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.