
**ORPHAN DISEASE CENTER
MILLION DOLLAR BIKE RIDE
PILOT GRANT PROGRAM**

The ODC MDBR Pilot Grant Program provides a one-year grant to support research related to a rare disease represented in the 2017 Million Dollar Bike Ride. Number of awards and dollar amounts vary per disease based on fundraising totals by each disease team.

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.

Letter of Interest Instructions:

Please visit our [website](#) to submit your Letter of Interest (LOI), which can also be found [here](#). This one-page LOI is due no later than **Monday, September 18, 2017 by 8pm (EST)**.

Full Application Instructions and Review Procedure

NOTE: Full Application is by invitation only after review of Pre-Application

Proposal Due Date: **Wednesday, October 18, 2017 no later than 8pm (EST)**

Full application documents are to be uploaded at

<http://www.med.upenn.edu/orphandisease/rare-disease-overview.html>

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]**
- NIH-style Biosketch with Other Support of PI and key personnel (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.
- 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: Jan 1, 2018 – Dec 31, 2018.
Total Budget depends on disease RFA:

Disease	# of Awards	Total Costs	Direct Costs	10% Indirect Costs
ALD	1	\$101,164.00	\$91,967.27	\$9,196.73
APBD	2	\$52,978.00	\$48,161.82	\$4,816.18
A-T	1	\$65,689.00	\$59,717.27	\$5,971.73
BPAN	2	\$50,507.00	\$45,915.45	\$4,591.55
Castleman	1	\$42,508.00	\$38,643.64	\$3,864.36
CDKL5 – Brain Samples	1	\$51,160.00	\$46,509.09	\$4,650.91
CDKL5 – Seizure Activity	1	\$51,160.00	\$46,509.09	\$4,650.91
CF	1	\$52,985.00	\$48,168.18	\$4,816.82
CHI	1	\$87,109.00	\$79,190.00	\$7,919.00
CMD	1	\$41,831.00	\$38,028.18	\$3,802.82
CRB1	2	\$50,497.00	\$45,906.36	\$4,590.64
DC	1	\$48,191.00	\$43,810.00	\$4,381.00
FD/MAS	2	\$53,614.00	\$48,740.00	\$4,874.00
GLA/GSD	1	\$80,185.00	\$72,895.45	\$7,289.55
GLA/GSD	1	\$52,109.00	\$47,371.82	\$4,737.18
Glut1 DS	1	\$48,918	\$44,470.90	\$4,447.09
LAM	2	\$50,060.00	\$45,59.09	\$4,550.91
ML4	1	\$71,939.00	\$65,399.09	\$6,539.91
MPS	2	\$59,449.00	\$54,044.54	\$5,404.45
NPC	2	\$49,645.00	\$45,131.82	\$4,513.18
Pitt Hopkins	2	\$49,263.00	\$44,784.55	\$4,478.45
RASopathies	1	\$47,189.00	\$42,899.09	\$4,289.91
Snyder-Robinson	2	\$42,866.00	\$38,969.09	\$3,896.91
Tay-Sachs	1	\$42,419.00	\$38,562.73	\$3,856.27

Total cost = direct costs plus 10% indirect costs (if relevant to your institution).
If your institution is willing to waive the IDCs, the total award amount can be used as direct costs.

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

- 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: 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.

Research Focus Areas for Pilot Grants:

1) Adrenoleukodystrophy (ALD): One \$101,164 pilot grant is available with a focus on a path towards treatment for Adrenomyeloneuropathy (AMN). Grants should focus on activities that lead towards a clinical trial. Adrenoleukodystrophy (ALD) is an X-linked metabolic disorder, characterized by progressive neurologic deterioration due to demyelination of the cerebral white matter. The adult form, Adrenomyeloneuropathy (AMN), develops in young adulthood and in general, progresses more slowly than ALD. Beginning in their 20s and 30s, men and ~60% of women carriers exhibit neurological-based motor lesions in their extremities. These lesions progress over many years and are characterized by progressive spasticity, ataxia, incontinence, and sexual dysfunction that can also be accompanied by fatigue and depression. ALD/AMN can lead to severe disability. All current treatments are symptomatic and do not address the progressive nature of the disease. This grant is made possible by Team Stop ALD and the Stop ALD Foundation.

2) Adult Polyglucosan Body Disease (APBD): Two \$52,978 grants are available to initiate or advance research of a treatment or a cure for this glycogen storage disease. These grants are made possible by the Tour de Friends bike team with the APBD Research Foundation.

3) Ataxia-Telangiectasia: One \$65,689 grant is available to identify and test therapeutic strategies for the neurodegeneration and motor control problems faced by patients affected by Ataxia-Telangiectasia. Projects may involve early, preclinical studies such as target identification, phenotypic screening, gene therapy vectors or the elucidation of disrupted neurocircuitry but must be novel and have a clear path for translation to a therapy. This grant is made possible by Team Derek's Dreams and the A-T Children's Project.

