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 2020 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 **Friday, September 18, 2020 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 26, 2020 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). **[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, 2021 – January 31, 2022. Total Budget depends on disease RFA:

Disease	Total Funds	# of Awards	Award Total
APBD	$121,268	1 or 2	$121,268 or $60,634
A-T	$129,898	1	$129,898
BPAN	$71,471	1	$71,471
CADASIL	$82,795	1	$82,795
Castleman	$64,590	1	$64,590
CHI	$73,190	1	$73,190
Choroideremia	$64,990	1	$64,990
CF	$64,010	1	$64,010
CMD	$84,812	1 or 2	$84,812 or $42,406
CMT	$55,090	1	$55,090
Cohen Syndrome	$100,786	1 or 2	$100,786 or $50,393
DC	$66,440	1	$66,440
FD/MAS	$66,263	1	$66,263
FOP	$80,000	2	$40,000
GLA/GSD	$81,965	1	$81,965
Glut 1DS	$64,200	1	$64,200
IBM	$68,245	1	$68,245
LAM	$70,769	1	$70,769
MPS	$64,485	1	$64,485
MPS Gene Spotlight	$65,040	1	$65,040
MSUD	$108,930	2	$54,465
NEHI	$103,066	1 or 2	$103,066 or $51,533
NPC	$47,630	1	$47,630
NUBPL	$75,360	1	$75,360
Pitt Hopkins	$71,643	1	$71,643
RASopathies	$69,885	1	$69,885
SETBP1	$80,746	1 or 2	$80,746 or $40,373
Snyder-Robinson	$68,840	1	$68,840
STXBP1	$143,316	2	$71,658
TBCK	$50,600	1	$50,600

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 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.

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; 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-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 $121,268 or two grants of $60,634 will be awarded depending on the merits of the applications received. Research proposals should focus on one of three areas:

- Identification of measurable biomarkers to quantify the amount of insoluble glycogen developing serially in tissues;
- The development of novel neuroimaging techniques for establishing correlations between disease symptomatology and pathology; and
- 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.

2) Ataxia-Telangiectasia (A-T): One grant of $129,898 has been made possible by Team Derek's Dreams and the A-T Children's Project to develop and train digitally based systems that can capture and analyze neurological data from children and young adults who have A-T. The awarded investigator will seek to use video, audio and multi-axis wearable device technologies to identify and validate data signatures that are specific to A-T and pattern changes that correlate with disease progression and severity of symptoms. A successful project will enable other researchers developing therapeutics for A-T to use these systems to make more precise and objective measurements of the A-T neurological phenotype in clinical trials, even when they are run across multiple sites. It is expected that artificial intelligence approaches such as unsupervised machine learning may be drawn on to identify clinically useful digital signatures.

3) Beta-propeller protein-associated neurodegeneration (BPAN)/Neurodegeneration with Brain Iron Accumulation Disorder (NBIA) disorders: One pilot grant for $71,471 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 International NBIA Patient Registry & Biobank. These grants are 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 $82,795 grant is available. This grant is made possible by Team CADASIL and cureCADASIL Association.

5) Castleman: One $64,590 pilot grant is available to perform further investigation into unicentric Castleman disease (UCD) and/or HHV-8-negative/"idiopathic" multicentric Castleman disease (iMCD). The 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 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-omics 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 Castleman Disease Collaborative Network (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) Choroideremia (CHM): One $64,990 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.

7) Charcot-Marie-Tooth disease (CMT) is one of the most commonly inherited nerve disorders, affecting an estimated 1 in 2,500 people in the United States. CMT is the most common of all the 7000 rare diseases reported in the US. Along with other inherited neuropathies, the disease causes problems with the sensory and motor nerves. Over time, this causes muscles in the feet, legs, and hands, as well as other parts of the body, to loose strength. Often, the muscle loss happens unevenly, which causes deformity as muscles waste

away (atrophy) at different rates. It can also have serious impacts on vision, hearing, breathing, speech and swallowing. The Hereditary Neuropathy Foundation (HNF) has developed the infrastructure to collect patient data in our proprietary patient registry, "Global Registry for Inherited Neuropathies" (GRIN), and targets patients to enroll in these virtual, natural and longitudinal studies for Charcot-Marie-Tooth/Inherited Neuropathies. In this unique era of COVID-19, the world is moving towards a more virtual research model to support therapy development. HNF, in collaboration with the University of Pennsylvania, is looking for a researcher with credentials as a psychometricinist to assist the CMT community. We require an expert to correlate the robust GRIN data (genotype, phenotype) to uncover correlations that have not previously been identified as a foundation for expansion of CMT research. We plan to evaluate, disseminate and update the CMT community with these findings. One grant of $55,090 is made possible by the Hereditary Neuropathy Foundation.

