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**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 2023 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. Prior MDBR award recipients must have current and updated project reporting to be eligible for selection.

**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 15, 2023 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 16, 2023 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, 2024 – January 31, 2025. Total Budget depends on disease RFA:

<b>Disease</b>	<b>Total Funds</b>	<b># of Awards</b>	<b>Award Total</b>
APBD	\$100,000	2	\$50,000
A-T	\$53,240	1	\$53,240
BPAN/NBIA	\$120,000	2	\$60,000
CACNA1A	\$73,731	1	\$73,731
CADASIL	\$109,856	1	\$109,856
Castleman	\$63,270	1	\$63,270
CHI	\$70,200	1	\$70,200
CDKL5	\$60,960	1	\$60,960
CHM	\$64,735	1	\$64,735
CLA	\$60,679	1	\$60,679
CMD	\$140,266	2	\$70,133
Cohen Syndrome	\$83,282	1	\$83,282
DUP15Q	\$47,158	1	\$47,158
FD/MAS	\$161,284	4	\$40,321
Glut 1DS	\$61,901	1	\$61,901
KCNT1	\$70,619	1	\$70,619
LAM	\$71,051	1	\$71,051
LNS	\$68,367	1	\$68,367
MPS	\$57,645	1	\$57,645
MPS Gene Spotlight	\$60,655	1	\$60,655
NPC	\$40,140	1	\$40,140
NEHI	\$100,621	1	\$100,621
Pitt Hopkins	\$73,473	1	\$73,473
RASopathies	\$60,755	1	\$60,755
Ring14	\$67,897	1	\$67,897
SCN2A	\$61,280	1	\$61,280
SETBP1	\$88,740	1	\$88,740
SynGAP	\$61,222	1	\$61,222
STXBP1	\$150,920	2	\$75,460
TBC1D24	\$86,962	1	\$89,962
Telomere	\$63,000	1	\$63,000
ZC4H2	\$61,815	1	\$61,815

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 2023 is \$212,100. For background and guidance, please refer to the following link: [https://grants.nih.gov/grants/policy/salcap\\_summary.htm](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 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 the 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. Of particular interest would be basic science or clinical studies aimed at biomarker development (including neurofilament light chain and glial fibrillary acidic protein assays) for development and design of future therapeutic trials or novel treatments. Studies that have a strong likelihood of future federal funding are a plus. **Two grants for \$50,000 each will be awarded.**

The primary focus for this grant opportunity is the identification of a biomarker(s) that could be used to demonstrate the effectiveness of a therapeutic for APBD. 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](mailto: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.

**2) Ataxia-Telangiectasia (A-T):** A grant of \$53,240 has been provided by Team Derek's Dreams and the A-T Children's Project to support a crucial research endeavor aimed at investigating the functional effects and potential therapeutic benefits of exon skipping in specific regions of the ATM gene for the treatment of ataxia telangiectasia (A-T). Targeted exon-skipping therapies, which have had success in other diseases, hold promise for children with A-T as they could potentially enable disease-causing mutations to be ignored. However, the application of this approach to A-T necessitates a more comprehensive understanding of the structure, function, and consequences of exon skipping within the ATM gene. By employing a combination of in silico and in vitro techniques to systematically examine each exon, the recipient of this grant will make groundbreaking contributions to the field, not only enlightening the A-T research community but providing actionable insights to developers of genetic medicines regarding regions within the ATM gene that could be omitted.

**3) Beta-propeller protein-associated neurodegeneration (BPAN)/Neurodegeneration with Brain Iron Accumulation Disorder (NBIA) disorders: Two pilot grants for \$60,000 each** are available for clinical and translational research studies related to the detection, diagnosis, or treatment of this rare, X-linked disorder caused by mutations in WDR45. BPAN typically is recognized in early childhood with delayed development and seizures. In adulthood, people with BPAN develop rapidly progressive parkinsonism. At the present time, symptoms may be treated but there is no cure.

