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 2022 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 **Friday, September 16, 2022 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 17, 2022 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, 2023 – January 31, 2024. Total Budget depends on disease RFA:

Disease	Total Funds	# of Awards	Award Total
APBD	$99,354	1 or 2	$99,354 or $49,677
A-T	$116,172	1	$116,172
BPAN/NBIA	$69,775	1	$69,775
CADASIL	$117,734	1	$117,734
Castleman	$60,570	1	$60,570
CHI	$70,920	1	$70,920
CDKL5	$50,240	1	$50,240
CHM	$61,760	1	$61,760
CLA	$68,650	1	$68,650
CMD	$113,008	1 or 2	$113,008 or $56,504
Cohen Syndrome	$100,474	1	$100,474
FD/MAS	$160,000	2, 3, or 4	$80,000, $53,333, $40,000
Glut 1DS	$61,855	1	$61,855
LAM	$75,110	1	$75,110
LNS	$85,779	1	$85,779
ML4	$53,634	1	$53,634
MPS	$60,350	1	$60,350
MPS Gene Spotlight	$60,000	1	$60,000
MSUD	$143,970	1 or 2	$143,970 or $71,985
NEHI	$87,145	1	$87,145
NUBPL	$120,465	1	$120,465
Pitt Hopkins	$71,650	1	$71,650
RASopathies	$60,100	1	$60,100
SCN2A	$61,068	1	$61,068
SETBP1	$91,664	1 or 2	$91,664 or $45,832
SynGAP	$65,705	1	$65,705
STXBP1	$174,250	2	$87,125
TBC1D24	$103,546	1	$103,546
TBCK	$40,000	1	$40,000
Telomere	$62,528	1	$62,528
ZC4H2	$93,692	2	$46,846

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 2022 is $203,700. For background and guidance, please refer to the following link: https://grants.nih.gov/grants/policy/salcap_summary.htm

☐ **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 an adult-onset, neurological form of glycogen storage disease type IV. APBD is caused by recessive mutations in the glycogen branching enzyme (GBE1) gene. Deficiency of GBE1 results in the pathogenic accumulation of polyglucosan bodies in the nervous system. APBD symptoms typically develop in the fourth or fifth decade of life and include bladder dysfunction, gait disturbance, sensory and motor

neuropathy, weakness, and fatigue. Cognitive decline is seen in approximately half of individuals with APBD. Progressive symptoms lead to wheelchair dependence and premature death. APBD is commonly misdiagnosed as multiple sclerosis, amyotrophic lateral sclerosis, and peripheral neuropathies. There are presently no treatments available for APBD.

The APBD Research Foundation is seeking research proposals that will advance the understanding of mechanisms of the disease or clinical phenotyping that will facilitate future treatment trials. Proposing studies with a clear therapeutic impact and a strong likelihood of future federal funding is a plus. A single grant of $99,354 or two grants of $49,677 will be awarded, depending upon the merits of the applications received.

The primary focus for this grant opportunity is the identification of a biomarker that could be used to demonstrate effectiveness of a therapeutic for the disorder.

Investigations related to the development of approaches that will prevent polyglucosan body accumulation or will facilitate its removal from the central and peripheral nervous systems will also be considered

Applicants are encouraged to collaborate with other scientists and clinicians and should include a statement on resource sharing in their proposal. Applicants are encouraged to use existing disease models (i.e., mouse models, cultured skin fibroblasts) and to contact the APBD Research Foundation (info@apbdrf.org) with any questions about these resources. All grant applications will be considered confidential. This grant is made possible by the APBD Research Foundation.

*Please submit a proposal for the total amount of $99,354. The ODC may choose to fund two awards at $49,677 each, at which point we will request a revised work plan and budget.

