

## Project CASK Grant Program 2024

Project CASK, in collaboration with the Orphan Disease Center, is seeking proposals to advance research that supports therapeutic development for CASK gene disorders.

### Background

The X-linked CASK gene provides instructions for making a protein called calcium/calmodulin-dependent serine protein kinase (CASK), which is primarily found in neurons and helps control the expression of other genes involved in brain development. Mutations on the CASK gene are currently associated with two disorders, microcephaly with pontine and cerebellar hypoplasia (MICPCH) and XL-ID with or without nystagmus. The spectrum of neurological phenotypes associated with CASK variants is broad and includes global developmental delays, intellectual disability, epilepsy, or other seizure disorders, hypotonia, swallowing or feeding challenges, hearing and vision issues, and other neurological symptoms.

### Eligibility

All individuals holding a faculty-level appointment at an academic institution or a senior position at a non-profit institution or foundation are eligible to respond to this RFA. Collaboration with existing CASK researchers is encouraged but not required.

Project CASK will consider applications that will make a significant impact on the CASK community and the prospects for accelerating therapeutic development in one of two categories:

**1) Grants to expand the study of disease mechanisms or to support clinical research. At least two awards of \$50,000 each for 12 months to the following:**

- Studies to perform molecular, cellular, and behavioral characterization of animal models for CASK-related disorders.
- Proposals to respond to key gaps in the knowledge of CASK disorders that are critical to the pursuit of therapeutic development. Proposals should explain therapeutic potential.
- Identification of short-term biomarkers (molecular and functional) that can monitor disease activity and treatment response.
- Establishment of outcome measures for future clinical trials.

**2) Grants for the development of potential therapeutic interventions. At least one award of up to \$250,000 for two years to the following:**

- Drug repurposing and small molecules.
- Gene therapies including innovative approaches that would address current limitations specific to the CASK gene.
- RNA-editing or other RNA-based approaches.
- Other novel techniques for x-linked neurological disorders.

### Letter of Interest Instructions

All applicants must first submit a one-page Letter of Interest (LOI) to be reviewed for consideration of a full application submission. Please specify the category (\$50,000/1 year or \$250,000/2 years). Please submit your LOI by February 16, 2024.

### Full Proposal

By invitation only, please submit your full application documents by April 5, 2024.

### FORMAT for documents

Font and Page Margins: Use Arial typeface, a 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.).

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. If files are not labeled properly, you will be asked to resubmit the PDFs before your application can be considered.

### CONTENT to be uploaded

Cover Page/Checklist/Institutional Signature Page [PDF].

An application template will be provided.

Biosketch/CV, with key personnel supporting the project (5 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. PI should add a section listing key personnel working on the project. Any Co-Is/Co-PIs, if present, should also provide a biosketch/CV.

Detailed Budget and Justification. [combined into one PDF]

Complete Excel budget sheet (to be provided). Describe justifications in a Word document including all subcontracts to co-investigators.

Research Plan (5 pages max) and Bibliography (1 page max) [combined into one PDF].

Include the following sections: Specific Aims, Background and Significance, Preliminary Studies/Data, Research Design and Methods. Research plan should address the following questions: 1) Do you require access to reagents, animal models, patient blood samples, IRB/ethical board approvals, and/or equipment necessary to complete work? If so, please describe your plan to gain access within the time-frame of this grant period. 2) Have you identified qualified personnel to complete this project within the grant period? If not, please provide your plan to do so. 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; maximum of 3 relevant reprints are also acceptable. Include IRB and/or IACUC approval letters if relevant. Include letters of support or letters of collaboration, if available.

**Project Disclosures and No Cost Extensions (NCE)**

- NCEs will be granted at the discretion of Project CASK.
- Awardees will be limited to 1 NCE request for their award.
- Maximum NCE time awarded will be 6 months.
- NCEs will be granted after a formal request prior to the NCE deadline with adequate justification.
- If granted an NCE, you are still required to submit an interim scientific report 6 months into the duration of the original award period, regardless of your new project end date.
- In your letter of interest, you will be required to certify that you have identified qualified personnel to complete this project within the grant period PRIOR to the start date of the award. If you have not, you will be required to provide your plan to engage said personnel. Only under extenuating circumstances will personnel issues be considered for NCE requests.
- In your letter of interest, you will also be required to state whether or not you require access to reagents, cell lines, animal models, IRB/ethical board approvals, and/or equipment necessary to complete your work. If so, you will be required to describe your plan to gain access within the time-frame of this grant period.
- In your letter of interest, please state if you are applying for \$50K or \$250K.

**Grant Review Procedure**

- Grants will be reviewed for scientific content and relevance to the goals of the RFA.
- Final decision of funding will be made by Project CASK.

**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? Is the research plan feasible within the time frame proposed?
- Clinical Impact - Is the answer to the study hypothesis important to our ability to understand the mechanisms behind CASK-related disorders? Will the proposed research lead to substantial advances and/or contribute to large leaps of understanding or knowledge that will aid efforts towards CASK-related disorders treatment?
- 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?

- o Investigator Qualifications - Do investigators hold a track record of outstanding accomplishment as evidenced by peer-review publications and funding awards in the area of proposed research? Do the investigators have access to the resources and environment necessary to complete the study as outlined? Is the research proposal appropriately designed to individual investigator area of expertise? Do investigators also have a track record of collaborative multi-institutional peer-reviewed publications?
- o Future Funding - Will the study generate preliminary data that will allow the PI to obtain further funding in the future? Will the outcome of this study put the PI in a position to continue their work in the CASK-related disorders space?

Proposed funding period is one or two years, beginning about one month after full applications are received.

#### 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
- IDCs of 10% are included in the total award amount

#### Unallowable costs

- 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