Grants are expected to generate essential information for the scientific community to advance knowledge about BPAN disease processes, and to produce preliminary data to enable national and international funding to carry the work forward. Examples of priority topic areas include: developing and exploiting disease models including computer 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 proposals should reflect knowledge of existing, ongoing studies and include a statement indicating how the proposed study would complement or integrate with existing studies. Moreover, proposals for 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) CACNA1A:** This RFA aims to advance the discovery or development of therapeutic treatments and/or cures for CACNA1A-related diseases. These are rare autosomal dominant neurodevelopmental disorders caused by a mutation in the CACNA1A gene, which encodes for the pore-forming alpha 1A subunit of the voltage-gated calcium ion channel Cav2.1. This channel plays a major role in fast synaptic neurotransmitter release in the brain. The spectrum of neurological phenotypes associated with CACNA1A variants includes hemiplegic migraine (sporadic and FHM1), episodic ataxia type 2 (EA2), epileptic encephalopathies, global developmental delays, intellectual disability, ASD, hypotonia, eye movement disorders, cerebellar atrophy, and neuropsychiatric disorders.

We seek applications for **one \$73,731 grant** that will strongly impact the CACNA1A community. Specific areas of interest include:

- Discovery and validation of biomarkers (molecular and functional). To date, no CACNA1A-specific biomarkers have been identified.
- Novel therapeutic approaches for CACNA1A-related disorders. The heterogeneity of symptoms requires the development of multiple therapeutic treatments for the CACNA1A community. Approaches we are interested in funding include (but are not limited to): drug repurposing, small molecules, gene therapies, and RNA-based therapies. While we are looking for approaches that will broadly impact the patient community, we will also support the development of disorder-specific treatments.
- Identification of disease mechanisms. Developing specific treatments highly depends on understanding how variants impact protein function and lead to disease phenotypes. There are over 300 unique pathogenic CACNA1A variants reported in Clinvar, with little molecular data. We are interested in funding work that expands the study of disease mechanisms among CACNA1A variants to accelerate therapeutic development.
- Variant Classification. In addition to functional characterization of variants, there is a need for a more comprehensive method of classifying CACNA1A variants. We seek

someone with expertise in designing a universal and systematic method for variant classification and identifying diverse but relevant criteria for incorporating data from sources including computational predictive models, cellular electrophysiology, and animal models, especially for a calcium ion channelopathy.

In addition, applicants are encouraged to collaborate with existing CACNA1A researchers and to leverage existing disease models and data (animal models, patient-derived cell models in our CombinedBrain biobank, CACNA1A Natural History Study, Citizen data, etc.) This grant is made possible by Team CACNA1A and the CACNA1A Foundation.

**5) 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, leukodystrophy, or neurodegeneration in CADASIL are not clear. Moreover, clinical markers that can be used to assess treatment efficacy are sparse.

cureCADASIL Association seeks applications for **one \$109,856 grant** for research that will advance the understanding of mechanisms of the disease or clinical phenotyping that will facilitate future treatment trials (e.g. 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. This grant is made possible by Team CADASIL and cureCADASIL Association.

**6) 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). **One \$63,270 grant is offered.**

- 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. 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>

**7) CDKL5 Deficiency Disorder (CDD):** This funding opportunity will focus on proposals with a strong likelihood of future federal funding to improve the health of patients affected by CDKL5 Deficiency Disorder (CDD). **One \$60,960 grant is available.** Examples of desirable research priorities include, but are not limited to:

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
3. Research to enhance our understanding of the cellular, molecular, genetic, and systems-level mechanisms contributing to the pathogenesis of CDD, facilitating the continued investigation of disease-modifying strategies.
4. Research aimed at improving CDD disease models (e.g., cell-based, tissue-based, or animal models) in an effort to assess the potential efficacy of therapeutic interventions against phenotypic deficits in the CDD patient population.

The International Foundation for CDKL5 Research encourages collaborative research that leverages existing resources (e.g., animal models, iPSCs, ICDD registry data). This grant is made possible by Team "CDKL5 Riding for a Cure" and the International Foundation for CDKL5 Research.

