

## **41. Data Management and Coordinating Center Summary**

### **Principal Investigator: Jeffrey Krischer, PhD**

The Data Management and Coordinating Center supports the Rare Diseases Clinical Research Network through the provision of technologies, tools and expertise:

- a. A public website that serves as a portal for the rare diseases community, including public and health care professionals, to provide information on research on rare diseases, consortium activities, practice guidelines and RDCRN protocols and sites. The public website is available in seven languages.
- b. A contact registry to permit the registration of individuals who self-select for their interest in participating in clinical research. The Contact Registry provides ongoing contact with over 24,671 individuals, alerting them when new studies and sites are available.
- c. A secure, password-protected Members' Website for 4,043 Consortium members from over 270 institutions that includes announcements, calendars, electronic case report forms and protocol management tools including systems for adverse event reporting and monitoring, research pharmacy drug management, biospecimen tracking, image processing, family history data collection and pedigree generation, desktop videoconferencing, and automated reporting.
- d. Remote monitoring tools including an Electronic Regulatory Binder and Electronic Site Delegation Log that replace the functionality and need for paper regulatory binders and site delegation logs.
- e. Mobile patient diary applications for the collection of medication adherence, diet and symptoms providing real time data collection and access and replacing the need for paper patient diary logs.
- f. Collaboration on study design and implementation for 127 actively accruing studies that have over 31,750 enrolled participants.
- g. Expertise and guidance for regulatory issues including HIPAA Privacy Rule, Global Data Protection Regulation (GDPR), Certificate of Confidentiality, IRB submissions, IND submissions, informed consent content and process, confidentiality agreements, Good Clinical Practice, data compliance, adverse event reporting, data sharing, etc.
- h. Auditing (review 10% of cases and select data points conducted within 18 months of first accrual, then annually thereafter for interventional studies and within 3 years thereafter for observational studies) and monitoring (review all subjects accrued and all data points every 3 months) of Network protocols. To date, the DMCC has conducted 1,299 protocol audits and 190 monitoring visits.
- i. OneIRB, an implementation model for use of a Single IRB of Record for multi-site studies. The OneIRB model includes a coordinating center function to reduce the burden on RDN investigators and study staff, as well as tools to support both study teams and IRBs. These tools include an IT platform to assist sites with sIRB coordination, reliance agreement template, standard operating procedures (SOPs) and local context review form.
- j. Collaboration and co-authorship of 145 scientific presentations and publications.
- k. Training (in-person and web-based) for consortia investigators and clinical research associates to ensure the high quality and completeness of submitted data and protocol compliance.
- l. Promulgation of data standards that provide consistency across research protocols and diseases to enhance the value of the research data collected.
- m. Database of clinical and laboratory findings that permits a close linkage between biological specimens and a well-characterized clinically followed population encoding 60,131,653 data points, photographs, CT scans, PET scans, x-ray images and videos.
- n. RDCRN Social Media presence on Facebook and Twitter including posts for protocol announcements, new site announcements, and consortium accomplishments. The RDCRN Facebook page currently has over 759 followers and the RDCRN Twitter account has over 4,254 followers.
- o. Direct-to-patient recruitment and referral of patients on social media which includes online screening, site selection and site referral tools.

Selected publications:

- Richesson RL, Krischer J. **Data standards in clinical research: gaps, overlaps, challenges and future directions.** *J. Am. Med. Inform. Assoc.* Nov-Dec 2007;14(6):687-696. PMID: 17712081, PMCID: PMC2213488
- Richesson RL, Malloy JF, Paulus K, Cuthbertson D, Krischer JP. **An automated standardized system for managing adverse events in clinical research networks.** *Drug Saf.* 2008;31(10):807-822. PMID: 18759506
- Richesson RL, Fung KW, Krischer JP. **Heterogeneous but "standard" coding systems for adverse events: Issues in achieving interoperability between apples and oranges.** *Contemp. Clin. Trials.* Sep 2008;29(5):635-645. PMID: 18406213, PMCID: PMC2575842
- Andrews JE, Patrick TB, Richesson RL, Brown H, Krischer JP. **Comparing heterogeneous SNOMED CT coding of clinical research concepts by examining normalized expressions.** *J. Biomed. Inform.* Dec 2008;41(6):1062-1069. PMID: 18328789, PMCID: PMC2605270
- Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, Nguyen T, Paulus K, Merkel PA. **Clinical research for rare disease: opportunities, challenges, and solutions.** *Mol. Genet. Metab.* Jan 2009;96(1):20-26. PMID: 19013090, PMCID: PMC3134795
- Richesson RL, Lee HS, Cuthbertson D, Lloyd J, Young K, Krischer JP. **An automated communication system in a contact registry for persons with rare diseases: scalable tools for identifying and recruiting clinical research participants.** *Contemp. Clin. Trials.* Jan 2009;30(1):55-62. PMID: 18804556, PMCID: PMC2640948
- Richesson RL, Smith SB, Malloy J, Krischer JP. **Achieving standardized medication data in clinical research studies: two approaches and applications for implementing RxNorm.** *J. Med. Syst.* Aug 2010;34(4):651-657. PMID: 20703919, PMCID: PMC2977947
- Richesson RL, Nadkarni P. **Data standards for clinical research data collection forms: current status and challenges.** *J. Am. Med. Inform. Assoc.* May 1 2011;18(3):341-346. PMID: 21486890, PMCID: PMC3078665
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- Krischer JP, Gopal-Srivastava R, Groft SC, Eckstein DJ. **The Rare Diseases Clinical Research Network's Organization and Approach to Observational Research and Health Outcomes Research.** *J. Gen. Intern. Med.* Aug 2014;29 Suppl 3:739-744. PMID: 25029976, PMCID: PMC4124127
- Merkel PA, Manion M, Gopal-Srivastava R, et al. **The partnership of patient advocacy groups and clinical investigators in the rare diseases clinical research network.** *Orphanet J. Rare Dis.* 2016;11(1):66. PMID: 27194034, PMCID: PMC4870759
- Tamura RN, Krischer JP, Pagnoux C, et al. **A small n sequential multiple assignment randomized trial design for use in rare disease research.** *Contemp. Clin. Trials.* Jan 2016;46:48-51. PMID: 26586608, PMCID: PMC4695231
- Krischer J, Cronholm PF, Burroughs C, et al. **Experience With Direct-to-Patient Recruitment for Enrollment Into a Clinical Trial in a Rare Disease: A Web-Based Study.** *J Med Internet Res.* 2017;19(2):e50. PMID: 28246067, PMCID: PMC5350442



## **42. Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) Clinical Research Consortium**

**Principal Investigators: Adam L. Boxer, MD, PhD. and Howard J. Rosen, MD**

[www.RareDiseasesNetwork.org/ARTFL](http://www.RareDiseasesNetwork.org/ARTFL)

The Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) consortium is a multi-center clinical research infrastructure for the study of Frontotemporal Lobar Degeneration syndromes. ARTFL was granted funding from the NIH through The National Center for Advancing Translational Sciences (NCATS) and the National Institute of Neurological Disorders and Stroke (NINDS), U54NS092089-02.

ARTFL includes 18 sites for clinical evaluation in the United States and Canada.

### **The Specific Aims of ARTFL in the first 5-year grant cycle include:**

1. To build a FTLD clinical trials network to facilitate the design and conduct of clinical trials in FTLD.
2. To determine the prevalence and clinical, genetic and systemic inflammatory cytokine profile of sporadic FTLD syndromes (Project 1).
3. To determine the natural history of presymptomatic f-FTLD (Clinical Dementia Rating [CDR] = 0) and symptomatic (CDR  $\geq$  0.5) f-FTLD over one year, the planned duration of trials of novel therapeutic agents, using novel clinical assessments in all individuals and longitudinal MRI scans sensitive to early disease pathology in presymptomatic gene carriers (Project 2).
4. To obtain pilot data using new tau-specific PET imaging agents in FTLD and other novel FTLD biomarkers and clinical assessment tools that may be employed in future FTLD clinical trials.
5. To train clinical researchers focused on biomarkers and treatment trials in FTLD.

**Diseases under study:** Frontotemporal Dementia (FTD), Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Semantic Variant Primary Progressive Aphasia, FTD with Amyotrophic Lateral Sclerosis (FTD-ALS), Frontotemporal Lobar Degeneration Spectrum disorders

### **Included clinical studies:**

**ARTFL Project 1: Sporadic FTLD Syndromes:** *actively enrolling*; current enrollment **631/650**

**ARTFL Project 2: Familial FTLD Syndromes:** *actively enrolling*; current enrollment **544/700**

### **Pilot Projects:**

**ARTFL Pilot Project: [11C]PBB3 PET imaging of human patients with predicted FTLD-tau and FTLD-TDP pathology.** *Completed*

**ARTFL Pilot Project: Whole exome sequencing to assess for new mutations and phenotype-genotype associations in FTD.** *In data analysis.*

**ARTFL Pilot Project: Communication Bridge: Web-based speech-language therapy for individuals with dementia.** *In data analysis.*

ARTFL has also integrated its infrastructure with the *Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)*, U01AG045390. Data sharing policies are available on the ARTFL website.

### **Training Program:**

The ARTFL Fellowship is an individually tailored training program of up to one year for physician-investigators who have demonstrated an interest in FTLD-spectrum disorders and wish to pursue a period of specialized training with an emphasis on translational and patient-oriented clinical investigation. The fellow must have previous training in behavioral neurology with exposure to FTLD spectrum disorders. The trainee may undertake the fellowship at their home ARTFL study site.

**Number of ARTFL Fellows:** Current: 1, Previous: 3

**Patient Advocacy Groups:** The Bluefield Foundation, The Association for Frontotemporal Degeneration (AFTD), Corticobasal Degeneration Solutions, CurePSP, and the Tau Consortium.

**Additional Funding:**

ARTFL has been successful in obtaining funding to supplement the RDCRN. Additional support for ARTFL projects comes from grants from The Bluefield Foundation and the Tau Consortium. ARTFL also obtained an NIH administrative supplement to increase biospecimen collection.





### **43. Autonomic Disorders Consortium (ARD)** **Principal Investigator: Italo Biaggioni, MD**

The Autonomic Rare Diseases Clinical Research Consortium (ARDCRC) brings together the five leading national referral centers for the research and treatment of autonomic disorders:

- Vanderbilt University Autonomic Dysfunction Center (Italo Biaggioni)
- Division of Autonomic Nerve Disorders, Mayo Clinic (Phillip A. Low and Wolfgang Singer)
- Dysautonomia Center at New York University (Horacio Kaufmann)
- Center for Autonomic and Peripheral Nerve Disorders at Beth Israel Deaconess Medical Center/Harvard Medical School (Roy Freeman)
- Clinical Neurocardiology Section of NINDS (David Goldstein).

The ARDCRC also has 17 collaborating sites, including 8 outside the USA.

We focus on **primary neurodegenerative autonomic disorders characterized by abnormal deposits of alpha-synuclein:**

- Multiple System Atrophy (MSA)
- Pure Autonomic Failure (PAF)
- Parkinson's Disease (PD) with autonomic impairment
- Dementia with Lewy Bodies (DLB) with autonomic impairment

The **Specific Aims of the ARDCRC** are to:

1. Develop the criteria to diagnose these conditions early in the disease process
2. Validate diagnostic criteria that differentiate between synucleinopathies and serve as predictors of phenoconversion
3. Define rate of progression of disease by identification and validation of biomarkers of disease severity
4. Explore therapies that will target disabling autonomic cardiovascular abnormalities and improve the quality of life of our patients
5. Continue to support Pilot & Feasibility studies that strengthen the overall goals of this Consortium
6. Attract and train the next generation of autonomic investigators

#### **Longitudinal Studies:**

**The Natural History of Synucleinopathies (RDCRN #6106).** A prospective observational longitudinal study to identify the natural history of synucleinopathies and identify predictive biomarkers of widespread central nervous system involvement. Current enrollment 956

**The Natural History of Synucleinopathies (skin nerve fiber biomarker) (RDCRN #6109).** A prospective, observational longitudinal study to determine the utility of the cutaneous phosphorylated/total alpha-synuclein ratio as a biomarker across the different alpha-synucleinopathy neurodegenerative disorders.

#### **Clinical Trials:**

**Intrathecal Autologous Mesenchymal Stem Cell Therapy in Multiple System Atrophy.** A phase I/II single-site dose-escalation study of intrathecal injection of autologous mesenchymal stromal cells (MSC) as a potential disease-modifying therapy in MSA. This trial showed not only adequate safety and tolerability but it also provided compelling efficacy signals with a lower rate of disease progression in MSC-treated patients.

**The Effects of Midodrine and Droxidopa on Splanchnic Capacitance in Autonomic Failure (RDCRN #6110).**

Orthostatic hypotension is the most disabling feature of synucleinopathies. Previous treatment efforts have focused on increasing upright blood pressure through arterial vasoconstriction. This study looks at a novel approach of reducing splanchnic capacitance to restore venous return and selectively improve upright blood pressure.

#### **Pilot Studies:**

**Vagal Stimulation in Postural Tachycardia Syndrome (POTS)-The Autonomic Inflammatory Reflex (RDCRN #6111).**

A randomized, interventional, double-blind, crossover study to compare the effects of transdermal vagal stimulation with that of sham stimulation and peripheral or central cholinesterase inhibition with that of each intervention alone on cardiovagal modulation in patients with Postural Tachycardia Syndrome (POTS). Improvement of parasympathetic function is a new approach to the treatment of patients with POTS.

**The ARDCRC Training Program** is designed to educate trainees on the difficulties inherent in rare disease clinical research and on ways to address these challenges. The Program is comprised of four major components: 1) a mentored research apprenticeship, 2) participation in a didactic curriculum, 3) participation in multidisciplinary conferences in

autonomic physiology and pathology, and 4) mentorship in career development. Members of the ARDCRC have had ~45 trainees since the inception of this program.

We have been fortunate to have various **patient advocacy groups (PAGs)** support us by promoting our research, educating patients and the community, and supplying materials. PAGs associated with the ADCRC actively promote autonomic research through research grants and travel awards to young investigators. We acknowledge that this Consortium will not succeed without regular interactions with the MSA Coalition, Dysautonomia Foundation, Dysautonomia International and others.

### Recent ARDCRC Accomplishments

- **Natural History Study.** We have shown that patients with synucleinopathies who present with an isolated peripheral autonomic neuropathy (pure autonomic failure) phenoconvert to disorders with CNS involvement (dementia of Lewy bodies, Parkinson's disease and MSA). We found that the presence of REM behavior disorder, anosmia and baseline catecholamine levels predict phenoconversion. We are looking now at other biological and imaging biomarkers, which will eventually allow us to target disease progression earlier.
- **Delaying progression of disease.** Current treatments for MSA patients focus on controlling symptoms, and none of these has halted or reversed the rapid disease progression. Intrathecal administration of adipose-derived MSCs in a single-site study, however, has demonstrated that the rate of progression, as measured with the Unified MSA Rating Scale, was markedly lower in treated patients compared to a matched control patient population.
- **Improving quality of life.** Orthostatic hypotension is the most disabling feature of synucleinopathies. Previous treatment efforts have focused on increasing upright blood pressure through arterial vasoconstriction. The fall in blood pressure on standing, however, is due to splanchnic venous pooling with reduced venous return and cardiac output. In an innovative approach to targeting this unrestrained venous pooling, we demonstrated that an automated abdominal binder that inflates to a sustained servo-controlled compression level of 40 mmHg, is as effective as pressor agents in maintaining blood pressure.
- **Discovery of new diseases.** The careful and systematic phenotyping we perform as part of this consortium has resulted in the discovery of new diseases that affect the synthesis of norepinephrine.
  - **CYB561 Deficiency.** *CYB561* encodes an enzyme that regenerates a critical co-factor for dopamine beta hydroxylase (DBH) function, and deficiency of the CYB561 protein interrupts norepinephrine synthesis. These patients lack norepinephrine from birth, but the enzymatic defect can be bypassed pharmacologically with droxidopa, which is converted to norepinephrine through dopa-decarboxylase.
  - **Familial Autonomic Ganglionopathy,** due to a mutation of the *CHRNA3* gene encoding the neuronal nicotinic receptor that mediates neurotransmission in autonomic ganglia. This defect interrupts both sympathetic and parasympathetic function, giving a clinical picture of a pandysautonomia.
- **Therapies and drug development in collaboration with industry.**
  - **Droxidopa.** We discovered DBH deficiency in the 1980s and found that droxidopa bypasses the enzymatic defect, being converted to norepinephrine by dopa-decarboxylase, the same enzyme that converts dopa to dopamine in the treatment of Parkinson's disease. More recently we played a role in the drug development and FDA approval of droxidopa for the treatment of orthostatic hypotension. This is an example of how research in rare diseases can impact common diseases.
  - **Norepinephrine Transporter (NET) blockers.** We previously discovered congenital NET deficiency as a cause of POTS. NET is responsible for the synaptic reuptake of norepinephrine, and NET deficiency potentiates norepinephrine activity. This led Cyndia Shibao, one of our trainees, to use the NET inhibitor atomoxetine for the treatment of orthostatic hypotension. She has since put together a phase 3 clinical trial funded by the FDA orphan drug program to repurpose atomoxetine for this new indication. We are also collaborating with drug companies interested in developing their own NET inhibitors for this indication. We designed and participated in a Phase II trial of a NET inhibitor for the treatment of orthostatic hypotension, and a Phase III will start shortly.





#### **44. Brain Vascular Malformations Consortium (BVMC)** **PI: Michael T. Lawton, MD; Co-PI: Helen Kim, PhD**

##### **Major Goals:**

The Brain Vascular Malformation Consortium focuses on three relatively rare vascular malformations: Familial Cerebral Cavernous Malformation (CCM), Sturge-Weber Syndrome (SWS), and Hereditary Hemorrhagic Telangiectasia (HHT). Each is poorly understood in terms of biological mechanisms, resource intensive to manage effectively, and has high probability of serious neurological morbidity, such as hemorrhage, seizures and focal neurological deficits. All three diseases share a common biological theme: a brain vascular phenotype based on failure of the normal physiological mechanisms of blood vessel formation or maintenance. Recent data also suggests that the three diseases share commonalities in their molecular signaling pathways. Each disease is characterized by a wide spectrum of phenotypes, for which biological risk factors are poorly understood. The identification of these risk factors would be of immediate significance for patient surveillance and for optimizing management. Further, although there are no specific medical therapies for these diseases, appropriate treatment trials will require biomarkers to risk stratify patients for selection and surrogate outcomes. In our original project period, we established information-rich patient registries for all three diseases, and made significant progress towards the identification of imaging, genetic, and biochemical biomarkers associated with specific clinical outcomes. In the second project period, we have expanded and continued recruitment and follow-up of patients with new specific aims as described below.

##### **Diseases under Study:**

Familial Cavernous Malformations (CCM)-Common Hispanic Mutation

Sturge-Weber Syndrome (SWS)-Leptomenigeal Angiomatosis

Hereditary Hemorrhagic Telangiectasia (HHT) associated Brain Arteriovenous Malformation (BAVM)

##### **Longitudinal Studies**

**Project 1 (6201): Modifiers of disease severity and progression in cerebral cavernous malformation (CCM).** The overall goal of Project 1 is to understand the natural history and identify modifiers of disease severity and progression in familial CCM1 disease. **Aim 1:** To continue longitudinal follow-up of BVMC enrolled CCM1 cases with the ‘Common Hispanic Mutation (CHM)’ to ascertain outcomes events and document lesion growth and burden. **Aim 2:** To build on our existing genome-wide association data to investigate the role of inflammation in a second replication cohort of familial CCM1 patients, expanding to all mutation carriers in CCM1. **Aim 3:** To assess changes in lesion permeability using dynamic-contrast enhanced permeability imaging. Cumulative enrollment: 483

**Progress:** We have identified several genetic modifiers in inflammatory and immune response genes associated with disease severity phenotypes in CCM. In addition, a collaboration with the University of Pennsylvania resulted in a recent Nature publication that established the gut microbiome as a risk factor for CCM brain lesion development in the mouse model, opening a potential new avenue for human study and ways to reduce lesion formation. Active collaborations are ongoing with our advocacy group, the Angioma Alliance, with successful publication of clinical guidelines and designation of the University of New Mexico and University of California-San Francisco as Angioma Alliance Centers of Excellence in CCM care and research. We have expanded the clinical phenotype of CCM1 with the finding of adrenal calcifications, and have been successful in using a trainee project to develop an automated counting algorithm for establishing lesion burden and longitudinal changes in disease burden. Two new related NIH grants were funded that utilize BVMC Project 1 data and investigators.