2) Ataxia-Telangiectasia (A-T): A grant of $116,172 has been made possible by Team Derek's Dreams and the A-T Children's Project to develop a brain-penetrant positron emission tomography (PET) tracer that binds to the ATM protein. A PET tracer will have tremendous value in neuroimaging in a clinical trial setting to confirm that a gene therapy approach has succeeded in producing protein in the brains of otherwise ATM-null patients, and in a preclinical setting as a powerful research tool for connecting ATM expression levels to downstream physiologic and functional MR metrics (diffusion, connectivity, blood flow, etc.).

3) Beta-propeller protein-associated neurodegeneration (BPAN)/Neurodegeneration with Brain Iron Accumulation Disorder (NBIA) disorders: One pilot grant for $69,775 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 is no cure.
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 $117,734 grant is available. This grant is made possible by Team CADASIL and cureCADASIL Association.

5) Castleman: One $60,570 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) patient, physician, and research communities have identified the following priority research questions (though applications to study additional areas will also be considered):

What are novel mechanisms involved in iMCD pathogenesis that may be therapeutic targets beyond IL6, mTOR, and JAK/STAT, particularly for treatment-refractory iMCD? What biomarkers can be used to improve diagnosis and tracking (predicting impending relapse) of iMCD? What are potential mechanisms underlying why some iMCD patients do not respond to anti-IL-6 therapy? What biomarkers can be used to predict a high likelihood of treatment response in individual patients? What is the etiological driver of 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 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 $50,240 grant available.

1. Research dedicated to furthering the understanding of CDKL5 function to inform the development of targeted, novel therapies.

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 $61,760 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 $100,474 grant is 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

9) Complex Lymphatic Anomalies (CLA): We are soliciting research applications for a $68,650 award focused on 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 laboratory or clinical research proposals with a strong likelihood of future federal funding. Areas of interest include, but are not limited to, genomic and/or proteomic analyses, biomarker identification/validation, cell line creation and characterization, and imaging. This award is 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 patients living with HI and should lead to: (1) an improved treatment; (2) novel endpoints for evaluating efficacy of treatments; (3) a better understanding of the patient experience including difficulty with feeding, fear of hypoglycemia, or the patient experience in resource limited settings; (4) knowledge of the cause of neurological damage; (5) novel or more effective methods for diagnosing hyperinsulinism at or near birth; or (6) enhanced management for HI. Multi-institution or multi-center collaboration is highly encouraged. Proposals that have the potential to benefit patients with all types of HI will be prioritized. 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. Please contact research@congenitalhi.org if you would like to discuss your proposed project. One grant of $70,920 is made possible by Team CHIbra and Congenital Hyperinsulinism International.

11) Congenital Muscular Dystrophy (CMD)
Funding: One $113,008 grant or Two $56,504 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
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.
Preference given to the continuation of previously funded research projects.

*Please submit a proposal for the total amount of $113,008. The ODC may choose to fund two awards at $56,504 each, at which point we will request a revised work plan and budget.

12) 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, three or four grants are available. Amounts vary per number of awards that are funded: two awards at $80,000, three awards at $53,333 or four awards at $40,000. 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 due to 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 $80,000. The ODC may choose to fund three awards at $53,333 or four awards at $40,000, at which point we will request a revised work plan and budget.

13) Glucose Transporter Type 1 Deficiency Syndrome (Glut1DS): One $61,855 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, identification of new biomarkers to make easier diagnosis and to measure the effectiveness of new treatments, 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, Determination for Dominic, Ride4Reed, and the Glut1 Deficiency Foundation.

14) Lesch-Nyhan Syndrome (LNS): Lesch-Nyhan Syndrome is a recessive, x-linked genetic disorder that impacts the HPRT1 gene. It is characterized by impaired kidney function, acute gouty arthritis, self-injurious behavior (such as lip/finger biting and head banging, among others), and severe motor impairments. Signs are usually seen as early as 6 months, although getting a diagnosis can be tricky due to the disease's rare nature and it is often misdiagnosed early as Cerebral Palsy. There have been treatments found that can greatly improve the body's ability to handle excess uric acid which can lessen related symptoms including kidney stones and gout. Currently no good treatments exist to manage the self-injurious behavior or motor impairment aspects of Lesch Nyhan Syndrome.

