



66. CPAG: Coalition of Patient Advocacy Groups

What is RDCRN-PAG?

The acronym RDCRN-CPAG stands for ‘Rare Diseases Clinical Research Network—Coalition of Patient Advocacy Groups. RDCRN-CPAG is the patient representative arm of the RDCRN. The activities and focus of RDCRN-CPAG is strictly limited to activities of the RDCRN. RDCRN-CPAG is not, then, a free-standing, independent patient organization, but one that provides input and support for RDRNC activities and is supported by the network in return.

One impressive feature of the RDCRN is the direct involvement of supporting patient advocacy groups in network operations, activities, and strategy. Each consortium in the network includes relevant patient advocacy groups in the consortium membership and activities. These patient advocacy group representatives serve in an advisory capacity within their own consortia.

Collectively, the Coalition of Patient Advocacy Groups (CPAG) represents the perspective and interests of all patient advocacy organizations associated with the clinical research consortia. The CPAG group meets frequently throughout the year via teleconference and face-to-face meetings. CPAG members influence the direction of the Rare Diseases Clinical Research Network as a whole. They participate in network-level discussions and meetings. The CPAG coalition is a voting member of the RDCRN Steering Committee.

CPAG Vision

Through collaboration, patient advocacy groups and researchers can make faster progress toward new treatment options and cures, which can improve the lives of all persons and families affected by a rare disease.

CPAG Purpose

The RDCRN CPAG promotes collaboration between PAGs and the RDCRN in order to facilitate better access to, and earlier benefit from, research conducted on rare diseases. As the patient advocacy arm of the RDCRN, the RDCRN CPAG and its members use their position to advance the cause of rare diseases research and improve patient outcomes.

CPAG Chair and Co-Chairs

CPAG operates under the direction of the ORDR who serve as advisers and facilitators of CPAG activities and who have final approval over all activities undertaken by CPAG. The leadership structure for CPAG leadership consists of a Chairperson (hereafter, "Chair") and two or more Co-Chairs selected from CPAG members.

The CPAG Chair serves as primary liaison between CPAG, ORDR, the Steering Committee of the RDCRN and the working group chairs of CPAG working groups. Co-Chairs assist in these functions, provide leadership on one or more CPAG working groups and are in line for the Chair position, if interested. The Chair and Co-Chairs are members of the Steering Committee of the RDCRN and have one vote as representatives of CPAG.

CPAG Advisory Group

CPAG leadership also includes a CPAG Advisory Group comprised of 6-8 CPAG members with demonstrated commitment to CPAG activities who work with the Chair and Co-Chairs to prioritize, initiate and manage projects and tasks and provide leadership for the three other working groups of CPAG outlined below. The CPAG Advisory Group also provides a qualified candidate pool for recruitment to Co-Chair and Chair positions. Responsibilities of the CPAG Advisory Group include, but are not limited to:

- Assessing the needs of the CPAG member groups as they relate to RDCRN activities and devising strategies to address identified needs
- Preparing policy recommendations regarding the patient needs of the RDCRN, and for the discussion and resolution of procedural issues that affect the operation and status of the CPAG as a whole.

- Ensuring CPAG working groups are staffed and fully functional
- Ensuring CPAG activities and meetings occur on schedule

RDCRN CPAG Working Groups

Working groups may be established to facilitate business in a variety of areas. They meet at a frequency determined by the working group members and outstanding business. Each working group has a Chair and co-Chair. The Chair and co-Chair should be members of different PAGs and represent different consortia.

Initially, working groups function in three main work areas:

- Communications, primarily focusing on internal communications;
- Outreach, which increase awareness outside of the current network; and
- Education, which will take responsibility for coordinating RDCRN CPAG calls and meetings.

RDCRN CPAG Meetings and Calls

The RDCRN CPAG group meets frequently throughout the year via teleconference and face-to-face meetings. Teleconference meeting times are tentatively scheduled for the same time each quarter (i.e. the second Wednesday of the month from 2-3 PM Eastern). Each quarter, the RDCRN CPAG Chair will determine whether the scheduled call will be held. Any member with a topic to discuss during a meeting should contact the RDCRN CPAG Chair. Additional meetings can be scheduled if desired.

Face-to-face meetings are scheduled annually. ORDR, NCATS provides travel reimbursement for one member of each PAG per face-to-face meeting.

67. 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, RDCRN-approved protocols and practice guidelines. This portal had over 600,000 visits in the last year.
- b. A patient contact registry to permit the registration of individuals who self-select for their interest in participating in clinical research. The Contact Registry also provides ongoing contact with over 9,800 individuals, alerting them when new studies are opened in the Network or approved studies open at new sites. New enhancements to the contact registry include registration for multiple diseases, collection of diagnostic criteria, and options to participate in online protocols and/or share information with Consortium PIs and PAGs.
- c. A secure, password-protected members' website for 2,290 Consortium members from 488 institutions that includes announcements, calendars, protocol management tools and electronic case report forms. Among the functions supported include systems for adverse event reporting and monitoring, research pharmacy drug management, biospecimen tracking, image processing, desktop videoconferencing, and automated reporting.
- d. Collaboration on study design and implementation for 77 actively accruing studies from 167 sites that now have over 11,600 enrolled patients.
- e. Ensured appropriate regulatory compliance with regard to adverse event reporting, HIPPA and DSMB oversight.
- f. Conducted and distributed reports for 317 audit site visits (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 75 monitoring visits (Review all subjects accrued and all data points every 3 months).
- g. Collaborated in preparation and co-authored 45 scientific presentations and publications.
- h. Conducted in-person and web-based training for consortia investigators and clinical research associates to ensure the high quality and completeness of submitted data and protocol compliance.
- i. Promulgation of data standards that provide consistency across research protocols and diseases to enhance the value of the research data collected.
- j. Established a data base of clinical and laboratory findings that permits a close linkage between biological specimens and a well-characterized clinically followed population encoding 22,542,917 data points, photographs, CT scans, PET scans, x-ray images and videos.

Network focused 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.
- 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.
- 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.
- 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.
- 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.
- Richesson RL, Sutphen R, Shereff D, Krischer JP. **The Rare Diseases Clinical Research Network Contact Registry update: Features and functionality.** *Contemp. Clin. Trials.* Mar 2 2012



68. 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

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 15 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 FTD-ALS, svPPA, and PSPS, clinical syndromes in which disease modifying FTLD therapies will initially be targeted (Project 1).
3. To determine the natural history of presymptomatic f-FTLD (Clinical Dementia Rating [CDR] = 0) and symptomatic (CDR ≥ 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 221/650

ARTFL Project 2: Familial FTLD Syndromes: *actively enrolling*; current enrollment 262/700

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

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

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

ARTFL has also integrated its infrastructure with the *Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS)*, U01AG045390.