**Project 2 (6202 and 6208): Innovative approaches to gauge progression of Sturge-Weber syndrome (SWS).** The overall goal of Project 2 is to understand the cerebral components of SWS, which is leptomenigeal angiomatosis, a poorly understood vascular proliferative condition that results in neurological morbidity. **Aim 1:** To examine vascular remodeling of the SWS birthmark as it relates to neurologic status and vascular factors. **Aim 2:** To determine the vascular remodeling of the deep draining intraparenchymal vessels as it relates to SWS neurologic status. **Aim 3:** To investigate the role of a somatic mutation causing SWS discovered during the last cycle (p.R183Q GNAQ) in phosphorylation of pathway proteins and angiogenesis factors in SWS tissue. Cumulative enrollment: 466

**Progress:** We found that the extent of the port wine birthmark may be a risk factor for severe neurological symptoms, that genetic factors identified through family history may contribute to common comorbidities, and that younger age of seizure onset is associated with more severe brain involvement. The ongoing sirolimus pilot trial (6209) involves a new collaboration with Pfizer who is providing study drug. New clinical research data obtained through the consortia is being used to design a multi-center clinical trial for presymptomatic treatment of infants with SWS; this trial is currently seeking funding. Data

from the Year 5 BVMC pilot project served as the foundation of a new funded NIH grant proposal to functionally characterize the GNAQ somatic mutation causing SWS. The Sturge-Weber Foundation, advocacy group, has expanded their clinical care network of centers that may be involved in the BVMC as new recruitment sites.

**Project 3 (6203): Cerebral hemorrhage risk in hereditary hemorrhagic telangiectasia (HHT).** The overall goal of Project 3 is to identify risk factors for hemorrhage from brain AVMs in HHT and provide better empirical data for informed clinical decision-making in HHT. Aim1: To characterize the risk of hemorrhage in HHT patients with brain AVM, and subgroups, leveraging our established HHT recruitment network to expand our HHT cohort. Aim 2: To investigate the hypothesis that multiple genetic alterations in the known HHT genes and other genes in the TGFB/BMP9 signaling pathway will modulate disease severity in HHT. Aim 3: To investigate the role of inflammation in brain AVM rupture in HHT using vessel wall imaging. Cumulative enrollment: 1624

Progress: We have continued to leverage our 6203 dataset to report outcomes of surgical and radiosurgical management of BAVMs in HHT, and have recently published the largest surgical series to date of HHT patients with BAVMs. HHT BAVM patients treated surgically had long-term functional outcomes comparable to nonsurgical/observational therapy with few unfavorable outcomes, suggesting surgical resection as a reasonable management option. Additionally, Spetzler-Martin grading does not appear to be a useful pre-operative predictive tool in this population, indicating that other predictive tools are needed. We also reported the prevalence and predictors of anemia in HHT, a first in the HHT field. Finally, we showed that multiple genetic hits to the TGFβ/BMP9 signaling pathway can modify disease severity in HHT. We found that a polymorphism in the ACVRL1-IVS3-35A>G was associated with organ AVM in ENG mutation carriers. Project 3 investigators were successful in obtaining DOD funding to study disease mechanism to new therapies in HHT.

### Pilot Studies

1. **6205**: Permeability MRI in Cerebral Cavernous Malformations Type 1 in New Mexico: Effects of Statins (PI: Morrison and Hart). Completed enrollment.
2. **6204**: Establishing reliability for Quantitative EEG, Transcranial Doppler, behavioral outcomes and Optical Coherence Tomography in SWS: A first step toward biomarker development (PI: Comi). Completed enrollment.
3. **6207**: Topical Anti-angiogenic Therapy for Telangiectasia in HHT: Proof of Concept (PI: Faughnan). Completed enrollment.
4. **6201 and 6203**: Urine biomarkers of angiogenesis in CCM and HHT (PIs: Morrison and Faughnan). Completed enrollment.
5. **6202**: Cellular characterization of GNAQ activating mutations in Sturge-Web.er syndrome (PI: Marchuk). Completed.
6. **6203**: Investigation of the functional effects of the ALK1-IVS3-35A>G polymorphism associated with sporadic BAVM and HHT AVMs (PIs: Marchuk and Pawlikowska). Completed.
7. **6208**: Trial of Sirolimus for Cognitive Impairments in SWS (PIs: Hammill, Franz, and Comi). Ongoing enrollment.
8. **6209**: Circulating miRNAs as biomarkers for brain VMs in HHT (PIs: Kutryk and Faughnan). Ongoing enrollment.

### Training Program Summary

1. Yasir Khan, MD, Project 1, Modifier Genes in Cerebral Cavernous Malformations
2. Takeo Nishida, MD, Project 3, Cerebral hemorrhage risk in HHT.
3. Eboni Lance, MD, Project 2, Innovative Approaches to gauge progression of Sturge-Weber Syndrome.
4. Helene Choquet, PhD, Project 1, Genetic/non-genetic modifiers influencing severity of familial CCM1
5. Michael J. Golden, MD, Project 1, The Longitudinal Brain Imaging Phenotype in CCM1-CHM
6. Xiaowei Zou, PhD, Project 1, Computer-aided cerebral microbleed detection and segmentation
7. Ali Tayebi-Meybodi, MD, Project 3, Surgical Outcome of AVMs in HHT and Sporadic AVMs
8. Giuseppe A. Latino, MD, Project 3, Diagn. Delays in Rare Disease: Identifying Factors and Strategies
9. Ryan Gill, MD, Project 2, Development of biomarkers for diagnosis & monitoring in Sturge-Weber
10. Sarah Wetzel-Strong, PhD, All Projects, Plasma biomarkers of angiogenesis and inflammation and disease severity phenotypes in familial CCM, HHT and SWS

### Patient Advocacy Groups

There are three advocacy groups involved in the BVMC: Angioma Alliance (Amy Akers), The Sturge-Weber Foundation, (Karen L. Ball), and Cure HHT (Marianne S. Clancy). The advocacy groups are involved in all aspects of BVMC functions and governance, specifically partnering with our Projects to help with overall recruitment.





**45. Brittle Bone Disorders Consortium**  
**Principal Investigator: Brendan Lee, MD, PhD**  
<https://www.rarediseasesnetwork.org/BBD>

The Brittle Bone Disorders Consortium (BBDC) is multi-center initiative focused on increasing our understanding and improving care for rare diseases characterized by bone fragility and fractures. The BBDC is a consortium within the Rare Diseases Clinical Research Network and is composed of 11 clinical sites in the United States and Canada. The BBDC partners with the Osteogenesis Imperfecta Foundation (OIF) to train a broad spectrum of health care providers in the diagnosis and treatment of osteogenesis imperfecta (OI).

**The goals of the Brittle Bone Disorders Consortium are to:**

- Conduct an observational cohort study, where subjects are followed over time gathering clinical, laboratory and radiological data as well as biospecimens
- Conduct a clinical trial to determine safety of the anti-TGF $\beta$  antibody fresolimumab in the treatment of OI
- Establish a patient contact registry
- Discover new biomarkers of disease that correlate with the clinical course and response to interventions
- Work with OI patient advocacy groups to facilitate participation in research.
- Train new, young investigators in the field of OI
- Construct and maintain an electronic website resource with significant information for clinicians, researchers, and patients

**Observational Studies:**

- BBDC 7701: Longitudinal Study of Osteogenesis Imperfecta. This is multidisciplinary investigation of the phenotypic spectrum, disease progression and response to therapies in individuals with dominant and recessive forms of OI. Actively enrolling (838/1000)
  - Scoliosis in growing children – observational study, response to interventions and impact on pulmonary function, physical function and quality of life
  - Vertebral compression fractures in haploinsufficient type I collagen OI – observational study of incidence, progression and effects of bisphosphonates
  - Oral health and impact on quality of life
- BBDC 7704: Dental Malocclusion and Craniofacial Development in OI. This study aims to describe dental malocclusion and craniofacial development in various forms of OI. The enrollment is complete (75/75) and we continue to follow patients longitudinally.
- BBDC 7705: Pregnancy in OI Registry
  - Enrollment complete (100/100). Compelling data on post-partum hemorrhage this survey study is supporting a larger and more in-depth study that is under development.

**Pilot Studies:**

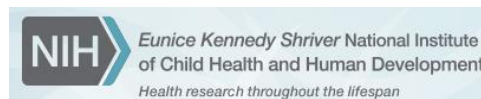
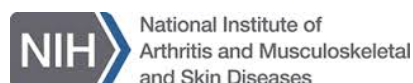
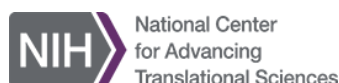
- BBDC 7702: PROMIS for OI patients – assessed the performance of various patient reported outcomes tools in OI compared to the general population.  
Enrollment complete (300/300) and these PRO tools are being incorporated into other studies
- BBDC 7703: Cross-linked Collagen Peptides as a Urinary Biomarker of OI Pathobiology  
Actively enrolling (21/25).

**Clinical Trial:**

- BBDC 7706: Phase I Trial Of Fresolimumab In Severe Osteogenesis Imperfecta (*Multicenter study to evaluate safety of fresolimumab in adults with moderate-to-severe Osteogenesis Imperfecta*)  
Actively enrolling (4/16). The 1<sup>st</sup> stage of the study will be completed by January 2019 with 2<sup>nd</sup> stage recruitment in February 2019.

### **Training Program and Community Outreach:**

- Through the Geisman Fellowship, the OIF has supported the development of 7 trainees interested in rare bone disease research.
- 5 BBDC Scholars were funded through the RDCRN T25 mechanism to foster clinical research in rare diseases. Projects from these Scholars include: Study of the *IFITM5* recurrent mutation and the disease-causing mechanism in OI type V, A Multicenter North American Study of Mobility in Osteogenesis Imperfecta, Effectiveness of OI Outreach, clinical evaluation of gait in the OI community, Musculoskeletal Biomechanics in Osteogenesis Imperfecta (OI), and Gait deviations in children with OI Type 1.
- The Regional Conference Program was implemented in 2014 to bring together OI physicians and researchers with the families they serve. The Regional and National meetings keep the families engaged in research. To date the regional conference attendance numbers are over 1,000 including approximately 100 medical professionals.
- Rare bone research symposium hosted in conjunction with the annual American Society for Bone and Mineral Research meeting attended by over 300 researchers and trainees.





## **46. Consortium of Eosinophilic Gastrointestinal Disease Researchers**

**Principal Investigator: Marc Rothenberg, MD, PhD**

<http://www.rarediseasesnetwork.org/cegir>

The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is a USA-based multi-center clinical research program focused on Eosinophilic Gastrointestinal Diseases (EGIDS), the first and only one in the world. CEGIR was first formed in 2014, as part of the third five-year cycle of Rare Diseases Clinical Research Network (RDCRN) (U54 AI117804) from the NIH through the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Science (NCATS) and funded by collaborative effort of NCATS, National Institute of Allergy and Infectious Diseases (NIAID) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

CEGIR includes 19 sites in the USA and a collaborating site in Europe.

### **The Specific Aims of CEGIR include:**

1. To promote collaboration among centers already focused on studying Eosinophilic Esophagitis (EoE), Eosinophilic Gastritis (EG), Eosinophilic Gastroenteritis (EGE) and Eosinophilic Colitis (EC)
2. To attract, train, and mentor highly qualified future investigators.
3. To collect longitudinal clinical data and biorepository specimens in a standardized way from patients dispersed over wide geographic areas into a centralized database.
4. To develop a better understanding of the disease natural history, developing appropriate diagnostic criteria, discovering and validating predictive biomarkers, validating patient-reported outcome (PRO) metrics and clinical outcome metrics (COMs) that meaningfully report and quantify clinical states, and gaining consensus about the best metrics to be used to monitor disease activity. Identification of these metrics will provide guidance to approval of novel therapeutic agents.
5. To optimize disease therapy, focusing on developing a less restrictive food elimination diet and the positioning of swallowed glucocorticoids (SGCs) for EoE.
6. To provide an opportunity for pilot studies designed to test novel clinical experimental hypotheses.
7. To make the accumulated clinical data available to patients, clinicians, investigators, and the general public via websites and other media, with the ultimate goal of improving the treatment and outcomes of patients with EoE, EG, and EC.
8. To develop a CEGIR website to provide a resource for patients, clinicians, and investigators; to develop a CEGIR Contact Registry for use in clinical research and education of patients.

**Diseases under study:** Eosinophilic Esophagitis, Eosinophilic Gastritis, Eosinophilic Gastroenteritis and Eosinophilic Colitis

### **Longitudinal Studies:**

**CEGIR 7801:** A Prospective, Multicenter Study to Compare and Validate Endoscopic, Histologic, Molecular, and Patient-Reported Outcomes in Pediatric and Adult Patients with EoE, EG and EC (OMEGA), *actively enrolling*, current enrollment 804 subjects of expected 1050.

*Multiple biomarker discovery projects (e.g. microbiome analysis) are linked to OMEGA. The biorepository has 6,189 samples including 658 DNA samples. Clinical Outcome Metrics (COM), histological criteria development, and natural history are being actively examined. In data collection, analysis phases; early findings and publications are emerging.*

### **Clinical Trials:**

**CEGIR 7802:** Six Versus One Food EoE Elimination Diet followed by Swallowed Glucocorticoid Trial (SOFEEED), *actively enrolling*, current enrollment 114/136.

### **Pilot Program**

**CEGIR 7803:** A preliminary open-label trial of losartan potassium in participants with EoE with or without a connective tissue disorder, *actively enrolling*, current enrollment 12/15.

**CEGIR 7804:** Role of the Microbiome in EoE, EG, and EC, *enrollment closed/data analysis & manuscript writing underway*, total enrollment: 416 biopsies and 172 stool samples collected.

**CEGIR 7808:** Use of unsedated transnasal esophagoscopy to monitor dietary management of EoE, *actively enrolling*, current enrollment 3/30.

**CEGIR 7809:** A Prospective Trial of Elemental Diet in Adults with EG & EGE. *Actively enrolling*; current enrollment 9/25.

### **Training Program**

The CEGIR Training Program is a structured training program for physician-investigators who have an interest in EGID and wish to pursue a period of specialized training with an emphasis on translational and patient-oriented clinical investigation. A series of lectures and discussions are provided to trainees. A video/slide-show library has been generated to facilitate training. CEGIR trainees may visit one of the CEGIR study sites for additional training and exposure to EGIDs. CEGIR trainees conduct research in conjunction with local and CEGIR mentors, with CEGIR oversight and guidance; research may involve utilization of CEGIR resources. CEGIR currently has four physician trainees, each at a different location. Overall, a total of 8 physicians have been trained in this program (including the four that are currently in the program).

**CEGIR 7806:** Demographics, clinical characteristics, and pathology of EG and EC in a multi-site cohort; enrollment completed with a total of 381 *patients enrolled across 6 sites*. Currently in the process of analyzing collected data.

**CEGIR 7807:** Validation of online cohort of EGID patients enrolled in CEGIR Contact Registry. *Actively enrolling*; current enrollment 185/1,352.

### **Patient Advocacy Groups:**

The American Partnership for Eosinophilic Disorders (APFED), Campaign Urging Research for Eosinophilic Disorders (CURED), Eosinophilic Family Coalition (EFC) and other patient advocacy groups are actively involved in CEGIR, promoting study participation and recruitment, advising on study design and implementation, participating in weekly teleconferences, attending CEGIR Investigator and Steering Committee meetings and participating in CPAG activities.

### **Additional Funding:**

CEGIR has been successful in obtaining funds from two of its associated PAGs (APFED and CURED), several institutions (e.g. Colorado Children's and Cincinnati Children's) as well as foundations (TIGERS) and leverages grants that utilize CEGIR resources including from NIAID (R01 AI124355).





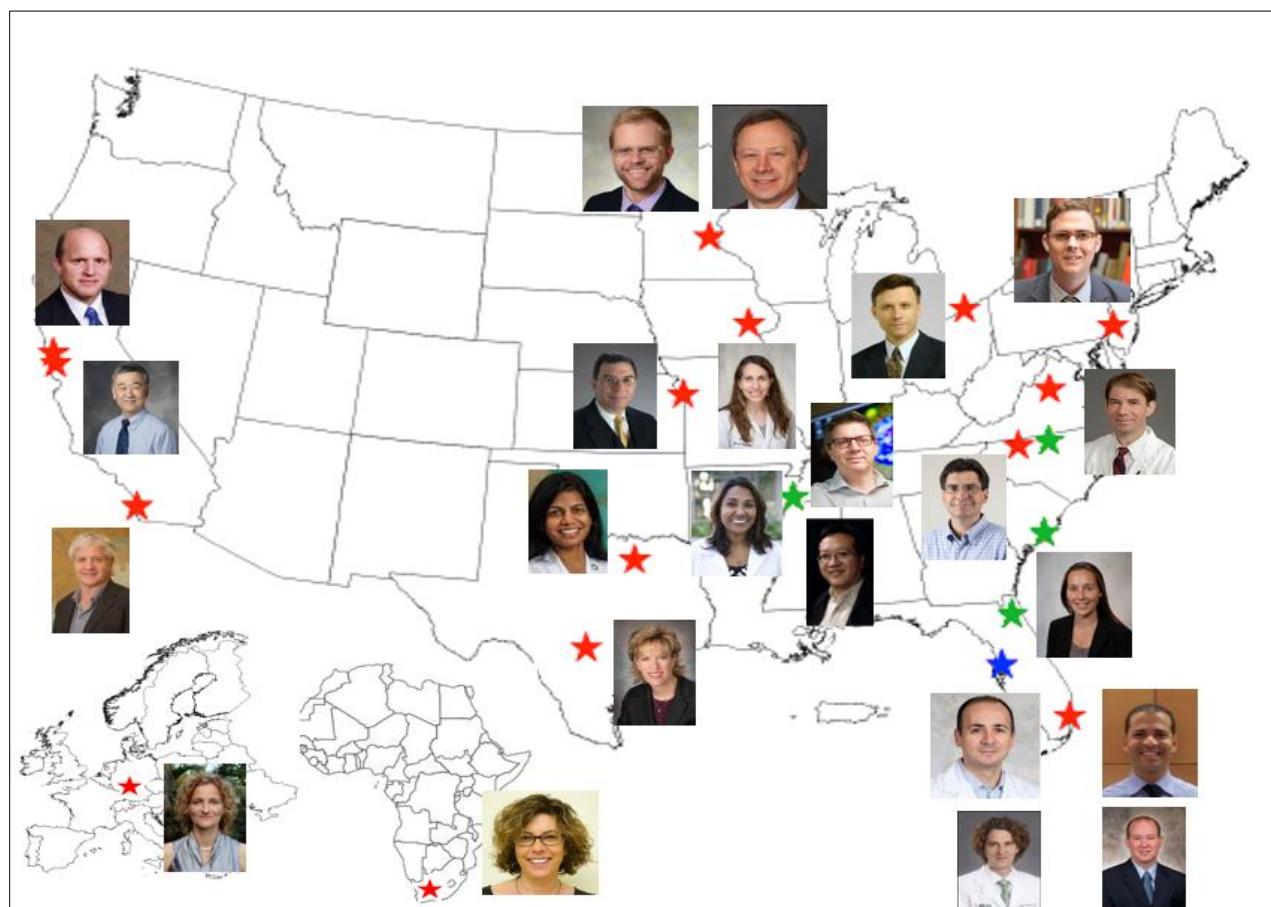
#### **47. Clinical Research in ALS and related disorders for Therapy development Consortium**

**Principal Investigator: Michael Benatar, MD, PhD**

[www.RDCRN.org/CReATe](http://www.RDCRN.org/CReATe)

The goal of the CReATe Consortium is to advance therapeutic development for sporadic and familial forms of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), primary lateral sclerosis (PLS), multisystem proteinopathy (MSP), hereditary spastic paraplegia (HSP), and progressive muscular atrophy (PMA). The CReATe consortium aims to support this goal through study of the relationship between clinical phenotype and underlying genotype, and also through the discovery and development of biomarkers.

The CReATe Consortium currently includes 13 clinical sites in the United States (University of Miami, Kansas University Medical Center, University of California San Diego, California Pacific Medical Center, University of Iowa, University of Virginia, University of Texas Southwestern, University of Texas Health Sciences Center San Antonio, Cleveland Clinic, Wake Forest University, Twin Cities ALS Research Consortium, and Stanford University), as well as two international sites (University of Tübingen in Germany and Cape Town University in South Africa). Dr. Richard Bedlack, MD, PhD (Duke) oversees outreach and advocacy activities. The CReATe Genetics Core is led by Drs. J Paul Taylor, Jinghui Zhang, Gang Wu and Evadnie Rampersaud (St. Jude Children's Hospital) along with Rosa Rademakers (Mayo Clinic Jacksonville) and Drs. Stephan Zuchner and Jake McCauley (University of Miami).





