ORPHAN DISEASE CENTER and LOULOU FOUNDATION
CDKL5 Program of Excellence
2021 PILOT GRANT PROGRAM

The ODC and Loulou Foundation CDKL5 Pilot Grant Program provides a one-year grant for $150,000.00 (total cost) to support research related to CDKL5 Deficiency Disorder (CDD). The number of awards is not fixed and may vary.

Background

CDKL5 Deficiency Disorder (CDD) is a monogenic, neurodevelopmental disorder characterized by treatment-resistant epilepsy and severe neurodevelopmental delay. The disease is caused by loss-of-function mutations in a protein kinase called CDKL5 which is responsible for normal neuronal function. The mechanisms by which loss of CDKL5 expression leads to this neurodevelopmental disorder remain unclear. The gene encoding this protein is located on the X chromosome, with heterozygous females primarily affected. The disease does not exhibit neurodegeneration, and animal models strongly suggest the potential for reversibility of phenotypes associated with loss of CDKL5. While clinical development of novel therapeutics is underway, there are currently no approved therapies for CDD, and the current standard of care is not effective at managing seizures or improving neurodevelopmental or motor deficits.

We are seeking grant applications that progress the discovery or development of treatments and/or cures for CDKL5 Deficiency Disorder. Because many gaps still remain in our understanding of the biology of CDKL5 and its role in neurological development and function, applications that address such gaps in basic science are welcome, provided that they are tethered to the development of a potential therapy. While the RFA is broad in scope, priority will be given to grants that cover the following areas:

1) **Novel therapeutic approaches for CDD,** including, but not limited to, techniques in genome editing, RNA-based mechanisms, biologics, novel cell-based therapeutics, network modulation, and development of novel therapeutic compounds, including through small molecule repurposing or screening in human cellular systems.

2) **Validation of phenotypes in CDKL5 function or disease pathophysiology** in cellular or animal disease models through rescue of molecular, cellular, or behavioral deficits with pharmacological or genetic / gene therapy techniques.
    a. Phenotypic reversal in rodent models will include the use of adult (*e.g.*, 6 months of age or older) animals, to address effects over the natural history of the phenotype in the animal model.
    b. Proposals are encouraged that will characterize individual CDKL5 protein isoforms (arising from alternative splicing / promoter usage, or post-translational modifications) or truncated protein forms capable of rescuing these phenotypes.
    c. Proposals are also encouraged to study phenotypic reversal in newly emerging biological domains, such as primary cilia function and microtubule dynamics, and peripheral organ systems, as well as potential novel functions of CDKL5 in distinct subcellular compartments (e.g., nucleus, post-synaptic density; nucleic acid binding).

3) **Systems biology and computational modeling approaches** to provide a deeper understanding of CDKL5 function, downstream effectors, intracellular signaling, protein:protein interactors, or genetic modifiers from model organisms and human cellular models, including regulators of CDKL5 gene expression.

4) **Novel application of imaging and functional techniques** to characterize the disease state of CDD pre-clinical models or in the clinical setting. A non-exclusive list of topics that would be responsive to this RFA is listed below:
   - Functional/structural MRI; diffusion tensor imaging (DTI)
   - Magnetic resonance spectroscopy (MRS)
   - EEG and stimulus-induced event-related potentials (*e.g.*, visual; auditory; TMS-stimulated motor)
   - Proposals are encouraged which would address potential reversal of these imaging and functional deficits by CDKL5 genetic / gene therapy or pharmacological interventions in CDD disease models

5) **Discovery and validation of CDKL5 biomarkers** (molecular and functional) with the goal of their translation to the clinical setting. Of particular interest are approaches to biomarker discovery using minimally invasive testing (*e.g.*, peripheral fluid analysis).

Eligibility

All individuals holding a faculty-level appointment at an academic institution or a senior scientific position at a non-profit institution or foundation are eligible to respond to this RFA. Biopharmaceutical companies are not eligible to apply; however, we will consider applications from contract research organizations that provide services responsive to the RFA, as collaborators with a qualified academic faculty-level staff member.

LOI Instructions and Review Procedure

All applicants must first submit a Letter of Interest (LOI) to be reviewed for consideration of a full application submission.

Format for the 1-page LOI:

- Project Title
- PI and Co-PIs, and associated institutions or organizations
- Overall goal of the project
- Why application is responsive to the RFA: please note that the applicant will not be invited to submit a full application if relevance to the RFA is not clearly described in the LOI.
- Brief background
- Specific Aims provided as a brief list
- Requested resources in terms of 1 year of funding. The total award amount is $150,000 (including direct and indirect costs). It is strongly preferred that applicant institutions waive indirect costs allowing the total amount to go towards research, but indirect costs up to a maximum of 10% could be accepted in exceptional cases.

