumor is invited to submit the model for validation and inclusion in the Collection. The process for submission of a PDX model for inclusion in the Collection is as follows:

1. Email the information requested in the Xenograft Submission Package (Appendix A) to **pcogswell@fibrofoundation.org**
2. Send 6-10 slides of both the original patient tumor (if available) and the PDX tumor for validation to:

Dr. Michael Wick
XenoSTART
4319 Medical Drive Suite 205
San Antonio, TX 78229
210-593-5296

The Fibrolamellar Cancer Foundation will provide a FedEx account number on request.

3. Once your Submission Package is approved and your model has been validated, execute the MTA Agreement for Distribution of Tumor Xenograft Lines ("Deposit Agreement") (Appendix B) to deposit your model in the Collection.
4. When the Agreement is in place:
 - a. XenoSTART can provide a kit for you to ship fresh tissue from the tumor, if available
 - b. If fresh tissue is not available, 6-10 cryopreserved PDX tumor fragments can be shipped on dry ice
 - c. Tumor fragments should be between the second and fifth passage

Samples should be shipped to:
Dr. Michael Wick
XenoSTART
4319 Medical Drive Suite 205
San Antonio, TX 78229
210-593-5296

The Fibrolamellar Cancer Foundation will provide a FedEx account number on request.

5. Upon validation and establishment of the PDX model, 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 PDX model deposited into the Collection.
6. 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 or the submission process, please email pcogswell@fibrofoundation.org

VALIDATION CRITERIA

The PDX model will be evaluated for inclusion in the Collection based on the following criteria:

1. The tumor from which the PDX model was derived is confirmed to be FLC or HCC with fibrolamellar-like features based on histology and immunohistochemical staining for markers including cytokeratin 7 and CD68.
2. PDX tumors from FLC express a fusion mRNA (*DNAJB1-PRKACA*), or contain a *DNAJB1-PRKACA* gene fusion confirmed by a fluorescence *in situ* hybridization (FISH) assay, or display some other molecular abnormality consistent with the activation of protein kinase A (PKA) signaling and previously associated with FLC (e.g., homozygous loss of a gene encoding a regulatory subunit of PKA such as *PRKAR1A*). For hepatocellular carcinomas with fibrolamellar-like features, molecular characterization consistent with abnormalities described by T. Hirsch et al. (2020) *J. Hepatol* 72:924-936 (e.g., *BAP1* mutation and activated PKA).
3. PDX tumors are histopathologically and genotypically similar to the primary tumor from which they were derived. If the originating tumor is not available, then the PDX tumor must at least have a rearranged genome as measured by SNP array in addition to a molecular abnormality consistent with FLC as noted in validation criterion #2.
4. Must be able to maintain growth for greater than two passages in immunodeficient mice.

TERMS AND CONDITIONS OF PRIZE

1. AWARD PROCESS

The decision to include a PDX model in the Collection and to award a \$10,000 prize to the xenograft’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 xenograft, as well as accompanying data regarding the tumor from which it was derived. Investigators will be notified in writing by the FCF whether or not xenograft(s) are selected for inclusion in the Collection. Upon validation, selection for inclusion in the Collection, execution of the Deposit Agreement and deposit of the xenograft at XenoSTART, 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 xenograft 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. Upon acceptance of the award, the FCF will be permitted to publicize the name of the institution and/or creator and the amount of the prize.

3. DISBURSEMENT POLICY

This prize is made to reward the creator of a FLC PDX model for contributing that xenograft to the FLC Xenograft Collection at XenoSTART. 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 Fibrolamellar Cancer Foundation, 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 Xenograft Submission Package

For a PDX model to be considered for inclusion in the Collection, the following must be submitted:

1. A completely deidentified pathology report from the tumor of origin.
2. A copy of the informed consent form used to collect the tumor from which the model was derived. The informed consent must allow for the use, storage and distribution of the xenograft for all research and development purposes and be clear that no profit from any commercial products derived from the xenograft will be returned to the patient.
3. Information about the tumor from which the model was derived:
 - a. Anatomic location of the tumor
 - b. Whether the tumor was primary, recurrent, or metastatic
 - c. Date tumor was resected or ascites fluid containing tumor cells was collected
 - d. Tumor size
 - e. Biochemical, cytogenetic, and immunophenotypic data from the tumor, if available
 - f. Molecular analysis for the *DNAJB1-PRKACA* gene arrangement, fusion mRNA, or encoded DNAJ-PKAc fusion protein, if available.
 - g. Indicate if a portion of the tumor was also preserved
4. Information about the patient from which the model was derived (if available):
 - a. Demographics, including: gender, age at diagnosis, ethnic origin
 - b. Treatment history including: prior surgery, chemotherapy, immunotherapy, and/or radiation
 - c. Patient outcome if known. Is the patient alive or deceased?
5. Summary of passage history in immunodeficient mice
 - a. Host mouse strain
 - b. Site of implantation (e.g., flank, orthotopic, or other)
 - c. Time from initial implantation to first harvest of a tumor from the mouse
 - d. Number of subsequent passages in mice and approximate times between passages
 - e. Molecular analysis of passaged PDX tumor for *DNAJB1-PRKACA* gene arrangement, fusion mRNA, or fusion protein, if available

Appendix B

LETTER OF AGREEMENT FOR THE TRANSFER OF MATERIALS ("Agreement")

PARTIES

Provider: _____
Address: _____

Recipient: The Fibrolamellar Cancer Foundation
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.

[signatures appear on following page]

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

Name:
Title:
Date:

Authorized Signature

Name:
Title:
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. 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.

11. 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 Scientist(s)

Date