One $85,779 grant available for research that will facilitate the development of an effective treatment for Lesch-Nyhan Syndrome. This would include, but is not limited to, biomarkers, model development, characterization of the natural history or therapeutic approaches.

15) Lymphangioleiomyomatosis (LAM): One $75,110 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.

16) 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 $143,970 grant or two $71,985 grants are 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 $100,415. The ODC may choose to fund two awards at $50,208 each, at which point we will request a revised work plan and budget.

17) 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 $53,634 grant is 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. We are particularly focused on research that is collaborative and that can show impact for patients. This grant is made possible byTeamCureML4, Pedal4Paul, Dream4Danielle, Love4Rose, LovingJackHenry, Treatments4Tommy, and Bike4Austin and our Israeli partners.

18) 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 $60,350 is made possible by Team MPS and the National MPS Society.

19) Mucopolysaccharidosis (MPS I) Gene Spotlight: a $60,000 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.

20) Neuroendocrine Cell Hyperplasia of Infancy (NEHI): One $87,145 grant available. 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.

21) NUBPL: A Mitochondrial Disease caused by mutations in the NUBPL Gene: One $120,465 grant is available for research related to treatments or cures of this form of mitochondrial disease, and/or the creation of natural history studies of the disease to advance future clinical trials or research studies. 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, 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"), studying or establishing gene therapies, establishing outcome measures to be used in clinical trials, and developing other essential resources to substantially prepare the NUBPL community for clinical trials. This grant is made possible by the NUBPL Foundation, Inc.

22) Pitt Hopkins Syndrome (PTHS): One $71,650 pilot grant available. Pitt Hopkins Syndrome is due to a deficiency in the TCF4 gene and is characterized by severe developmental delays, including most being non-speaking and many being non-ambulatory. Other symptoms include extreme gastrointestinal issues (76%), debilitating anxiety (55%), episodic hyperventilation and/or breath-holding (34%), recurrent seizures/epilepsy (25%), 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 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 $60,100 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.

24) SCN2A: The FamilieSCN2A Foundation is excited to announce that one $61,068 grant is available for research to accelerate the development of therapeutic treatments and disease-modifying advancements for those living with autism and/or epilepsy due to changes in the SCN2A gene. We are interested in funding work that advances understanding of the cellular,

molecular, genetic, and systems-level mechanisms of SCN2A-related disorders. hopes Specific areas of interest include but are not limited to:

1. Investigating de-risked drugs as treatment for SCN2A-related disorders (ie. repurposing FDA-approved drugs or investigating non-approved “shelved” drugs but with validated clinical safety profiles)
2. Understanding the prevalence of SCN2A-related disorders in the population
3. Patient level functional analysis on all variants / genotype-phenotype assessment.

Priority will be given to innovative projects which could potentially lead to therapeutic treatments or cures for those with SCN2A-related disorders.

In addition, applicants are encouraged to collaborate with existing SCN2A researchers and to leverage existing disease models and data (e.g. animal models, Simons Searchlight registry and biobank, CTRS, Ciitizen/Invitae data.)

25) 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 (SETBP1-HD). One grant for $91,664 or two grants for $45,832 are 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-HD
- Identifying novel drugs or therapies for SETBP1-HD
- Investigating language, cognitive, behavioral and/or attention clinical profiles through natural history studies to further delineate the SETBP1-HD 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 future 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.

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 $91,664. The ODC may choose to fund two awards at $45,832 each, at which point we will request a revised work plan and budget.