**The specific goals of CReATe are as follows:**

1. **Team Science:** Promote and facilitate collaborative research in the field of ALS and related disorders
2. **Trials Preparation:** Establish a firm foundation for future clinical trials in homogeneous patient populations by defining phenotype (observable characteristics)-genotype (genetic code) relationships in ALS and related disorders
3. **Biomarkers:** Identify and develop biomarkers (both wet and dry) of disease progression that may enhance therapeutic development efforts
4. **Education:** Train clinician-scientists focused on therapy development for people living with ALS and related disorders
5. **Relevance** to other rare diseases: Pioneer an innovative approach to the study of phenotype-genotype relationships that is relevant and applicable to other rare diseases
6. **Outreach/Advocacy:** Engage both the lay- and scientific-community stakeholders in a partnership that will enhance scientific research and therapeutic development for people living with ALS and related disorders
7. **Biorepository:** Develop and maintain a repository of biological samples from phenotypically well-characterized individuals, for use by Consortium members and the broader scientific community, for future biomarker development

**Clinical Projects**

- 8001 – Phenotype, Genotype and Biomarkers (actively enrolling)
- 8002 – Clinical Procedures To Support Research - CAPTURE (actively enrolling)
- 8003 – A Patient Centric Motor Neuron Disease Activities of Daily Living Scale- PADL-ALS (actively enrolling)
- 8004 – Innate Lymphoid Cells in ALS (actively enrolling)
- 8005 – Limited Phenotype DNA Sequencing – LPSeq (ongoing)
- 8006 – CReATe@home (in development)
- 8007 – Study of ALS Reversals- St.A.R. Protocol 2 (actively enrolling)
- 8008 – Biomarkers of axonal degeneration in Hereditary Spastic Paraplegia (activated)
- 8009 – TRIAL READY (pending activation)

**Training Program**

The CReATe Scholars program solicits applications annually. Fellows, post-docs and junior faculty, as well as both MDs and PhDs are encouraged to apply. To date we have provided funding for eight CReATe Scholars.

**Patient Advocacy Groups**

The ALS Association (ALSA), Muscular Dystrophy Association (MDA), Spastic Paraplegia Foundation (SPF), the Association for Frontotemporal Degeneration (AFTD), Target ALS, Prize4Life and ALS Recovery Fund.

**Additional Funding**

CReATe has been successful in securing additional funding to supplement our parent grant from NINDS and NCATS, including the ALS Association (16-TACL-242, 17-LGCA-331) CDC/ATSDR (R01 TS000244), MDA (376132), Target ALS, NINDS (U01 NS107027), NCATS (U54NS092091-04S1 and U54NS092091-04S2) and Avanir Pharmaceuticals.







**48. Developmental Synaptopathies Consortium**  
**Principal Investigator: Mustafa Sahin, MD, PhD**  
[www.rarediseasesnetwork.org/DSC](http://www.rarediseasesnetwork.org/DSC)

The Developmental Synaptopathies Consortium (DSC) is an 11-site consortium aimed at comprehensively characterizing the developmental, biological, and neurological phenotypes of three rare neurogenetic disorders - Tuberous Sclerosis Complex (TSC), Phelan-McDermid Syndrome (PMS), and PTEN Hamartoma Tumor Syndrome (PTEN) with high penetrance of autism spectrum disorder/intellectual disability (ASD/ID). The short-term goals are to better characterize the neurodevelopmental phenotype of these three groups of patients longitudinally and identify biomarkers that predict risk for disease severity/progression. Leveraging the shared molecular pathway of TSC, PMS, and PTEN, the DSC aims to shed light on molecular pathways and targets relevant to ASD/ID.

**The Specific Aims of the DSC**

1. Maintain the administrative and clinical infrastructure necessary to conduct longitudinal multi-center studies
2. Complete follow up of enrolled participants for three longitudinal studies for TSC, PMS, and PTEN populations
3. Continue enrolling and finish follow up of currently enrolled participants in the pilot studies described below
4. Conduct a multicenter, randomized, double-blind, placebo controlled phase I/II trial aimed at investigating the safety and efficacy of everolimus on neurocognition in PTEN
5. Continue supporting training fellowships through the DSC and associated Patient Advocacy Group (PAGs)

**Patient Populations included in these studies:** Tuberous Sclerosis Complex (TSC), Phelan-McDermid Syndrome (PMS), PTEN Hamartoma Syndrome (PTEN), Autism Spectrum Disorder (ASD)

**Longitudinal Studies**

**DSC 7901:** Autism Spectrum Disorder (ASD) and Intellectual Disability (ID) Determinants in Tuberous Sclerosis Complex (TSC); *enrollment complete: 106*

**DSC 7902:** Mapping the Genotype, Phenotype, and Natural History of Phelan-McDermid Syndrome; *enrollment complete: 100*

**DSC 7903:** Natural History of Individuals with Autism and Germline Heterozygous *PTEN* Mutations; *enrollment complete: 103*

**Pilot Studies**

**DSC 7905:** Electrophysiological Biomarkers of Phelan-McDermid Syndrome; *actively recruiting, current enrollment: 59/100*

**DSC 7906:** Mapping the Phenotype in Adults with Phelan-McDermid Syndrome; *actively recruiting, current enrollment: 8/30*

**DSC 7907:** Access to Resources for Patients with PTEN Hamartoma Tumor Syndrome; *actively recruiting, current enrollment: 12/100*

**Clinical Trial**

**DSC 7904:** A Randomized Double-Blind Controlled Trial of Everolimus in Children and Adolescents with PTEN Mutations (RAD001XUS257T); *actively recruiting, current enrollment: 17/40*

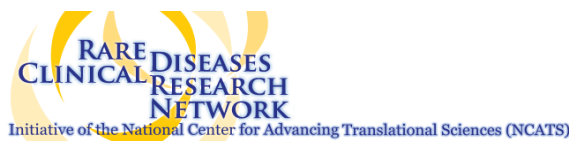
**DSC Associated Training Programs**

The DSC aims to provide a one-year training fellowship in rare disease research to medical professionals seeking to learn more about or working with individuals with rare neurogenetic diseases. The trainee undertakes the fellowship at one of the participating sites, and the fellowship rotates from one disease population to the next each year. Dr. Farach was selected to be the first NIH Certificate Training Fellow for the TSC sub-study. As part of her fellowship project, she has characterized a genotype for TSC to have a mild phenotype and is in the process of writing a manuscript summarizing these results. She is collaborating on a study to determine the underlying cause of TSC in patients with no mutation identified; results are currently pending and she has done preliminary studies for a project involving modifier genes including whole exome sequencing of 10 patients with TSC. Additionally, two fellows (Ishka Frances Que and Takae Brewer) have been chosen at

Cleveland Clinic and will complete their projects in PTEN, while for PMS, Jessica Zweifach has been chosen at Mount Sinai Medical Center.

### Patient Advocacy Groups

The DSC works closely with representatives from the patient advocacy groups associated with each of the rare diseases included in this study: Tuberous Sclerosis Alliance (TSC); Phelan-McDermid Syndrome Foundation (PMS); and PTEN Hamartoma Syndrome Foundation, PTEN Research Foundation UK, PTEN World (PTEN). The DSC has worked with the respective groups to host syndrome specific webinars about the study and ongoing research and actively involves the groups in promoting recruitment and research participation. The PAGs have also contributed financially to the DSC to support the pilot projects and training program.





## **49. Dystonia Coalition**

### **Principal Investigator: Hyder A. Jinnah, MD, PhD**

#### **Major Goals:**

Our major goals are to conduct projects that address bottlenecks in clinical and translational research to facilitate clinical trials for a family of disorders known as the dystonias. Some key examples include:

1. Develop a more complete understanding of the natural history of all isolated dystonias to provide background data for future studies of disease-modifying clinical trials.
2. Establish internationally acceptable diagnostic criteria to aid selection of subjects for clinical trials.
3. Establish internationally acceptable instruments appropriate for monitoring disease severity in clinical trials.
4. Create a resource for exploring potential biomarkers that could be used for diagnosis or severity.

#### **Main diseases under study:**

The main diseases under study include all of the isolated dystonias. They are disorders of excessive muscle activity that lead to involuntary abnormal twisting or repetitive movements. The main subtypes are included below:

1. Cervical dystonias (torticollis)
2. Craniofacial dystonias (blepharospasm, oromandibular dystonia, or Meige syndrome)
3. Laryngeal dystonias (including spasmodic dysphonia)
4. Limb dystonias (arm or leg)
5. Segmental dystonia (any combination of the above in contiguous body areas, including hemidystonia)
6. Multi-focal dystonia (any combination of the above in non-contiguous body areas)
7. Generalized dystonia (multiple body regions affected)

#### **Major Clinical Studies:**

*Project 1: Natural History & Biorepository for Isolated Dystonias (Joel Perlmutter, Washington Univ. St. Louis).*

This study is ongoing. The goal is to develop a better understanding of the clinical features and progression of the isolated dystonias, so that we may improve the treatment of affected patients by collecting clinical data longitudinally. A secondary goal is to create a biospecimen repository linked to valuable clinical data, so that we may begin to explore potential biomarkers and diagnostic measures. As of November 2018, 40 centers contributed to the enrollment of 3037 subjects. This is the largest publicly available resource in the world.

*Project 2: Comprehensive Rating Tools for Cervical Dystonia (Cynthia Comella; Rush University).*

This study has been completed. The goal was to develop a unified, comprehensive assessment device, the Combined Cervical Dystonia Rating Scale for cervical dystonia, and to develop a training tape for proper use of this scale. A total of 10 domestic centers recruited 209 patients, and a new rating scale was created and published. Several follow-on studies are ongoing with data collected for this project including international validation of the new scale.

*Project 3: Diagnostic and Rating Tools for Laryngeal Dystonia (Christy Ludlow; James Madison University).*

This study has been completed. The goal was to develop diagnostic criteria for the major subtypes of the laryngeal dystonias. A total of 4 domestic centers with teams of otolaryngologists, neurologists, and speech pathologists recruited 187 patients with various voice disorders, and diagnostic criteria were established using the Delphi process. Several follow-on studies are ongoing, including strategies that might be used to assess severity.

*Project 4: Diagnostic and Rating Tools for Blepharospasm (Mark Hallett; NINDS, NIH).*

This project is nearly complete. The goal was to develop diagnostic criteria and measurement tools for blepharospasm. Eight centers in four countries have so far completed recruitment of 184 blepharospasm patients for an international multicenter study. Data analysis will begin when recruitment of the disease control groups is completed, which is likely to be before the end of 2018.

#### **Pilot Projects Program:**

The Dystonia Coalition received 74 applications from 68 different investigators in 6 different countries. To date, 15 applications (20%) were approved for funding. In addition, we provided data or materials collected during the course of the four main projects above for >30 pilot projects with alternative sources of funding. These sources included other NIH or country-specific grants, local institutional resources, and private foundations. Together, these activities contributed to 82 publications, and several have led to multiple independently funded grants.

### **Career Development Program:**

The Dystonia Coalition offers a development/training award program to junior faculty members interested in dystonia research. To date, the Dystonia Coalition Development Program has reviewed 30 different applications from investigators in 5 different countries and 14 have been awarded (47%). Each award is approximately \$50,000 over 1-2 years. All of these were co-funded by the relevant Patient Advocacy Group.

### **Role of Patient Advocacy Groups:**

Patient Advocacy Groups play a key role in all aspects of the Dystonia Coalition. There have been as many as 19 groups, although some have now closed down. They are involved in the Executive Committee and invited to help plan and attend all of our Annual Meetings. They are engaged in selecting and designing our Main Clinical Research Projects. They are involved in selecting and funding projects submitted to the Pilot Projects Program and candidates applying for the Career Development Award. In addition, they manage a dystonia patient registry that has 5,431 registrants as of October 2018.

### **Highlights of Some Accomplishments:**

#### *International Consensus Definition for Dystonia*

One of the biggest accomplishments of the Dystonia Coalition relates to the very definition of dystonia. Prior to our start, the definition of dystonia varied in different parts of the world. This variability led to enormous confusion and conflict regarding virtually every study, because of diagnostic uncertainties of the patient cohorts studied. The Dystonia Coalition sponsored a series of meetings with private foundations in America and Europe to develop an internationally accepted consensus on its definition. The results of the consensus group were published in 2013, they were accepted internationally almost immediately, and the article has been cited more than 300 times already. The significance of this simple task for all of dystonia research cannot be underestimated.

#### *International Consensus Classification for All Dystonias*

Dystonia is not a single disorder, but a family disorder with more than 100 different causes. The same international consensus working group that re-defined dystonia also presented a new classification for the many subtypes. This was published in the same article noted above. This new classification system has also been internationally accepted, and now facilitates collection of specific groups of related dystonia populations for clinical trials and other clinical studies.

#### *Biobank for Dystonia Research*

Dystonia Coalition investigators have accumulated a biobank of more than 3000 DNA samples from patients with various types of dystonia for new gene discovery. This is the largest and most carefully clinically annotated biobank in the world. This biobank contributed to the discovery of the first gene for cervical dystonia, a large candidate gene screening study, and a GWAS has been completed. These large-scale studies would not have been possible without the collaborative effort of multiple investigators who agree to collect samples in a uniform way for sharing. The biobank also has more than 200 serum samples for future biomarker discovery.

#### *Novel Diagnostic Criteria for Laryngeal Dystonia and Blepharospasm*

Prior to our start, there were no widely accepted diagnostic criteria for any form of dystonia. We have established diagnostic criteria for laryngeal dystonia and blepharospasm. The latter group is now subject to an international validation study that will be completed by December 2018.

#### *Overall publication productivity*

The Dystonia Coalition has been remarkably effective over its 8 years of funding. Its members have contributed to the following:

1. Peer-reviewed publications: 77
2. Reviews/commentaries/chapters/letters: 58
3. Abstracts/poster presentations: 53
4. Lectures/seminars: 334 (119 supported by the Dystonia Coalition)



## **50. Genetic Disorders of Mucociliary Clearance Consortium**

### **Principal Investigator: Michael R Knowles, MD**

**Major Goals-** Define the clinical phenotypes of inherited, non-asthmatic disorders of mucociliary clearance, and establish the underlying pathophysiological and molecular etiologies.

**Diseases -** Primary Ciliary Dyskinesia (PCD); variant CF; Idiopathic Bronchiectasis.

#### **Protocol 5901 - Longitudinal Study of Primary Ciliary Dyskinesia: Participants 5-18 Years of Age.**

Between Aug 2006 and Sep 2009, 120 participants were enrolled into this 5 year longitudinal study. Currently, we are in a 5 year extension phase for this longitudinal study in which participants are evaluated at intervals of every 2-3 years. As of May 29, 2018, 63 participants have completed at least one extension visit. Of the 120 enrollees, 104 have definite PCD (confirmed by electron microscopy and/or genetics), including 93 (89%) with defined biallelic gene mutations in one of 18 different PCD-associated genes identified within this population, providing a very rich dataset for analyzing effect of gene type on severity of lung disease. Dr. Leigh (PI for 5901) and Dr. Davis (PI for 5903) have worked with Hye-Seung Lee, PhD at the DMCC to perform a “combined” analyses. A cross-sectional analysis of the data from the initial visit for 118 confirmed PCD participants in 5901 and 5903 showed those with certain mutated genes (*CCDC39* and *CCDC40*) had lower FEV1 % predicted than those with mutations in genes associated with outer dynein arm defects (Davis SD et al: Am J Respir Crit Care Med. 191:316-24, 2015). A subsequent longitudinal analysis of 5 year follow-up of 137 participants with confirmed PCD showed that percent predicted FEV1 decline was heterogeneous with a mean decline of 0.57% predicted/year. The group with inner dynein arm defect/microtubular disorganization/central apparatus defect (IDA/MTD/CA; n=41) had younger age at diagnosis, younger age at entry into the study, and lower % predicted FEV1 than the group with outer dynein arm defect (ODA; n=51). Similarly, the group with mutated *CCDC39* or *CCDC40* genes (n=34) (the most prevalent genes within the IDA/MTD/CA group) had lower % predicted FEV1 than group with mutated *DNAH5* (n=36) (the most prevalent mutated gene within the ODA group), providing further evidence for worse lung disease in individuals with mutated *CCDC39* or *CCDC40*. (Davis SD et al: Am J Respir Crit Care Med, In Press 2018).

**Protocol 5902 - Rare Genetic Disorders of the Airways: Cross-sectional Comparison of Clinical Features, and Development of Novel Screening and Genetic Tests.** Protocol enrollment has been completed, and several important discoveries regarding diagnostic approaches are already impacting on clinical care (see below for details). These discoveries derived from our rigorous diagnostic protocol, which emphasized a complete assessment of phenotypic, physiologic, ciliary ultrastructural, and genetic characterization of patients. We now have nearly 450 patients with confirmed PCD with hallmark ultrastructural ciliary defects and/or biallelic PCD-causing genetic mutations. It is now clear that the presence of respiratory distress in term neonates is a very strong marker of PCD, as 85% of PCD patients <18 yrs give this history. Thus, respiratory distress in term neonates, along with year-round congestion and daily cough from birth, coupled to chronic middle-ear disease, should create a high index of suspicion for PCD. Since half of PCD patients have *situs inversus* (or *situs ambiguous*), an educated and experienced clinician can now readily recognize the clinical phenotype and the likelihood of PCD, and proceed with the appropriate diagnostic workup. In addition, we have now identified ~ 35 PCD-causing genes, and we can now identify ~65% of PCD patients by genetic testing, which is now available in the U.S. at a reasonable cost at CLIA-approved labs. Exome sequencing for discovery of additional PCD genes is now underway in > 100 PCD patients. We have already identified 2 genes (*CCDC39* and *CCDC40*) associated with more severe PCD clinical disease, and one gene (*RSPH1*) with milder disease. Now that we have genetic data on a large number of patients, we will begin extensive analyses of genotype and clinical phenotype across the entire population.

#### **Protocol 5903 - Early Onset and Progression of Primary Ciliary Dyskinesia Lung Disease Prior to 10 Years of Age.**

Recruitment for Protocol 5903 (Early Onset and Progression of Primary Ciliary Dyskinesia Lung Disease Prior to 10 Years of Age) is complete. Fifty-four participants were enrolled into this 5 year longitudinal study, of which 37 have confirmed PCD, 11 were withdrawn later when persistent respiratory symptoms improved decreasing likelihood of PCD. Children with a confirmed PCD had chronic, daily cough, nasal congestion and recurrent otitis media, usually starting before 1 year of age, as well as abnormal chest CTs, and > 80% had neonatal respiratory distress. These findings demonstrate significant disease burden in children with PCD <5 years old and emphasize the need for further study to determine risk factors for disease progression. Dr. Davis (PI of 5903) and Dr. Leigh (PI of 5901) have worked with Hye-Seung Lee to perform a “combined” cross-sectional and longitudinal analysis of all participants (described above for Protocol 5901).



**Protocol 5904 - Cross-sectional Characterization of Idiopathic Bronchiectasis**

This protocol was designed to characterize clinical features, body morphometrics, and respiratory microbiology in patients with non-PCD/non-CF (“idiopathic”) bronchiectasis, stratified by gender and presence/absence of non-tuberculous mycobacterial (NTM) respiratory tract infection. Enrollment is complete with 271 patients enrolled from 7 sites. Preliminary assessment of our phenotype data supports past findings on morphotypic traits in bronchiectasis patients with NTM. Specifically, NTM patients were diagnosed with bronchiectasis at an older age and have a higher FEV1% predicted, higher incidence of scoliosis and a higher incidence of tree in bud infiltrates in comparison to non-NTM patients. The race and ethnicity enrollment show a predominance of whites with much lower prevalence of Asian, Black, or Hispanic, which reflects the known racial and ethnic distribution of bronchiectasis in the US (Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots R. [Trends in bronchiectasis among Medicare beneficiaries in the United States, 2000 to 2007](#)). Ongoing studies are testing the hypothesis that these idiopathic bronchiectasis patients have an increased burden of variants in heritable disorders of connective tissue genes, which would be congruent with our recent report (Daniels, LA, 2016, Ann Am Thorac Soc) that these patients have dilation of the dural sac (dural ectasia), as seen in Marfan Syndrome.

**Protocol 5905 – Research Genetic Testing for Primary Ciliary Dyskinesia Using a Panel of Genes**

This protocol (approved and started in February, 2015) was designed to identify PCD-causing mutations in patients with clinical phenotypes consistent with PCD, and define prevalence of biallelic mutations in subjects who fulfill rigorous criteria for PCD. A secondary objective is to identify PCD patients who do not have mutations in known PCD genes, so they can be exome sequenced to discover novel genes associated with PCD. As of August, 2018, we have enrolled 317 of our target enrollment of 320 subjects. After genetic testing is completed in a collaborative effort with Invitae, we will determine the prevalence of biallelic PCD-causing mutations in two groups: 1) Patients who fulfill rigorous clinical criteria for PCD, and have high likelihood of having PCD. 2) Patients who have some clinical manifestations of PCD, but do not fulfill diagnostic criteria (*e.g.*, they have “Probable or possible PCD”). We anticipate that the prevalence of biallelic mutations in these patients is likely to be <70%, since some of these patients may not have PCD.