4) BPAN- A Neurodegeneration with Brain Iron Accumulation Disorder: Two \$50,507 pilot grants are available for clinical and translational research studies related to the detection, diagnosis, or treatment of this rare, X-linked disorder caused by mutations in *WDR45*. BPAN typically is recognized in early childhood with delayed development and seizures. In adulthood, people with BPAN develop rapidly progressive parkinsonism. At the present time, symptoms may be treated but there are no cures.

Grants are expected to generate essential resources for the scientific community, advance knowledge about BPAN disease processes, and produce preliminary data to enable national and international funding to carry the work forward. Examples of priority topic areas include developing disease models that complement existing models, identifying biomarkers, delineating the molecular cascade that leads to early cellular changes, developing rational therapeutics, establishing outcome measures to be used in clinical trials, and developing other essential resources to substantially prepare the BPAN community for clinical trials. Natural history studies must have a component that includes participation in the International NBIA Patient Registry & Biobank. These grants are made possible by Team NBIA and BPAN families with the NBIA Disorders Association.

5) Castleman Disease: A \$42,508 pilot grant is available to perform critical investigations into the etiology and pathogenesis of HHV-8-negative/"idiopathic" multicentric Castleman disease (iMCD). We seek to fund research that will improve understanding of the etiology, genomic aberrations, aberrant cell populations, dysregulated signaling pathways, and/or effector cytokines in iMCD. Applications that include strong preliminary data from discovery-level studies that need funding for targeted function characterizations of suspected pathological genomic aberration(s) are preferred. Functional validation studies should provide information on the genomic aberration identified, functional studies to demonstrate the effect of the aberration and hypothesized mechanisms for how the aberration leads to iMCD pathogenesis. If preliminary data suggests that the aberration is acquired, proposals should also include studies to identify the harboring cell population. The Castleman Disease Collaborative Network (CDCN) will support the project through sample procurement, as needed, and can provide its expertise and guidance to facilitate the success of the project. This grant is made possible by the Castleman Disease Collaborative Network and Team CDCN.

6) CDKL5: Two \$51,160 grants are available, made possible by The International Foundation for CDKL5 Research and Team CDKL5.

1) CDKL5 Postmortem Brain Samples (\$51,160)

Research focused on genetic, molecular and anatomical studies of postmortem brain samples of CDKL5. There are CDKL5 postmortem samples at the Harvard Brain Bank under the Rett Syndrome special collection. This area is completely underrepresented in any current CDKL5 research, and can inform the future of other aspects of CDKL5 research. IFCR will assist the awardee with gaining access to this tissue.

2) Mechanisms of CDKL5 Seizure Activity (\$51,160)

Research focused on seizures in CDKL5, including but not limited to causation, treatment, or evaluation. This can include drug screening.

7) Congenital Hyperinsulinism (CHI): One \$87,109 grant available for an innovative, pre-clinical or clinical study that has the potential to lead to: (1) faster and more accurate diagnoses of congenital hyperinsulinism (HI); (2) better HI treatment; (3) a cure for HI; or (4) quality of life improvement for those affected by HI. This grant is made possible by Team Raring to Go for CHI, and Congenital Hyperinsulinism International.

8) Congenital Muscular Dystrophy (CMD): One \$41,831 grant available. CMD are a group of genetically inherited multi-system disorder with symptom onset at birth and progressive muscle weakness, respiratory insufficiency, contractures and scoliosis. Failure to thrive, cardiac arrhythmias, subclinical cardiomyopathy and seizures may complicate disease course. The purpose of this RFA is to promote discovery of underlying disease mechanisms and preclinical development of potential therapies, as well as the clinical translation of those efforts. Areas of interest include, but are not limited to, understanding the cause of disease, unraveling pathways involved in disease, identifying novel drug targets or gene therapies, and testing new strategies to treat disease or any of its incapacitating consequences (e.g. contractures). In addition, applications may propose to create or improve disease models (e.g. animal models, patient-derived cell models), biomarkers or functional outcome measures to assess therapeutic impact.

Priority will be given to research projects targeting Collagen VI (Ullrich). This grant is made possible by Team Cure CMD and the Cure CMD organization.