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: 1

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





69. Autonomic Disorders Consortium (ARD)

Principal Investigator: David Robertson, MD – Vanderbilt University

Major Goals	Diseases Studied
- To develop novel therapies for improving quality of life and altering course of disease - To standardize the evaluation of autonomic function - To learn more about the long-term prognosis of the disorders - To develop patient registries - To develop data/specimen banks - To discover biomarkers to facilitate disease diagnosis and inform disease progression	- Hyperadrenergic Postural Tachycardia (POTS) - Pure Autonomic Failure (PAF) - Multiple System Atrophy / Shy-Drager Syndrome (MSA) - Autoimmune Ganglionopathy (AAG) - Autoimmune Autonomic Neuropathy - Parkinsonism with Autonomic Failure - Lewy Body Disease - Dopamine β-Hydroxylase Deficiency - Norepinephrine Transporter Dysfunction - Familial Dysautonomia - Baroreflex Failure - Neurally Mediated Syncope - Pheochromocytoma - Mastocytosis - Takotsubo Syndrome

Study Title	Goals	Status
6103 Norepinephrine Transporter Blockade in Neurogenic Orthostatic Hypotension	To determine if the pressor response to atomoxetine can distinguish between patients with pre-ganglionic lesions versus those with post-ganglionic lesions	Closed to enrollment. Follow-up and data analysis ongoing.
6106 Natural History Study of Synucleinopathies	To test the hypothesis that pure autonomic failure (PAF) is a neurodegenerative synucleinopathy that remains confined to the autonomic nervous system and does not develop into a motor or cognitive disorder. To define the natural history of multiple system atrophy (MSA) to establish the rate of disease progression and disease-specific milestones.	Enrollment continues.
6108 Reduction in Splanchnic Capacitance Contributes to Sympathetically Dependent Hypertension in Autonomic Failure	To determine if autonomic blockade with trimethaphan increases splanchnic venous capacitance. To compare hemodynamics and segmental vascular volumes when abdominal compression is added to trimethaphan or placebo.	Ready to initiate enrollment.
6109 Natural History of Synucleinopathies – Skin Biopsies	To determine the utility of cutaneous alpha-synuclein measured in skin biopsies as a biomarker in different synucleinopathies with autonomic failure.	Not yet enrolling.

Study Title	Goals	Status
6110 Effects of Midodrine and Droxidopa on Splanchnic Capacitance	To compare the effects of midodrine and droxidopa on stroke volume during head-up tilt. To determine whether droxidopa or midodrine in combination with abdominal compression has an additive pressor effect during head-up tilt	Not yet enrolling.
6111 Vagal Stimulation in Postural Tachycardia Syndrome (POTS)	To compare the effects of transdermal vagal stimulation with that of sham stimulation and peripheral (aim 1) or central (aim 2) cholinesterase inhibition on cardio vagal modulation in POTS patients. To compare the effects of the combination of transdermal vagal stimulation and peripheral (aim 1) or central (aim 2) cholinesterase inhibition with that of each intervention alone on cardio vagal modulation in POTS patients.	Not yet enrolling.

Training

The primary focus of the Training Component is the career development of Consortium Scholars through mentored research experiences to increase their knowledge about Rare Autonomic Disorders. The institutions in the Autonomic Rare Diseases Consortium have developed formal curricula related to the conduct of clinical research, as well as autonomic physiology and neurology. Approximately 30 PhD's and MD's have participated in our training program. Several previous trainees have transitioned to faculty and staff positions.

Role in Advocacy Groups

We have been fortunate to have various advocacy groups to support us by promoting our research, educating patients and the community, and supplying materials and funding whenever possible. We acknowledge that this Consortium will not succeed without regular interactions with these organizations. We therefore confer with leaders of the support groups about research projects, recruitment, education, and patient needs. Consortium members regularly meet with support group representatives at the annual conference of the American Autonomic Society and/or the Academy of Neurology.

The following is a partial list of advocacy groups that share our vision: MSA Coalition, Dysautonomia Foundation, Dysautonomia International, National Dysautonomia Research Foundation, and Dysautonomia Information Network. The MSA Coalition has provided financial support for ARD 6106 and has assisted with an initiative to form a transatlantic alliance to unite North American and European MSA Centers.





70. Brain Vascular Malformations Consortium (BVMC)

PI: Michael T. Lawton, MD; Co-PI: Douglas A. Marchuk, 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)-Leptomeningeal 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: 373

Project 2 (6202): 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 leptomeningeal 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: 311

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. Aim 1: 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: 1324

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). Ongoing 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 Weber syndrome (PI: Comi). Ongoing
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). Ongoing.
7. **6208:** Trial of Sirolimus for Cognitive Impairments in SWS (PIs: Hammill, Franz, and Comi). Pending enrollment.
8. **6209:** Circulating miRNAs as biomarkers for brain VMs in HHT (PIs: Kutryk and Faughnan). Pending enrollment.

Training Program Summary

The BVMC has supported eight trainees to date:

1. Yasir Khan, MD, Project 1, Modifier Genes in Cerebral Cavernous Malformations
2. Takeo Nishida, MD, Project 3, Rare Disease Clinical Research Consortia for the Rare Disease Clinical Network.
3. Eboni Lance, MD, Project 2, Innovative Approaches to gauge progression of Sturge-Weber Syndrome.
4. Helene Choquet, PhD, Project 1, Genetic and 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, Comparative Anatomy and Surgical Outcome of AVMs in HHT and Sporadic AVMs
8. Giuseppe Latino, MD, Project 3, Diagnostic Delays in Rare Disease: Identifying Factors and Developing Strategies to Address.

Contact Information/Consortium Projects

Project 1: Modifier Genes in Cerebral Cavernous Malformations

Leslie Morrison, MD, Leader

University of New Mexico

Helen Kim, PhD, Co-Leader

University of California, San Francisco

Project 2: Innovative Approaches to Gauge Progression of Sturge-Weber Syndrome

Anne Comi, MD, Leader

Kennedy Krieger Institute

Douglas A. Marchuk, PhD, Co-Leader

Duke University

Project 3: Cerebral Hemorrhage Risk in Hereditary Hemorrhagic Telangiectasia

Marie E. Faughnan, MD, Leader

University of Toronto

Michael T. Lawton, MD, Co-Leader

University of California, San Francisco

Genetic and Statistical Analysis Core

Charles E. McCulloch, PhD, Leader

Ludmila Pawlikowska, PhD, Co-

University of California, San Francisco

Pilot/Demonstration Project Core

Michael T. Lawton, MD, Leader

Douglas A. Marchuk, PhD, Co-

University of California, San Francisco
Duke University

Training (Career Development) Core

Charles E. McCulloch, PhD, Leader

Michael T. Lawton, MD, Co-Leader

University of California, San Francisco

Participating Clinical Sites:

University of California, San Francisco, CA	University of Utah, Salt Lake City, UT
University of New Mexico, Albuquerque, NM	Mayo Clinic, Rochester, MN
Dignity Health/Barrow Neurological Institute, Phoenix, AZ	University of California, Los Angeles, CA
Angioma Alliance, Norfolk, VA	Johns Hopkins University, Baltimore, MD
Duke University, Durham, NC	University of North Carolina, Chapel Hill, NC
Hugo W. Moser at Kennedy Krieger, Baltimore, MD	Cure HHT, Monkton, MD
The Children's Hospital Corporation, Boston, MA	Augusta University Research Institute, Augusta, GA
Children's Hospital Medical Center, Cincinnati, OH	Washington University, St. Louis, MO
New York School of Medicine, New York, NY	Wayne State University, Detroit, MI
Research Institute at Nationwide Children's, Columbus, OH	Sturge Weber Foundation, Mt. Freedom, NJ

International:

St. Michael's Hospital/University of Toronto	Sick Kids, The Hospital for Sick Children, Toronto
Centre Hospitalier de l'Université de Montréal, Montréal	St. Antonius Hospital, Nieuwegein, Utrecht

Patient Advocacy Groups: There are three advocacy groups involved in the BVMC: Angioma Alliance (Amy Akers), The Sturge-Weber Foundation, (Karen L. Ball), and CureHHT (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.