**Training Section:** Over the past 14 years, the GDMCC has been successful in training and mentoring the next generation of rare lung disease investigators, with trainees as lead or contributing authors on 71 peer-reviewed publications, 9 book chapters, and 66 abstracts at national conferences. Of the 31 trainees who have completed post-graduate and fellowship training, 27 have positions at academic medical centers. Currently, we have an extensive training program in effect that includes 10 active trainees, including Fellows and post-doctoral students. The desire by the PCD Foundation to expand the network of PCD clinical centers, coupled to the recognition by academic pulmonary divisions that it is important to be recognized as having expertise in PCD, has led to an expanded opportunity to our Consortium to educate young trainees, as well as both junior and senior faculty who are “new” to PCD.

**Role of Advocacy Groups:** The PCD Foundation has played a key role in our progress over the past decade. With this improved understanding of the disorder and diagnosis, the PCD Foundation is now establishing a growing network of PCD clinical care and research centers throughout North America, and is developing a Registry to aid in future research efforts.

There are three primary patient advocacy groups involved with the GDMCC, all of whom fully support the consortium and its research goals:

- The Primary Ciliary Dyskinesia (PCD) Foundation
- The Cystic Fibrosis (CF) Foundation
- NTM Information and Research (NTMIR)

The PCD Foundation and NTMir Organization are involved in bi-monthly conference calls, and contribute to planning and execution of studies and educational programs.





## 51. The Inherited Neuropathy Consortium

### Principal Investigator: Michael E. Shy, MD

**The Inherited Neuropathy Consortium (INC) RDCRC** is a network of clinical investigators dedicated to developing the infrastructure necessary to evaluate therapies for patients with heritable peripheral neuropathies, collectively known as Charcot-Marie-Tooth disease (CMT). Supplemental funding from the Muscular Dystrophy Association (MDA) and Charcot Marie Tooth Association (CMTA), two of our five Patient Advocacy Groups (PAGs), has allowed the INC to expand from 6 to 20 sites. The >90 genes that cause CMT can be divided into three major groups - dominantly inherited demyelinating neuropathies (CMT1), dominantly inherited axonal neuropathies (CMT2), and recessively inherited neuropathies (CMT4). These are the groups of disorders we investigate. Michael Shy MD, professor of Neurology at the University of Iowa, is the Principal Investigator (PI) of the INC. The INC has enrolled > 10,000 participants into our protocols including > 5,000 patients into our natural history projects. We have developed CMT specific clinical outcome assessments (COA) used to measure disability in adults and children with CMT, including both functional and patient reported outcomes (PRO). INC investigators have identified biomarkers including MRI imaging that correlate with our COA in CMT1A, the most common form of CMT. INC investigators have just been awarded a U01 award to “Accelerate Clinical Trials in CMT (ACTCMT) for CMT1A. We have relationships with pharmaceutical and academic partners to share clinical data for trial readiness. We have had a Critical Path Innovation Meeting (CPIM) meeting with the FDA. The INC has also been actively involved in identifying novel genetic causes of CMT including 23 during the past five years. We have utilized GWAS to identify SIPA1L2 as the first genetic modifier for CMT1A and shown that this gene is a potential therapeutic target. We have initiated the CMT Variant Browser which promotes international sharing of genetic information on CMT and developed GENESIS software to share exome data internationally. We are now poised to expand these studies into phenotypic sharing and whole genome analysis. The INC Website has also allowed us to directly interact with > 3600 participants who constitute the INC Contact Registry who have helped us develop the CMT Health Index (CMT-HI), a PRO measure of disease burden, among other publications. We have developed the CMT-International Database (CMT-ID), a group of national registries from around the world that use the same CMT Minimal Dataset that is used by the INC. We have successfully trained 11 young investigators who have all obtained or are on track to obtain faculty positions in fields related to CMT.

### NATURAL HISTORY STUDIES

We have performed cross sectional analysis on over 900 children with various types of CMT with the CMTPedS scale that we designed and validated in RDCRN2. We extended our normative data for all our COAw including CMTPedS by evaluating over 1,000 individuals without CMT of all ages and genders. We have performed longitudinal analysis of children with CMT1A using CMTPedS demonstrating that children with assorted disability progress at 12-15% above previous baseline on a yearly basis with a Standard Response Mean (SRM) of 0.49. We have developed and validated a pediatric infant and toddler scale (CMTInf) to measure progression from birth up until age 5. We have extended CMTPedS into adulthood by developing and validating a CMT Functional Outcome (CMT-FOM) scale. We have also developed and validated two PRO instruments; the Disability Severity Index (DSI) and the CMT-Health Index (CMT-HI). INC investigators have identified elevated levels of NFL as a biomarker in multiple subtypes of CMT which we believe will serve as a potential biomarker for axonal degeneration in CMT. We have identified potential biomarkers of disease activity and progression from skin biopsies. We have extended our MRI investigations of IMFA in calf muscle to show similar results in two INC sites which demonstrate significant progression of free fat accumulation to the extent that the SRM can be as high as 2.44 demonstrating potential for requiring < 50 patients/arm as an outcome in clinical trials.

### NEXT GENERATION SEQUENCING

Next Generation Sequencing: Protocol 6602 has been to utilize WES sequencing to identify novel forms of CMT from our patients who lacked a genetic diagnosis and to identify potential modifier genes that affect the phenotype of patients with CMT1A, the most common hereditary neuropathy. Exome Sequencing: To date we have identified 22 new CMT genes in the last four years and have identified another 3 genes that have been being confirmed or are in the review process. The recently published CMT and CMT-related genes from INC investigators include *ATL1/HSN1D*, *ATPA1/CMT2*, *ATP7A/SMAX3*, *BICD/SMALD2*, *BAG3*, *DRP2/CMTX*, *DST/HSAN6*, *DYNC1H1/SMALD1*, *FBX038/HMS2D*, *HARS/CMT2W*, *HINT1/* neuromyotonia and axonal neuropathy, *MARS/CMT2U*, *MME/CMT2*, *MORC2/CMT2Z*, *NAGLU/CMT2V*, *NEFH/CMTCC*, *PDK3/CMTX6*, *PMP2/CMT1*, *PRDM12/HSAN8*, *SCYL1/syndrome with neuropathy*, *SLC5A7/HMN7A*, *SLC25A46/syndrome with neuropathy*, *SCL52A2/HMN* and *SCL52A3/HMN*, *SYT2/CMS7*, *WARS/HMN2*, and CMTX3 insertion at Xq27.1.

Dr. Züchner from our Miami site has also developed a password protected genetic analysis platform called GENESIS (formerly GEM.app), which is a web-based application can be used from any desktop computer and allows investigators inside and outside the INC to analyze data from exomes and genomes that they have submitted. The wide usage of this platform inside INC has been at the core of the successful gene discoveries via genetic matchmaking. The exome/genome data aggregation combined with phenotypic details in this software is also the foundation for larger statistical projects, such as the genetic modifier study and rare variant burden analysis, such as in the MME gene, which we co-discovered. Further, we have developed the INC Neuropathy Variant Browser and a paper has been published on it. This Variant browser allows the INC to review alleles in known CMT genes, add novel alleles to form clinical reports, and generally aims at reducing the number of Variants of Unknown Significance.

Modifier studies: Identifying modifier gene(s) for CMT1A through Genome Wide Association Studies (GWAS) was a major goal of protocol 6602. We have accrued 1,000 DNA samples from patients with CMT1A and correlated these with their clinical outcome measures on 6601. We have now identified kinase *SIPA1L2* as the first demonstrated modifier gene for CMT1A, demonstrated that it is expressed in Schwann cells, is regulated by SOX10 like other myelin genes and modifies *PMP22* mRNA levels; this is the first proven modifier gene in CMT1A and identifies *SIPA1L2* as a therapeutic target to suppress *PMP22* mRNA expression in CMT1A.

## TRAINING PROGRAM SUMMARY

The INC has targeted trainees who typically had completed a neuromuscular fellowship (or equivalent) and either were at advanced post-doctoral stage or ready to assume junior faculty levels in the US or senior specialist registrars (SPRs) in neurology who were at an equivalent developmental position in the UK. We designed 1 and 2 year fellowship programs to train investigators in all forms of clinical research including research methods for clinical assessment and natural history studies (including clinical pattern recognition, neurophysiologic methodologies, neuromuscular imaging, nerve pathology and genetic testing). All fellowships included either a clinically relevant clinical or related laboratory-based research project or a dedicated module to develop expertise in clinical trial design and biostatistics. An ideal training program should be comprehensive and flexible and our program design allowed us to offer individualized programs for each trainee to specifically address their personal needs and to allow us to recruit trainees with varying degrees of previous exposure to inherited neuropathies. This meant we were able to attract very high level trainees who have all successfully transitioned or are transitioning towards clinical academic careers in inherited neuropathies, 10 of which were 100% supported by the INC. We also successfully developed funding partnerships with other RDCRCs and academic partners to fully exploit training opportunities. Two examples are *Maiya Kugasthan* and *Wolfgang Pernice*. *Maiya Kugasthan* was initially jointly funded for her fellowship by the INC and the MRC centre in London and subsequently successfully obtained a MRC training fellowship to continue her work on the pathogenesis and developing outcome measures for HSN1. *Wolfgang Pernice*, a basic scientist with a background and major interest in inherited neuropathies caused by mitochondrial genes is a current post-doctoral fellow jointly funded by the INC and the North American Mitochondrial Consortium (NAMDC) RDCRC led by Michio Hirano benefitting from the combined neuropathy and mitochondrial expertise of both RDCRCs. We also involved 66 other trainees in our centres (including neurologists, basic scientists and therapists) who benefitted directly from the training opportunities arising from having the INC in the participating INC centres and from the various research projects of the INC. Our 11 core trainees have published 66 papers, 88 abstracts and presented 54 oral presentations and 62 posters at national and international meetings based on the work done in their fellowships to date as well as won various prizes for their work including a recent fellow, *Andrea Cortese* being selected competitively from all RDCRC trainees to present his work at the recent RDCRC steering committee in Washington in May 2018.

## INC PATIENT ADVOCACY GROUPS (PAG)

Our PAGs are an important component of the IAB, have been incredibly supportive of the INC and have allowed us to expand from our original 6 sites to our current total of 20 sites. The Muscular Dystrophy Association provides grant support that allows us to provide support to five additional sites. **Amanda Haidet-Phillips**, Scientific Program Officer for the MDA, will continue to serve the INC MDA representative on the IAB. The Charcot Marie Tooth Association provides the INC with a grant to support additional sites in the consortium. **Amy Gray**, CEO of the CMTA, has served and will serve as the INC CMTA representative. **Allison Moore**, CEO and Founder of the HNF will serve as HNF representative and has pledged to provide support for INC sites. **Karen Butcher** will continue to serve as the INC representative from CMT United Kingdom (CMTUK). **Dr. Anna Ambrosini**, the head of the Research Program Development for Telethon will continue to serve as their representative to the INC (see letter). We are also pleased to add CMTA Australia as a PAG. **Darryl Beitsch**, President of CMTAA has joined our IAB and will work to expand the presence of the INC in Australia.



## **52. The Lysosomal Disease Network (LDN)**

**Chester B. Whitley, PhD, MD; Principal Investigator**  
**James C. Cloyd, PharmD; Administrative Director**

The combined, integrated effort of researchers in the Lysosomal Disease Network (LDN) is concentrated on using available resources to create a network of clinical research centers focused on solving major challenges in diagnosis, disease management, and therapy for these complex, rare disorders. Solutions for clinical and social problems associated with lysosomal disease have direct impact on patients and inform medical practice.

Toward that goal, the LDN facilitates clinical research in rare diseases through a program that supports:

1. Collaborative research via nine longitudinal and three pilot project studies that each strive to find answers to the fundamental issues of a given disease.
2. Supportive cores providing integral services to investigators across the network
3. Train clinical investigators in lysosomal disease research
4. Provide access to information related to lysosomal conditions by submission of data to the Data Management and Coordinating Center (DMCC), dbGAP, via presentations at conferences and meetings, and by following the tenets of the NIH public access policy.
5. Active involvement of patient advocacy groups (PAG) in the recruitment, scientific advisement, and transmission of research results to the community at large.

Because central nervous system (CNS) involvement is prevalent in lysosomal conditions—while being difficult to measure and treat—we include a major emphasis on qualitative analysis of CNS structure, function, and the discovery of biomarkers for relevant conditions including: mucopolysaccharidosis (MPS), mucopolipidosis IV, Batten disease, and the gangliosidoses (including Tay-Sachs disease). Systematically collected data on brain effects, will help us develop outcome measures that are specific and sensitive to change in disease status.

In order to drive cutting-edge research in what are multi-system diseases, we also have projects focused on immune modulation in Pompe disease, kidney structure and function in Fabry disease, and the role of oxidative stress in Gaucher disease. We also continue to emphasize the collection of natural history data for those lysosomal conditions for which there are no current therapies: Krabbe disease, mucopolipidosis type IV, and Sanfilippo syndromes type C and D.

### **Longitudinal Studies**

Project 1(6727): “Podocytes in Fabry Renal Disease.” S. Michael Mauer (University of Minnesota). Dr. Mauer and colleagues will utilize kidney biopsy to study the correlation between age at initiation of therapy and severity of kidney disease in Fabry patients. Satellite site: University of Washington

Project 2 (6703): “Longitudinal Study of Brain Structure and Function in MPS I, II, and VI.” Chester B. Whitley (University of Minnesota). This study aims to identify abnormalities of CNS structure and function using neuropsychological, behavioral, and MRI imaging techniques. Satellite sites: Oakland Children’s Hospital, University of California-San Francisco, New York University, Emory University, Hospital for Sick Children-Toronto, LABioMed-UCLA.

Project 3 (6704): “The Natural History of Mucopolipidosis type IV.” Raphael Schiffmann (Baylor Research Institute). Dr. Schiffmann aims to catalogue the neurocognitive characteristics of patients with MLIV with regard to brain volume and developmental function using DTI, MRI and EEG.

Project 4 (6705): “Longitudinal Study of Bone and Endocrine Disease in Children with MPS I, II, and VI: A Multi-Center Study of the Lysosomal Disease Network.” Lynda Polgreen MD (LABioMed-UCLA). Dr. Polgreen hypothesizes that biomarkers for inflammation and bone and cartilage turnover can predict the severity of skeletal disease over time in MPS patients. Satellite sites: Oakland Children’s Hospital and University of Minnesota.

Project 5 (6709): “Long-Term Follow-Up and Treatment Outcomes for Individuals with Infantile Pompe Disease.” Priya Kishnani, MD (Duke University). Dr. Kishnani aims to characterize the emerging natural history of IPD survivors and assess the efficacy of immune tolerance induction and suppression algorithms.

Project 7 (6716): “Biomarkers for Disease Severity and Therapeutic Response in LINCL.” Douglas Ballon PhD and Jonathan Dyke PhD (Weill Medical College, Cornell University). This study hypothesizes that advanced MRI techniques in

combination with quantitative evaluation of CSF metabolites can be exploited to develop a comprehensive set of biomarkers for assessing disease severity and therapeutic response in children with LINCL.

### Interventional Studies

Project 6 (6728): “An Extension Study of Intrathecal Enzyme Replacement for Cognitive Decline in Mucopolysaccharidosis Type I.” Agnes Chen MD (Biomedical Research Institute at UCLA-Harbor). This study aims to evaluate the long-term safety and efficacy of IT ERT for the treatment of cognitive impairment in MPS I. Satellite sites: University of Minnesota.

Project 8 (6722): “Role of Oxidative Stress and Inflammation in Type 1 Gaucher Disease (GD1): Potential Use of Antioxidant/Anti-Inflammatory Medications.” James C. Cloyd PharmD and Reena Kartha, PhD (University of Minnesota). The central hypothesis of this study is that relative to healthy subjects, GD1 patients exhibit increased systemic and brain oxidative stress and inflammation. Further, we hypothesize that antioxidant/anti-inflammatory therapy can improve oxidative stress/inflammation in GD1 patients. Satellite sites: NYU Langone Medical Center and Gaucher and Fabry Disease Clinic.

Project 9 (6713 and 6729): “Natural History of Hexosaminidase Deficiency and Other Gangliosidoses and Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G).” Jeanine Utz PharmD, Chester B. Whitley PhD, MD (University of Minnesota). To characterize and describe disease progression and heterogeneity in the gangliosidosis disorders. To evaluate a combination, multi-targeted therapy for pediatric gangliosidoses, using miglustat with the ketogenic diet—and pyrimethamine for patients with responsive mutations—will improve neurodevelopmental outcomes compared to data reported in previous natural history studies, and previous studies using monotherapy with miglustat.

### Pilot Project (PP) Program

LDN pilot studies will maximize research in lysosomal diseases to advance knowledge and provide approaches to answering the important questions in the field. Pilot studies are selected through a competitive process. Five pilots were selected in first two years; two are ongoing at this time, and two are complete; one is opening to enrollment in this final year of LDN funding.

PP2 (LDN 24) Magnetic Resonance Spectroscopy (MRS) to Determine Neuroinflammation and Oxidative Stress in MPS I” Igor Nestrail, MD, PhD (University of Minnesota). The goal of this project is to explore the utility of MRS as a means of identifying biomarkers of inflammation in MPS I participants as compared to controls.

PP 3 (6723): “Natural History Study for MPS IIIC and MPS IIID.” Paul Levy MD (Montefiore Medical Center). LDN Partnership with Jonah’s Just Begun Foundation. The aim of this project is to expand our knowledge of the clinical features of MPS IIIC and MPS IIID disease by carrying out a prospective natural history study.

PP 4 (6726): “Long Term Follow Up for Krabbe Disease.” Thomas Langan MD (University of Buffalo School of Medicine). LDN Partnership with Hunter’s Hope Foundation. We hypothesize that children with positive screens for this condition will exhibit distinct developmental outcomes, which can be measured by standardized phone interview protocols.

### Trainee Projects:

**Note that Drs. Reena Kartha and Mari Mori have presented their work at RDCRN Steering Committee Meetings and Dr. Kartha will present at the CCRRD conference**

- “Immune Response to Intrathecal Enzyme Therapy in Mucopolysaccharidosis I Patients” (Moin Vera MD Fellow, PI).
- “Discovery of genetic modifier(s) linking Gaucher disease & hematologic malignancy” (Sara Lo PhD, Fellow, PI)
- “MPS Longitudinal Study of Brain Structure and Function” (Julie Eisengardt PhD, Fellow, PI)
- 1.) “Urinary GAG and Its Role as an Outcome Measure in Mucopolysaccharidoses; 2) Classifying and Managing Infusion Reactions to Enzyme Replacement Therapy; 3) Combination Therapy for MPS VI; 4) Medication Therapy Management for Patients with Inherited Metabolic Disorders; 5) Combination Oral Therapies for the Gangliosidoses.” (Jeanine Utz PharmD, Fellow, PI)
- 1.) “Urinary GAG and Its Role as an Outcome Measure in Mucopolysaccharidoses; 2) Assessing and Managing Fabry Disease Pain: The role of gabapentin. (Jonica Hazert PharmD, Fellow, PI)
- “Novel Transporters for MPS I and MPS III A Enzyme Replacement Therapy” (Wenyong Tong PhD, Fellow, PI)
- “Longitudinal Studies of Brain Structure and function in MPS Disorders; current project is to evaluate phenotype and genotype relationship in Mucopolysaccharidosis Type I” (Alia Ahmed MD, Fellow, PI).
- “Placebo Controlled Trial Evaluating Gabapentin for the Treatment of Small Fiber Neuropathic Pain in Patients with Fabry Diseases. 2. Synergistic Enteral Regimen for Treatment of the Gangliosidoses .3) Comparative Neuroimaging

Brain Volume Studies of Childhood Gangliosidoses Using Semi-Automated Systematic Manual Volumetric Technique  
4. Metabolomic Study of Gangliosidosis Diseases” (Patrick Sorgen, PharmD, Fellow, PI)

- “An Exploratory Study of Psychological and Executive Functioning in MPS I Patients” (Kelly King, PhD, Fellow, PI)
- “Evaluation of Oral N-acetylcysteine Pharmacokinetics and Pharmacodynamics in Gaucher Disease” (Lisa Coles PhD, Fellow, PI)
- “Hypothyroidism in Pompe disease” (Joe Schneider PharmD, Fellow, PI)
- “Proteomics to identify signature proteins in patients likely to mount an immune response to enzyme replacement therapy in infantile Pompe disease” (Zoheb Kazi PhD, Fellow PI)
- “Identification of candidate genes for Pompe disease phenotype modifier genes” (Mari Mori PhD, Fellow, PI)
- “Evaluation of transcytosis mechanisms in lysosomal storage disease brains” (Melani Solomon PhD, Fellow, PI)
- “Delayed Infusion Reaction to Enzyme Replacement Therapies” (Zahra Karimian PharmD, Fellow, PI)
- “Role of Oxidative Stress and Inflammation in Type 1 Gaucher Disease: Potential Use of Antioxidant/Anti-inflammatory Medications” (Reena Kartha PhD, Fellow, PI)
- “Motivational Interviewing to assess patient based outcomes in Fabry disease” (Kwangchae Yoon, PharmD, Fellow, PI)
- “Development of mesenchymal stromal cells for the treatment of corneal disease in Morquio A patients” (Michael Flanagan PhD, Fellow, PI)
- “Proteomics and metabolomics analysis of lysosomal diseases to identify diagnostic and therapeutic targets” (Li Ou, PhD, Fellow, PI)
- “Metachromatic leukodystrophy: Characterization of genetic mutations, age of onset, and clinical subtypes” (Laura Adang MD, PhD, Children’s Hospital of Philadelphia)
- “Genotype Phenotype correlation in Morquio syndrome” (Todd Vanyo PharmD, University of Minnesota)

#### **Patient Advocacy Groups:**

LDN patient groups provide: insight into study design, make recommendations for inclusion of projects into grant applications, and co-fund may LDN projects; their involvement in the LDN is invaluable.