8) 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/). HIGR must be used as a data source or a tool to collect study data. If the project proposes collecting new data as a sub-study to HIGR on the IamRare platform, $11,000 of the grant funding must be allocated for platform implementation costs. If the project proposes to use existing HIGR surveys as a data source, there is no implementation fee. One grant of $73,190 is made possible by Team CHIbra and Congenital Hyperinsulinism International.

9) Congenital Muscular Dystrophy (CMD): Two $42,406 grants or one $84,812 grant will be awarded depending on the merit, feasibility, and budget justification (please indicate solicited budget level on your LOI).

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-CMD closer to Clinical Trial Readiness.

10) 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.

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 including human growth hormone (HGH), granulocyte-colony stimulating factor (G-CSF), and others on the relevant symptoms.

One grant for $100,786 or two grants for $50,393 will be awarded

11) Complex Lymphatic Anomalies: One $81,965 grant is available for basic science and/or clinical research on the Complex Lymphatic Anomalies – Gorham-Stout disease (GSD), generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA) or central conducting lymphatic anomaly (CCLA). 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).

12) 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.

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 Fibrous Dysplasia Foundation (FDF) 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.

A single grant of up to $66,263 will be awarded. The grants are made possible by Team FD/MAS and the FDF. First-time applicants are encouraged. Previous FDF and MDBR grant 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 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 FDF and MDBR, must be freely accessible without restrictions and/or deposited in a public repository. Members of labs that have previously received support from FDF or MDBR but that have not complied with this guidance are not eligible to apply for new grants.

13) Fibrodysplasia Ossificans Progressiva (FOP): Two grantees will each be awarded $40,000 to advance Fibrodysplasia Ossificans Progressiva (FOP) research. 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 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.

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

14) Glucose transporter 1 deficiency syndrome (Glut1DS): One $64,200 pilot grant is available and will be awarded to research that has the potential to lead to a cure, better treatment options, or quality of life improvement for those affected by Glut1DS. Potential topics of interest may include but are not limited to: genomic medicines, the blood brain barrier, translational studies, clinical studies, alternative treatment theory, new collaboration linking to other diseases, or disease mechanisms relevant to Glut1DS. Preference may be given to novel concepts and collaborative/team approaches. This grant is made possible by the generous support of donors to teams Miles for Millie, Determination for Dominic, Team Glut1 Hope in Motion, and the Glut1 Deficiency Foundation.

15) Inclusion Body Myositis (IBM): One $68,245 grant is available for inclusion body myositis (IBM) research. IBM is a rare muscle disease characterized by inflammation, degeneration, and mitochondrial pathology.

Proposals for funding should be focused on investigating potential treatments which may slow, stabilize, or reverse the progression of muscle weakness that characterizes IBM.

Examples may include, but are not limited to:

- Identification of candidate drugs
- Early development of therapeutic compounds that are designed to be treatments for IBM
- Investigation of already existing drugs for repurposing as possible IBM treatments
- Investigation of compounds, such as Creatine and Vitamin B3 complex, that may improve mitochondrial function in people with IBM.
- Exercise as therapy

This grant is made possible by Cure IBM.

16) Lymphangioleiomyomatosis (LAM): One $70,769 pilot grant 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) 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. Two grants are available for applied (not basic) MSUD research.

The first grant is to support the development of technology to be used to individually measure blood levels of the branched chain amino acids (BCAAs) vital to treatment. These BCAAs include leucine, isoleucine, and valine, with leucine being the most important. The technology should be usable in the home by MSUD patients as well as by clinics and provide a rapid (<1

hour) assessment. This project will be funded at $54,465.

A second grant of $54,465 will support one of the following areas: (a) a project to identify possible neurological biomarkers in the brain of MSUD patients and/or evaluate the neurocognitive health of individuals with MSUD; or (b) innovative applied research leading to improvements in the quality of life of MSUD patients or potentially lead to a cure.

18) Mucopolysaccharidoses (MPS): 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, and secondary metabolic manifestations from MPS including cardiac, lung, and bone issues. One grant of $64,485 is made possible by Team MPS and the National MPS Society.