71. 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 understanding and providing better 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 9 clinical sites in the United States and Canada. The consortium is funded by the National Institutes of Health through the Office of Rare Diseases Research (U54 AR 068069), and a collaboration between NCATS and the National Institute of Dental and Craniofacial Research (NIDCR), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Patient Advocacy Group:

The BBDC is partnering 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 OIF is the only voluntary national health organization dedicated to helping people cope with the problems associated with OI.

The goals of the Brittle Bone Disorders Consortium are:

1. Conduct an observational cohort study (where subjects are followed over time and clinical, laboratory and radiological data as well as blood samples specifically for research are collected at regular intervals).
2. Conduct a clinical trial to determine safety of fresolimumab in the treatment of OI.
3. Establish a patient contact registry.
4. Discover new laboratory markers of disease that will lead to better treatment and deeper scientific understanding of the causes of these diseases.
5. Develop improved methods for studying OI.
6. Work with OI patient support groups to help those patients who wish to be involved in research connect with those doctors conducting the research.
7. Train new, young investigators in the field of OI.
8. Construct and maintain an electronic website resource with significant information for clinicians, researchers, and patients.

Observational Studies:

- BBDC 7701: Longitudinal Study of Osteogenesis Imperfecta
Actively enrolling (466/1000).
- BBDC 7704: Dental Malocclusion and Craniofacial Development in OI
Actively enrolling as of October 2016.
- BBDC 7705: Pregnancy in OI Registry
Anticipate enrollment start date December 1, 2016.

Pilot Studies:

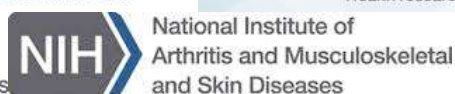
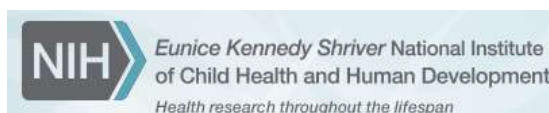
- BBDC 7702: PROMIS for OI patients
Enrollment goal has been reached (300/300). Data analysis currently underway.
- BBDC 7703: Cross-linked Collagen Peptides as a Urinary Biomarker of OI Pathobiology
Actively enrolling (9/25).

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*)
Anticipate enrollment start date February 2017.

Training Program:

- Through the Geisman Fellowship, the OIF has supported the development of 4 trainees interested in rare bone disease research. Results from these projects provided preclinical data for the Phase I Trial of Fresolimumab in Severe OI study.
- 5 BBDC Scholars were funded through the RDCRN T25 mechanism to foster clinical research in rare diseases. Projects from these Scholars include: Effectiveness of OI Outreach, clinical evaluation of gait in the OI community, Musculoskeletal Modeling in children with OI, and Bone fracture risk during tasks for Osteogenesis Imperfecta.





72. 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 16 sites in the USA and a collaborating site in Europe.

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

The Specific Aims of CEGIR include:

1. To promote collaboration among centers already focused on studying Eosinophilic Esophagitis (EoE), Eosinophilic Gastritis (EG), 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.

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 250 subjects of expected 1050.

Multiple biomarker discovery projects (e.g. microbiome analysis) are linked to OMEGA. The biorepository has 931 samples including DNA from 109 subjects. 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 14/136.

Pilot Program

CEGIR 7803: A preliminary open-label trial of losartan potassium in participants with EoE with or without a connective tissue disorder; *NIH/cIRB approval pending*; current enrollment 0/20.

CEGIR 7804: Role of the Microbiome in EoE, EG, and EC, *actively enrolling*, current enrollment 20 stool samples of 108.

CEGIR 7808: Use of unsedated transnasal esophagoscopy to monitor dietary management of EoE; *NIH/cIRB approval pending*; current enrollment 0/20.

CEGIR 7809: A Prospective Trial of Elemental Diet in Adults with EG. *NIH/cIRB approval pending*; current enrollment 0/20.

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 undertake fellowships at one of the CEGIR study sites. CEGIR trainees conduct research in conjunction with mentors and CEGIR oversight and guidance; research may involve utilization of CEGIR resources. CEGIR currently has five physician trainees, each at a different location; three of these trainees are supported by NIH K08 grants.

CEGIR 7806: Demographics, clinical characteristics, and pathology of EG and EC in a multi-site cohort; *NIH/cIRB approval pending*.

CEGIR 7807: Validation of online cohort of EGID patients enrolled in CEGIR Contact Registry

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 PCORI and NIAID (R01 AI124355).





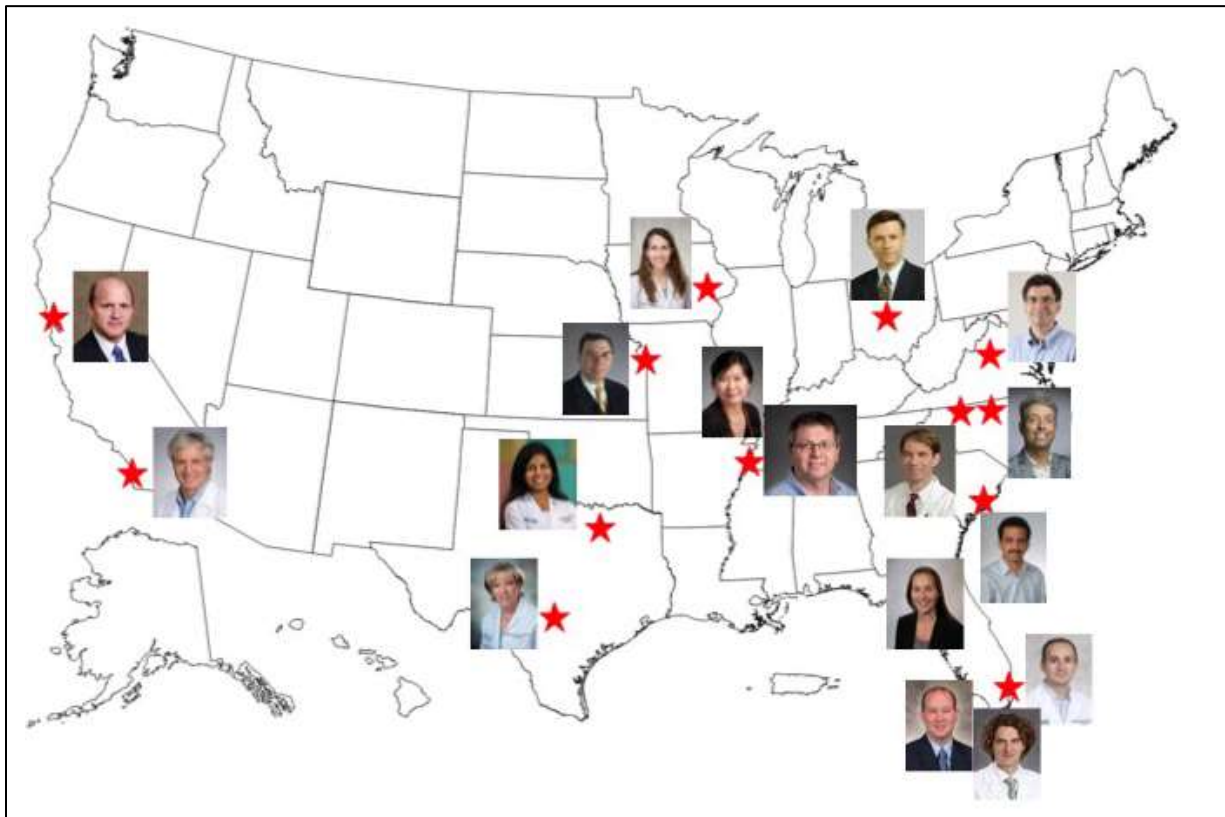
73. Clinical Research in ALS and related disorders for Therapy development Consortium