National Tay-Sachs and Allied Diseases Association; National Mucopolysaccharidosis Society; International Society for Mannosidosis and Related diseases; Cystinosis Research Network; Association for Glycogen Storage Disease; Fabry Support and Information Group; The Fabry Disease Foundation; Children’s Gaucher Disease Research Fund; National Gaucher Foundation; Hide and Seek Foundation; Hunter’s Hope Foundation; The Children’s Rare Disease Network; Mucopolipidosis IV Foundation; Adrenoleukodystrophy Foundation; MLD Foundation; United Leukodystrophy Foundation; National Niemann-Pick Disease Foundation The Ara Parseghian Medical Research Foundation; Batten Disease Support and Research Association; Acid Maltase Deficiency Association, Ryan Foundation.

#### **Consortium Progress**

The annual meeting of LDN Principal Investigators, support staff, DMCC support staff, and representatives from NIH took place February 9<sup>th</sup>, 2018 in San Diego CA. This year, our annual meeting focused on crafting the competitive renewal due October 9<sup>th</sup>, 2018 at NIH. In brief, anyone interested in being part of the “new LDN” submitted an outline, and then defended their proposal in front of a panel of reviewers in San Diego. The LDN strives for complete transparency in all activities and this is one way we ensure an open process. At the conclusion of the presentations, the panel met for a debrief and to provide opinions.

**Moving forward**, as we look to the next 5 years of funding, the LDN will take on a new form; in the next grant cycle the LDN will be comprised of 12 Centers of Excellence, each contributing participants to our five research projects. Each center was chosen for its experience and excellence as a clinical site for lysosomal disease, and its geographic location—LDN Centers of Excellence will have a regional dispersal making it convenient for any patient to reach a center, and thus participation in an LDN study.





### **53. Nephrotic Syndrome Study Network (NEPTUNE)** **Principal Investigator: Matthias Kretzler, MD**

#### **Specific Aims**

The Nephrotic Syndrome Study Network (NEPTUNE) is a collaborative investigational infrastructure of 26 sites across North America encompassing 38 recruitment centers for conducting clinical and translational research on three rare diseases presenting as Nephrotic Syndrome (NS): Focal and Segmental Glomerular Sclerosis (FSGS), Minimal Change Disease (MCD), and Membranous Nephropathy (MN). The NEPTUNE specific aims are to: 1) maintain a collaborative, integrated, investigational infrastructure for conducting clinical and translational research in FSGS, MCD, and MN; 2) perform longitudinal observational cohort studies on patients with biopsy proven FSGS, MCD and MN, and with pediatric patients with incipient Nephrotic Syndrome prior to biopsy; 3) support a pilot and ancillary project program; 4) support a training program for post-doctoral/junior faculty trainees preparing for clinical and translational research in glomerular disease; and 5) collaborate with the RDCRN DMCC and patient advocacy groups using for outreach to lay people, physicians, and scientists.

#### **NEPTUNE Clinical Studies**

Longitudinal observational cohort studies include: 1) adults and children with incident, biopsy-proven FSGS, MCD, or MN, recruited at the time of biopsy; and 2) children with incident NS at time of first presentation before diagnostic kidney biopsy. The first cohort began with the initiation of NEPTUNE in 2010; the latter cohort was added with the second funding cycle of NEPTUNE. All participants are prospectively followed in 4 to 6 monthly intervals, for a minimum of 36 months, ascertaining the two primary outcomes: remission of proteinuria and progressive loss of renal function. Study participants in the non-biopsy cohort additionally receive daily text messages (SMS) for the first 90 days of enrollment, and then weekly text messages for the first year. 502 participants with the core diagnoses (MCD, FSGS and MN) have been enrolled and actively followed in the biopsy cohort, with 94% consented to genetic testing, 91% case report form completion, and 89% biosample collection across all visits. Mean follow-up time is 32 months. In the Children's Non-Biopsy Cohort, 127 children have been enrolled and actively followed, with 97% consented to genetic testing, 94% participated in mobile health data collection (SMS), 99% case report form completion, and 93% with biosample collection. Follow-up visits are currently ongoing.

#### **Pilot and Ancillary Studies**

The Ancillary Studies Program (ASP) leverages NEPTUNE datasets, biosamples, and whole slide images for goals that extend beyond core NEPTUNE specific aims. Some ancillary studies may require collection of additional data and/or biosamples or may nest a clinical trial within the NEPTUNE cohort. NEPTUNE welcomes all qualified scientists, whether or not they are members of the NEPTUNE consortium to use NEPTUNE resources for their own ancillary research. The study development process typically begins with data exploration and completion of a short ancillary study. NEPTUNE utilizes a data sharing tool called tranSMART, an open-source, cloud-based systems biology analysis and visualization platform. The tranSMART platform allows user-specified exploration of cohort study datasets along the entire genotype-to-phenotype continuum, using the i2b2 data model with extensions for multi-omics analysis. Ancillary Investigators can explore patient population characteristics based on clinical and molecular data to define patient populations and/or generate hypotheses. NEPTUNE data are uploaded on a quarterly basis into tranSMART.

Investigators complete an application provided on the study website. The NEPTUNE Data Analysis and Coordinating Center and Ancillary Studies Committee (ASC) review the application for burden to the consortium, participant burden, new data/sample generation plans, bioinformatics and statistical resources on the ancillary team, adherence to the network's guidelines for public-private interactions, suitability for integration into NEPTUNE archive, and scientific merit, if the study proposal will not have external funding review. NEPTUNE ASC and Steering Committee must approve ancillary studies before inception of research activities or submission of a proposal for external funding. The ASC reviews approved ancillary studies annually. Ancillary Investigators who are actively seeking funding for their studies may apply for an extension of the study approval and sample encumbrance. For ancillary studies underway, the ASC reviews annual study updates that include number of samples/patients analyzed, challenges, preliminary results, and plans to complete the project.

Ancillary investigators are required to return their study data back to the NEPTUNE consortium, to be available for use by other investigators. Return of the ancillary study data is required within 24 months or upon publication, whichever comes



first. Across both funding cycles, 112 applications were reviewed and 107 applications were approved by the ASC. Many ancillary study applications originated outside of consortium member sites, reflecting NEPTUNE's visibility to the investigative community and the value of its research platform.

The NephCure Kidney International (NKI)-NEPTUNE Pilot Project Program is a special component of the NEPTUNE ASP that provides extramural funding dedicated specifically to funding NEPTUNE-related pilot studies. A "pilot project" is defined as a short duration ( $\leq 1$  year) preliminary clinical or translational study focused on clinical, translational or basic science issues in mechanisms, management or treatment of MCD, FSGS or MN. These projects generate feasibility data to advance promising concepts for subsequent funding and can include, but are not limited to, projects that develop clinical assays, protocols, or early phase clinical trials. Application for the Pilot Project Program occurs in two steps: 1) evaluation and approval by NEPTUNE as a NEPTUNE ancillary study, and 2) grant submission, independent review, and funding by NKI. NEPTUNE uses its ancillary study procedures and review criteria for its evaluation of pilot projects prior to NKI referral for final evaluation.

### **NEPTUNE Training Program**

The NEPTUNE Training Program is designed for advanced post-doctoral and junior faculty trainees, or established investigators interested in redirecting their investigative focus, who are preparing to become independent investigators in clinical and translational research in human glomerular disease. Key components of the NEPTUNE training program include: a) a mentored research project, b) an individualized training program with formal didactic training, c) associated career development activities, d) training in responsible conduct of research, and e) subsequent research experiences. The trainees have access to the rich NEPTUNE resources, the diverse expertise of NEPTUNE-affiliated investigators, and a growing menu of career-enhancing activities. Fellowship duration is one year and NEPTUNE allocates \$57,500 direct costs per year to support one trainee salary. The application process is competitive. NEPTUNE trainees are actively engaged in focused working groups, committees and meeting presentations. Since its inception in 2009, nine trainees have received a NEPTUNE training grant. In addition, the career development environment, created by NEPTUNE for glomerular disease research, has resulted in five NIH-sponsored career development awards (K-awards).

### **Patient Advocacy in NEPTUNE**

NephCure Kidney International (NKI) has worked with NEPTUNE since its inception. NKI is an outstanding and highly effective patient interest group dedicated to identifying treatments and ultimately a cure for NS. Founded in 2001 by a group of parents of children with steroid-resistant FSGS, this organization successfully raises funds, educates Congress and the NIH on behalf of patients, and educates the public via regional patient seminars and the NKI website. Over the years, NKI and NEPTUNE have jointly developed patient outreach material for NEPTUNE recruitment and retention. In addition, NKI is proficient in using social media for outreach, education and advocacy, including the "NephSpace".

The Halpin Foundation likewise has worked with NEPTUNE since its inception. This group was funded by a family who was affected by MN. They support training, education, registries, and research (including biomedical and genetic research). In addition, NEPTUNE recently developed the NEPTUNE Patient Advisory Council for Therapies (NPACT) which is primarily comprised of NEPTUNE participants of all ages, and includes parents of children. The overall goal of NPACT is to enhance research success in NS by guiding effective research methodologies with patient and caregiver-focused input. NPACT goals are to provide timely feedback on research study design and patient-facing study materials, while providing insight for study-specific assessment of key patient-reported outcomes and experiences to NEPTUNE investigators. NEPTUNE has a patient contact registry at the RDCRN DMCC (<http://rarediseasesnetwork.epi.usf.edu/registry/>) for patients with NS. As a consequence of outstanding outreach efforts by NKI, there are 1873 patients self-registered in the NS category.



## **54. North American Mitochondrial Disease Consortium (NAMDC)**

### **Principal Investigator: Michio Hirano, MD**

A member of the Rare Diseases Clinical Research Network (RDCRN), the North American Mitochondrial Disease Consortium (NAMDC) was established in 2009 with an ARRA grant. Since then, NAMDC has expanded from the original 9 sites to 17 (Akron Children's Medical Center, Baylor College of Medicine, Boston Children's Hospital, Children's Hospital of Philadelphia, Children's National Medical Center, Columbia University Medical Center [CUMC], Case Western Reserve, Cleveland Clinic, Massachusetts General Hospital, Mayo Clinic, McMaster University, Stanford University, Seattle Children's Medical Center, University of Florida Gainesville, University of Pittsburgh, University of Colorado, and University of California San Diego). NAMDC has also launched the virtual site (remote enrollment platform) that functions as an additional NAMDC site to recruit mitochondrial patients to the NAMDC Registry. The mission of NAMDC is to improve the diagnosis, natural history, and treatment of mitochondrial diseases due to defects of the respiratory chain (RC).

#### **1. NAMDC Overall Structure and Interactions:**

NAMDC has strengthened its critical relationship with the United Mitochondrial Disease Foundation (UMDF). UMDF has generously continued funding for a full-time NAMDC Project Manager, who works in the Department of Neurology under Dr. Michio Hirano. The current NAMDC Project Manager, Dr. Xiomara Q. Rosales, also serves as the NAMDC Clinical Team Liaison, and has established and led the NAMDC Remote Recruitment program. The UMDF also provides the venue for the annual NAMDC site investigator face-to-face meetings, which is held at the UMDF Annual Meeting. The NIH Program and Scientific Officials, Drs. Adam Hartman, and Danuta Krotoski, have been intimately involved in all NAMDC activities. They have actively participated in all of the NAMDC conference calls and NAMDC site investigator meetings, reviewed all of the NAMDC study protocols, reviewed pilot study grant applications (DK), and monitored all interactions with the DMCC.

**2. NAMDC Central IRB:** To facilitate implementation of study protocols, NAMDC has established a Central Institutional Review Board (CIRB) at Columbia University Medical Center. The CIRB conducts reviews of research requirements and regulations at each of the 17 NAMDC sites at CUMC.

**3. "NAMDC Clinical Registry and Biorepository" [Protocol 7401]:** NAMDC received NIH approval of the NAMDC Clinical Registry and Biorepository protocol on April 20, 2011. As of October 1, 2018, 1396 patients have been enrolled in the registry. A remote enrollment platform has also been established to recruit mitochondrial patients nationwide. The virtual site is now available in English and Spanish. The NAMDC Biorepository for blood, DNA, skin biopsies, and cultured skin fibroblasts has been established at the Mayo Clinic. As of October 1, 2018, samples from 292 patients had been shipped to the NAMDC Biorepository. In addition, NAMDC has established a NAMDC Virtual Fibroblast Biorepository. This database allows web-based data entry on human fibroblast lines available at each NAMDC site. To date, 119 fibroblast lines from eight NAMDC sites have been entered into this Virtual Fibroblast Biorepository, which allow access to any scientific investigator.

**4. NAMDC Diagnostic Criteria:** Because of the vast clinical and genetic heterogeneity of mitochondrial disease, diagnosing these disorders is challenging, but critical to assess natural histories, define prognoses, study pathogenic mechanisms, and develop clinical trials. To facilitate accuracy and uniformity of the diagnosis of mitochondrial disease, Drs. Jaya Ganesh (Camden Medical Center), Geogirene Vladutiu (SUNY Buffalo), and Valentina Emmanuele (Columbia University) have developed NAMDC Diagnostic Criteria, which are being applied on a research basis to the NAMDC Registry.

**5. "Natural History of MNGIE (NAHIM)" [Protocol 7402]** a natural history study of MNGIE has been initiated by Dr. Michio Hirano since 2012. We have enrolled ten patients in the study.

**6. "MNGIE AHSCT (Allogeneic Hematopoietic Stem Cell Transplantation) Safety Study" (MASS) [Protocol 7403].** The Primary Aim of this one-arm, interventional phase 1 study is to evaluate the safety of Allogeneic Hematopoietic Stem Cell Transplant (AHSCT) for MNGIE in terms of primary graft failure and mortality, while minimizing risk, through 100 days post-transplant, using a well-specified adaptive, two-stage safety stopping rule. No patients have been enrolled yet.

**7. “Natural History of Alpers-Huttenlocher Syndrome” [Protocol 7405]** This is a 3-year, multi-site, non-randomized, prospective, observational study of patients with AHS and their siblings. The objectives are to characterize the natural history of AHS. This study is an extension of the NAMDC Clinical Registry. Patient data are collected at regularly-scheduled standard of care appointments, at least every 6 months. Asymptomatic siblings accompany their affected siblings to visits whenever possible and have the same assessments as their affected siblings.

**8. “Natural History of Pearson Syndrome” [Protocol 7408].** The purpose of this 3-year, multi-site, non-randomized, prospective, observational study is to characterize the natural history of Pearson Syndrome. Part of the cohort has now been followed for several years. Patients have been seeing Dr. Parikh along with Ophthalmology and electrophysiology (Cardiology) along with other specialists as needed.

**9. Natural History and Advanced Genetic Study of Pyruvate Dehydrogenase Complex Deficiencies” [Protocol 7412].** Drs. Suzanne DeBrosse, Jirair Bedoyan, and Douglas Kerr (Case Western Reserve University School of Medicine) are PIs of this study, which establish an ongoing database within the NAMDC patient registry specific to PDC deficiency and integrate medical and family reported clinical features, outcomes, advanced genetic analyses, and reported benefits of various interventions and treatments.

#### **NAMDC Pilot Study Program**

**10. “Prototype development of an exome variant analysis pipeline and public interface for the community-wide Mitochondrial Disease Sequence Data Resource (MSeqDR)” [Protocol 7407]** Dr. Marni Falk (Children’s Hospital of Philadelphia) directs this resource development project to produce software for DNA exome variant analysis and public interface for the Mitochondrial Disease Sequence Data Resource (MSeqDR). NAMDC has provided \$25,000 pilot study funding to this project.

**11. “Natural History of Pearson Syndrome” [Protocol 7408]** Dr. Sumit Parik (Cleveland Clinic) is leading this study of the natural history of Pearson syndrome and progression to chronic progressive external ophthalmoplegia (CPEO) and Kearns Sayre syndrome (KSS) as described above.

**12. “Citrulline for MELAS Dose Finding Study [RDCRN Protocol 7416].** Dr. Fernando Scaglia (Baylor College of Medicine) is PI of this pilot project. In this 2-year pilot study, the primary aim is to establish the safest maximal dose of an amino acid, citrulline, which will be used as potential treatment for adult patients with a disorder of energy metabolism called Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS). Together with Drs. Rosales, and Kathy Camp (ODS), Dr. Scaglia has obtained IND to proceed with the clinical trial to start on January 2019.

#### **NAMDC Survey Studies**

**13. “Survey regarding the use of Oocyte Nuclear Transfer in Mitochondrial Disease (Oocyte)” [Protocol 7404].** Recent developments in oocyte mitochondrial replacement therapy (OMRT) as well as pronuclear transfer (PNT) between zygotes may offer new options to prevent transmission of mtDNA-disease. However, it remains to be seen if the non-scientific community in the US will approve of zygotes that contain DNA from three people. Our aim was to survey the level of support for developing these techniques among mtDNA point mutation carrier females and healthy oocyte donors. Ninety-two women carriers, representing 13 distinct mtDNA mutations, completed the “ONGT carrier survey”. The survey indicates that the majority of mtDNA carriers and oocyte donors support the development of ONGT techniques to prevent transmission of mtDNA-diseases. The Journal of Human Reproduction has published the results.

**14. “Survey Regarding NAMDC Research Diagnostic Criteria” [Protocol 7406].** Richard Buchsbaum and Johnston Grier (CUMC) have conducted a survey of NAMDC investigators to assess their opinions regarding the NAMDC research diagnostic criteria. The survey seeks to identify causes of discordant diagnoses generated by NAMDC clinicians and diagnoses generated by the NAMDC diagnostic criteria. Dr. Jaya Ganesh (Cooper Hospital, Camden, NJ) together with members of the NAMDC Diagnostic Committee is using the survey data to revise the diagnostic criteria.

**15. “Nutritional Supplement Use in Mitochondrial Disease” Survey [RDCRN Protocol NAMDC 7411].** Mitochondrial disease physicians’ surveys through the Mitochondrial Medicine Society have shown that virtually all providers recommend a variety of dietary supplements to their patients. In this survey led by Dr. Amel Karaa (Massachusetts General Hospital, Harvard Medical School), patients and parents of patients were asked about their experience taking these dietary supplements as part of their treatment for mitochondrial disease. The manuscript was published by Molecular Genetics and Metabolism.

**16. “Survey on Cardiovascular Events in Patients with Metabolic Disease on Chronic Carnitine Supplementation” [Protocol 7412]** Carnitine intake has lately been shown to increase cardiovascular risks for CAD. Several patients with mitochondrial and other metabolic diseases have been on chronic carnitine supplementation. Dr. Karaa directed this survey, which attempted to capture the cardiac health/events in-patient who are/have been on carnitine. The survey is complete and an abstract was presented at the 2015 UMDF meeting.

**17. “Survey on Motivations and Barriers for Participation in Clinical Trials by Individuals with Mitochondrial Disease” [Protocol 7413]** Dr. Marni Falk directed this RDCRN contact registry survey on the motivations and barriers for participation in clinical trials among individuals with self-reported mitochondrial diseases. The survey is complete. Preliminary results were presented at the NIH Dietary supplement use in Mitochondrial Disease Workshop in December 2014 and by Dr. Zarazuela Zolkipli at the 2015 UMDF meeting.

**18. “Diagnostic Odyssey Survey” [RDCRN Protocol NAMDC 7414].** Johnston Grier designed and implemented this survey under the supervision of Dr. Hirano. The purpose of this survey is to gain an understanding of the “diagnostic odyssey” patients with mitochondrial disease undergo. The survey is complete and data was published was published by Molecular Genetics in April 2018. A second phase of this survey is currently ongoing.

