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 2021 Million Dollar Bike Ride. Number of awards and dollar amounts vary per disease based on fundraising totals by each disease team.

Eligibility
This RFA is open globally. International applicants are invited to apply. 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 **Thursday, September 16, 2021 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 18, 2021 no later than 8pm (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/PI, including Other Support). **[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, 2022 – January 31, 2023. Total Budget depends on disease RFA:

Disease	Total Funds	# of Awards	Award Total
APBD	$99,025	1 or 2	$99,025 or $49,513
A-T	$70,966	1	$70,966
BPAN/NBIA	$66,366	1	$66,366
CADASIL	$120,456	1 or 2	$120,456 or $60,228
Castleman	$64,205	1	$64,205
CHI	$73,045	1	$73,045
CDKL5	$74,775	1	$74,775
Choroideremia	$64,360	1	$64,360
CF	$117,655	1	$117,655
CLA	$106,921	2	53,460
CMD	$97,752	1 or 2	$97,752 or $48,876
Cohen Syndrome	$162,161	1 or 2	$162,161 or $81,080
FD/MAS	$161,374	2 ,3 or 4	$80,687, $53,791, or $40,343
FOP	$64,000	1	$64,000
Glut 1DS	$64,465	1	$64,465
LAM	$73,491	1	$73,491
ML4	$64,335	1	$64,335
MPS	$64,015	1	$64,015
MPS Gene Spotlight	$64,645	1	$64,645
MSUD	$119,555	1 or 2	$119,555 or $59,777
NEHI	$82,000	1 or 2	$82,000 or $41,000
NPC	$50,010	1	$50,010
NUBPL	$50,198	1	$50,198
Pitt Hopkins	$78,530	1	$78,530
RASopathies	$75,431	1	$75,431
SETBP1	$91,466	1 or 2	$91,466 or $45,733
Snyder-Robinson	$74,691	1	$74,691
STXBP1	$160,141	2	$80,070
TBCK	$50,400	1	$50,400
Telomere	$65,445	1	$65,445

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

* Beginning in May 2020, PI salary on all ODC Pilot awards will be applicable to the National Institutes of Health Executive Level II Salary Cap. The current NIH Salary Cap for the year 2020 is $197,300. For background and guidance, please refer to the following link: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-065.html

☐ **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 timeframe 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.

All previous MDBR grant awardees must include a statement of outcomes including publications, patents and additional funding granted as a result of data generated from those grants. Specific aims must be different from those in previous applications.

☐ **Appendix [combined into one PDF]**
Limited to 5 pages of supplemental information pertaining to proposal or preliminary data only. In addition to 5 pages of supplemental information, 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 timeframe of this grant period.

Research Focus Areas for Pilot Grants:

1) Adult-onset Polyglucosan Body disease (APBD) is a recessively inherited form of glycogen storage disease, associated with reduction in glycogen branching enzyme activity (GBE) to 10-20% of normal. Symptoms generally develop in the fourth or fifth decade with bladder dysfunction, gait disturbance, sensory and motor neuropathy, weakness, and fatigue. Mild attention and memory deficits may occur with brain white abnormalities noted on neuroimaging. By their early 60's patients require a walker and are subsequently wheelchair

dependent. The actual prevalence of the disease is probably much greater than reported due to misdiagnoses such as multiple sclerosis, Charcot-Marie-Tooth disease, ALS and spinal muscular atrophy (Schwartz L, et al. Am J Rare Dis: Diagn Ther. 2020;3(1):004-008.)
The APBD Research Foundation was established in 2005 to foster research in APBD and to provide patient and family support. Under their auspices, much has been learned about the genetic bases for tissue storage of polyglucosan bodies. Animal models have been established for the two major mutations in the GBE1 gene, and repurposed drugs have been examined for their ability to enhance glycogen branching activity. Substrate synthesis inhibition has been examined to reduce endogenous polyglucosan body formation.

A single grant of $99,025 or two grants of $49,513* will be awarded depending on the merits of the applications received. The primary focus for this grant opportunity is:

- Identification of measurable biomarkers to quantify the amount of insoluble glycogen developing serially in tissues.