Principal Investigator: Michael Benatar, MD, PhD

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 10 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 and Wake Forest University), as well as one site (University of Tübingen) in Germany. Dr. Richard Bedlack, MD, PhD (Duke) oversees outreach and advocacy activities. Drs. J Paul Taylor, Jinghui Zhang and Evadnie Rampersaud (St. Jude Children's Hospital) along with Drs. Stephan Zuchner and Jake McCauley (University of Miami) and Rosa Rademakers (Mayo Clinic Jacksonville) oversee C9orf72 and whole genome sequencing and analysis.



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 (in development)
- 8003 – CReATe Connect Registry-based protocol (pending IRB approval)
- 8004 – Innate Lymphoid Cells in ALS (actively enrolling)

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 three fellows, with two more planned for 2017.

Patient Advocacy Groups

The ALS Association (ALSA), Muscular Dystrophy Association (MDA), Spastic Paraplegia Foundation (SPF), the Association for Frontotemporal Degeneration (AFTD), PatientsLikeMe, 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 (R01TS000244) and Avanir Pharmaceuticals.





74. Developmental Synaptopathies Consortium
Principal Investigator: Mustafa Sahin, MD, PhD
www.rarediseasesnetwork.org/DSC

The Developmental Synaptopathies Consortium (DSC) is 10-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. Continue enrolling for three longitudinal studies for TSC, PMS, and PTEN populations
3. Continue enrolling in a pilot study aimed at characterizing electrophysiological biomarkers in PMS
4. Conduct a multicenter, randomized, double-blind, placebo controlled phase I/II trial aimed at investigating safety and efficacy of everolimus on neurocognition in PTEN
5. Continue supporting training fellowships through the DSC and associated patient advocacy group foundations

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); *actively recruiting, current enrollment: 41/100*

DSC 7902: Mapping the Genotype, Phenotype, and Natural History of Phelan-McDermid Syndrome; *actively recruiting, current enrollment: 68/105*

DSC 7903: Natural History of Individuals with Autism and Germline Heterozygous *PTEN* Mutations; *actively recruiting, current enrollment: 58/100*

Observational/ Outcome Measure Studies

DSC 7905: Electrophysiological Biomarkers of Phelan-McDermid Syndrome; *actively recruiting, current enrollment: 2/50*

Clinical Trials

DSC 7904: A Randomized Double-Blind Controlled Trial of Everolimus in Children and Adolescents with PTEN Mutations (RAD001XUS257T), *expected to enroll January 2017*

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. In the past year 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. The next training fellowship will be within the PTEN sub-study.

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, PTENworld, PTENlife (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.





75. Dystonia Coalition

Principal Investigator: H. A. Jinnah, MD, PhD

19 October 2016

Main diseases under study:

The main diseases under study include all of the isolated dystonias (previously called “primary 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 Goals:

Our major goals are to select projects that both investigators and patient advocacy groups can agree are the most relevant and important for advancing translational sciences and supporting future clinical trials.

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.

Major Clinical Studies:

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

This study is ongoing. The primary 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 1 October 2016, 33 centers contributed to the enrollment of 2497 subjects.

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

This study has been completed, although several follow-on studies are ongoing. The overall 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. This rating scale is now being validated for use by centers internationally.

Project 3: Diagnostic and Rating Tools for Spasmodic Dysphonia (Christy Ludlow; James Madison University)

Recruitment for this study has concluded, with 3 centers enrolling nearly 200 subjects. Results are being analyzed. The overall goal was to demonstrate validity of a novel diagnostic instrument for spasmodic dysphonia and to determine validity/reliability of two measures for detecting change in symptoms.

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

This study has just begun recruiting. The plan is for 10 centers to recruit a total of 200 subjects, along with disease controls. The overall goal is to test the utility of diagnostic and severity tools that were developed as Pilot Projects.

Pilot Projects Program:

To date, the Dystonia Coalition Pilot Projects Program has reviewed 68 different applications from investigators in 6 different countries and 14 have been granted funding (20%). Another 18 studies were reviewed and provided with data or materials from the Major Clinical Research Projects, but no financial support. A summary of the projects given financial support by the DC is provided below. Several of these were co-funded by the relevant Patient Advocacy Group:

Table 1. Pilot Project Grants Supported With Dystonia Coalition Funds

Recipient	Institution	Year	Grant Title
Mark Ledoux, MD PhD	Univ TN, Memphis	2009	THAP1 sequence variants in dystonia
Gianni DeFazio, MD PhD	Univ Bari, Italy	2010	Diagnostic guidelines & rating tools for blepharospasm
Emmanuel Roze, MD	Salpêtrière, Paris, France	2010	Cerebellar cortical plasticity in focal dystonia
Kailash Bhatia, MD FRCP	Univ Coll London, UK	2010	DYT6: A window to mechanisms in primary dystonia?
David Peterson	Univ Calif, San Diego	2010	Increasing CERTainty in blepharospasm
Christine Klein, MD	Univ Lubeck, Germany	2011	Endophenotypes in focal dystonias
Henry Houlden, MRCP, PhD	Univ Coll London, UK	2011	Neuropathology of DYT1 and DYT6 dystonia
Stephen Frucht, MD	Mt. Sinai School of Med, NY	2013	Rating scales for musician's dystonias
Sheila Eichenseer, MD	Rush Univ, Chicago	2013	A novel method for rating scale assessment in cervical dystonia
Mark LeDoux, MD PhD	Univ Tenn, Memphis	2013	Targeted sequencing in primary dystonias
H.A. Jinnah, MD PhD	Emory Univ	2013	Dystonia Coalition iPS resource
Scott Norris, MD	Washington Univ, St Louis	2013	fMRI in laryngeal dystonia and MTD
Katja Lohmann, PhD	Univ Luebeck, Germany	2013	Whole genome sequencing in focal dystonias
Jonathon Mink, MD	Univ Rochester, NY	2015	Development and validation of rating scales for children

Abbreviations: ACTSI, Atlanta Clinical and Translational Sciences Institute (CTSA); BEBRF, Benign Essential Blepharospasm Research Foundation; BSDPF, Bachmann-Strauss Dystonia Parkinson's Foundation; iPS, induced pluripotent stem cell. A complete list of presentations that includes those noted in this table is provided in the Overall Description of the Dystonia Coalition.