**19. NAMDC Clinical Investigator Training Program.** Dr. Richard Haas (University of California at San Diego) is the PI of the NAMDC training program, which train the next generation of mitochondrial disease clinical investigators. This fellowship program has trained six clinicians to date. The fellows spend at least 6 months at USCD and do two additional rotations at other NAMDC sites to gain further clinical experience. Dr. Haas has implemented highly successful monthly videoconferences as training tools, where NAMDC investigators have presented their research and interesting cases.





THE PORPHYRIAS CONSORTIUM

## **55. Porphyrias Consortium**

**Principal Investigator: Robert J. Desnick, PhD, MD,  
Icahn School of Medicine at Mount Sinai, NY, NY**

**For the past nine years the Porphyrias Consortium (PC) has been focused on improving the diagnosis, treatment, and quality-of-life for patients suffering from the inborn errors of heme biosynthesis, the Porphyrias.**

### **Disorders under study**

- Acute Hepatic Porphyrias: Acute Intermittent Porphyria (AIP), Hereditary Coproporphyria (HCP), Variegate Porphyria (VP), and Aminolevulinic Acid Dehydratase Deficiency Porphyria (ADP)
- Cutaneous Porphyrias: Porphyria Cutanea Tarda (PCT), Congenital Erythropoietic Porphyria (CEP), Erythropoietic Protoporphyria (EPP), and X-Linked Protoporphyria (XLP)

### **PC Sites**

<b>Institution</b>	<b>Investigator</b>
Icahn School of Medicine at Mount Sinai	Robert J. Desnick, MD, PhD
University of Texas Medical Branch	Karl E. Anderson, MD
University of California at San Francisco	D. Montgomery Bissell, MD
University of Alabama	Brendan McGuire, MD
Wake Forest University	Herbert L. Bonkovsky, MD
University of Utah	John D. Phillips, PhD
<b>Satellite Sites</b>	
University of Washington	Sioban Keel, MD
University of Miami	Cynthia Levy, MD
University of Illinois at Chicago	John Quigley, MD

### **Coordination with the American Porphyria Foundation (APF)**

The Consortium remains closely aligned with the APF:

- The PC Steering Committee, which includes the APF Executive Directors, Mrs. Desiree Lyon Howe and Mrs. Kristen Wheeden, meets monthly by phone to discuss Consortium progress, plans, and issues, and quarterly in person;
- The APF monthly Newsletter and their website continues to inform patients and families of our efforts, emphasizing the importance of enrolling in the Contact Registry and participating in Consortium studies, thus playing an active role in the identification and enrollment of study subjects;
- The APF continues to provide financial support for PC Trainees as part of their “Protect the Future” Program.

### **Ongoing Studies**

- 7201 Longitudinal Study of the Porphyrias:** a longitudinal observational study investigating the clinical presentation, biochemical findings, genetic status, complications, and therapeutic outcomes of diagnostically confirmed individuals with any of the acute or cutaneous porphyrias. Over 840 subjects enrolled to date at all sites.
- 7203 A double-blind, randomized, placebo-controlled, parallel group trial on the efficacy and safety of Panhematin<sup>TM</sup> in the treatment of acute attacks of porphyria:** a single site Phase II interventional study to evaluate the clinical efficacy and safety of Panhematin<sup>TM</sup> compared to glucose treatment started early for acute attacks of porphyria. Actively enrolling at UTMB, 20 subjects have been enrolled to date and an interim analysis is underway.
- 7204 Clinical Diagnosis of Acute Porphyrias:** an observational study to determine the prevalence of abnormal lab tests and porphyria-like symptoms in adult family members of index cases of acute porphyrias, to devise a clinical index for the likelihood of acute porphyria genetic carrier state. Closed to enrollment, data



analysis underway.

4. **7206 Therapeutic Studies of PCT:** a pragmatic study comparing the standard treatments for PCT by assessing time to remission, the rates of recurrence of symptoms, and the effects of susceptibility factors.
5. **7207 Erythropoietic Protoporphyrins: Natural History, Genotype-Phenotype Correlations, and Psychosocial Impact:** an observational study of the natural history, complications, psychosocial impact, genotype-phenotype correlations, and therapeutic outcomes in people with erythropoietic protoporphyria. Closed to enrollment, 150 subjects in follow up.
6. **7208 Evidence-Based Assessment of Medication Sensitivity in Acute Hepatic Porphyrins:** an innovative online protocol through the Contact Registry to collect reports from patients with an acute porphyria, in which an acute attack was triggered by a medication. The goal is to develop an evidence-based list of medications that are safe/not safe in patients with acute porphyria and to assess the degree of risk.
7. **7209 Effect of Oral Iron Therapy on Erythrocyte Protoporphyrin Levels in the Erythropoietic Protoporphyrins:** a pilot clinical trial to determine the efficacy and safety of oral iron administration in the protoporphyrias, as the literature has conflicting reports of the benefit of iron in these patients.
8. **7210 Newer Direct-Acting Anti-Viral Agents as Sole Therapy of Porphyria Cutanea Tarda in Subjects with Chronic Hepatitis C:** an open-label study with a non-inferiority design, to assess whether Harvoni is an effective treatment of PCT, as the literature indicates PCT clearing when the underlying HCV is treated

### Completed Studies

1. **7202 Mitoferrin-1 Expression in Patients with Erythropoietic Protoporphyria:** an observational study to determine if abnormal *mitoferrin-1* (*MFRN1*) expression contributes to the phenotype in patients with the genetic/metabolic disorder erythropoietic protoporphyria (EPP). Results will be published soon.
2. **7205 Quantification of the Effects of Isoniazid Treatment on Erythrocyte and Plasma Protoporphyrin IX Concentration and Plasma Aminolevulinic Acid in Patients with Erythropoietic Protoporphyria:** an interventional pilot study to determine whether INH lowers the plasma concentration of protoporphyrin IX in patients with EPP and XLP. Eleven patients completed the study and results were presented at the International Congress on Porphyrins and Porphyrins.

### **Training Program**

**Objective:** To address the shortage of physicians and scientists and lack of knowledge about porphyrias among physicians, patients and the general public by:

1. Training more physicians and scientists to become qualified as experts in the field of the porphyrias and to be the next generation of porphyria experts and scientists in the U.S.,
2. Providing information and training to primary care and specialist physicians to provide appropriate diagnosis and clinical management services to a widespread population of patients with multiple types of porphyria in the U.S., and
3. Educating patients, their families, and the public so they will have an appropriate level of understanding of porphyrias.

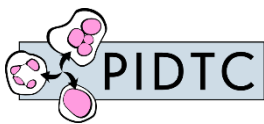
### **Accomplishments:**

1. Since the inception of the PC in 2009, 59 individuals have been trained, of whom 39 were post-graduates or junior faculty, and 9 were students. 8 trainees achieved grant funding.
2. Each Trainee has an active role in the diagnosis and management of porphyria patients, clinical and basic research, publication and education.
3. Four Satellite Sites of the Porphyrias Consortium have been established with support from the APF as part of the “Protect the Future” program; Cynthia Levy, MD, University of Miami; Sioban Keel, MD, University of Washington; Angelika Erwin, MD, PhD, Cleveland Clinic (closed); and John Quigley, MD, University of Illinois at Chicago.
4. An R13 supported research conference titled “Heme Biosynthesis and the Porphyrias: Recent Advances,” was held in Orlando, FL from January 12-14, 2018 with the aim of advancing understanding of heme biosynthesis and treatment of the porphyrias by bringing together basic scientists, clinical investigators, and trainees. A total of 130 attendees registered for the conference, including 35 trainees.



### **Recent Publications**

1. Balwani M, Wang B, Anderson KE, Bloomer JR, Bissell DM, Bonkovsky HL, Phillips JD, Desnick RJ; Porphyrias Consortium of the Rare Diseases Clinical Research Network. Acute Hepatic Porphyrias: Recommendations for Evaluation and Long Term Management. *Hepatology*. 2017;66(4):1314-1322. PMID: 28605040
2. Singal AK, Venkata KVR, Jampana S, Islam F-U, Anderson KE. Hepatitis C treatment in patients with porphyria cutanea tarda. *American Journal of Medical Sciences* 2017, 353(6): 523-528. PMID: 28641714. PMCID: PMC5484053
3. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. *NEJM*. 2017;377:862-72. PMID: 28854095
4. Salameh H, Sarairah H, Rizwan M, Kuo YF, Anderson KE, Singal AK. Relapse of porphyria cutanea tarda after treatment with phlebotomy or 4-aminoquinoline antimalarials: a meta-analysis. *Br J Dermatol*. 2018 Epub PMID: 29750336
5. Indika NLR, Kesavan T, Dilanthi HW, Jayasena KLSPKM, Chandrasiri NDPD, Jayasinghe IN, Piumika UMT, Vidanapathirana DM, Gunarathne KDAV, Dissanayake M, Jasinge E, Arachchi WK, Doheny D, Desnick RJ. Many pitfalls in diagnosis of acute intermittent porphyria: a case report. *BMC Res Notes*. 2018;11(1):552. PMID: 30071891
6. Chen B, Solis-Villa C, Erwin AL, Balwani M, Nazrenko I, Phillips JD, Desnick RJ, Yasuda M. Identification and characterization of 40 novel hydroxymethylbilane synthase mutations that cause acute intermittent porphyria. *J Inherit Metab Dis*. 2018 Epub. PMID: 29594648
7. Lala SM, Naik H, Balwani M. Diagnostic Delay in Erythropoietic Protoporphyria. *J Pediatr*. 2018 Epub PMID: 30041937
8. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute Hepatic Porphyrias--Review and Recent Progress. *Hepatology Communications*. 2018 *In press*.
9. Gou E, Weng C, Greene T, Anderson KE, Phillips JD. Longitudinal Analysis of Erythrocyte and Plasma Protoporphyrin Levels in Patients with Protoporphyria. *Journal of Applied Laboratory Medicine*. 2018 Epub.



## **56. Primary Immune Deficiency Treatment Consortium (PIDTC)** **Principal Investigator: Jennifer Puck, M.D.**

The Primary Immune Deficiency Treatment Consortium (PIDTC) is a unique multi-institutional collaboration now comprising 44 specialized centers across North America with interest and expertise in primary immunodeficiency (PID) diseases. The PIDTC was established to collect and analyze uniform data from large patient cohorts and to enlist immunologists, transplant physicians, researchers, and patient advocacy groups (PAGs) to pose and answer questions regarding best treatment approaches to lead to optimal outcomes for these rare diseases.

### **Major Goals and Diseases:**

- Conduct multi-center studies of PID diseases, organized into four Projects: Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease (CGD), Wiskott-Aldrich Syndrome (WAS) and Primary Immune Regulatory Disorders (PIRD). Goals are to expand understanding and improve treatments and outcomes for patients with rare PIDs.
- Recognize, train and encourage new leaders in PID to foster growth of future innovative research.
  - Fund timely, innovative research through the Pilot/Feasibility Core.
  - Provide Career Enhancement for new PID investigators.
- Engage Patient Advocacy Groups to share information between patients, parents, clinicians and scientists about up-to-date approaches PID.
- Learn from and contribute to Rare Disease Research by collaborating with RDCRN partners.

### **PID Studies – Current/ Proposed:**

#### **Severe Combined Immunodeficiency (SCID) Studies:**

**Protocol 6901: A Prospective Natural History Study of Diagnosis, Treatment and Outcomes of Children with**

**SCID Disorders.** (opened Aug 2010; will close Aug 2019)

**Protocol 6902: A Retrospective and Cross-Sectional Analysis of Patients Treated for SCID Since January 1, 1968.**

(opened Dec 2010; will close Aug 2019)

**Protocol 6907 SCID** (proposed for Sep 2019 opening)

The goal of the SCID studies is to advance the understanding, diagnosis, management, and treatment of SCID to define how best to achieve survival and full immune reconstitution after allogeneic hematopoietic cell transplant (HCT) or gene therapy. Results to date include demonstration that the specific genotype (from over 20 causative loci) plays a major role in outcome. Thus, it is vital to ascertain the underlying genetic cause in all patients. 279 patients have been enrolled to date in a prospective study and 741 in a retrospective/cross-sectional study. While most infants have known genotypes, those without a gene diagnosis will be studied with deep sequencing and mechanistic studies. These cohorts will be combined for future longitudinal studies with continuing enrollment of new patients. SCID has undergone a major change in presentation with newborn screening, now nearly universal in the USA and in place in several Canadian provinces. Infections observed despite newborn screening and conditioning regimens in very young infants require further systematic study for development of best practices.

#### **Chronic Granulomatous Disease (CGD) Studies:**

**Protocol 6903: Analysis of Patients Treated for Chronic Granulomatous Disease Since January 1, 1995.** (opened Jan 2014; will close Aug 2019)

**Protocol 6908 CGD** (proposed for Sep 2019 opening)

The goal of the CGD studies is to define optimized curative transplant strategies and to understand and treat auto-inflammatory disease pre- and post-allogeneic HCT or gene therapy, a previously underestimated component of the disorder. A novel finding has been that successful HCT alleviated not only susceptibility to infection, but also auto-inflammatory complications. 379 patients have been enrolled to date.

#### **Wiskott-Aldrich Syndrome (WAS) Study:**

**Protocol 6904. Analysis of Patients Treated for Wiskott-Aldrich Syndrome Since January 1, 1990.** (opened Oct 2013; will close Aug 2019)

The goal of the WAS study has been to define the critical clinical factors and biologic markers that predict survival and other outcomes of children with WAS following HCT or medical therapies and to characterize the long-term outcomes. The overall study closed to new enrollment in September 2018, with publications to include outcomes and quality of life in 129 long-term survivors who received HCT after 2005. 306 patients have been enrolled.

**Primary Immune Regulatory Disorders (PIRD) Study** (proposed for Sep 2019 opening):

The goal of the PIRD study is to define natural history and long-term outcomes in PIRD following treatment with HCT, biologics and small molecules, while also providing basic insights into mechanisms of disease pathogenesis and therapeutic responsiveness.

**Pilot/Feasibility Core:** This core is responsible for soliciting, reviewing and overseeing the Pilot Projects awarded each year. Proposals with high scientific merit and potential to advance the field in an impactful manner are chosen. Pilot Projects may focus on PIDs already under study by the PIDTC or disorders under consideration for potential addition to the PIDTC disease list. The PIDTC has awarded 7 Pilot Projects to date, each selected after competitive and stringent review and funded for 1-2 years.

**Career Enhancement Core:** This core encourages involvement in rare disease research at the level of fellows and early faculty, and to promote interactions with senior physician scientists active in the field. An Annual PIDTC Scientific Workshop and Education Day offer opportunities for networking and career advancement for PID researchers in the PIDTC as well as RDCRN investigators in allied fields. The PIDTC has granted 20 fellowship awards to date. Our awardees have continued to contribute to PID research; all remain in academic positions.

**PIDTC Patient Advocacy Groups (PAGs):** The PIDTC engages multiple immunodeficiency PAGs – the Immune Deficiency Foundation (IDF), Jeffrey Modell Foundation (JMF), SCID Angels for Life Foundation, CGD Foundation and Wiskott-Aldrich Foundation – in every facet of our organization. Members of the PIDTC Steering Committee and Scientific Planning Committee serve on PAG boards, assist in development of PAG patient-family education materials, summarize each major PIDTC publication in lay language on the PIDTC and pertinent PAG websites, and also participate in PAG national and regional meetings. Representatives of our PAGs have contributed to the PIDTC website, the Annual PIDTC Scientific Workshops, and PIDTC publications. PAG members are represented on each PIDTC Protocol, serve on the PIDTC Scientific Program Committee and assist in protocol development and recruitment of subjects.



## **57. Rare Kidney Stone Consortium (RKSC)**

**Principal Investigator: Dr. Dawn Milliner; Co-P.I. Dr. John Lieske**

Patients with primary hyperoxaluria (PH), cystinuria, adenine phosphoribosyltransferase deficiency (APRTd), and Dent disease experience recurring stones from childhood on and are at risk for chronic kidney disease (CKD). These conditions are rare enough that there has been minimal sharing of information and expertise among clinicians and scientists, a situation that has slowed progress toward effective treatments. The Rare Kidney Stone Consortium (RKSC) was formed to advance understanding and treatment of these disorders.

**The goals of the Rare Kidney Stone Consortium (RKSC) are to: (1) Integrate and engage patients and patient advocacy groups (PAGs) as partners in research work to improve disease outcomes, (2) Identify patients at risk of progressive loss of kidney function, (3) Identify pathways of kidney injury, and (4) Identify novel therapeutic targets for potential pilot studies.**

A secure web-based patient registry and a tissue bank for each disease supports clinical studies, and to generate and test new hypotheses. We have developed a robust infrastructure to support our patient cohorts. Longitudinal data collection is in use to define the natural history of each disease over the lifetime of individual patients. Complementary analyses of prospective cohort and retrospective registry information are continuously expanding knowledge regarding clinical expression of each of these hereditary stone diseases, in order to provide clues about potentially modifiable factors that influence disease severity including factors leading to kidney injury. The registries provide well-characterized patient cohorts available for clinical trials as promising new treatments become available. Prospective urine and blood samples from the longitudinal cohorts added to the biobank expand our study potential and ability to assess the inflammatory and metabolomic biosignatures of the cohorts. The Consortium also supports a vigorous Pilot Project and Clinical Training program for new investigators.

### **Patient Advocacy Groups**

Goals of the RKSC are achieved through close collaboration with our PAG partners: The Oxalosis and Hyperoxaluria Foundation (OHF), International Cystinuria Foundation (ICF), Lowe Syndrome Association (LSA), the Dent Disease Foundation, and the APRTd Patient Support Group. Web sites and newsletters of the PAGs inform their members regarding disease manifestations and treatments, results of ongoing research, and alert their members to RKSC studies open for enrollment. The RKSC maintains an active social media presence through Facebook, Rare Share, and Twitter. In partnership with our PAGs, patient and family meetings have been held for the purpose of informing patients and their family members about their disease, raising awareness of research, encouraging their participation in registries and clinical studies, and providing peer support. Importantly, these meetings also promote direct communication among patients, family members, clinicians, and investigators. These conversations inform clinicians and scientists of disease burden experienced by those with the disease, and can provide guidance as to future research direction.

### **Active Protocols**

#### **Hereditary Causes of Nephrolithiasis and Kidney Failure (RDCRN 6401)**

To advance understanding of disease expression and factors associated with renal injury in PH, cystinuria, Dent disease and APRTd with the goal of developing new treatments directed at protecting renal function, and reducing nephrocalcinosis and stone formation. Longitudinal data collection defines the natural history of each disease over the lifetime of individual patients, allowing identification of risk factors for disease progression.

#### **Biobank Protocol (RDCRN 6404)**

To obtain high quality biological samples from well characterized patients with PH, cystinuria, APRTd, and Dent disease, and from their family members for use in research.

#### **Genetic Characterization and Genotype/Phenotype Correlations in Primary Hyperoxaluria (RDCRN 6406)**

#### **Health-Related Quality of Life in Rare Kidney Stone Formers (RDCRN 6408)**

### **Proteomics of Primary Hyperoxaluria Type I (PHI): A Rare Calcium Oxalate Stone Disease (RDCRN 6409)**

Urine aliquots from PHI patients & healthy sibling controls; and longitudinally collected 24 hr. urine from patients with PHI are examined to determine unique proteomic markers of PHI vs. healthy (intra-familial) controls.

### **Role of Phosphorus and FGF23 in Patients with Dent Disease (RDCRN 6414)**

To determine the role of FGF 23 in the impaired calcium and phosphorus metabolism in Dent disease; to evaluate if supplementation with phosphorus for 2 weeks may reduce hypercalciuria; to compare Dent patients with idiopathic calcium stone patients with and without phosphate leak.

### **Descriptive Analysis of Gut Microbiome Alterations in Hyperoxaluric Patients (RDCRN 6416)**

To characterize the microbiome in 4 groups of participants (primary hyperoxaluria type 1 (PH1), idiopathic CaOx stone, enteric hyperoxaluria (EH) and healthy participants) by comparing the number of species and diversity of the microbial populations and pathway for oxalate metabolism by paralleling the gene expression in enzymes involved in oxalate degradation by gut bacteria.

### **Prospective Research Rare Kidney Stones (ProRKS) (RDCRN 6417)**

To establish prospective longitudinal study of cohorts of patients with PH, enteric hyperoxaluria, cystinuria, Dent disease, Lowe syndrome (Dent type 2), and APRT deficiency and identify biomarkers associated with disease progression.

### **Characterization of Monogenic Stone Diseases (RDCRN 6419)**

To identify and define the etiology of monogenic diseases causing nephrolithiasis and nephrocalcinosis and to provide definitive genetic information for research diagnostics, using a screening panel of > 100 genes and next generation sequencing.

### **Effect of Increasing Doses of Tiopronin on Cystine Capacity in Patients with Cystinuria (RKSC 6421)**

To determine the minimum effective dose of the cysteine binding thiol drug (CBTD) Tiopronin on urine cystine capacity, (a measure of cystine solubility in the urine), in patients with cystinuria to evaluate the effect of escalating doses of cystine binding thiol drugs. The overall goal will be to help guide therapy and ultimately minimize unnecessary side effects caused by larger doses.