**8) Choroideremia (CHM):** One **\$64,735 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.

**9) Complex Lymphatic Anomalies (CLA):** We are soliciting research applications for a **\$60,679 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), Team LGD Alliance Europe 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](mailto:research@congenitalhi.org) if you would like to discuss your proposed project. **One grant of \$70,200** is made possible by Team CHIbra and Congenital Hyperinsulinism International.

### **11) Congenital Muscular Dystrophy (CMD)**

#### **Funding: Two \$70,133 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 the COL6-related dystrophy (COL6-RD) subtype of congenital muscular dystrophy (CMD).

Areas of Interest: Including but not limited to,

1. understanding the pathomechanisms 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.

**12) 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 \$83,282 grant 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

**13) Dup15q Syndrome** is a clinically identifiable neurodevelopmental disorder that occurs when a key portion of chromosome 15 is duplicated at the 12.1-13.2 region. The syndrome, a leading genetic causes of autism, also leads to hypotonia, GI issues, epilepsy, motor and speech delays and intellectual disability. There are currently no approved therapeutics targeted at Dup15q syndrome despite a significant unmet medical need. We are soliciting applications for **one \$47,158 grant** that supports work towards a potential therapeutic.

While we are keeping the opportunity broad in scope, preference will be given to awards that focus on three areas:

- A formalized Natural History study that will support clinical trials and the creation of key outcome measures that can be leveraged in clinical trial design
- Model systems that explore any aspect of the pathophysiology of the syndrome to include, but not limited to, identification/confirmation of the role of the duplicated genes, genotype/phenotype correlation, biomarkers
- Exploration of novel approaches to therapeutic development; ASOs, siRNA, small molecule inhibitors of the enzyme, PROTACs

**14) 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 Gs $\alpha$  cAMP signaling pathway. Skeletal manifestations include bone pain, fractures, deformity, and osteomalacia/rickets.

- **Four grants are available at \$40,321 each.**
- **A project may be considered for up to \$80,642 in funding if the researcher has an outstanding project and submits two proposals for \$40,321 each.**

Studies focusing on the pathogenesis of FD/MAS or clinical studies to address any 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 Gs $\alpha$ , PKA, Wnt, or other signaling pathways; and studies of the pathophysiology, such as the role of RANKL, IL6, 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 a previous grant(s) and must describe how the new proposal is distinct or extends from the previous funding. Projects that feature collaborations across multiple institutions are encouraged.

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

**15) Glucose Transporter Type 1 Deficiency Syndrome (Glut1DS): One \$61,901 grant is available** to support a project that will lead to a deeper understanding of this disease so it can be diagnosed earlier and treated more easily and more effectively.

Glut1 Deficiency Syndrome is a rare genetic condition that impairs brain metabolism. It is caused by variants in the *slc2a1* gene, which encodes the glucose transporter protein type 1 (GLUT1). GLUT1 is the principal transporter of glucose and also moves other important sugars across the blood-brain barrier. Impaired glucose transport associated with Glut1 Deficiency creates a metabolic crisis in the brain and often results in a range of neurological symptoms such as seizures, speech and movement disorders, and developmental delays. Not all patients experience all symptoms, and there is a wide spectrum of severity. Symptoms may change and evolve over time.

Potential areas of emphasis for this RFA 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 as metabolic therapies; basic science to better understand underlying disease mechanism; identification of new biomarkers and outcome measures to be used in future clinical studies; and understanding how the involvement of GLUT1 in different diseases can lead to the development of better treatments for Glut1 Deficiency. Projects with novel concepts and collaborative/team approaches are especially encouraged.

This grant is made possible by the generous support of the Orphan Disease Center, Miles for Millie, Team Glut1, and the Glut1 Deficiency Foundation.

