**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 2018 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 10, 2018 by 8pm (EST).**

## Full Application Instructions and Review Procedure

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

Proposal Due Date: **Monday, October 15, 2018 no later than 12pm (EST)**
Full application documents are to be uploaded on our website, by invitation only.

**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 Excel budget sheet (to be provided). Describe justifications in a Word document. Award will be for one year. Proposed funding period: February 1, 2019 – January 31, 2020. Total Budget depends on disease RFA:

| Disease | Total Funds | # of Awards | Award Total |
|---|---|---|---|
| APBD | $106,911 | 2 | $53,455 |
| Angelman Syndrome | $44,030 | 1 | $44,030 |
| A-T | $87,164 | 1 | $87,164 |
| BPAN | $102,040 | 2 | $51,020 |
| Castleman | $102,150 | 1 | $102,150 |
| CDKL5 Function | $51,382 | 1 | $51,382 |
| CDKL5 Biomarker Development | $51,382 | 1 | $51,382 |
| CHI | $84,080 | 1 | $84,080 |
| Choroideremia | $101,740 | 1 | $101,740 |
| CF | $53,668 | 1 | $53,668 |
| CMD | $101,399 | 2 | $50,699 |
| CRB1 | $100,625 | 2 | $50,312 |
| DC | $100,373 | 1 | $100,373 |
| FD/MAS | $272,742 | 4 | $68,185 |
| FOP | $75,266 | 2 | $37,633 |
| GLA/GSD | $101,070 | 2 | $50,535 |
| LAM | $100,485 | 2 | $50,242 |
| ML4 | $68,992 | 1 | $68,992 |
| MPS | $111,985 | 2 | $55,992 |
| MPS Gene Spotlight | $103,560 | 1 | $103,560 |
| MSUD | $112,893 | 2 | $56,446 |
| NPC | $62,340 | 1 | $62,340 |
| Pitt Hopkins | $102,284 | 2 | $51,242 |
| RASopathies | $74,830 | 1 | $74,830 |
| Snyder-Robinson | $109,548 | 2 | $54,774 |

Institutions may opt to take up to 10% IDCs from their award totals. Awarded amounts will not exceed Award Totals listed above.

**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, cell lines, animal models, 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; a maximum of 3 relevant reprints are also acceptable. Include IRB and/or IACUC approval letters if relevant.

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

- NCEs will be granted at the discretion of the ODC.
- 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 through this form found on the ODC website prior to the NCE deadline with adequate justification.
- If granted a 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.

**Research Focus Areas for Pilot Grants:**

**1) Adult Polyglucosan Body Disease (APBD):** Two $53,455 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.

**2) Angelman Syndrome (AS):** One $44,030 grant is available to develop a consensus statement on standardization of care focusing on currently available therapy for individuals living with Angelman Syndrome. The proposal should include a discussion of the consensus building process (i.e. telecons with other KOLs, etc.), assessment, and deliverables. This grant is made possible by the Foundation for Angelman Syndrome Therapeutics.

**3) Ataxia-Telangiectasia**: One $87,164 grant, made possible by Team Derek's Dreams and the A-T Children's Project, 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. Please note that the following *will not* be considered for funding through this grant mechanism:

- Neuroscience-related research proposals using Atm-/- mice as a model system.
- Research to generate iPS cell lines derived from A-T patient cells or by disrupting the ATM gene in normal or carrier cells.

**4) BPAN -- A Neurodegeneration with Brain Iron Accumulation Disorder:** Two $51,020 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 Disorders and BPAN families with the NBIA Disorders Association.

**5) Castleman Disease:** One $102,150 grant is available to perform investigation into the presence and role of auto-antibodies and auto-reactive cell populations in HHV-8-negative/"idiopathic" multicentric Castleman disease (iMCD). iMCD is a poorly-understood and deadly disorder involving systemic inflammation, polyclonal lymphoproliferation, cytopenias, and multiple organ dysfunction due to an idiopathic cytokine storm. It's not clear whether iMCD should be considered an autoimmune, autoinflammatory, neoplastic, or infectious disorder. iMCD's defining histopathologic lymph node features have also been observed in autoimmune diseases, and ~30% of published cases of iMCD are reported to have auto-antibodies and/or autoimmune hemolytic anemia.