Investigations related to the below will also be considered:

- The development of novel neuroimaging techniques for establishing correlations between disease symptomatology and pathology
- Identification of therapeutic targets that will prevent polyglucogon body storage or facilitate its removal from vital organs such as the brain and peripheral nervous system.

Grantees are expected to have access to senior mentors who can provide guidance and if needed, additional resources to accomplish the proposed work. Close collaboration with other scientists and clinicians knowledgeable about APBD is strongly encouraged. Proposals should include a sharing of data statement, and make use of available patient specimens such as cultured skin fibroblasts and animal models. It is hoped that the data generated by this funding mechanism will enable investigators to successfully compete for larger multi-year grants to carry forward their research and translate their results to improvement in the clinical care of patients.

*Please submit a proposal for the total amount of $99,025. The ODC may choose to fund two awards at $49,513 each, at which point we will request a revised work plan and budget.

2) Ataxia-Telangiectasia (A-T): A grant of $70,966 has been made possible by Team Derek's Dreams and the A-T Children's Project to pursue one of three objectives: 1) to demonstrate a technique that uses multiple viral vectors or a non-viral vector to deliver and express the entire 9.2kb coding length ATM gene, potentially making gene replacement therapy possible for children with A-T, 2) to demonstrate a gene editing technique (rather than a whole-gene delivery method) that can correct ATM gene mutations observed in children with A-T by targeting small insertions, deletions and base swapping, and then confirming success with a functional assay, or 3) to identify and validate a clinically useful blood or CSF biomarker, other than NfL and AFP, that correlates with the neurological deterioration seen in A-T patients and that can be used to determine whether a potential therapeutic is having a positive benefit in a clinical trial.

3) Beta-propeller protein-associated neurodegeneration (BPAN)/Neurodegeneration with Brain Iron Accumulation Disorder (NBIA) disorders: One pilot grant for $66,366 is 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 TIRCON International NBIA Patient Registry & Biobank. This grant is made possible by Team NBIA Disorders and BPAN families with the NBIA Disorders Association.

4) CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is the leading genetic cause of stroke, vascular cognitive impairment and vascular dementia and is linked to cysteine-altering mutations in NOTCH3. The precise mechanisms driving vascular dysfunction in CADASIL are not clear. Moreover, clinical markers that can be used to assess treatment efficacy are sparse. cureCADASIL Association seeks applications for research that will advance the understanding of mechanisms of the disease or clinical phenotyping that will facilitate future treatment trials (eg. identification of biomarkers or clinical predictors). Disease model initiatives and drug repurposing projects are of interest. Both basic laboratory and clinical projects will be considered. One $120,456 grant or two $60,228 grants are available. This grant is made possible by Team CADASIL and cureCADASIL Association.

*Please submit a proposal for the total amount of $120,456. The ODC may choose to fund two awards at $60,228 each, at which point we will request a revised work plan and budget.

5) Castleman: One $64,205 pilot grant is available to perform investigation into unicentric Castleman disease (UCD) and/or HHV-8-negative/"idiopathic" multicentric Castleman disease (iMCD). The Castleman Disease Collaborative Network's (CDCN) Scientific Advisory Board has identified the following priority research questions (though applications to study additional areas will also be considered): What is the role of JAK/STAT signaling in iMCD? What is the role of MAPK/ERK signaling in iMCD? What mouse model (xenograft, mutant, etc.) can be developed to be an effective model of human UCD or iMCD? What causal inferences or associations can be identified from whole exome sequencing and SNParrays of constitutional DNA from a cohort of 200-300 iMCD patients (grants intending to address this question would propose performing analyses of these datasets being generated)? What is the role of specific auto-antibodies identified through auto-antibody screens in iMCD? What proteomic patterns may be present in the serum of the 100 iMCD patients who have had auto-antibody profiling performed? What is the role of CXCL13 in iMCD? What insights can be gained from multi-omic profiling of lymph node tissue from iMCD and/or UCD patients (grants intending to address this question would propose performing multi-omic analyses)? Proposals should seek to explore one of the above priority research questions. We expect the investigator's application to provide information on the preliminary data that exist, hypotheses being tested, relevant experiences performing similar work, and the experimental plan. Proposing studies with a clear therapeutic impact is a plus. All grant applications will be considered confidential. The CDCN will support the project through sample procurement, as needed, and can provide its expertise and guidance throughout the grant. For a complete listing of CDCN studies, visit: https://www.cdcn.org/research-pipeline

6) CDKL5 Deficiency Disorder: One $74,775 grant available.
1. Research dedicated to furthering the understanding of CDKL5 function to inform the development of targeted, novel therapies and disease-modifying strategies.