Development (Training) 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 11 have been awarded (47%). Each award is approximately \$50,000. A summary of the awards made is provided below. 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. 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 now has nearly 5,000 registrants.

Table 2. Career Development Awards

Recipient	Institution	Year
Maren Carbon-Corell, PhD	Feinstein Inst, NY	2009
Mateusz Zurowski, MD*	Univ Toronto, Canada	2010
Alberto Espay, MD	Univ Cincinnati	2010
Morvarid Karimi, MD	Washington Univ, St Louis MO	2011
Teresa Kimberley, PT, PhD	Univ Minnesota, Minneapolis	2011
Brian Berman MD	Univ Colorado, Denver	2012
Aparna Wagle-Shukla, MD	Univ FL, Gainesville	2012
Mateo Bologna, MD	Univ Rome, Sapienza, Italy	2013
Sarah Pirio-Richardson, MD	Univ New Mexico, Albuquerque	2013
David Peterson, PhD	Univ Calif, San Diego	2013
David Arkadir, MD	Hadassah Univ, Israel	2013
Michael Hammer, PhD	Univ Wisconsin, Madison	2015
Aasef Shaikh, MD PhD	Case Western Reserve, Cleveland	2015
Kaviraja Udupa, MD PhD	Univ Toronto, Canada	2015

All

All of the groups below have participated, although some of them have since closed: Action for Dystonia, Diagnosis, Education, & Research, American Dystonia Society, Bachmann-Strauss Dystonia and Parkinson Foundation, BeatDystonia, Benign Essential Blepharospasm Research Foundation, Cure Dystonia Now, Dystonia, Inc, Dystonia Ireland, Dystonia Medical Research Foundation, Dystonia Medical Research Foundation – Canada, The Dystonia Society, Dystonie-Qc, European Dystonia Foundation, Foundation for Dystonia Research, National Spasmodic Dysphonia Association, National Spasmodic Torticollis Association, Tyler's Hope, WE MOVE.



76. 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.

Longitudinal Studies, Clinical Trials and Pilot Studies (listed below)

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

Recruitment and 5 year follow-up for the first phase of Protocol 5901 (Longitudinal Study of Primary Ciliary Dyskinesia: Participants 5-18 Years of Age) is complete, and 120 participants were enrolled in this 5 year longitudinal study. A cross-sectional analysis of the first 103 enrollees show a wide spectrum of lung disease. Some children had widespread bronchiectasis and normal spirometry, and some had no bronchiectasis on chest CT, but marked airflow obstruction. This discordance emphasizes the need for both spirometry and CT of chest to track early lung disease. We have now obtained a 5 year extension to this longitudinal study. As of May 1, 2016, 46 participants have completed their first extension visit. Most recently, 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” longitudinal analysis of all participants.

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 consented and enrolled into the study, of which 28 have completed the initial 5 years of followup; 17 were withdrawn due to no longer meeting inclusion criteria, parental request, or loss to follow-up. Preliminary findings have demonstrated that among children with a confirmed PCD diagnosis, all had chronic, daily cough, nasal congestion and recurrent otitis media, usually starting before 1 year of age, as well as abnormal chest CTs; > 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 and optimal disease management. We have now obtained a 5 year extension to this longitudinal study in which participants will be followed for an additional 4-5 years. During this extension period, participants are evaluated at 2-3 year intervals. Most recently, Dr. Davis (PI of 5903) and Dr. Leigh (PI of 5901) have worked with Hye-Seung Lee to perform a “combined” longitudinal analysis of all participants.

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 the phenotype data from the 5904 Protocol was recently completed and was presented in poster format at the 2016 American Thoracic Society Conference in San Francisco. This study supports past findings on morphotypic traits in bronchiectasis patients with NTM, including

older age of diagnosis, lower BMI, and high incidence of scoliosis. Comparisons by strata revealed significant differences between NTM and non-NTM patients. 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. When comparing NTM women to NTM men, women were diagnosed at a younger age, have a lower FEV1% predicted, and have a lower BMI than men. In comparison of NTM women to non-NTM women, NTM women were older at age of diagnosis and have a lower BMI than non-NTM women. Similarly, in comparing NTM men to non-NTM men, NTM men were older at age of diagnosis, have a higher FEV1% predicted, and have a higher incidence of scoliosis. 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

The protocol was approved and started in February, 2015. This protocol 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. The initial target enrollment is 280 patients; to date, we have enrolled 246 subjects, which has occurred so rapidly that we are considering a request to increase our target enrollment. After genetic testing is performed 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. Technical validation of our DNA samples has been completed by Invitae, and we have already submitted DNA samples on the first 120 PCD patients to define the genetic etiology of their PCD, and anticipate submitting more samples in the next 6 months. We expect that ~ 2/3 of those PCD subjects will have defined biallelic mutations in PCD genes.

Training Section: The goal is to provide trainees with the professional research skills needed to be productive academic leaders in rare lung diseases. Over the first 10 years of this Consortium, we had 34 trainees involved in GDMCC-related research. Of the 16 trainees who have completed all their training, 13 have academic positions. Currently, we have an extensive training program in effect that includes 10 active trainees, including Fellows and post-doctoral students. Importantly, we have seen multiple (n=13) previous trainees ascend to academic faculty positions, and continue to participate in rare disease research. RDCRN Conferences on Clinical Research for Rare Diseases (Rockville, MD, 2007, 2010, 2012, 2014, 2016) – which has the goals of supplementing general training in clinical research in rare diseases and attracting trainees, junior faculty and new investigators into this field. These successful trainees are also writing manuscripts, and thus have high visibility. 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. The PCD Foundation sponsors an annual conference, “PCD on the Move”, which has been held in Bloomington, Minnesota in August, 2015, and September, 2016. This conference is well attended by trainees and other consortium personnel. Thus, our training efforts are escalating, because of this new opportunity. In September, 2016 two trainees presented 3 posters at the PCD Foundation “On the Move” national conference, 4 presented at the ATS and 3 had abstracts accepted for the ATS conference. Five trainees have submitted abstracts for the November 2016 CCRD conference. Trainees participate in bi-monthly conference calls and are involved in helping to establish a clinical (treatment) trial network. Our trainees are also co-authors on important manuscripts emanating from our Consortium, and are helping to lead workshops and working groups charged with developing clinical care guidelines for the diagnosis and management of PCD.

Role of Advocacy Groups: Genetic disorders of mucociliary clearance are associated with a host of clinical problems, the most serious being severe lung disease, and the PCD Foundation has played a key role in our progress over the past decade. GDMCC research has helped redefine the genetic picture of these disorders, enabling faster, more accurate diagnosis, improving ability to identify individuals at risk for developing difficult to treat lung infections, and promising that in the future these disorders will be in line to potentially benefit from a new generation of therapies that target genetic mutations. Because of natural history studies done by the GDMCC, we are now able to distinguish PCD from other disorders using phenotypic features and a novel, non-invasive

screening test (nasal nitric oxide). This monumental advancement in diagnostic capability addresses a serious problem with delayed and/or missed diagnosis that has plagued the PCD community for decades and has resulted in increased, preventable morbidity. 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.