19) Mucopolysaccharidosis (MPS I) Gene Spotlight: a $65,040 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): Two $51,533 grants or one $103,066 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.

21) Niemann Pick Type C (NPC): One $47,630 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) Nonsense Mutations in Cystic Fibrosis: One $64,010 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.

23) NUBPL: A Mitochondrial Disease caused by mutations in the NUBPL Gene: One $75,360 grant is available for research into this disease, with an emphasis on developing treatments or a cure for this form of mitochondrial disease, and/or the creation of a natural history study of the disease to advance future clinical trials or 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"), 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 $71,643 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), Costello syndrome (CS), and Neurofibromatosis type 1 (NF1) which share many clinical features, such as developmental delay, gastrointestinal difficulties, skeletal abnormalities, hematologic abnormalities, and growth delay. One $69,885 grant is available.This grant will be awarded to initiate or advance research in RASopathies specifically in the adult population (those over 18 years of age). Research can be of one of the following and must demonstrate how it will shed light on the other of the following RASopathies: CFC, CS, NS. This grant is made possible by Team RASopathies Network Riders and the RASopathies Network.

26) SETBP1: One grant in the amount of $80,746 or two grants in the amount of $40,373 are available. The purpose of this RFA is to promote discovery of underlying disease mechanisms and pre-clinical development of potential therapies and tools for SETBP1 disorder. Areas of interest include, but are not limited to, unraveling pathways involved in this disease, rescuing symptoms in disease models, identifying novel drug targets, and characterizing mouse models. In addition, applicants must collaborate with existing SETBP1 researchers and the preference is to leverage existing disease models (e.g. animal models at JAX, patient-derived cell models at Max Planck Institute of Psycholinguistics and McGill University, and in development by Simons Searchlight) to assess therapeutic impact. This grant is made possible by Team SETBP1Strong and SETBP1 Society.

27) Snyder-Robinson Syndrome (SRS) is a genetic condition resulting in the dysfunction of Spermine Synthase (SMS). SMS catalyzes the conversion of spermidine to spermine is the last step in the polyamine pathway and polyamine levels are altered in SRS. There is some evidence that SMS may have additional functions.

Clinical features include intellectual disability, seizures, developmental delay, and osteoporosis with fractures in the absence of trauma, along with defects in other organ systems. There is a wide range of severity among individuals with SRS.

Mouse models with alterations in SMS are available for research studies through The Jackson Laboratory.

One $68,840 grant is available for SRS. Research focus areas include new studies into understanding pathophysiology or mechanisms by which SRS causes disease, as well as corresponding treatment options.

There is particular interest in the following areas, however, other novel approaches are encouraged:

1. Examine whether the loss of the ability of the SMS protein to synthesize spermine accounts for all of the changes seen in SRS. Structural studies on the SMS protein have identified mutations leading to stable but inactive protein that could be used for such investigations.
2. Determine if an existing pharmaceutical and or other technique can rescue some or all of the phenotype in an SRS mouse model by reducing spermidine and/or resulting toxins in circulation and target tissues.
3. Develop an inexpensive and convenient assay for SMS activity.

These funds have been made available by Team SRS.

28) STXBP1 Encephalopathy: Two $71,658 grants are available to advance research into the development of new therapies for STXBP1 disorders. Projects addressing any stage of therapeutic development will be considered, spanning both clinical and basic science applications. Particular areas of interest include:

1. Functional characterization of patient-derived iPSC-neurons harboring STXBP1 mutations as a model system to study STXBP1 disorders and test novel therapies.
2. Evaluation of gene therapeutic approaches to correct STXBP1 haploinsufficiency.
3. Drug repurposing efforts to treat STXBP1 disorders.
4. Development of novel therapeutic approaches.
5. Development of clinical trial readiness including non-seizure clinical endpoints.

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

29) Telomere Biology Disorders, including Dyskeratosis Congenita: One $66,440 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.

30) TBCK Syndrome: One $50,600 grant is available to initiate or advance research towards a treatment or cure for TBCK Syndrome. TBCK is an autosomal recessive disease causing severe hypotonia, intellectual and developmental disabilities, and epilepsy. Certain mutations of the disease are neurodegenerative, with the majority of diagnosed patients being severely

impacted, but a small minority with more minor impairments. Applications will be considered for research methods that will potentially have interventions to mitigate symptoms and eventually a treatment. This grant is made possible by The TBCK Foundation and their generous supporters.

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 full application), 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.