LOI Due Date: LOI document is to be uploaded no later than 5pm (EST) on Friday, February 26, 2021, via this form.
Applicants will be notified via email on Monday, March 1, 2021, with a decision regarding their LOI, which, if successful, will invite the applicant to submit a full application.

Full Application Instructions and Review Criteria
NOTE: Full Application is by Invitation only after review of LOI

Proposal Due Date: **Friday, March 26, 2021, no later than 8pm (EST).** Full application documents are to be uploaded at https://www.orphandiseasecenter.med.upenn.edu/grants

FORMAT for documents:
Font and Page Margins: Use Arial typeface, black font color, and a font size of 11 points. A symbol font may be used to insert Greek letters or special characters. Use 0.5 inch margins (top, bottom, left, and right) for all pages, including continuation pages. Print must be clear and legible; all text should be single-spaced.

Header: There should be a header at the top right on all pages of the PDF indicating the full name of the PI (e.g., **PI: Smith, John D.**).
For your convenience, a continuation page template is included at the end of the application document.

File names: ALL files to be uploaded should start with the LAST NAME of the PI followed by the brief name of the document. Examples: SMITH CV, SMITH Cover Page, SMITH Budget

CONTENT to be uploaded:

☐ **Cover Page/Checklist/Institutional Signature Page [PDF]**

☐ **NIH-style Biosketch with Other Support of PI and key personnel** (4 pages max) **[PDF]**
The PI must include accurate and complete information regarding all other sources of grant support (current and pending), including title, abstract, annual and total amount of grant, inclusive funding period, and percent effort.

☐ **Detailed Budget and Justification [combined into one PDF]**
Complete attached Excel budget sheet. Describe justifications in a Word document. Award will be for one year. Proposed funding period: May 1, 2021 – April 30, 2022.

Allowable direct costs

- Salary for PI
- Salary/stipend and related benefits for graduate student/postdoctoral fellow/technical support
- Travel (up to $1500)
- Laboratory supplies and other research expenses

Unallowable costs

- Salary/consultant costs
- Tuition
- Professional membership dues
- Equipment >$5,000
- General office supplies, institutional administrative charges (e.g., telephone, other electronic communication, IT network, etc.)
- Pre-award charges
- Any other expenses not directly related to the project

☐ **Research Plan** (5 pages max) and **Bibliography** (1 page max) **[combined into one PDF]**
Include the following sections: Lay Summary (one paragraph; to be shared publicly if grant is awarded), Specific Aims, Background and Significance, Preliminary Studies/Data, Research Design and Methods.
Text citations should use a numbered format. Include all author names in the reference list.

☐ **Appendix [combined into one PDF]**
Limited to 5 pages of supplemental information pertaining to proposal or preliminary data only; a maximum of 3 relevant reprints are also acceptable. Include IRB and/or IACUC approval letters if relevant.

Grant Review Criteria:

1) Grants will be reviewed for scientific content and relevance to the goals of the RFA.
2) Proposal Content and Review Criteria: The following criteria will be utilized in proposal review. *Project Proposal*. Is the proposed project of high scientific quality? Is the budget fully justified and reasonable in relation to the proposed project?
    - Background – Is the fundamental objective of the study and hypothesis to be addressed clearly defined?
    - Scientific Approach - Will the proposed specific aims answer the study hypothesis? Will the scientific approach effectively test and answer each specific aim? Are the study goals supported by existing data?
    - Clinical Impact - Is the answer to the study hypothesis important to our ability to treat CDKL5 Deficiency Disorder? Will the proposed research lead to substantial advances and/or contribute to large leaps of understanding or knowledge that will contribute to an improved quality of life, better control of seizures, improved cognition, and/or greater survival rate?
    - Research Significance - Does the study address an important question that is not likely to be addressed without this funding? Does the proposed study offer a unique opportunity to explore an important issue and/or employ a novel approach to this disease research? Will the study outcomes advance our knowledge of this disease and/or contribute to changes in the focus of future research questions or the way we conduct research on this issue?
    - Investigator Qualifications – One consideration is to attract new talent in to CDKL5 research. While it is important for the investigator to have access to the resources and environment necessary to complete the proposed work, this RFA is not limited to scientists currently working on CDKL5. However, we encourage junior and senior investigators not previously working in this area to apply.

AWARD INFORMATION

The following terms and conditions will apply to the awarded grantee/institution and subcontract institutions.