### **Pilot Studies**

- Establishment of primary cultures from PHI hepatocytes, Hari Koul
- New drugs for cystinuria, Amrik Sahota
- CLCN5 Allelic Heterogeneity of Dent's Disease, E. Tosetto
- Novel assay for the determination of urinary 2,8-dihydroxyadenin and other key urinary purine metabolites, V. Edvardsson
- Descriptive and functional analyses of gut microbiome alterations in hyperoxaluria, L. Nazzal
- Proteomics of crystalline nephropathy, C. Langman and E. Brooks
- Screening of monogenic stone formers and recurrent stone formers for disease causing mutations, P. Harris
- Characterization of specific renal cellular activation or injury in primary hyperoxaluria. M. Jayachandran
- Prevalence of Adenine Phosphoribosyltransferase Deficiency, V. Edvardsson
- Dent disease and glomerular damage: The role of CIC-5 in podocytes, L. Ganesello
- Inhibition of oxalate synthesis by RNA interference, K. Wood
- The isolated live perfusion for studying hepatic oxalate transport in PH, J. Whittamore

### **Training Program**

- Dr. Lada Beara Lasic, Dent Disease: Role of phosphorus and FGF 23 in patients with Dent disease
- Dr. Hatem Amer, Transplant nephrocalcinosis: Incidence, risk factors and graft function
- Dr. Larissa Kovacevic, Urine proteomic analysis in cystinuric patients with renal stones
- Dr. Whittamore, Primary Hyperoxaluria: Acid-base regulation of intestinal oxalate transport
- Dr. Lama Nazzal, Descriptive analysis of gut microbiome alterations in hyperoxaluric conditions



- Dr. David Sas, Characterization of urinary microbiome in primary hyperoxaluria and cystinuria
- Dr. Min-Hwang Chang, Mechanistic studies of CLCN5 point mutations to understand genotype-phenotype correlations in Dent disease
- Dr. Min-Hwang Chang, Chemical chaperones of CLC-5 R345W mutations and new Dent disease animal model.

### **RDCRN R25 Rare Disease RKSC Trainees:**

Past RKSC Trainees: L. Nazzari, MD, MSc (NYU, 2016), D. Sas, DO, MPH (Mayo Clinic, 2017), M. Chang, PhD (Mayo Clinic, 2017)

Current RKSC Trainee: S. Fargue, MD, PhD (UAB, 2018)

New RKSC Trainees (start 2018): H. Runolfsdottir, MD (Landspítali-The Nat'l U. Hospital of Iceland), F. Shen, PhD and M. Jayachandran, PhD (Mayo Clinic), K. Wood, MD (UAB) and L. Ganesello, PhD (University of Padua, Padova, Italy)





**58. Rare Lung Diseases Consortium**  
**Principal Investigator: Bruce C. Trapnell, MD**  
[www.RareDiseasesNetwork.org/RLDC](http://www.RareDiseasesNetwork.org/RLDC)

The Rare Lung Diseases Consortium (RLDC) and its affiliated clinical network, the Rare Lung Diseases Clinic Network, is an international, multi-center, clinical research infrastructure devoted to multi-center research for rare lung diseases. The RLDC is one of the founding consortia within the Rare Diseases Clinical Research Network (RDCRN) [U54RR019498] and was granted funding for a second 5-year period from the NIH through the Office of Rare Diseases Research (ORDR) and the National Heart, Lung, and Blood Institute (NHLBI) [U54HL127672].

**The RLDC and its affiliated Rare Lung Diseases Clinic Network includes 31 clinical sites in the United States and 24 international sites.**

**The Specific Aims of the RLDC in this second 5-year grant cycle include:**

1. Establish a highly integrated clinical research infrastructure focused to the study of Lymphangiomyomatosis (LAM), Pulmonary Alveolar Proteinosis (PAP), Hermansky-Pudlak Syndrome (HPS), and other rare lung diseases
2. Conduct longitudinal and therapeutic clinical studies related to LAM, PAP and HPS
3. Conduct a pilot and demonstration project program within the RLDC
4. Provide clinical research training related to rare lung diseases at RLDC clinical centers
5. Develop rare lung disease educational materials for patients, doctors, and the public

**Diseases under study:** Birt-Hogg Dube, HPS, LAM, Pulmonary Alveolar Microlithiasis, PAP, Pulmonary Langerhans Histiocytosis

**Longitudinal/Cohort Studies:**

**RLD 5701:** QUANTitative chest computed tomography UnMasking emphysema progression in alpha-1 antitrypsin deficiency, *recruitment complete*, 49 participants

**RLD 5709:** Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS), *actively enrolling*, current enrollment 372/600

**RLD 5710:** A Longitudinal Study of Hermansky-Pudlak Syndrome Pulmonary Fibrosis, *actively enrolling*, current enrollment 64/80

**RLD 5712:** Longitudinal Evaluation of Pulmonary Alveolar Proteinosis; *actively enrolling*, current enrollment 21/100

**Clinical Trials:**

**RLD 5702:** Multicenter International Lymphangiomyomatosis Efficacy and Safety of Sirolimus Trial, *recruitment complete*, 89 participants

**RLD 5713:** Multicenter Interventional Lymphangiomyomatosis Early Disease Trial (The MILED Trial), *actively enrolling*, current enrollment 16/60

**RLD 5717:** Evaluation of the Safety, Pharmacokinetics and Pharmacodynamics of Inhaled Sargramostim in Patients with Autoimmune Pulmonary Alveolar Proteinosis, *actively enrolling*, current enrollment 5/10

**Observational Studies**

**RLD 5714:** Assessment of Safety of Air Travel in Patients with Diffuse Cystic Lung Disease, *actively enrolling*, current enrollment 260/300

**RLD 5715:** Retrospective Review of CT Images in Rare Lung Diseases, *recruitment complete*, 68 participants

**RLD 5716:** Use of Hyperpolarized <sup>129</sup>Xe MR Lung Imaging in Children and Adults, *recruitment complete*, 17 participants

**Cross-Sectional Studies**

**RLD 5706:** Multicenter International Cross-Sectional Evaluation of Pulmonary Alveolar Proteinosis, *recruitment complete*, 134 participants

**RLD 5711:** A National Registry for Pulmonary Alveolar Proteinosis, *actively enrolling*, current enrollment 114/500

### FDA approval

**Rapamune (sirolimus)** is the first drug approved (May 2015) by the U.S. Food and Drug Administration to treat lymphangioleiomyomatosis (LAM).

### RLDC Scholars Program:

This is a training program for physician-investigators who have developed an interest in rare lung diseases and wish to pursue a period of specialized training with an emphasis on translational and patient-oriented clinical investigation. The fellowship is designed to provide a balance of clinical, basic, and translational research training. The fellow will develop the skills needed to identify important and answerable clinical problems, design experiments that provide pivotal preclinical data, and design and execute effective clinical trials. RLDC Scholars at Cincinnati Children's Hospital Medical Center and University of Cincinnati Medical Center will participate in the Rare Lung Disease/Genetic Pulmonary Disease Fellowship. However, scholars may participate in this program at one of the other RLDC sites. **Number of RLDC Fellows:** Current: 1, Previous: 6

### Patient Advocacy Groups:

Alpha-1 Antitrypsin Foundation, Children's Interstitial and Diffuse Lung Disease (chILD) Foundation, Hermansky-Pudlak Syndrome (HPS) Network, Inc, Histiocytosis Association, Lymphangiomatosis and Gorham's Disease Alliance (LGDA), The LAM Foundation, PAP Foundation, Sjogren's Syndrome Foundation. Advocacy Groups are actively involved in the RLDC by promoting study participation and recruitment, advising on study design and implementation, and participating in CPAG activities.

International Meetings and Educational Opportunities: In 2016, the RLDC and The LAM Foundation hosted RLDC 2016 & LAMposium, which was the largest and most comprehensive international rare lung disease meeting in history, bringing together more than 450 physicians, scientists, patients, families, and patient advocates from 21 countries to discuss RLD research and advancements in diagnostics and clinical care. The RLDC infrastructure provided the opportunity to solicit more than 30 sponsors and nearly \$400,000 in support from industry, academic institutions, the NIH, patients and families, and patient advocacy groups. In 2018, the RLDC and The LAM Foundation built upon the success of the RLDC 2016, again bringing together over 500 physicians, scientists, patients, families, and patient advocates from 23 countries to discuss RLD research and advancements in diagnostics and clinical care. The RLDC collaborative infrastructure led to the engagement of 29 sponsors and nearly \$400,000 in support from industry, academic institutions, the NIH, patients and families, and patient advocacy groups for this educational conference. The conference offered 14.5 CME credit hours and attracted four new educational partners.

### Additional Funding:

The RLDC has been successful in obtaining funding to supplement the RDCRN. Additional support for RLDC projects comes from grants from NCATS 3UL1TR001425-02S1 (RLD 5717), NHLBI U01HL131755 (RLD 5713) and 3U54HL127672-02S1 (RLD 5715 and RLD 5716), the Translational Pulmonary Science Center in Cincinnati, the LAM Foundation, Industry partners, and other sources.





## **59. Rett Syndrome, MECP2 Duplication Disorder, and Rett-related Disorder Consortium**

**Principal Investigator: Alan Percy, MD – University of Alabama at Birmingham (UAB)**

**Study Administrator and Co-PI: Jeffrey Neul, MD, PhD – Vanderbilt University (VU)**

**Project Manager: Jane Lane, RN BSN – University of Alabama at Birmingham (UAB)**

**Disorders:** Rett Syndrome; *MECP2* Duplication Disorder; *CDKL5* Disorder; *FOXG1* Disorder

### **Study sites (site PI):**

Baylor College of Medicine: Daniel Glaze  
Children's Hospital of Philadelphia: Eric Marsh  
Cleveland Clinic: Sumit Parikh  
Greenwood Genetic Center: Steve Skinner  
Rush Medical Center: Peter Heydemann  
University of California San Diego: Richard Haas  
Vanderbilt University: Sarika Peters

Boston Children's Hospital: Mustafa Sahin  
Cincinnati Children's Hospital: Shannon Standridge  
Gillette Children's Hospital: Art Beisang  
Oakland Children's Hospital: Mary Jones  
University of Alabama at Birmingham: Alan Percy  
University of Colorado: Tim Benke  
Washington University St. Louis: Robin Ryther

### **Major Goals, Status, and Results**

- 1: a) Longitudinal studies of disorders under study including clinical progress, genotype-phenotype correlations, and survival surveillance, clinical severity assessments, and quality of life measures;  
b) Currently >850 enrolled (goal = 1200 enrollees) in addition to >1200 enrolled in initial study;  
Results described under publications.
- 2: a) Neurophysiologic studies of visual and auditory evoked potentials with high density EEG analysis;  
b) Currently 100 enrolled (goal = 250 and 50 controls);  
c) Results reveal differences from controls and between each disorder;  
d) Abstract submitted to American Academy of Neurology on delta/alpha differences in EEG power spectral analyses in RTT.
- 3: a) Biobanking of blood for plasma, DNA, and RNA and skin biopsy for induced pluripotent stem cells;  
b) Currently 173 enrolled (goal = 1500 samples);  
c) Results from initial metabolomics assessment are pending; second phase analyses to follow.

### **Pilot Studies**

- 1: Development of a Rett-specific behavioral outcome measure: The first round of 100 parent participants has been completed. Preliminary psychometric analyses revealed good to excellent properties. A Bayesian factor analysis is being completed in preparation for the possible reorganizing of items and conduct of the second phase, assessing the response in 250 parents.
- 2: Metabolomics assessment to identify potential biomarkers: The initial round of metabolomics testing has been analyzed and a report on this phase is being generated. We are currently collecting additional plasma samples (see Biobanking project above) for the second phase analysis.
- 3: Development of a reliable, valid global severity scale: Employing item response theory, NHS data from 5201 and 5211 will be used to develop a global severity outcome measure for use in Rett syndrome treatment trials, examine its reliability and validity, and conduct preliminary sensitivity analyses. The analyses are being conducted through RTI in the North Carolina research triangle.

### **Clinical Trials (involving consortium sites but not part of Consortium activities)**

- 1: **IGF-1 Phase 2 Trial:** Boston Children's Hospital, Rush Medical Center, and Greenwood Genetic Center
- 2: **Trofinetide Phase 2 Trials (Neuren Pharmaceuticals):** Involved 12 of 14 Consortium sites.
- 3: **Sarizotan Trial (Newron Pharmaceuticals):** Involves 5 of 14 Consortium sites
- 4: Four additional trials are in various stages of planning, all involving RTT Consortium sites.

**Training Program:** Training is progressing well with two trainees now participating and four having completed their training, two in the two-year program supported by RS.O, and two in research-related studies through UAB. The two current trainees, Carrie Buchanan and Cary Fu participate in the R25 RDCRN training initiative. The two trainees who have completed the two-year program also participated in the R25 program.

**Role and Involvement of Patient Advocacy Groups:** Patient advocacy groups are integral to the RTT consortium. These include Rettsyndrome.org (RS.O), Rett Syndrome Research Trust, MECP2 Duplication Foundation, International Foundation for *CDKL5* Research, LouLou Foundation, and International FOXG1 Foundation. The Patient Advocacy Groups participate in on-going consortium activities and stimulate active recruitment of participant enrollment, particularly through their websites. RS.O provides funding for the three major goals, the pilot projects, and training and supports the clinical trial initiatives. Rettsyndrome.org also provides funding for the sites at Cincinnati Children's, Gillette Children's, and Washington University St. Louis sites. The International Foundation for *CDKL5* Research provides funding for the Cleveland Clinic site.

### Representative publications:

Neul JL, Fang P, Barrish J, et al. Specific Mutations in Methyl-CpG-Binding Protein 2 Confer Different Severity in Rett Syndrome. **Neurology** **70**:1313-1321,2008 [PMID: PMC2677974]

Lane JB, Lee H-S, Smith LB, et al. Clinical severity and quality of life in children and adolescents with Rett Syndrome. **Neurology** **77**:1812-1818, 2011. [PMID: PMC3233210]

Tarquinio D, Motil K, Hou W, et al. Growth Failure in Rett Syndrome: Specific Growth References. **Neurology** **79**:1653-1661, 2012. [PMID: PMC3468773]

Cuddapah VA, Pillai RB, Shekar KV, et al. *Methyl-CpG-binding protein 2 (MECP2)* mutation type is associated with disease severity in Rett syndrome. **J Med Genet** **51**:152-158, 2014. [PMID: PMC4403764]

Neul JL, Lane JB, Lee H-S, et al. Developmental delay in Rett syndrome: data from the natural history study. **Journal of Neurodevelopmental Disorders** 2014, 6:20 [PMID: PMC4112822]

Killian JT, Lane JB, Cutter GR, et al. Pubertal Development in Rett Syndrome Deviates from Typical Females. **Pediatr Neurol** **51**:769-775, 2015. [PMID:PMC4254166]

Tarquinio D, Hou, W, Neul JL, et al. Age of diagnosis in Rett syndrome: patterns of recognition among diagnosticians and risk factors for late diagnosis. **Pediatr Neurol** **52**:585-591,2015 [PMID:PMC4442062]

Tarquinio DC, Hou W, Neul JL, et al. The changing face of survival in Rett syndrome and *MECP2*-related Disorders. **Pediatr Neurol** **53**:402-411,2015. [PMCID: PMC4609589]

Killian, Jr. JT, Lane JB, Lee H-S, et al. Caretaker Quality of Life in Rett Syndrome: Disorder Features and Psychological Predictors. **Pediatr Neurol** **58**:67-74, 2016. [PMCID: PMC4899118]

Sajan, SA, Jhangiani SN, Muzny DM, et al. Rett Syndrome that is not caused by mutations in *MECP2*, *CDKL5*, and *FOXG1* is genetically complex, heterogeneous, and enriched in mutations in chromatin regulators. **Genet in Med.** [PMCID: PMC5107176]

Ward CS, Huang T-W, Herrera JA, et al. Loss of MeCP2 causes urological dysfunction and contributes to death by kidney failure in mouse models of Rett Syndrome. **PloS One** PONE-D-16-11130R1, 2016. [PMCID: PMC5102405]

Tarquinio DC, Hou W, O'Leary H, et al. Longitudinal Course of Epilepsy in Rett Syndrome and Related Disorders. **Brain** **140**(Pt 2):306-318, 2017. [PMID: PMC6026556]

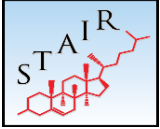
Lane JB, Salter AR, Jones NE, et al. Assessment of Caregiver Inventory for Rett Syndrome. **Journal of Autism and Developmental Disorders**, **47**:1102-1112, 2017. [PMCID: PMC5357458]

Killian JT, Lane JB, Lee H-S, et al. Scoliosis in Rett Syndrome: Progression, Comorbidities, and Predictors, **Pediatr Neurol** **70**:20-25, 2017 [PMID: PMC5461984]

Glaze DG, Neul JL, Percy A, et al. A Double-Blind, Randomized, Placebo-Controlled Clinical Study of Trofinetide in the Treatment of Rett Syndrome. **Pediatr Neurol** **76**:37-46, 2017. [PMID: PMC28964591]

Tarquinio DC, Hou W, Neul JL, et al. The course of awake breathing disturbances across the lifespan in Rett syndrome. **Brain & Dev**, 2018 doi.org/10.106/j.braindev.2018.03.010. [PMID: PMC6026556]





## **60. Sterol and Isoprenoid Diseases Consortium (STAIR)**

**Principal Investigator: William B. Rizzo, MD**

The **Sterol and Isoprenoid Research Consortium (STAIR)** is dedicated to the investigation and elucidation of rare inherited metabolic diseases that are associated with defects in the metabolic pathways for sterols, isoprenoids and sterol related lipids, such as bile acids, neurosteroids and plant sterols. These diseases comprise a clinically heterogeneous group with considerable phenotypic variation. The major goals of STAIR are:

- To promote advances in the diagnosis and treatment of STAIR diseases by developing an effective research infrastructure that brings together expert physicians/scientists with highly committed Patient Advocacy Groups (PAGs) to carry out clinical research studies.
- To train the next generation of young physicians/scientists to become leaders in STAIR diseases.
- To actively participate in RDCRN activities to support research on rare diseases.

STAIR diseases include Smith-Lemli-Opitz Syndrome (SLOS), Sjögren-Larsson syndrome (SLS), Sitosterolemia, Mevalonate Kinase Deficiency (MKD/Hyper IgD syndrome), Cerebrotendinous Xanthomatosis (CTX), Peroxisome Biogenesis Disorders (PBD), Succinic Semialdehyde Dehydrogenase deficiency (SSADHD), Methylsterol Oxidase deficiency (MSO) and others. Because STAIR is based on a *biochemical pathway* rather than a specific phenotype, diseases may be added to STAIR to take advantage of new scientific advances in disorders that affect sterol and isoprenoid metabolism.

### **Current Studies in STAIR**

- *STAIR 7004*: Sjögren-Larsson Syndrome: A Longitudinal Study of Natural History, Clinical Variation and Evaluation of Biochemical Markers.
- *STAIR 7007*: The Role of Fish Oil, Colesevelam and Ezetimibe Combination Therapy for Sitosterolemia
- *STAIR 7010*: Caregiver Reported Symptoms and Quality of Life Surveys in Zellweger Spectrum Disorders
- *STAIR 7012*: Smith-Lemli-Opitz Syndrome: A Pilot Study of Cholic Acid Supplementation

### **Trainees Supported by STAIR**

- *Dr. Andrea DeBarber* (Oregon Health & Science University): developed a new LC-MS/MS method for diagnosing CTX patients; now exploring newborn screening for CTX.
- *Dr. Miao He* (Children's Hospital of Philadelphia): described the first patient with Methylsterol Oxidase (MSO) deficiency; currently developing laboratory diagnostic methodologies for rare metabolic diseases.
- *Dr. Shibani Kanungo*: short-term STAIR trainee explored the feasibility of newborn screening for MSO deficiency and a therapeutic trial of this disease.
- *Dr. Semone Myrie* (University of Manitoba): established therapeutic benefit of ezetimibe for Sitosterolemia; Co-PI for an ongoing STAIR pilot project to determine the optimal combination therapy for Sitosterolemia.
- *Dr. Mousumi Bose*: (Montclair State University): currently directing STAIR caregiver quality of life studies on Zellweger Spectrum Disorders and other STAIR diseases.

**STAIR Trainee Accomplishments:** discovery of a new STAIR disease (He), exploration of newborn screening (Kanungo), improved diagnostic methods for CTX (DeBarber), advances in treatment of STAIR disease (Myrie) and understanding the impact of devastating diseases on parental and family dynamics (Bose).