Inherited Neuropathies Consortium

77. The Inherited Neuropathy Consortium

Principal Investigator: Michael E. Shy, MD

Charcot-Marie-Tooth disease (CMT) is the eponym for heritable peripheral neuropathy and is named for three investigators who described it in the late 1800s. CMT affects ~1 in 2500 people (approximately 120,000 Americans) and is among the most common inherited neurological disorders. CMT is inherited in an autosomal dominant pattern, X-linked dominant or autosomal recessive pattern. The majority of CMT neuropathies are demyelinating, although up to one third appear to be primary axonal disorders. Most patients have a “typical” CMT phenotype characterized by onset by early adulthood, distal weakness, sensory loss, and foot deformities. However, many patients develop severe disability in infancy or early childhood, while others develop few if any symptoms of neuropathy until adulthood.

Despite the clinical similarities among patients with CMT, the group is highly genetically heterogeneous. At present, mutations in more than 90 genes have been identified that cause inherited neuropathies. These genes are largely separable into three major groups: dominantly inherited demyelinating neuropathies (CMT1); dominantly inherited axonal neuropathies (CMT2); and recessively inherited neuropathies (CMT4). Although there have been extensive advances into the cell biology of many genes and proteins causing CMT1, CMT2, and CMT4 there are no therapies available for any of these disorders. The overarching goal of our RDCRC is to provide a translational approach to the development of rationally based therapies for all three groups of the inherited neuropathies.

Overview of the INC

The overarching goal of the INC is to provide a translational approach to the development of rationally based therapies for CMT. To achieve this, we have developed several projects in collaboration with clinical sites around the world where patients with CMT are routinely evaluated. **Clinical Research Project 1** is a natural history study for all forms of CMT with a particular emphasis on CMT1B, CMT2A, and CMT4A and CMT4C. This is a 10 year longitudinal study following both adults and children with CMT. We have currently enrolled **4075** patients into this protocol. We have developed and published new clinical outcome instruments for adults (CMTNSv2, in the *Journal of the Peripheral Nervous System*) and children (CMTPedS, in the *Annals of Neurology*) with CMT, and have tested almost **800** children with CMT using the CMTPedS. Both these instruments are already in use internationally and will be the standard outcome measures for upcoming clinical trials in CMT. These also allow us to measure the natural progression of CMT, and when we know how a disease progresses without a treatment intervention, we are able to better evaluate if a treatment is actually working – if it is slowing or stopping the rate of progression. We also have a **Pilot Project** underway which is to develop an outcome instrument for infants with CMT (CMTInfs) as it ultimately may prove necessary to start treatments in early childhood to prevent disease progression.

Clinical Research Project 2 is to identify new genetic causes of CMT along with genetic modifiers of the most common form of CMT, CMT1A, which is caused by a duplication of the *PMP22* gene. In the CMT1A genetic modifier project we have been utilizing genome-wide association studies (GWAS) on over 1000 patients who have CMT1A. By using the outcome measures we developed and validated, we are looking at genes that lead to milder or more severe impairment in patients. The second part of this project is to use exome sequencing to identify new causes of CMT by testing patients and families who have not been able to be genetically confirmed. By using this method and collecting samples from patients across the consortium, the INC has helped to identify over half of the currently known 90+ genes that have been identified as causing CMT.

Clinical Research Project 3 has established a Website Resource for the inherited neuropathies, for patients, families and investigators. We have over **2500** patients in our patient contact registry and are conducting two research protocols based on interactions with the contact registry. We also have clinical information for physicians on almost all forms of inherited neuropathy on the website. This also includes our Inherited Neuropathy Variant Browser, which is a way for physicians and researchers to look up variants identified in patients with CMT to see if that variant has been seen or reported before. With the ever expanding number of genes and variants being described, this is an invaluable tool for the future as we document variants and help people to know if they are disease causing. The variant browser can be found online at

http://hihg.med.miami.edu/code/http/cmt/public_html/index.html#/.

Including the CMTInfs, we have multiple **Pilot Projects** that we are also working on through the INC. These include the collection of samples for identifying biomarkers on some of the most common causes of CMT which could also be used during clinical trials to look at disease progression. Another way of looking at disease progression is by using MRI imaging of the calf muscle to look at the

fat infiltration in the muscle which we have shown can measure disease progression in just one year. We are also developing and validating variety of Quality of Life measures for both children and adults with CMT to have patient reported outcome (PRO) instruments that can be used longitudinally when clinical trials become available. This incorporates the patients' perspectives of disability and defines disease severity based on its impact on the overall quality of life of a patient. The goal of developing all of these measures are so we have reproducible items that can be performed at multiple visits and compared over time at multiple sites to show statistical differences over time.

Trainees:

The INC has supported 100% of the salaries for eight outstanding young trainees; we have a clinical trial design track and a basic translational research track. The training programs are designed to be variable in length to allow for more trainees to be able to participate. They also incorporate multiple sites across the consortium, so trainees are able to work with specialists across the US and internationally. Trainees have gone on to help with projects such as using iPSC technology to develop cell lines of CMT, along with developing new specialty centers in other countries which then collaborate with the INC. We have had 30 trainees come through our program that have funding from other sources, and we are proud of the accomplishments of all of these trainees and are confident that they will remain leaders in the field of genetic neuropathy research for years to come.

Patient Advocacy Groups (PAGs)

We are very pleased to have several outstanding Patient Advocacy Groups (PAG) associated with the INC RDCRC. These groups include the Muscular Dystrophy Association (MDA), the Charcot Marie Tooth Association (CMTA), CMT United Kingdom (CMTUK), Telethon (Italy) and CMTA Australia. We work closely with the PAGs, and appreciate their insight in the projects that we are working on along with the helping with the direction of the consortium. The PAGS participate in our monthly conference calls. Several also provide financial support that has allowed us to expand our consortium sites. Many of the people who work across the consortium serve on the medical advisory boards for the PAGs, and in turn the PAGs help to encourage the patient population to participate in our registry and attend our consortium sites. It is a partnership that has allowed us to grow both in number and in knowledge.

In summary we all remain excited to be members of the RDCRN and look forward to working together to advance the care of patients with inherited peripheral neuropathies. We have published over **175** manuscripts that involve the inherited neuropathies. It is our expectation that within the next few years we will be conducting multicenter clinical treatment trials for different genetic types of CMT; trials that would not have been possible without the establishment of the INC RDCRC.



78. The Lysosomal Disease Network (LDN)

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

The combined, integrated efforts of researchers involved in the Lysosomal Disease Network (LDN) continue to focus on using limited resources to create a network of clinical research centers focused on solving the major challenges in diagnosis, disease management, and therapy for these complex, rare disorders. Finding solutions to both the clinical and social problems associated with lysosomal disease will have direct impact on patients and inform medical practice.

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

1. Collaborative research via nine longitudinal and five 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, and through presentation at conferences and meetings; and
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, the search for undiagnosed Fabry patients in high-risk populations, 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, MD (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 Disorders.” Chester B. Whitley, PhD, MD (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; and L.A. Biomed-UCLA.

Project 3 (6704): “The Natural History of Mucopolipidosis Type IV.” Raphael Schiffmann, MD (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 (L.A. Biomed-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 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 7 (6716): “Biomarkers for Disease Severity and Therapeutic Response in LINCL.” Douglas Ballon, 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.