We wish to understand the role of auto-antibodies/autoimmune mechanisms in iMCD through

this grant. Identifying a sensitive and specific auto-antibody or auto-reactive cell population would re-direct research efforts and could improve diagnosis, particularly if it can help to separate out iMCD cases from mimics. Investigators who have experience performing discovery-level auto-antibody screening to identify candidate auto-antibodies in iMCD should apply. Proposals should include performing validation and functional studies of candidate auto-antibodies, with the goal to generate data to understand iMCD etiology and pathogenesis. We expect the investigator's application to provide information on the screening platform and functional assays to demonstrate the effect of the auto-antibodies/self-reactive cell populations. All grant applications will be considered confidential. The Castleman Disease Collaborative Network (CDCN) will support the project through providing samples, as needed, and can provide its expertise and guidance to facilitate functional assay development. For a complete listing of CDCN studies, visit: https://www.cdcn.org/research-pipeline

**6) CDKL5:** Two $51,382 grants are available, made possible by The International Foundation for CDKL5 Research and Team CDKL5.

1. **CDKL5 Function:** Research dedicated to furthering the understanding of CDKL5 function to inform the development of targeted, novel therapies and disease-modifying strategies.

2. **CDKL5 Biomarker Development:** Development of sensitive biomarkers with temporal specificity that may be useful in determining the clinical efficacy of a potential therapy.

**7) Choroideremia:** One $101,740 grant is available to initiate or advance research towards a treatment or cure for Choroideremia (CHM). CHM is an X-linked retinal disease causing progressing loss of vision and eventual blindness. Applications will be considered for research including gene therapy, CRISPR, stem cell therapy, or other methods that will potentially halt the progression of CHM and/or restore retinal functioning. This grant is made possible by Team CHM and the Choroideremia Research Foundation.

**8) Congenital Hyperinsulinism (CHI):** One $84,080 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.

**9) Congenital Muscular Dystrophy (CMD):** Two $50,699 grants or one $101,399 grant will be awarded depending on the merit, feasibility, and budget justification (please indicate solicited budget level on your LOI). The purpose of this RFA is to promote discovery of underlying disease mechanisms and pre-clinical development of potential therapies for **Collagen VI-Congenital Muscular Dystrophy,** 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), bio markers or functional outcome measures to assess therapeutic impact. This grant is made possible by Team Cure CMD and Cure CMD

**10) CRB1-CRUMB1 degenerative retinal disorder:** CRB1-CRUMB1 degenerative retinal disorder: Two $50,312 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 Rod-cone Dystrophy or Macular 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.

**11) Nonsense Mutations in Cystic Fibrosis:** One $53,668 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.

**12) Dyskeratosis Congenita & Telomere Biology Disorder:** One $100,373 grant available to investigators conducting basic or clinical research on all aspects of Dyskeratosis Congenita / Telomere Biology Disorders. Dyskeratosis Congenita is a progressive, genetic condition caused by defects in telomeres, the protective caps at the ends of chromosomes. Impaired telomere maintenance in Dyskeratosis Congenita/Telomere Biology Disorders results in problems throughout the body, notably including blood, liver, and lung disease, and cancer. Proposals that seek to advance understanding of the genetics, biology, pathophysiology, disease manifestations, treatment, including late effects of stem cell transplant, natural history and/or outcomes of Dyskeratosis Congenita and telomere diseases will be considered. This grant is made possible by Team Josh's DCO Riders.

**13) Fibrous Dysplasia/McCune Albright Syndrome:** Four grants available, each for up to $68,185 to promote balance between funding basic and clinical research projects. At least one grant will go to a clinical research project.

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, Gsα, 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: studies that characterize existing mouse models or generate novel mouse models; studies to understand the mechanism and/or treatment of FD-related bone pain; development/testing of therapeutics, especially those targeting Gsα, PKA or Wnt signaling pathways; studies of the molecular etiology, especially the role of RANKL, IL6, cAMP and FGF23; projects that feature collaborations across multiple institutions are encouraged. These grants are made possible by Team FD and the Fibrous Dysplasia Foundation.

