ADLD Center / Orphan Disease Center
Grant Pilot Program

The ADLD Center, in collaboration with the Orphan Disease Center, will provide a 1-year grant to support research related to Autosomal Dominant Leukodystrophy (ADLD). Up to 2 awards will be granted at $50,000 each.

Background

Adult-onset Autosomal Dominant Leukodystrophy (ADLD) is a rare genetic disorder that develops symptoms in the fourth or fifth decade due to nerve damage that slowly progresses. The onset often includes autonomic conditions such as bowel or bladder dysfunction, male impotence, loss of fine motor skills, and orthostatic hypotension. Later symptoms include difficulties using and controlling legs and arms, ultimately leading to paralysis and problems swallowing, and eventually developing into intellectual impairment. ADLD is a fatal disorder, but it is slowly progressive; patients often survive for several decades.

ADLD can be caused by one of two genetic defects - either a duplication of the gene LMNB1 that encodes for the protein Lamin B1, or an upstream deletion. Lamin B1 is a protein that is present in every cell in the body and plays an essential role in cell structure. Either of the two aforementioned genetic changes results in toxic overexpression of Lamin B1. Although Lamin B1 is present in all cells in the body, overexpression of Lamin B1 mainly causes problems in the central nervous system where it causes demyelination.

The ADLD Center, in collaboration with Orphan Disease Center, is seeking grant applications for multidisciplinary teams of scientists that aim to further progress our understanding of the disease, the available therapeutic options, and investigating strategies to establish outcome measurements. The RFA could focus on one, or several, of the following aims to further advance ADLD research and therapeutic approaches:

1. Identification of short-term biomarkers that can monitor disease activity and treatment response.
2. Establishment of outcome measures for future clinical trials.
3. Development of therapeutic approaches in early symptomatic patients.
4. Supporting pilot clinical trials, preclinical trials, or animal model trials that promote drug repurposing strategies.
5. Development of a standardized evaluation criteria for clinical projects allowing uniformity of patients as well as the severity and progression of the disease.
6. Development of cellular models (i.e., oligodendrocytes) for evaluation of therapeutic options to translate for clinical use.
7. Evaluate pre-clinical patients (MRIs, genetic testing).

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.

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 submit your LOI by **January 9, 2023**.

Full Proposal: By invitation only, please submit your full application documents by **February 24, 2023**.

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.**).
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. **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.

Proposed funding period is one year, 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

☐ **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 the ADLD Center
- 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.

Grant Review Procedure

- Grants will be reviewed for scientific content and relevance to the goals of the RFA.
- Full applications proceed through a two-step review process. The first step includes external review and rating with an assessment of the strengths and weaknesses of each application based on the defined review criteria described below. During the second step, funding recommendations are determined based on an assessment of the reviewer scores and written comments. Final decision of funding will be made by Center Leadership.
- 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 ADLD? Will the proposed research lead to substantial advances and/or contribute to large leaps of understanding or knowledge that will aid efforts towards ADLD 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?
    - **Investigator Qualifications and Consortium Structure** - 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?

- **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 ADLD space?