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

7) Choroideremia (CHM): One $64,360 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) Cohen Syndrome (CS) is a rare autosomal recessive disorder caused by loss-of-function mutations in VPS13B. This is a transmembrane protein thought to function in vesicle-mediated transport and sorting. Individuals with CS present diverse clinical features including intellectual disability, developmental and motor planning challenges, microcephaly, hypotonia, joint laxity, truncal obesity, intermittent neutropenia, progressive high myopia and retinal dystrophy. Loss of vision generally begins in early childhood and advances to legal blindness over time.

One $162,161 grant or two $81,080 grants are available*. While research opportunities in this area are broad in scope, priority will be given to grants that cover one of the following areas:

1. Studying the functions of VPS13B and underlying pathways to understand the molecular basis of CS
2. Development of potential therapeutic interventions including drug repurposing, small molecules, oligonucleotides, gene and cell therapies or protein replacement therapies
3. Collection of clinical and genetic data from at least 50 CS patients worldwide to assess phenotypic variability and to evaluate the effect of various treatments on the relevant symptoms.

*Please submit a proposal for the total amount of $162,161. The ODC may choose to fund two awards at $81,080 each, at which point we will request a revised work plan and budget.

9) Complex Lymphatic Anomalies (CLA): We are soliciting applications for two $53,460 awards focused on translational research for Complex Lymphatic Anomalies (CLAs), including Gorham-Stout disease (GSD), generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA) and central conducting lymphatic anomaly (CCLA). Priority will be given to proposals with a strong likelihood of future federal funding, that use patient samples, patient data and/or preclinical models and have the potential to positively impact human health. Areas of interest include, but are not limited to, genomic and/or proteomic analyses, biomarker identification/validation, 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).

10) Congenital Hyperinsulinism (HI) includes many subtypes that all cause hypoglycemia due to the overproduction of insulin, which can lead to permanent brain damage or death. The consequences of HI are preventable – however, HI is often overlooked, misdiagnosed, or even when detected, mistreated. We are seeking applications for an innovative clinical or pre-clinical study that has the potential to benefit all types of HI and lead to: (1) a better understanding of the patient experience and/or natural history of HI; (2) novel or more effective diagnostics; (3) a quality-of-life improvement for those affected by HI; or (4) enhanced management or new treatments for HI. Multi-institution or multi-center collaboration is highly encouraged. The HI Global Registry (HIGR) is a global patient-powered congenital hyperinsulinism patient registry and consists of a series of thirteen surveys made up of questions related to a patient's HI experience over their lifetime (https://www.higlobalregistry.org/). It is highly recommended that

HIGR be used as one of the data sources or tools to collect study data. Applicants are encouraged to contact CHI to explore how to utilize HIGR. One grant of $73,045 is made possible by Team CHIbra and Congenital Hyperinsulinism International.

11) Congenital Muscular Dystrophy (CMD)
Funding: One $97,752 grant or Two $48,876 grants available*
Purpose: Promote the discovery of underlying disease mechanisms and the preclinical development of potential therapies, as well as the clinical translation of those efforts for Collagen VI Congenital Muscular Dystrophy.
Areas of Interest: Including but not limited to, 1) understanding the cause of disease, 2) understanding tissue-specific phenotypes, 3) unraveling pathways involved in disease, 4) identifying novel drug targets or gene therapies, and 5) testing new strategies to treat disease or any of its incapacitating consequences (e.g. contractures, respiratory function decline). We will also accept applications proposing to create or improve disease models (e.g. animal models, patient-derived cell models), and encourage applications on biomarker discovery or functional outcome measures to assess therapeutic impact in an effort to bring COL6-RD closer to Clinical Trial Readiness.

*Please submit a proposal for the total amount of $97,752. The ODC may choose to fund two awards at $48,876 each, at which point we will request a revised work plan and budget.