### **RDCRN STAIR Patient Contact Registry**

Maintained by University of South Florida (RDCRN Data Management Coordinating Center), the STAIR Patient Contact Registry currently has 369 registrants including PBD (149), SLOS (75), SSADHD (58), MVK/HIDS (45), and SLS (21). The Registry notifies registrants of STAIR studies and facilitates disease-related surveys.

### **STAIR Patient Advocacy Groups**

All PAGs provide invaluable support for conducting STAIR studies.

STAIR Patient Advocacy Groups (PAG)		
Smith-Lemli-Opitz/RSH Foundation (SLO/RSH)	<a href="http://www.smithlemliopitz.org">www.smithlemliopitz.org</a>	Helped organize the SLOS Scientific conferences (2011, 2014, 2017); supported a Young Investigators/Junior Faculty/Diversity Travel Award program for the Conferences.
United Leukodystrophy Foundation (ULF)	<a href="http://www.ulf.org">www.ulf.org</a>	Supported the 2 <sup>nd</sup> International Cerebrotendinous Xanthomatosis (CTX) Scientific Conference (July 2012) and CTX Newborn Screening meetings (2016, 2017).
Foundation for Ichthyosis & Related Skin types (FIRST)	<a href="http://www.firstskinfoundation.org">www.firstskinfoundation.org</a>	Supports STAIR 7004 SLS study, advertised study and recruited patients to STAIR.
Succinic Semialdehyde Dehydrogenase Deficiency Association	<a href="http://www.ssadh.net">www.ssadh.net</a>	Provides support, education and physician referrals for patients. Works with STAIR to support studies of SSADHD.
Sitosterolemia Foundation	<a href="http://www.sitosterolemiafoundation.org">www.sitosterolemiafoundation.org</a>	Supports sitosterolemia patients and contributed to the success of STAIR 7002 ezetimibe.
Global Foundation for Peroxisomal Disorders (GFPD)	<a href="http://www.thegfpd.org">www.thegfpd.org</a>	Recruits subjects and contributed to success of STAIR Contact Registry surveys (STAIR 7010). STAIR Trainee Dr. Mousumi Bose is the Scientific Liaison for GFPD and on Board of Directors.

### STAIR Publications (partial list)

1. Merkins MJ, Sinden NL, Brown CD, Merkens LS, Rouillet J-B, Nguyen T, Steiner RD. Feeding impairments associated with plasma sterols in Smith-Lemli-Opitz syndrome. *J Pediatr* 165:836-41, 2014. PMID: 25039049, PMCID: PMC4177270.
2. DeBarber AE, Luo J, Giugliani R, Souza CF, Chiang JP, Merkens LS, Pappu AS, Steiner RD. A useful multi-analyte blood test for cerebrotendinous xanthomatosis. *Clin Biochem* 47:860-3, 2014. PubMed PMID: 24769274; PubMed Central PMCID: PMC4175980.
3. Rouillet J, Rizzo WB. Sjögren-Larsson Syndrome: An Inborn Error of Fatty Aldehyde Metabolism. In: *Encyclopedia of the Neurological Sciences*. 2nd ed. Daroff R, Aminoff MJ, editors. Academic Press, Salt Lake City, Chapter 92, 2014.
4. Ajagbe BO, Othman RA, Myrie SB. Plant sterols, stanols and sitosterolemia. *J AOAC Int*. 98:716-23, 2015. PMID: 25941971, PMCID: PMC4514516.
5. Jack LS, Benson C, Sadiq MA, Rizzo WB, Margalit E. Segmentation of retinal layers in Sjögren-Larsson syndrome. *Ophthalmology* 122:1730-32, 2015. PubMed PMID: 25784589. PMCID: PMC4520310.
6. Freeman KA, Olufs E, Tudor M, Rouillet J-B, Steiner RD. A pilot study of the association of markers of cholesterol synthesis with disturbed sleep in Smith-Lemli-Opitz syndrome. *J Develop Behav Pediatr* 37:424-30, 2016. PMID: 27244299, PMCID: PMC4890614.
7. Rizzo WB. Genetics and Prospective Therapeutic Targets for Sjögren-Larsson Syndrome. *Expert Opin Orphan Drugs* 4:395-406, 2016. PMID: 27547594, PMCID: PMC4989507.
8. Othman RA, Myrie SB, Mymmin D, Rouillet J-B, Steiner RD, Jones PJH. Effect of ezetimibe on low- and high-density lipoprotein subclasses in sitosterolemia. *Atherosclerosis* 260:27-33, 2017. PMID:2834036, PMCID: PMC5419426
9. Othman RA, Myrie SB, Mymmin D, Rouillet J-B, DeBarber AE, Steiner RD, Jones, PJH. Thyroid hormone status in sitosterolemia is modified by ezetimibe. *J Pediatr* 188:198-204, 2017. PMID:28625503, PMCID: PMC5572543.
10. Eroglu Y, Nguyen-Driver M, Steiner RD, Merkens L, Merkens M, Rouillet JB, Elias E, Sarpahare G, Porter FD, Li C, Tierney E, Nowaczyk MJ, Freeman KA. Normal IQ is possible in Smith-Lemli-Opitz syndrome. *Am J Med Genet A* 173:2097-2100, 2017 PMID: 28349652, PMCID: PMC6016830.
11. Hidalgo ET, Orillac C, Hersch A, Harter DH, Rizzo WB, Weiner HL. Intrathecal Baclofen therapy for the treatment of spasticity in Sjögren-Larsson syndrome. *J Child Neurol* 32:100-103, 2017. PMID:28257279, PMCID: PMC5339737.

### Acknowledgments

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## 61. Urea Cycle Disorders Consortium

**Principal Investigator: Andrea Gropman, MD**

OVERVIEW	
<b>Major Goals:</b>	<p>1) <b>To advance our understanding of the pathophysiology of urea cycle disorders (UCD)</b> by performing collaborative clinical research.</p> <p>2) <b>To nurture development of the next generation of orphan disease</b> researchers by training this still-nascent cadre to become expert in the clinical investigation of rare disorders, especially UCD.</p> <p>3) <b>To identify promising new approaches to UCD care</b> by performing pilot/demonstration (proof of concept) clinical research projects which will deploy state-of-the-art methodologies.</p> <p>4) <b>To disseminate knowledge</b> and improve the care of UCD by providing ready access to information to all individuals whose efforts will impact outcome, including researchers, physicians, allied healthcare professionals, patients, families, representatives in government and the lay public.</p>
<b>Disorders Studied:</b>	<ol style="list-style-type: none"> <li>1. N-acetylglutamate synthetase (NAGS) deficiency</li> <li>2. Carbamyl phosphate synthetase I (CPSI) deficiency</li> <li>3. Ornithine transcarbamylase (OTC) deficiency</li> <li>4. Argininosuccinate synthetase (AS) deficiency (citrullinemia)</li> <li>5. Argininosuccinate lyase (AL) deficiency (argininosuccinic aciduria)</li> <li>6. Arginase (ARG) deficiency (argininemia)</li> <li>7. Citrulline (CITR) deficiency (citrullinemia type II)</li> <li>8. Hyperornithinemia, hyperammonemia, homocitrullinuria (HHH) syndrome</li> </ol>
STUDIES	
<b>Introduction:</b>	<p>The UCDC is now in its third 5-year funding cycle. In addition to numerous pilot and trainee projects, 10 major studies have been conducted resulting in 93 publications. The following is a summary of studies funded in this grant cycle. In addition to the studies listed below, the UCDC continues the Carbaglu Surveillance Protocol (RDCRN 5111), initiated in a previous grant cycle. PCORI funding was secured to help answer one of the Longitudinal Study's research questions (treatment comparisons) and expanded the analysis to include patient and health care provider qualitative data through collaboration with the George Washington School of Public Health through the "Comparative effectiveness of therapy in rare diseases: Liver transplantation vs. conservative management of urea cycle disorders" study (RDCRN 5117).</p>
<b>Major Protocol 1:</b>	<p><b>Longitudinal Study of Urea Cycle Disorders (RDCRN 5101)</b>  PIs: Andrea Gropman, MD, Children's National Health System, Sandesh Nagamani, MD, Baylor College of Medicine, and Shawn McCandless, MD, Children's Hospital Colorado</p>
<b>Objective(s):</b>	<p>To conduct a longitudinal multidisciplinary investigation of the natural history, morbidity, and mortality of people with UCD.</p>
<b>Status:</b>	<p>Active, recruiting  Enrolled: 839 participants as of 10/31/18    Target: 550    Limit: 1,100</p>
<b>Results:</b>	<p>This study has allowed the UCDC to data mine the natural history of UCDs and publish 21 papers (and several other related papers using 5101 data) including cross sectional analysis, liver dysfunction and hepatocellular injury, neuropsychological outcomes, hyperammonemic event triggers, the association between vaccination and metabolic decompensation, the incidence of UCD, and improvement in long term outcomes.</p>
<b>Major Protocol 2:</b>	<p><b>Biomarkers of Neurological Injury and Recovery in Urea Cycle Disorders (RDCRN 5113)</b>  PI: Andrea Gropman, MD, Children's National Health System</p>
<b>Objective(s):</b>	<p>To characterize metabolic, structural and cognitive changes in UCDs at baseline, and to validate biomarkers for the effect of hyperammonemia and its treatment on the brain. Glutamine and myoinositol will be measured in the brain (using 1H MRS) in affected participants with OTCD. N-acetyl-L-aspartate, citrulline, and argininosuccinic acid will be measured in those with distal UCDs. Additionally, fractional anisotropy as a measure of white matter microstructural damage (by DTI) and brain activation pathways alterations with tasks probing working memory (fMRI) will be measured in all the conditions. A secondary objective is to correlate the findings from neuroimaging with cognitive functioning.</p>

<b>Status:</b>	Active, recruiting Enrolled: 17 participants have been enrolled as of 10/31/18 Target: Aim 1 – 24 (12 subjects/12 controls), Aim 2 - 25, Aim 3 – 24 (12 subjects/12 controls)
<b>Major Protocol 3:</b>	<b>Nitric Oxide Supplementation as a Therapeutic Intervention in Argininosuccinate Lyase Deficiency (RDCRN 5114)</b> PI: Sandesh Nagamani, MD, Baylor College of Medicine
<b>Objective(s):</b>	The urea cycle enzyme argininosuccinate lyase (ASL) is a regulator of nitric oxide (NO) production. Thus, some patients with ASL deficiency (ASLD) can have NO deficiency, which could contribute to the long-term complications including hypertension, and neurocognitive deficiencies that are observed in this disorder. In preclinical models and in proof-of-concept human studies, we have shown that supplementation of NO could be of potential therapeutic benefit. We now aim to determine if short-term NO supplementation will be tolerated as well as used safely and effectively to treat endothelial dysfunction in patients with ALSD and if long-term NO supplementation can be tolerated and used safely to improve executive functioning in patients with ALSD.
<b>Status:</b>	Active, recruiting Enrolled: 8 Target: 16
<b>Pilot Studies:</b>	10 papers have been published on UCDC pilot projects to date. Pilot projects in this grant cycle include: <b>Manipulating the Microbiome in UCDs (RDCRN 5115)</b> , PI: Nicholas Ah Mew, MD, Children's National Health System <b>Targeted Massively Parallel DNA Sequencing for Newborn Screening for Proximal UCDs (RDCRN 5116)</b> , PI: Shawn McCandless, University Hospitals Cleveland Medical Center <b>UCD Practice Patterns and Outcomes Assessment (RDCRN 5112)</b> , PI: Jeffrey Krischer, DMCC, University of South Florida <b>Prospective Cross-sectional Non-invasive Assessment of Chronic Liver Disease in UCD (RDCRN 5118)</b> , PI: Lindsay Burrage, Baylor College of Medicine
<b>Trainee Studies:</b>	34 papers have been published on UCDC pilot projects to date. Pilot projects in this grant cycle include: <b>Enzyme Replacement Therapy in Mouse Models of Arginase Deficiency</b> , PI: Lindsay Burrage, Baylor College of Medicine <b>Development and Evaluation of Handheld Blood Ammonia Meter</b> , PI: Omar Ayuub, PhD, Children's National Health System <b>Pre-clinical Gene Editing for Arginase-1 Deficiency</b> , PI: Yuan Yan Sin, MBBS, PhD, Hospital for Sick Children <b>Clinical and Molecular Characterization of Citrin Deficiency in the U.S.</b> , PI: Kimihiko Oishi, MD, Icahn School of Medicine at Mount Sinai (funding to begin August 1, 2017)

## TRAINING

The RDCRC NIH grant and two related foundation grants provide support for 1-2 year training periods for 1-2 trainees/year. To date, the UCDC provided funding for the training of 21 graduate students, clinical genetics/ metabolism fellows and junior faculty members in rare disease research.

## PATIENT ADVOCACY GROUP INVOLVEMENT

The UCDC continues to maintain a strong relationship with the National Urea Cycle Disorders Foundation (NUCDF). Cindy Le Mons, the Executive Director of NUCDF, has been a voting member of the executive leadership of the UCDC since its inception and is now a co-PI of the Consortium. Ms. Le Mons participates in leadership meetings, monthly conference calls, and face-to-face meetings (which are held in conjunction with the NUCDF family conference every 2 years). The NUCDF assists with UCDC recruitment efforts and is collaborating with several investigators on data mining and research projects. Several UCDC PIs serve on NUCDF's medical advisory board. The success of the collaboration between NUCDF and UCDC has led to the NUCDF becoming a PAG role model.



## **62. Vasculitis Clinical Research Consortium**

**Principal Investigator: Peter A. Merkel, MD, MPH**  
[www.RareDiseasesNetwork.org/VCRC](http://www.RareDiseasesNetwork.org/VCRC)

The Vasculitis Clinical Research Consortium (VCRC) is an international, multi-center, clinical research infrastructure for the study of vasculitis. The VCRC is the major multi-center clinical research program in North America and one of the major international vasculitis research networks. The VCRC was one of the founding Consortia within the Rare Diseases Clinical Research Network (RDCRN) [U54 RR019497] and was granted funding for a third 5-year period from the NIH through the Office of Rare Diseases Research (ORDR) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) [U54 AR057319].

**Study Sites:** The VCRC includes >20 sites in the United States and Canada >90 additional international collaborating centers.

### **The Specific Aims of the VCRC include:**

1. Maintain and expand the administrative and scientific infrastructure of the VCRC
2. Expand enrollment and observation period for the five VCRC Longitudinal Studies, and initiate a new Longitudinal Study to support the VCRC Clinical Data Repository and VCRC Biospecimen Repository.
3. Continue to conduct novel projects within the VCRC Biomarker Discovery and Genetic & Genomics Programs including genome-wide analyses, whole exome sequencing, gene expression projects, and epigenetics studies.
4. Conduct a series of projects to i) study clinical outcomes in vasculitis; and ii) develop and validate new outcome measures for vasculitis for use in clinical research and integrate these new measures into our clinical trials and the Longitudinal Studies.
5. Conduct new Phase I and II studies of promising new therapeutics for vasculitis within the VCRC Pilot Project Program.
6. Conduct large, multicenter, randomized, controlled clinical trials in various forms of vasculitis facilitated by the U54 infrastructure but funded through additional external funding and industry partners.
7. Expand the VCRC Patient Contact Registry and continue to use this unique resource to conduct novel internet-based research projects, including collection of patient-reported outcomes and investigating novel methods of conducting trials.
8. Continue and expand the VCRC Fellowship Program to train young investigators in methodology for clinical and translational research in vasculitis
9. Maintain and expand the VCRC Website to provide a resource for patients, clinicians, and investigators; maintain and expand the VCRC Contact Registry for use in clinical research and education of patients

**Diseases under study:** Aortitis, Behçet's syndrome, cryoglobulinemic vasculitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), giant cell arteritis, granulomatosis with polyangiitis, IgA vasculitis (Henoch Schönlein), isolated cutaneous vasculitis, microscopic polyangiitis, polyarteritis nodosa, Takayasu's arteritis, urticarial vasculitis

### **Longitudinal Studies:**

**5502:** Giant Cell Arteritis; *actively enrolling*, current enrollment 406

**5503:** Takayasu's Arteritis; *actively enrolling*, current enrollment 219

**5504:** Polyarteritis Nodosa; *actively enrolling*, current enrollment 106

**5505:** Granulomatosis with Polyangiitis & Microscopic Polyangiitis; *actively enrolling*, enrollment 1,009

**5506:** Eosinophilic granulomatosis with polyangiitis; *actively enrolling*, current enrollment 270

**5507:** Aortitis; *actively enrolling*, current enrollment 8

*Multiple biomarker discover projects are linked to Longitudinal Studies and >20 projects in different stages: currently underway; in data analysis phases; completed and published; and several more projects are schedule to start this year*



**5510:** Genetic Repository One Time DNA protocol; six diseases; current enrollment 805 [in addition to the 2018 cases from the VCRC Longitudinal Studies for a total of 2823 cases of vasculitis with DNA samples and extensive clinical phenotyping. *Several candidate gene and microarray studies using stored DNA samples and linked comprehensive clinical phenotyping are under way.*

**5511:** VCRC Tissue Repository; *actively enrolling.* This unique repository includes the tissue blocks, digital copies of slides, and pathologic reports from hundreds of patients with various forms of vasculitis who are enrolled in any of the VCRC protocols. These samples are linked to the clinical data and other biospecimens.

### **Pilot Studies:**

**5522:** Abatacept for mild relapsing Wegener's granulomatosis, *recruitment complete, 20/20*

**5562:** A randomized multicenter study for isolated skin vasculitis (ARAMIS), *actively enrolling, current enrollment 21*

**5563:** Clinical transcriptomics in systemic vasculitis (CUTIS), *actively enrolling, current enrollment 36*

*Several new pilot studies of promising agents for the treatment of vasculitis are under consideration by the Steering Committee.*

### **Clinical Trials:**

**5523:** Abatacept for giant cell arteritis and Takayasu's arteritis (AGATA); *recruitment complete, 80*

**5524:** Plasma exchange and glucocorticoid dosing for ANCA-Associated Vasculitis (PEXIVAS); *recruitment complete, 704*

**5525:** Randomized controlled trial comparing rituximab and azathioprine for ANCA-associated vasculitis (RITAZAREM); *recruitment complete, 188*

**5526:** Randomized controlled trial of prednisone in granulomatosis with polyangiitis (TAPIR); *actively enrolling, current enrollment 92*

**5527:** Randomized, placebo controlled trial of abatacept in granulomatosis with polyangiitis (ABROGATE); *actively enrolling, current enrollment 38*

### **Observational Studies:**

**5515:** Imaging study of MRI and PET/CT scans in Takayasu's arteritis; *recruitment complete, 26*

**5531:** Vasculitis Reproductive Health Survey; *recruitment complete, 467*

**5532:** Vasculitis pregnancy registry (V-PREG); *actively enrolling, current enrollment 20*

**5533:** Vasculitis illness perception study; *recruitment complete, 707*

**5534:** Vasculitis educational needs study; *recruitment complete, 386*

**5535:** Validation of Patient-Reported Diagnostic Data; *recruitment complete 198*

**5536:** Impact of Vasculitis on Employment and Income Study; *recruitment complete, 426*

### **Outcome Measures**

**5540:** Development of Disease-Specific Outcomes in Vasculitis

**5541:** Validation of PROMIS for use in Vasculitis

OMERACT Vasculitis Working Groups for ANCA-Associated Vasculitis, Large-Vessel Vasculitis, and Behçet's Syndrome

**Online Research Resources:** The VCRC conducts research and patient outreach through two linked internet-based, interactive patient registries: the VCRC Patient Contact Registry and the Vasculitis Patient-Powered Research Network.

### **Training Program: The Vasculitis Clinical Research Consortium-Vasculitis Foundation Fellowship**

The VCRC-VF Fellowship is a structured training program of up to two years for physician-investigators who have developed an interest in vasculitis and wish to pursue a period of specialized training with an emphasis on translational and patient-oriented clinical investigation. The trainee undertakes the fellowship at one of the VCRC study sites. Fellows who have developed an interest in vasculitis are recruited from Rheumatology, Nephrology, Pulmonology, Neurology, Vascular Medicine/Cardiology or other subspecialties. This fellowship is a partnership between the VCRC and the Vasculitis Foundation.

**Number of VCRC Fellows trained:** Current: 1, Previous: 15

**Patient Advocacy Groups:** The Vasculitis Foundation is actively involved in the VCRC, promoting study participation and recruitment, attending Steering Committee meetings, and participating in CPAG activities.

**Additional Funding:** The VCRC has been successful in obtaining funding to supplement the RDCRN. Addition support for VCRC projects has been provided from grants from the NIAMS (1RC1 AR058303; P60 AR047785; U01 AR51874; HHSN2682007000036C; R01 AR064153), the FDA (R01 FD003516), the NHLBI (R01 HL115041), PCORI, and the Vasculitis Foundation, and industry partners [Bristol-Myers Squibb, Genentech, Kypha, and TerumoBCT].