9) CRB1 degenerative retinal disease: Two \$50,497 grants are available for work toward treatments for CRB1 retinal disease. Applications including gene therapy, CRISPR, cell therapy or other methods that will halt the progression of CRB1 retinal disease and ultimately restore retinal function will be considered. CRB1 retinal disease is a rare disease causing Leber's Congenital Amaurosis (LCA), Retinitis Pigmentosa (RP) or Cone Rod Dystrophy. Children with CRB1 are blind or visually impaired from a very early age (at birth in LCA) and most are Braille readers and white cane users. This grant is made possible by Team Bike4Sight and the Curing Retinal Blindness Foundation

10) Nonsense Mutations in Cystic Fibrosis: One \$52,985 grant available. Cystic fibrosis is a genetic condition affecting the lungs and digestive system. The grant will be awarded to advance research and understanding of a treatment or cure that would impact people carrying a nonsense mutation. The research should include, but not be limited to, the R1158X gene mutation. This grant is made possible by Team Movin' for Mallory: Cure Cystic Fibrosis! and the Movin' for Mallory organization.

11) Dyskeratosis Congenita & Telomere Biology Disorder: One \$48,191 pilot grant available to investigators conducting clinical studies or basic science research on all aspects of Dyskeratosis Congenita or Telomere Biology Disorders. Dyskeratosis Congenita is a progressive, genetic condition caused by defects in telomere biology and results in problems in areas with high rates of cell regeneration. Proposals that seek to advance understanding of the manifestations of the disease will be considered. This research could involve the examination of late effects of the disease—including late effects of stem cell transplant; the development of a comprehensive database that characterizes clinical complications and or treatments; focus on gene discovery; or address any of the unmet needs of DC/TBD

patients. This grant is made possible by Team Josh & the DCO Riders and Dyskeratosis Congenita Outreach, Inc.

12) Fibrous Dysplasia/McCune Albright Syndrome: Two grants available, each for up to \$53,614. Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a rare disease caused by somatic mutations in GNAS. The mutation results in constitutive activation of the signaling protein, Gs α , and downstream cAMP signaling. Skeletal manifestations include bone pain, fractures, deformity, and osteomalacia/rickets. Any study that focuses on the pathogenesis of FD/MAS, or clinical investigative studies to address any of the unmet needs in FD/MAS patients and their management will be considered. Research priorities for the Fibrous Dysplasia Foundation include: generation of new mouse models to study FD/MAS; studies to understand the mechanism and/or treatment of FD-related bone pain; development/testing of therapeutics, especially those targeting Gs α , PKA or Wnt signaling pathways, including through the use of oligonucleotides; or studies of the molecular etiology, especially the role of RANKL, IL6, cAMP and FGF23. These grants are made possible by Team FD and the Fibrous Dysplasia Foundation.

13) Generalized Lymphatic Anomaly (GLA; a.k.a. lymphangiomatosis) and Gorham-Stout Disease (GSD): Two grants are available for basic science and/or clinical research on GSD or GLA. One is for \$80,185 and the other is for \$52,109. Areas of interest include, but are not limited to, genetic analysis, biomarker identification, cell line creation and characterization, and imaging. These grants are made possible by Team LGDA (Lymphangiomatosis & Gorham's Disease Alliance) and Team LMI (Lymphatic Malformation Institute).

14) Glucose Transporter Deficiency Syndrome (Glut 1DS): Glut 1 DS is a rare genetic disorder caused by a mutation in the SLC2A1 gene, which regulates the glucose transporter type 1 (Glut1). Glucose is not transported properly into the brain, leaving it starving for the energy it needs to grow & function. One \$48,918 pilot grant is available and will be awarded to research focused on identifying and investigating innovative research projects that involve basic research including blood brain barrier, translational studies, clinical studies, alternative treatment theory, or gene therapy relevant to Glut 1DS. This grant is made possible by the generous support by friends of Team Miles for Millie.

15) Lymphangiomyomatosis (LAM): Two \$50,060 pilot grants will be available focusing on translational proposals with strong likelihood of future federal funding, that use LAM samples, models or patient data, and which have the potential to favorably impact human health will be given priority. Examples of desirable topic areas include identification of molecular targets, biomarker development, and biomarker driven small pilot trials. In 2017, LAM research grant proposals from early career investigators (three years or less into their first faculty appointment) who are working in the laboratories of established LAM researchers or conducting research with the mentorship of established LAM researchers will be given priority. These grants are made possible by Team LAM Foundation Easy Breathers and The LAM Foundation.

16) Mucopolipidosis Type IV (ML4): One \$71,939 pilot grant available. Mucopolipidosis Type IV is caused by a single-gene mutation in p19 which encodes for MCLON1. Most patients experience total loss of this transmembrane protein resulting in severe psycho-motor delays, neurodegeneration, and blindness. We offer this grant to investigators conducting research on all aspects of disease including disease pathogenesis and clinical studies. Preference will be given to those research projects developing new therapies for MLIV, and translational research projects that improve our understanding of the disease state and pathogenesis, such as biomarkers or functional outcome measures to assess therapeutic impact. This grant is made possible by Together4Ido, TeamCureML4, Climb4Carin, Pedal4Paul, Danny4theGirls, and MayaanHikes4Meira.