This award is based on the application for the above-referenced project submitted to, and as approved by the University of Pennsylvania and is subject to the terms and conditions below.

The Award is contingent upon the availability of funds and is subject to the Terms and Conditions herein, which may be revised from time to time. By accepting an Award, the Principal Investigator and the Grantee Institution agree to be bound by the Terms and Conditions.

Funding for this Award is provided by the generous contribution of the Loulou Foundation (the “LLF”). LLF and ODC have partnered in establishing a Program of Excellence (the “POE”) in CDLK5 research within ODC with the goal of developing effective treatments for patients with a deficiency of CDKL5.

PAYMENT

Funds will be issued through cost reimbursement mechanism executed by purchase order from the University of Pennsylvania. We have been advised by our Office of Research Services that due to the nature of this award, unless your institution objects, we will be able to forego the institutional signatory process (subaward agreement) and proceed directly with creating a purchase order for monthly invoicing of award. Any changes to this schedule will be confirmed with the Grantee Institution upon a prior written notice.

TERMS AND CONDITIONS

1. Funds for this Award are provided by private philanthropy by LLF and administered by the University of Pennsylvania. All funds shall be used exclusively for the purposes provided for in the Award Application and in strict compliance with the approved Budget.

2. The total award amount is $150,000 (including direct and indirect costs). It is strongly preferred that applicant institutions waive indirect costs thereby allowing the total amount to go towards research, but indirect costs up to a maximum of 10% could be accepted in exceptional cases.

3. Travel <$1,500 is allowed, including international travel, as long as it is related to the Research Project.

4. Equipment >$5,000 is not allowed. Equipment qualifying as a capital asset is defined as an item with an acquisition cost of $5,000 or more. The acquisition cost of equipment includes installation charges and freight. Capitalized equipment can be identified as having all of the following characteristics:
    a) Acquisition cost equal to or greater than $5,000;
    b) Life span in excess of one (1) year;
    c) Contains or is made of non-expendable material; and
    d) Is not made for consumption

5. Reallocations between budget categories (Personnel, Supplies, Other Expenses) of 10% or less are allowable. Budget revisions in excess of 10% between categories require justification and prior approval by the University of Pennsylvania.

6. Oversight for use of animals and/or humans is the responsibility of the Grantee Institution. The Grantee Institution and Principal Investigator agree that animal and/or human use will comply with all applicable laws and regulations, including but not limited to current EPA, FDA, USDA, and NIH guidelines. Please note: no work on animals or humans may proceed until current IACUC or IRB approvals are received by the University of Pennsylvania.

7. Appropriate citation of all collaborations must be included in all publications resulting from the Award.

8. All final data sets and observations must be shared openly with the full scientific community, and all reagents and/or research tools developed under this Award must be made accessible upon request.

9. Policies for managing intellectual property resulting from research utilizing the Award and sharing of potential licensing revenue are determined by the LLF. Prior to release of funding for approved Awards, the University of Pennsylvania must receive signed confirmation that

the Grantee Institution and the LLF have agreed to the management of intellectual property resulting from research utilizing the Award and sharing of potential licensing revenue, in the form attached hereto as Exhibit 1. Any disputes regarding such intellectual property/licensing revenue sharing must be adjudicated between the LLF and the Grantee Institution. The terms of the LLF Patent Policy shall survive termination of the Award Terms and Conditions.

10. The University of Pennsylvania reserves the right to share the full application, as well as progress reports and the final report with the LLF, which they will be receiving under confidentiality. LOIs and full applications will also be shared with external reviewers, after they sign a confidentiality agreement. The University of Pennsylvania reserves the right to share the following information about the Award with the public: Principal Investigator name, Award amount, title of Award/Research Project, and a non-confidential, lay-language final report and project summary (provided during the application process).

11. The Principal Investigator of the award will be expected to attend an annual meeting for the CDKL5 POE (Forum). LLF will reimburse such representative directly for reasonable, pre-approved travel expenses related to this meeting. This expense reimbursement is independent of any travel expenses requested/provided within the PoE grant award.

For additional information, please contact Samantha Charleston at scharle@upenn.edu or 215-573-6822.