**16) The KCNT1 Epilepsy Foundation** is seeking proposals for a **\$70,619 award** for a translational research project focused on the development of therapies for KCNT1 disorders. The goal of this grant is to support research that can lead to the development of effective treatments for KCNT1 disorders. The project should focus on one or more of the following areas:

- Define the non-conductance functions of KCNT1 as a way to further disease understanding and find alternative treatment targets. Proposals should emphasize therapeutic potential.
- Understand cellular mechanisms, splice variants, and gene modifiers that potentially influence KCNT1 and could serve as a potential therapeutic target. Proposals should emphasize therapeutic potential.
- Preclinical testing of FDA-approved drugs previously identified in repurposing screens: This may include in vitro and/or in vivo work, to investigate efficacy for multiple patient mutations. The proposal should state why additional preclinical testing is necessary before patients are treated.
- Organization and execution of clinical trials for drugs already identified in repurposing screens: The proposal should include details of the clinical trials design, recruitment strategy, inclusion and exclusion criteria, primary and secondary outcomes, and statistical analysis plan.
- Validation of assessment tools in KCNT1 patients for use in clinical trial outcome measures, especially non-seizure outcomes: The proposal should include details of the assessment tools to be validated, the validation process, and the expected outcomes.
- Investigation of symptoms/pathophysiology outside of the brain, such as the role of KCNT1 in the lungs or cardiac symptoms. Proposals may include clinical studies or translational lab research.
- Development of gene therapies: The proposal should include details of the gene therapy approach, preclinical data, and the proposed plan for clinical translation.

Applicants are encouraged to collaborate with existing KCNT1 researchers and to leverage existing disease models and data (e.g., animal models, Citizen data, registry data, biobank, cell lines, etc.) and should include a statement on resource sharing in their proposal. This grant is made possible by the KCNT1 Epilepsy Foundation, its generous supporters, and the Orphan Disease Center.

**17) 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. There are treatments that decrease uric acid buildup which reduces renal and skeletal symptoms (including kidney stones and gout) but have no effect on the neurological aspects of LNS.

**One \$68,367 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.

**18) Lymphangi leiomyomatosis (LAM): One \$71,051 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 the 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 act as endpoints 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.

**19) Mucopolysaccharidosis (MPS) and Mucopolipidosis II/III (ML II/III):** These disorders comprise a group of 14 different lysosomal storage diseases, each a monogenic disease due to a specific single enzyme defect, but all of which lead to multiorgan pathologies due to either primary glycosaminoglycan storage or other abnormal metabolic changes. Neuropathology and/or connective tissue pathology, are primary features of these disorders. We seek applications directed to treating the life limiting central nervous system manifestations, cardio-respiratory disease, and/or bone and connective tissue issues. **One grant of \$57,645** is made possible by Team MPS and the National MPS Society.

**20) Mucopolysaccharidosis (MPS I) Gene Spotlight: a \$60,655 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): One \$100,621 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.

**22) Niemann Pick Type C (NPC): One \$40,140 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) Pitt Hopkins Syndrome (PTHS): One \$73,473 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.

**24) 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 \$60,755 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.

**25) Ring chromosome 14 syndrome** is a rare chromosomal abnormality where the 14th chromosome forms a ring like structure r(14). The disorder is characterized by early onset refractory epilepsy, intellectual disability, autism spectrum disorder and a number of diverse health issues. There is a heavy health burden associated with Ring14 which affects the whole the family.

**One \$67,897 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 Ring Chromosome 14 and related disorders. Potential topics of interest may include but are not limited to: open source resource development (cell lines – in particular, direct

differentiated neuronal cell lines as iPSCs are unstable for ring chromosomes, assays, functional studies, etc.), basic science to understand disease mechanisms relevant to Ring Chromosome 14, clinical studies to better define the national history, and translational studies. Preference may be given to novel concepts and collaborative/team approaches.

## **26) SCN2A:** The FamilieSCN2A Foundation

**One \$61,280 grant** 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 innovative projects that will advance development of therapeutic treatments for SCN2A-related disorders (SRDs).