26) SynGAP1-related intellectual disability: SYNGAP1-related intellectual disability is autosomal dominant disorder caused by haploinsufficiency of the Syngap1 gene that leads to a rare genetic developmental and epileptic encephalopathy (DEE) characterized by developmental delay, generalized epilepsy, intellectual disability and autism spectrum disorder (ASD). One $65,705 grant is available. We seek applicants that propose rigorous and comprehensive experiments to define endogenous regulation of SYNGAP1. Priority will be given to proposals that investigate the underlying signaling, transcriptional, epigenetic and genetic mechanisms of SYNGAP1 gene activation. Experimental strategies to exogenously activate SYNGAP1, in either human cells or animal models, will be especially well received.

27) STXBP1 Encephalopathy: Two $87,125 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. Areas of priority interest include, but are not limited to:

1. Development of clinical trial readiness, including identification of novel biomarkers and non-seizure clinical endpoints.
2. Determining the trajectory of STXBP1 disorders from pediatric to adult presentations.
3. Understanding pathomechanisms and genotype-phenotype relationships of STXBP1 disorders.
4. Developing or advancing therapeutic approaches to correct STXBP1 disorders, including the repurposing of FDA-approved drugs.

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

28) TBC1D24: Mutations in the TBC1D24 gene can cause individuals to have epilepsy, deafness, shortened nails, fingers, and toes. Mutations in this gene also cause hypotonia (low muscle tone), and developmental delays in babies and toddlers, continuing throughout adulthood. There is a wide spectrum of severity, ranging from the mild Familial infantile Myoclonic Epilepsy with normal intellect to the severe and early death causing EIEE 16.

The TBC1D24 Foundation, with funding from generous donors, is accepting applications for one grant of $103,546 for scientific and/or clinical research studies related to natural history, treatment and research. Consideration will be given to applicants in the field of neurology, genetics and behavior. This grant is offered to encourage meritorious scientific and clinical studies designed to improve the diagnosis or therapy of individuals with a TBC1D24 gene mutation. Proposals that focus on defining the natural history, early detection and diagnosis, or novel treatment strategies will be given priority.

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 other potential treatments and people who have model systems of TBCK. One grant of $40,000 is made possible by The TBCK Foundation.

30) Telomere Biology Disorders, including Dyskeratosis Congenita: One $62,528 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.

31) ZC4H2 Associated Rare Disorders (ZARD) is an ultra-rare genetic condition with central and peripheral nervous system involvement caused by pathogenic variant of the ZC4H2 gene. ZC4H2 is located on the X chromosome and encodes the ZC4H2 (zinc finger C4H2-type containing) protein essential for normal development. ZARD can manifest in a broad range of

clinical severity. Clinical presentations of affected individuals who carry the same pathogenic ZC4H2 gene variant can vary within families and between families. Males and females can be affected. To date, approx. 250 cases have been diagnosed worldwide.
There is currently very limited understanding of the function of the ZC4H2 gene and its protein. The focus for this grant opportunity is to a) understand the protein function of ZC4H2 and b) advance the search for viable therapies to treat this condition.

For this purpose, two equal grants of USD 46,846 each, will be offered to research projects on:

1. Studies on the function of ZC4H2 protein: Proteomic/transcriptomic profiling to identify protein function using patient-derived iPSCs (provided).
2. Novel therapeutic approaches for ZC4H2 Associated Rare Disorders (ZARD), including, but not limited to, X-reactivation, drug repurposing, techniques in genome editing, RNA-based mechanisms, biologics, novel cell-based therapeutics, and development of novel therapeutic compounds.

Applicants are expected to collaborate with other scientists and clinicians currently or previously involved in ZC4H2 research, and should include a statement on resource sharing in their proposal. Applicants are encouraged to use existing tools (e.g., existing viable and validated animal models, antibodies, fibroblasts, LCLs, iPSCs) and to contact the ZC4H2 Research Foundation (info@zc4h2foundation.com) with any questions about these resources. This grant is made possible by the ZC4H2 Research Foundation and the Orphan Disease Center.

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.

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.