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 (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, Dr. Cloyd hypothesizes 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): “A Natural History Study of the Gangliosidoses” and “Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G).” Jeanine Utz, PharmD and Chester B. Whitley, PhD, MD (University of Minnesota). To characterize and describe disease progression and heterogeneity in the gangliosidosis disorders (6713). Using miglustat with the ketogenic diet as a combined, multi-targeted therapy for pediatric gangliosidoses, to evaluate if this combination will provide improved clinical outcomes compared to what is currently known about the natural course of the disease (6729).

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; new studies will be evaluated and selected in year two.

PP 1 (6725): “Podocyturia, a Non-Invasive Predictor of Renal Dysfunction in Fabry Nephropathy.” Behzad Najafian, MD (University of Washington). The proposed study seeks a non-invasive biomarker which can be regularly checked to identify FD patients, especially children, with greater risk of developing Fabry nephropathy, for the purpose of making decisions for treatment options or ERT dose-adjustment. Satellite site: University of Minnesota.

PP 2 (6724): “MR Spectroscopy to Determine Neuroinflammation and Oxidative Stress in MPS I.” Igor Nestrail, PhD, MD (University of Minnesota). Dr. Nestrail hypothesizes that neurochemical profiles will differ between MPS I Hurler (post-HCT), Hurler-Scheie (ERT), and age-matched controls; and that inflammation and oxidative stress will be more pronounced in ERT patients than post-HCT patients.

PP 3 (6723): “Natural History Study for MPS IIIC and MPS IIID.” Paul Levy, MD (Montefiore Medical Center). LDN Partnership with the 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 the Hunter’s Hope Foundation. Dr. Langan hypothesizes that children with positive screens for Krabbe disease will exhibit distinct developmental outcomes, which can be measured by standardized phone-interview protocols.

PP 5 (6711): “The Role of *GLA* Gene Variants in Heart and Kidney Disease.” Raphael Schiffmann, MD (Baylor Research Institute). The goal of this study is to determine the frequency of occurrence of persons with clinically-relevant *GLA* variants, among patients with heart and kidney disease in the general population.

Trainee Projects

- “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) “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 IIIA 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)
- 1) “Placebo Controlled Trial Evaluating Gabapentin for the Treatment of Small Fiber Neuropathic Pain in Patients with Fabry Disease” 2) “Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)” 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)
- “Proteomic Analysis to Identify Potential Biomarkers and Elucidate Pathology Mechanisms of MPS I Disease” (Li Ou, PhD, Fellow, PI)
- “Development of Mesenchymal Stromal Cells for the Treatment of Corneal Disease in Morquio A Patients” (Michael Flanagan, PhD, Fellow, PI)

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. Some of these patient groups are: Batten Disease Support & Research Association; National Tay-Sachs & Allied Diseases Association; New Hope Research Foundation; National Mucopolysaccharidosis Society; Sanfilippo Foundation for Children; Jonah's Just Begun—Foundation to Cure Sanfilippo, Inc.; United Pompe Foundation; International Society for Mannosidosis and Related Diseases; LAL Solace; The Cystinosis Foundation; Cystinosis Research Network; Cystinosis Research Foundation; Association for Glycogen Storage Disease; Fabry Support & Information Group; National Fabry Disease Foundation; Children's Gaucher Disease Research Fund; National Gaucher Foundation; Hunter's Hope Foundation; Mucopolysaccharidosis IV Foundation; Adrenoleukodystrophy Foundation; MLD Foundation; United Leukodystrophy Foundation; National Niemann-Pick Disease Foundation; The Ara Parseghian Medical Research Foundation; Acid Maltase Deficiency Association; The Ryan Foundation.



79. Nephrotic Syndrome Study Network (NEPTUNE)

Principal Investigator: Matthias Kretzler, MD

Overview

The Nephrotic Syndrome Study Network (NEPTUNE) is a collaborative investigational infrastructure of 23 sites across North America for conducting clinical and translational research on three diseases that are a part of a group of rare kidney disease presenting as Nephrotic Syndrome (NS): Focal and Segmental Glomerular Sclerosis (FSGS), Minimal Change Disease (MCD), and Membranous Nephropathy (MN).

Specific Aims

The NEPTUNE specific aims are: a) perform longitudinal observational cohort studies on patients with incipient NS, b) institute a pilot/ ancillary study program using the unique NEPTUNE resources, c) administer a training program to prepare young investigators for clinical and translational research in glomerular diseases, and d) collaborate with the RDCRN and patient advocacy groups to disseminate information.

NEPTUNE Clinical Cohort Studies

To implement the overall goal and specific aims listed above, NEPTUNE is using a multicenter, prospective cohort study with un-blinded standardized evaluation of clinical and molecular outcomes in two separate and parallel cohorts of study participants: 1) adults and children with incident, biopsy-proven FSGS, MCD, or MN 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. With the addition of second cohort to NEPTUNE, we have a unique opportunity to study patients from the onset of disease, allowing not just the collection of data, but valuable biosamples that have not been affected by time or medications.

Study participants in the biopsy cohort are recruited at the time of first biopsy. Study participants for both cohorts provide biosamples and clinical data at 4-6 month intervals for a minimum 36 months of follow-up. Study Participants in the non-biopsy cohort additionally receive daily text messages for the first 90 days that they are in the study, and then weekly text messages for the first year. Participants are asked about proteinuria, edema, potential triggers, as well as time missed from school or work due to NS to capture the dynamic nature of the disease process.

Data resources further encompass standardized digital histopathology scoring, morphometry, cytokine and chemokine panel in blood and urine, renal biopsy gene expression profiles, whole genome sequencing, exome chip genotyping, high depth targeted sequencing across 21 steroid resistance NS genes, and APOL1 genotyping. Data and samples are made available to interested researchers through the Pilot and Ancillary Studies Program. As of September 15, 2016, 560 participants were actively enrolled in the study.

Pilot and Ancillary Studies

Central to NEPTUNE's goals for facilitating translational science in NS is the maintenance of an infrastructure that encourages investigators with diverse interests and expertise to use NEPTUNE's intellectual resources, observational clinical data, biospecimens, digital pathology archive, and derived data sets. The consortium has a web-based tool called tranSMART, which provides available clinical, biospecimen, and biomarker data in an organized ontology. This allows investigators to: explore patient population characteristics based on clinical and molecular data, generate hypotheses, and develop ancillary study concepts. As of October, 2016, the NEPTUNE Steering Committee has approved 68 pilot and ancillary studies, with 34 currently in-progress. Out of the 68 studies, 23 have been submitted to NIH for funding, with 9 of 23 proposals awarded grants. A half-dozen studies have been funded by non-profit organizations or industry.

For the second NEPTUNE grant cycle, NKI agreed to provide funding for pilot studies for up to \$150,000 each year so to advance clinical and translational research in glomerular disease. In total, this program received 24 applications in the first two years of the program with two awards to-date. We are currently in the process of preparing for the next funding cycle.

Pilot and ancillary study investigators participate in a wide-range of opportunities within the consortium, such as steering committee meetings, working groups and manuscripts. Already, 17 manuscripts have been published to-date that resulted from pilot and ancillary studies. In addition to the 68 approved studies, there are 8 proposals under review as of October, 2016.