Specific areas of interest include but are not limited to:

1. Exploring safe drug options for treating SCN2A-related disorders, such as repurposing FDA-approved drugs or investigating previously shelved drugs with established clinical safety records.
2. discovery and validation of novel biomarkers for SCN2A-related disorders
3. Discovery of compensatory mechanisms that arise due to SCN2A mutations in development and evaluation of their therapeutic potential
4. Evaluation of mechanisms that lead to phenotypic variability within SCN2A variants.
  - A. Screens for genetic modifiers of the SCN2A lof or gof phenotypes
  - B. Characterization of autonomic dysfunction in SCN2A animal models (if possible - not sure)
  - C. Preclinical efficacy and safety study of any therapeutic (repurposed, "shelved" or novel) in SCN2A animal model or iPSCs

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.)

**27) 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 \$88,740 grant 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

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 or COMBINEDBrain biorepositories, etc.) to assess therapeutic impact. This grant is made possible by Team SETBP1Strong and SETBP1 Society.

**28) STXBP1 Encephalopathy: Two \$75,460 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, which may arise from multi-omics interrogations.
2. Determining the trajectory of STXBP1 disorders from pediatric to adult presentations.
3. Understanding pathomechanisms and genotype-phenotype relationships of STXBP1 disorders. This may include the development of novel murine or iPSC-based models to determine pathomechanisms of missense variants.
4. Developing or advancing novel therapeutic approaches to correct STXBP1 disorders, including the repurposing of FDA-approved drugs based on mechanistic identification.

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

**29) SYNGAP1-related intellectual disability:** Requests research proposals to advance research that supports therapeutic development for SYNGAP1 disorders. Projects addressing any stage of pre-clinical to clinical development will be considered. **One \$61,222 grant available.** 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 SYNGAP1 disorders from pediatric to adult presentations.
3. Understanding pathomechanisms and genotype-phenotype relationships of SYNGAP1 disorders, including a focus on variants of unknown significance (VUS).
4. Developing or advancing therapeutic approaches to correct SYNGAP1 disorders, including the repurposing of FDA-approved drugs.

**30) TBC1D24: One \$86,962 Grant Available**

Focus Areas: TBC1D24 gene mutation variants, related seizure research, related symptom research; other topics welcome.

The TBC1D24 Foundation, with funding from generous donors, is accepting applications 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. We welcome questions, comments, ideas, and of course, completed applications.

We appreciate your interest and efforts in furthering understanding of the TBC1D24 gene mutation and the impact it will have on our families.

Research Objectives: The TBC1D24 Foundation 2023 Grant is being established 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.

Support: We aim to partner with you in research by providing access to patient data (where available) and to our board members.

**31) Telomere Biology Disorders, including Dyskeratosis Congenita: One \$63,000 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.

**32) 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.

Among the many symptoms affecting an individual with ZARD, neuromuscular manifestations (impaired movement, mobility and orthopedic disorders) are consistently ranked within the ZARD community as the most impactful in terms of diminishing quality of life.

There is currently very limited understanding on the role of the ZC4H2 gene and its protein in the development and function of the human muscular system. The focus for this grant opportunity is to understand the impact of pathogenic ZC4H2 variants in the physiology and function of the human skeletal muscles.

For this purpose, **one grant of \$61,815**, will be offered to research projects on:

Studies on the pathology, physiology, morphology, anatomy and neural activation of human skeletal muscles affected by pathogenic mutations of the ZC4H2 gene: the studies may involve

in-vivo, in-situ and/or in-vitro human materials and in-vivo and in-vitro animal materials. The in-situ and in-vivo human studies should not be invasive.

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.org](mailto:info@zc4h2foundation.org)) with any questions about these resources.

This grant is made possible by the ZC4H2 Research Foundation and the Orphan Disease Center (under the Million Dollar Bike Ride initiative).

### **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; our expert reviewers sign a CDA in advance of the review process. 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 upon request.

**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](mailto:scharle@upenn.edu).