12) Cystic Fibrosis: One $117,655 grant available. Cystic fibrosis is a genetic condition affecting the lungs and digestive system. The grant will be awarded to target research to better understand exercise physiology in CF in the era of CFTR modulators, to implement and maintain exercise (fitness) programs in CF clinics, and/or to define the impact of research on health and outcomes in CF. This grant is made possible by Team Movin' for Mallory: Cure Cystic Fibrosis! and the Movin' for Mallory organization.

13) Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a rare multisystem disease caused by somatic mutations in GNAS. The mutation results in constitutive activation of the Gsα cAMP signaling pathway. Skeletal manifestations include bone pain, fractures, deformity, and osteomalacia/rickets.

Two to four grants are available. Amounts vary per number of awards that are funded: two awards at $80,867, three awards at $53,791, or four awards at $40,343. Studies that focus on the pathogenesis of FD/MAS or clinical studies to address any of the unmet needs in the care of FD/MAS patients will be considered. Research priorities for the FD/MAS Alliance include: studies that characterize mouse models; studies to understand the mechanism and/or treatment of FD-related bone pain; development or testing of therapeutics, such as those targeting Gsα, PKA, Wnt, or other signaling pathways; and studies of the pathophysiology, such as the role of RANKL, IL6, cAMP, and FGF23

The grants are made possible by Team FD/MAS and the FD/MAS Alliance. First-time applicants are encouraged. Previous awardees must describe progress, publications, and other funding awarded as a result of data generated from previous grant(s) and must describe how the new proposal is distinct or extends from previous one(s). Projects that feature collaborations across multiple institutions are encouraged.

Reagents and research tools, including animal models that are generated or studied using support from FD/MAS Alliance and MDBR, must be freely accessible without restrictions and/or deposited in a public repository.

*Please submit a proposal for the total amount of $80,867. The ODC may choose to fund three or four awards at $53,791 or $40,343 each, at which point we will request a revised work plan and budget.

14) Fibrodysplasia Ossificans Progressiva (FOP): All individuals holding a faculty-level appointment at an academic institution or a senior scientific position at a nonprofit institution or foundation are eligible to respond to this RFA. One $64,000 grant available. The two areas of FOP research focus for grant consideration are:

1. Research that seeks to identify biomarkers, including novel imaging techniques, capable of measuring and predicting early FOP disease progression and/or treatment response.
2. Research that investigates and further elucidates the immunologic mechanism in FOP.

Awardees 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's FOP Biobank, if needed. Please contact the IFOPA at grants@ifopa.org for further details on these resources.

15) Glucose Transporter Type 1 Deficiency Syndrome (Glut1DS): One $64,465 pilot grant is available and will be awarded to research that has the potential to lead to better understanding and better treatments to improve the quality of life for those affected by Glut1DS. Potential topics of interest may include but are not limited to: open source resource development (cell lines, assays, functional studies, etc.), Glut1 at the blood brain barrier, brain glucose metabolism, ketogenic diets, basic science to understand disease mechanisms relevant to Glut1DS, and translational and clinical studies. Preference may be given to novel concepts and collaborative/team approaches. This grant is made possible by the generous support of donors to Team Glut1, Miles for Millie, Mission for Macie, and the Glut1 Deficiency Foundation.

16) Lymphangioleiomyomatosis (LAM): One $73,491 pilot grant available focusing on 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:

- Better understanding of the molecular derangements in LAM with an aim to identify targets for future development of novel therapeutics
- Improving the existing models or creating new models to study disease pathogenesis
- Biomarker development to enable non-invasive diagnosis, better prognosticate the risk of disease progression, predict the response to treatment, or to act as end points in clinical trials. A biomarker is broadly defined as any objective modality that can measure disease activity and could include quantified biological variables (e.g., blood- or urine-based tests), novel imaging techniques, or patient-reported outcomes
- Molecular pathogenesis-guided pilot clinical trials

These grants are made possible by Team LAM Foundation Easy Breathers and The LAM Foundation.

17) Maple Syrup Urine Disease (MSUD) is an inherited disorder affecting an estimated 1:190,000 births in which the body is unable to properly process branched-chain amino acids. The condition is characterized by poor feeding, vomiting, lethargy, and developmental delay. Depression, anxiety, and learning disabilities are common. If untreated, MSUD can result in seizures, coma, and death. One $119,555 grant or two $59,777 grants available*. We seek proposals which will address one of the following objectives:

- Technologies aimed at enabling in-home monitoring of branched-chain amino acid levels,

• Applied research leading to improvements in quality of life of MSUD patients including but not limited to improvements in metabolic formulas and treatment of cognitive dysfunction,
• Improved therapies and projects which may potentially lead to a cure of MSUD.