**14) Fibrodysplasia Ossificans Progressiva (FOP):** Up to two $37,633 grants are available to further research in Fibrodysplasia Ossificans Progressiva (FOP). FOP is a rare genetic disorder that causes bone to form in muscles, tendons, ligaments and other connective tissues. Bridges of extra bone develop across joints, progressively restricting movement and forming a second skeleton that imprisons the body in bone. These grants are made possible by Team #cureFOP and the International Fibrodysplasia Ossificans Progressiva (FOP) Association.

Proposals for funding should be focused on one of the following two research areas:

- Research that seeks to identify biomarkers, including novel imaging techniques, capable

of measuring and predicting early FOP disease progression and/or treatment response;

- Research that investigates and further elucidates the immunologic mechanisms in FOP. Winners of the research funding may have access to the IFOPA's FOP Mouse Model (IFOPA will support the cost of animal models with the exception of shipping) or available samples from the IFOPA Biobank, if needed. Please contact the IFOPA at grants@ifopa.org for further details on these resources.

**15) Generalized Lymphatic Anomaly (GLA; a.k.a. lymphangiomatosis) and Gorham-Stout Disease (GSD):** Two $50,535 grants are available for basic science and/or clinical research on GSD or GLA. 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).

**16) Lymphangioleiomyomatosis (LAM):** Two $50,242 pilot grants available focusing on translational proposals with strong likelihood of future federal funding, that use LAM samples, animal 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. These grants are made possible by Team LAM Foundation Easy Breathers and the LAM Foundation.

**17) Mucolipidosis Type IV (ML4):** One $68,992 grant available. Mucolipidosis 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 focusing on biomarkers, functional outcome measures to assess therapeutic impact, and natural history research. This grant is made possible byTeamCureML4, Pedal4Paul, Cycle4Scott, Treatments4Tommy and Bike4Austin.

**18) Mucopolysaccharidoses (MPS):** Two $55,992 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 and the National MPS Society.

**19) MPS Gene Spotlight: Mucopolysaccharidosis (MPS I):** One $103,560 pilot grant is available for proposals focused on translational or clinical research to treat MPS I that have a strong likelihood of future federal funding. MPS I results from reduced enzymatic activity of alpha-L-iduronidase that leads to abnormal metabolic storage products and multi-organ pathologies. We are seeking proposals for oral or parenteral drugs that will slow the progression of central nervous system (CNS) manifestations of this disease or new methods for measuring CNS disease progression. This grant is made possible by Gene Spotlight.

**20) Maple Syrup Urine Disease:** Two $56,446 grants are available for work towards improved treatment and/or a cure of MSUD, a life-threatening disease characterized by an inability to metabolize branched-chain amino acids. Our intent is to award one grant for a gene therapy project and one grant for a non-gene therapy approach to treatment. The non-gene therapy approach may include research to develop a home monitor to measure leucine levels in a patient's blood. These grants are made possible by the MSUD Family Support Group.

**21) Niemann Pick Type C (NPC):** One $62,340 grant 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 (upon confirming no redundancies exist i.e. multiple dosing studies on pipeline drugs.) Consideration will further be given to gene therapy proposals. Research exploring 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 and have a direct impact on translation of new treatments to patients is encouraged. Studies looking to understand variants in the population to formulate targeted supportive care and therapy are welcome. This grant is made possible by Team NPC.

**22) Pitt Hopkins Syndrome (PTHS):** Two $51,242 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.

**23) RASopathies:** One $74,830 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.

**24) 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 systems. There is a wide range of severity among individuals with SRS.

Research Focus Area for Snyder-Robinson Syndrome: Two grants in the amount of $54,774 are available to focus on research related to potential treatments, which will cure and/or improve quality of life of individuals with SRS. Examples may include but are not limited to applications using mouse models, and evaluation of urine and other tissues of SRS individuals to identify the potential loss of exported diacetylspermine or increase in monoacetylspermidine. Additional novel measurements in urine or tissues would be welcomed. These funds have been made available by Team SRS.

**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, 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.
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?

**Fund Disbursement:**

Funds will be issued through a 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.