ORPHAN DISEASE CENTER and LOULOU FOUNDATION
CDKL5 Program of Excellence
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 may vary.

**Background**

CDD is a monogenic, orphan condition characterized by treatment-resistant epilepsy and severe cognitive and motor disability. The disease is driven by the loss of a kinase called CDKL5 which is responsible for normal neuronal development, synapse formation and signal transmission. The mechanism(s) by which CDKL5 Deficiency leads to CNS disease is 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. There are no approved therapies and standard of care is not effective at managing seizures or improving cognitive or motor deficits.

We are seeking grant applications that progress the discovery or development of treatments and/or a cure for CDKL5 Deficiency. We recognize, however, that many gaps exist in the basic understanding of CDKL5 and its role in neurologic development. Therefore, basic science projects that address these gaps are welcome as long as 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, network modulation, and development of novel therapeutic compounds, including through small molecule repurposing.

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 (6 months of age or older) animals.
   b. Proposals are encouraged that will identify individual CDKL5 protein isoforms (arising from alternative splicing / promoter usage, or post-translational modifications) 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, as well as potential novel functions of CDKL5 in distinct subcellular compartments (e.g., nucleus, post-synaptic density).

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, 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 the impact of CDKL5 genetic / gene therapy or pharmacological interventions on these imaging and functional deficits 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 who provide services that are responsive to the RFA.
Full Application Instructions and Review Criteria
NOTE: Full Application is by Invitation only after review of LOI

Proposal Due Date: **Friday, April 5, 2019, no later than 8pm (EST)**. Full application documents are to be uploaded at [http://www.med.upenn.edu/orphandisease/rare-disease-overview.html](http://www.med.upenn.edu/orphandisease/rare-disease-overview.html)

**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]**


**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? 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.

For additional information, please contact Dr. Sheridan Carrington at sjcarr@upenn.edu
or 215-746-8508