*Please submit a proposal for the total amount of $119,555. The ODC may choose to fund two awards at $59,777 each, at which point we will request a revised work plan and budget.

18) Mucolipidosis Type IV (ML4): 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. One $64,335 grant available. 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 gene therapy development, biomarkers, functional outcome measures to assess therapeutic impact, and natural history research. This grant is made possible byTeamCureML4, Pedal4Paul, Dream4Danielle, Love4Rose, LovingJackHenry, Treatments4Tommy, Bike4Austin, Love4ZinetandAssen.

19) Mucopolysaccharidosis (MPS): The MPSs comprise a group of 11 MPS types, each a monogenic disease due to a specific single enzyme defect, but all of which lead to primary glycosaminoglycan storage, other abnormal metabolic changes and storage products, and multiorgan pathologies. Neuropathology is a feature of a majority of the MPS types. We are seeking applications directed to treating the central nervous system manifestations, and other primary manifestations from MPS including cardio-respiratory disease and bone and connective tissue issues. One grant of $64,015 is made possible by Team MPS and the National MPS Society.

20) Mucopolysaccharidosis (MPS I) Gene Spotlight: a $64,645 pilot grant is available for proposals focused on translational or clinical research to treat MPS I Scheie or MPSI Hurler-Scheie that have a strong likelihood of future federal funding or where the grant amount can be matched. MPS I S/HS 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, including identification of novel disease-related functional, structural or biochemical changes. This grant is made possible by Gene Spotlight, Inc.

21) Neuroendocrine Cell Hyperplasia of Infancy (NEHI): Two $41,000 grants or one $82,000 grant* will be awarded depending on the merit, feasibility, and budget justifications (solicited budget level must be indicated on your LOI).
The purpose of this RFA is to advance research or projects already in progress or to initiate new research or studies. Examples of priority topics include but are not limited to (1) increasing understanding of pathology (including Genetics); (2) quicker and more accurate diagnosis; (3) quality of life improvements; (4) development of treatments or cure.
Previous awardees of grants supported by NEHI Research Foundation must describe progress, publications, and other funding awarded as a result of data generated from those grants. They should also describe how the new proposal is distinct from previous one(s).
This grant is made possible by NEHI Research Foundation.

*Please submit a proposal for the total amount of $82,000. The ODC may choose to fund two awards at $41,000 each, at which point we will request a revised work plan and budget.

22) Niemann Pick Type C (NPC): One $50,010 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 or research considered along with any other research for a treatment or cure for Niemann Pick Type C. 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.

23) NUBPL: A Mitochondrial Disease caused by mutations in the NUBPL Gene: One $50,198 grant is available for research into this disease, with an emphasis on developing treatments or a cure for this form of mitochondrial disease. This grant can advance research or projects already in progress, or be used to initiate new research or studies. Examples of priority topic areas include developing, advancing, or continuing disease models, life studies, identifying potential therapeutics whether they consist of drugs, vitamins, diets, or supplements that are currently in the market, or the development of novel molecules, studying the effectiveness of therapies currently in use for mitochondrial disease in this form of the disease (including components of what is known as the “Mitochondrial Cocktail”), establishing outcome measures to be used in clinical trials, gathering data, and developing other essential resources to substantially prepare the NUBPL community for clinical trials. These grants are made possible by the NUBPL Foundation, Inc.

24) Pitt Hopkins Syndrome (PTHS): One $78,530 pilot grant 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.

25) 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), and Costello syndrome (CS) share many clinical features, including developmental delay, gastrointestinal difficulties, skeletal abnormalities, hematologic abnormalities, and growth delay. One $75,431 grant is available. This grant will be awarded to academic researchers to initiate or advance RASopathies research - specifically CFC, Costello, and/or Noonan syndrome. Grants will be reviewed based on the quality of the science and its potential impact on any one of the RASopathies. All things being equal, however, we will favor research that is relevant across multiple RASopathies.