17) Mucopolysaccharidoses (MPS): Two \$59,449 pilot grants available. Mucopolysaccharidoses represent a broad array of diseases due to enzyme defects that lead to abnormal metabolic storage products and multi-organ pathologies. We are seeking applications directed to treating the central nervous system manifestations or antibody response of these diseases. These grants are made possible by Team MPS, the National MPS Society and the Ryan Foundation.

18) Niemann Pick Type C (NPC): Two \$49,645 pilot grants available. Consideration will be given to research projects developing new therapies for NPC as well as those designed to complement therapies presently in the pipeline. Consideration will further be given to gene therapy proposals; studies focused on problems, including psychiatric issues, impacting quality of life through the lifespan of the patient population and research projects that improve our understanding of the biology, pathogenesis and disease state (i.e., biomarkers or functional outcome measures to assess therapeutic impact) and have a direct impact on translation of new treatments to patients. This grant is made possible by Team NPC, the Andrew Coppola Foundation, Jammin' for JP, Chase the Cure and iPedal4Chad.

19) Pitt Hopkins Syndrome (PTHS): Two \$49,263 pilot grants available. Pitt Hopkins Syndrome is due to a deficiency in the TCF4 gene and is characterized by severe intellectual disability and developmental delay. Other symptoms include episodic hyperventilation and/or breath-holding (55%-60%), recurrent seizures/epilepsy (40%-50%), gastrointestinal issues, and distinctive facial features. The Pitt Hopkins Research Foundation would like to focus this research on finding therapeutics and a cure for this debilitating syndrome and are not interested in natural history studies at this time. These grants are made possible by Team Pitt Hopkins Pedalers with the Pitt Hopkins Research Foundation.

20) RASopathies: One \$47,189 pilot grant available. RASopathies are a group of genetic conditions caused by mutations in genes on the Ras-MAPK pathway. These conditions, including Noonan syndrome/Noonan-related conditions (NS), cardio-facio-cutaneous syndrome (CFC), Costello syndrome (CS), and Neurofibromatosis type 1 (NF1) share many clinical features, such as developmental delay, gastrointestinal difficulties, skeletal abnormalities, hematologic abnormalities, and growth delay. This grant should be directed toward the development of a treatment or cure for the RASopathies, and must include NS, CFC, and CS. This grant is made possible by Team RASopathies Network Riders and the RASopathies Network.

21) Snyder-Robinson Syndrome: Snyder-Robinson Syndrome (SRS) is a genetic condition resulting in the dysfunction of Spermine Synthase (SMS). This enzyme conversion is the last step in the polyamine pathway. Polyamines are ubiquitous and SRS is the only known condition involving a polyamine inborn error of metabolism. Clinical features include intellectual disability, seizures, developmental delay, and osteoporosis with fractures in the absence of trauma, along with defects in other organ systems. There is a wide range of severity among individuals with SRS.

Two \$42,866 grants are available for Snyder-Robinson Syndrome. Research focus includes further understanding of pathophysiology and/or mechanisms by which SRS causes disease as well as potential treatments, which will cure and/or improve quality of life of those with SRS. These grants are made possible by the Snyder-Robinson Team and the Snyder-Robinson Foundation.

22) Tay-Sachs, Sandhoff, GM-1, or Canavan Disease: One \$42,419 pilot grant is available focusing on forms of Tay-Sachs, Sandhoff, GM-1, or Canavan disease. We are soliciting proposals for innovative research projects that involve basic research, translational studies or clinical studies relevant to the diseases mentioned above. Projects may be focused on (1) pre-clinical and clinical research needs, such as clinical outcome measures, registries, animal models, or biomarkers or (2) technology approaches such as stem cells, molecular chaperones, substrate inhibitors, small molecule drug screening, gene therapy, novel drug delivery to the brain. This grant is made possible by Team NTSAD and the National Tay-Sachs & Allied Diseases Association.

Grant Review Procedure:

- 1) Grants will be reviewed for scientific content and relevance to the goals of the RFA.
- 2) 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, reviewers' scores are averaged and funding recommendations are determined based on an assessment of the ranked scores and written comments. Final decision of funding will be made by Center Leadership.
- 3) 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 or reduce rare disorders/disease incidence and/or mortality? Will the proposed research lead to substantial advances and/or contribute to large leaps of understanding or knowledge that will contribute to reductions in disease incidence and/or mortality within the decade?
 - **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** – Does the investigator hold a track record of outstanding accomplishment as evidenced by peer-reviewed publications and funding awards? Does the investigator have access to the resources and environment necessary to complete the study as outlined?

Award mechanism:

Funds will be issued through cost reimbursement mechanism executed by purchase order from the University of Pennsylvania. Details of invoicing schedules and reporting requirements will be made available upon award.

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