

**ORPHAN DISEASE CENTER and LOULOU FOUNDATION
CDKL5 Program of Excellence
2025 PILOT GRANT PROGRAM: REQUEST FOR APPLICATIONS**

The ODC and Loulou Foundation CDKL5 Pilot Grant Program provides a one-year grant for \$150,000 (total cost) to support research related to CDKL5 Deficiency Disorder (CDD). The number of awards is not fixed and may vary. The deadline for submission of a **Letter of Intent** in response to this Request for Applications (RFA) is **Tuesday, February 18, 2025, by 5 PM (EST)**.

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 the CDKL5 gene, which encodes a protein kinase whose expression is required for proper 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, the current standard of care is not fully effective at managing seizures in all patients, or in the treatment of non-seizure symptoms such as 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 against validated phenotypes in human cellular systems. Also encouraged are novel delivery systems for gene therapy and genome editing cargoes.
- 2) **Establishment of a link between molecular function of CDKL5 and disease pathophysiology** in cellular or animal disease models through rescue or modulation of molecular, cellular, or behavioral deficits via pharmacological or genetic / gene therapy interventions.

- a. Projects are considered that will expand our understanding of the genomics, biochemistry, and cell biology of the CDKL5 gene, mRNA, and protein kinase, including upstream regulation of the gene or protein; and broader understanding of downstream kinase targets, as contributors to pathology and/or possible therapeutic interventions.
 - b. Phenotypic reversal in rodent models should include the use of adult (*e.g.*, 4 months of age or older) animals, to address effects over the natural history of the phenotype in the animal model.
 - 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), provided that a link to pathophysiology can be established or hypothesized.
- 3) **Systems biology and computational modeling approaches** to provide a deeper understanding of CDKL5 function, downstream effectors, intracellular signaling, protein:protein interactor networks, or genetic modifiers from model organisms and human cellular models, including regulators of CDKL5 gene expression, or the expression of CDKL family members.
- 4) **Discovery and validation of CDKL5 biomarkers** (molecular and functional) and clinical outcome development with the goal of translation to the clinical setting.
- a. **Molecular biomarker discovery and validation of candidate biomarkers** in patient and model system fluids such as plasma and CSF.
 - b. **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; magnetic resonance spectroscopy (MRS); diffusion tensor imaging (DTI).
 - EEG and stimulus-induced event-related potentials.
 - 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, and potential mechanisms of CDKL5 function in these systems.
 - Clinical outcome development for CDD, including in domains such as visual function, fine motor/hand use skills, etc.

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 for-profit organizations that provide services responsive to the RFA, as collaborators with a qualified academic faculty-level staff member.

For project proposals utilizing CDD patient-derived induced pluripotent stem cell (iPSC) lines, the Loulou Foundation and the Orphan Disease Center, along with the Coriell Institute for Medical Research, have made available to the CDKL5 research community a panel of iPSC lines, with isogenic controls, from several patients with distinct mutations in the CDKL5 gene. More information regarding these lines, their characteristics, and how to order them, is found at: <https://www.coriell.org/1/Orphan-Disease-Center-Collection/CDKL5-BioRepository/Overview>

Awardees of CDKL5 Program of Excellence Pilot Grants for 2025 may be invited to submit a (non-competitive) continuation grant proposal for a second year of funding, with a maximum of \$150,000 in support. Invitations to apply for this continuation funding will be extended towards the end of the pilot grant period, provided the pilot grant project has been successfully executed.

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 Tuesday, February 18, 2025, via [this form](#).

Applicants will be notified via email on Wednesday, February 19, 2025, with a decision regarding their LOI, which, if positive, 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 21, 2025, no later than 5 pm (EST)**. Full application documents are to be uploaded at <https://www.orphandiseasecenter.med.upenn.edu/grant-opportunities>

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, 2025 – April 30, 2026.

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 (in addition to the 5-page supplemental information). 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 used in proposal review:
 - Project Proposal – Is the proposed project of high scientific quality? Is it feasible for a one-year project? Is the budget fully justified and reasonable for 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? Are their projected plans for the project beyond the experiments proposed in this pilot grant phase, including through funding by alternative sources (NIH, other grantee institutions)?
 - 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 of this pilot grant program is to attract new talent 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; we encourage junior and senior investigators not currently 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. All invoices for payment should be submitted in, and will be paid in, US dollars (US\$). 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 forgo 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, and by the characteristics below. 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. **Intellectual Property:** 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 (CDKL5 Forum). In 2025, the CDKL5 Forum will be held in Boston, MA, USA, on October 27-28, 2025, with a grantees-only pre-meeting scheduled for October 26, 2025. LLF will reimburse such representative directly for reasonable, pre-approved travel expenses and hotel lodging related to these meetings. This expense reimbursement by LLF is independent of any travel expenses requested/provided within the PoE grant award.

For additional information, please contact Jasmine Carter at jlcarter@upenn.edu.