26) SETBP1: The purpose of this RFA is to promote understanding of underlying disease mechanisms and pre-clinical development of potential therapies and tools for SETBP1 haploinsufficiency disorder, also known as SETBP1 disorder. One $91,466 grant or two $45,733 grants available*. Areas of interest include, but are not limited to:

-Identifying molecular pathways involved in this disease
-Investigating repurposing of existing FDA approved drugs as a treatment for SETBP1 disorder
-Identifying novel drugs or therapies for SETBP1 disorder
-Investigating language, cognitive, and attention clinical profiles through natural history

studies to further delineate the SETBP1 disorder phenotype and develop diagnostic and/or predictive biomarkers for clinical trials with a preference for virtual administration with multi-language support

-Identify Proteomics, Metabolomics, & Transcriptomics biomarkers to be used in clinical trials

In addition, applicants are encouraged to collaborate with existing SETBP1 researchers and to leverage existing disease models (e.g. animal models at JAX, patient-derived cell models at SFARI biorepository, etc.) to assess therapeutic impact. This grant is made possible by Team SETBP1Strong and SETBP1 Society.

*Please submit a proposal for the total amount of $91,466. The ODC may choose to fund two awards at $45,733 each, at which point we will request a revised work plan and budget.

27) Snyder-Robinson Syndrome (SRS) is a genetic condition caused by mutations in Spermine Synthase (SMS). SMS catalyzes the conversion of spermidine to spermine and the dysfunction of SMS results in altered elevated levels of spermidine and reduced levels of spermine in SRS. There is some evidence that SMS may have additional functions. Clinical features of SRS include intellectual disability, seizures, developmental delay, kyphoscoliosis and osteoporosis with fractures in the absence of trauma, as well as defects in other organ systems. There is a wide range of severity among individuals with SRS. There is some evidence to suggest possible immune suppression and/or overactivation is present in some patients with SRS. Mouse models with alterations in SMS are available for research studies through The Jackson Laboratory.

Research focus area: One $74,691 grant is available for SRS. There is interest in new studies focused on understanding the pathophysiology or mechanisms by which mutations in SMS cause SRS including how they may affect the immune systems. Applications addressing treatment options are welcomed. These funds have been made available by Team SRS.

28) STXBP1 Encephalopathy: Two $80,070 grants are available to advance research that supports therapeutic development for STXBP1 disorders. Projects addressing any stage of pre-clinical to clinical development will be considered, including applications exploring the fundamental science of STXBP1 disorders. Areas of interest include, but are not limited to:

1. Pathomechanisms and genotype-phenotype relationships of STXBP1 disorders.
2. Gene editing and gene replacement approaches to correct STXBP1 disorders.
3. Development of novel therapeutic approaches.
4. Development of clinical trial readiness, including non-seizure clinical endpoints.

These grants are made possible by Lulu's Crew/Team STXBP1

29) TBCK Syndrome is a very rare disease that causes epilepsy, severe hypotonia, and intellectual and developmental disability. We are seeking applications directed to research that supports investigations into the impact of branch chain amino acids as a possible intervention for TBCK Syndrome and/or investigations into potential treatments that support development. One grant of $50,400 is made possible by The TBCK Foundation.

30) Telomere Biology Disorders, including Dyskeratosis Congenita: One $65,445 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 the understanding of the genetics, biology, pathophysiology,

disease manifestations, treatment, natural history and/or outcomes of telomere diseases, including late effects of stem cell transplant, will be considered. This grant is made possible by Team Telomere.

Grant Review Process:

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?

Anonymous reviewer feedback is shared upon the request of the applicant at the discretion of the Orphan Disease Center where appropriate.

Confidentiality:

The MDBR Grant Program is a confidential process and all content of the LOIs and Full Applications will be kept confidential by the ODC. In order to encourage sharing of new techniques and findings to advance science, after funding decisions are made, the ODC will share a non-confidential lay summary of the research proposals received (required with your letter of intent), including those that were not funded, with each participating funding organization. The ODC aims to respect and protect the integrity of your work, and thus will not release any proprietary information.

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.

A notice about COVID-19: ODC will continue to monitor the global pandemic and will work with awardees to accommodate extensions that allow research aims to be completed safely in a mutually agreeable timeframe.