Exhibit C
Loulou Foundation Patent Policy

1. This Patent Policy shall govern the relationship between Loulou Foundation ("LLF") and each grant recipient ("Grantee") with respect to any Inventions as a result of conducting research pursuant to the Grant.

    a. Procedures for Notification of Invention(s). The Grantee shall promptly notify LLF after the disclosure of any Invention(s) by Principal Investigator, or by any person working under the supervision and direction of the Principal Investigator. An invention initially conceived or reduced to practice / further developed as a result of the Grant funding shall constitute an "Invention" for purposes of this Patent Policy.

    b. Election to Pursue Intellectual Property Protection for Invention(s).

        i. Grantee may elect, at Grantee's sole discretion, to pursue patent protection, copyright registrations or other intellectual property registrations or protection (collectively, "IP Registrations") for any Invention(s).
        ii. Grantee agrees to notify LLF within a reasonable period of time, not to exceed one hundred eighty (180) days after the disclosure of an Invention(s) to LLF, of Grantee's election to pursue, or not to pursue, IP Registration(s) for any such Invention or whether Grantee elects to treat such Invention as a trade secret.
        iii. If Grantee elects to pursue IP Registration for an Invention, Grantee further agrees, as soon as practicable thereafter, to file an application for IP Registration for such Invention in the relevant country or countries and to provide confirmation of such filing to LLF in writing within sixty (60) days after filing.
        iv. Thereafter, Grantee agrees to notify LLF in writing within sixty (60) days after either the issuance of an IP Registration or a final confirmation or determination that such IP Registration will not issue.

    c. Obligation to Apply Good Faith Research Efforts. Grantee agrees to use good faith efforts necessary to advance the Invention in the field for which the scientific research was funded ("the Field") during and after the Grant Period, and then promptly thereafter to exercise good faith efforts to seek a third party licensee to commercialize the Invention. Grantee shall provide progress reports to LLF on an annual basis outlining the actions Grantee has taken to license the Invention. If Grantee grants a license for such Invention(s), Grantee agrees that any such licenses so granted shall provide that:

        i. the license grant shall include an obligation on behalf of licensee to exercise Commercially Reasonable Efforts to bring such licensed Invention(s) to practical application within the Field and provide annual progress reporting to Grantee, so that Grantee can furnish annual progress reports to LLF outlining the development program progress by the licensee;
        ii. the license grant shall include reasonable development diligence events and timelines that the licensee must meet in order to maintain the license and advance their product development program, with customary recourse for the Grantee

(licensor) if such development diligence in not achieved as outlined in the license agreement.; and

iii. a requirement of prompt notice to Grantee if the licensee intends to sublicense the license.

d. Grantee encourages LLF to assist it in seeking licensees of an Invention and may include LLF in Grantee's negotiations with a potential third party licensee if Grantee determines LLF's inclusion in such negotiations will be productive.

e. Notice of Transfer or Assignment of Rights. Grantee shall not assign or transfer rights to any funded Invention without the prior consent of LLF.

2. Grantee shall make reagents (e.g., animals models, expression plasmids, antibodies, permanent cell lines) and detailed protocols for their use available, upon request, to qualified scientists working for academic and to other organizations working with LLF, exerting best efforts to make these available as quickly as possible, as well as post any related protocols on the CDKL5 Forum portal, upon request. Recipients will be expected to acknowledge the source of the reagents consistent with customary scientific standards in resulting publications.

3. In consideration for this Grant, the Grantee shall pay to LLF a portion of the Net Income (as hereinafter defined) received by the Grantee calculated by multiplying Net Income by a fraction, the numerator of which is the amount of the Grant, and the denominator of which is the total direct costs incurred by the Grantee with respect to the Invention, provided that, without regard to the application of the foregoing fraction, the portion of the Net Income payable to either LLF or the Grantee shall not be less than twenty percent (20%) For these purposes, "Net Income" shall mean any amount received by the Grantee from third parties as a result of licensing the Invention ("Gross Income") less the following: (i) costs incurred by the Grantee with respect to IP Registration or enforcement of the Invention; (ii) the portion of any Gross Income that the Grantee is contractually obligated to pay to the Principal Investigator and other inventors of the Invention and the Inventor's laboratories pursuant to the Grantee's Patent Policy; and (iii) any additional legal costs incurred by the Grantee associated with licensing of the Invention not to exceed $25,000, to the extent in each of (i), (ii) and (iii) above is not reimbursed to Grantee by the licensee for the Invention.

[Signature Appears on Following Page]

I hereby certify that I have read and understand Loulou Foundation's Patent Policy applicable to the Invention and I will comply with all provisions thereof relating to the Invention. All notifications hereunder shall be sent to Loulou Foundation, 4 Old Park Lane, Mayfair, London W1K 1QW, United Kingdom, or via email to contact@louloufoundation.org

SEEN AND AGREED

Grantee Institution:_____

By:_____

Name:_____

Title:_____

Date:_____

Research Project: _____