NEPTUNE Training Program

NEPTUNE provides a unique opportunity for training scientists dedicated to studying glomerular disease. Due to insufficient opportunity in the past, few potential investigators were drawn to this area. NEPTUNE helped to transform this environment by assembling a talented community of scientists with diverse backgrounds, by collecting unique resources, and by uncovering outstanding research opportunities that can be exploited to expand the pool of scientists who employ modern experimental approaches for work in glomerular diseases.

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, e) subsequent research experiences. NEPTUNE trainees are actively engaged in focused working groups, committees and meeting presentations.

The program has spanned 6 years, with over 25 applications and eight selected trainees who have completed the program. The eight funded trainees and their career development projects are:

1. Vimal Derebail, MD, MPH, University of North Carolina, *A novel mechanism for venous thromboembolism in nephrotic syndrome*
2. Tanya Pereira, MD, University of Miami, *Role of soluble urokinase (suPAR) in early onset Nephrotic Syndrome*
3. Rivka Ayalon, MD, Boston University, *The value of anti-PLA2R for diagnosis and monitoring of membranous nephropathy*
4. Pietro Canetta, MD, Columbia University, *Genetic risks for common mechanisms of injury among distinct nephrotic diseases*
5. Larysa Wickman, MD, University of Michigan, *Urinary podocyte-specific mRNA ratio as a marker of glomerular disease*
6. Ying M. Chen, MD, PhD, Washington University in St Louis, *Podocyte Endoplasmic Reticulum Stress and Focal Segmental Glomerulosclerosis*
7. Jarcy Zee, PhD, *Statistical Methods for Analysis of Glomerular Disease Morphology Data*
8. Debora Malta C.s. Santos, PhD, *The role of the miR-17~92 microRNA cluster in glomerulopathies*

Patient Advocacy Groups in NEPTUNE

Since the first cycle of funding in NEPTUNE, two Patient Advocacy Groups have played an important role: NephCure Kidney International (NKI) and the Halpin Foundation. Both groups actively participate in the NEPTUNE Steering Committee. NKI is engaged in the Recruitment and Retention Committee, and overall help with informational tools for patients, such as brochures and website content focused on the key diseases of interest to NEPTUNE. NKI has further worked with NEPTUNE on informational sheets for research coordinators, with the goal of supporting them in their efforts to interact with patients who have nephrotic syndrome (NS). Supplying the right information at the right time to study participants will enhance their study experience, which we hope will increase their likelihood to stay engaged and active throughout the study.

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 1844 patients self-registered in the Nephrotic Syndrome category.



80. Nephrotic Syndrome Study Network (NEPTUNE) Training Program in Clinical and Translational Research in Human Glomerular Disease

Matthias Kretzler¹, Larry Holzman², The NEPTUNE Consortium, Tina Mainieri¹

University of Michigan¹, University of Pennsylvania²

Objectives. 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. Training is individually tailored for each trainee, combining a didactic program with a mentored research experience that employs the resources of NEPTUNE.

This poster will describe the design, structure and components of the NEPTUNE training program, highlight the unique aspects of the NEPTUNE career development environment, formal mechanisms for administering the program, and trainee outcomes.

Methods. The program aims are to: 1) maintain a rich career development environment for those who benefit from NEPTUNE datasets and biomaterials, the activities of the scientific community created by NEPTUNE-affiliated investigators, and by participating in its working groups and committees; and 2) to provide a mechanism to evaluate, prioritize and fund career development fellowships.

Trainees combine a mentored research project with an individualized formal training component. They have access to the clinical data and biospecimens collected by the consortium sites, unique derived NEPTUNE datasets, and the consortium investigator community of experts in glomerular sciences and their intersecting proficiency in clinical intervention, epidemiology, human genetics, bioinformatics, statistics, renal pathology, glomerular biology, and biomarker discovery. Trainees have the opportunity to define research projects from within a diverse yet integrated bench-to-bedside program.

The program has a formal administrative structure that entails its own application requirements, advertisement across broad spectrum, scientific review and selection process, and ongoing monitoring of progress.

Results. The program has spanned 6 years, with over 25 applications and eight selected trainees who have completed the program. Five of six are now pursuing independent scientific careers of their own.

Conclusions. NEPTUNE provides a unique opportunity for training scientists dedicated to studying glomerular disease. Due to insufficient opportunity in the past, few potential investigators were drawn to this area, and accordingly, few established investigators emerged to conduct glomerular disease research. NEPTUNE has transformed this environment by assembling a talented community of scientists with diverse backgrounds, by collecting unique resources, and by uncovering outstanding research opportunities that can be exploited to expand the pool of scientists who employ modern experimental approaches for work in glomerular disease.

81. 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 16 (Akron Children's Medical Center, Baylor College of Medicine, 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). The mission of NAMDC is to improve the diagnosis, natural history, and treatment of mitochondrial diseases due to defects of the respiratory chain (RC). Mitochondrial diseases are clinically and genetically heterogeneous due to primary mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA).

NAMDC has strengthened its critical relationship with the United Mitochondrial Disease Foundation (UMDF), National Institutes of Health (Katrina Gwinn, MD, NAMDC Program Official, National Institute of Neurological Disease and Stroke [NINDS]; Danuta Krotoski, PhD, NAMDC Scientific Official, National Institute of Child Health and Development [NICHD]; Katherine Camp, PhD, Office of Dietary Supplements); and David Eckstein (National Center for Advancing Translational Sciences [NCATS]), and, via the Statistical Analysis Center (SAC, Columbia University Mailman School of Public Health), the RDCRN Data Management Coordination Center (DMCC).

NAMDC has expanded a powerful patient registry (which has >900 patients), a website for education and recruitment of patients, a NAMDC biorepository (Mayo Clinic, Rochester, MN), and essential diagnostic guidelines for consensus research. In addition, seven clinical studies have been initiated: a therapeutic safety study, three natural history studies (one funded as a pilot study), six survey studies, and three pilot studies. The therapeutic trial (PI, Michio Hirano, MD, New York, NY) will assess the safety of allogeneic hematopoietic stem cell transplant (HSCT) in an autosomal recessive fatal disorder of young adults (MNGIE, mitochondrial neurogastrointestinal encephalomyopathy). The first natural history study (PI Russell Saneto, OD, PhD, Seattle, WA) focuses on Alpers syndrome, a lethal childhood-onset hepatocerebral disease. The second (PI Michio Hirano, MD) investigates MNGIE to identify clinical outcome measures, which are critical for therapeutic trials. The third natural history study (PI Sumit Parikh, MD) is characterizing the progression of patients with early childhood onset Pearson syndrome due to mtDNA single deletion mutations with support of a NAMDC pilot award. The four patient surveys have assessed: 1) attitudes of women carrying mtDNA mutations and healthy egg donors regarding oocyte nuclear transfer to prevent transmission of maternally transmitted defects (Kris Engelstad with Drs. Hirano and Mark Sauer); 2) nutritional supplement use in mitochondrial disease (Dr. Amel Karaa, Harvard Medical School); 3) cardiovascular events in patients with metabolic diseases on chronic carnitine supplementation (Dr. Karaa); and 4) motivations and barriers for participation in clinical trials by individuals with mitochondrial diseases (Dr. Marni Falk, Children's Hospital of Philadelphia). In addition, a survey of NAMDC investigators regarding the NAMDC Research Diagnostic Criteria and a survey of patients' diagnostic experiences, have been completed. The pilot study (PI Fernando Scaglia, MD, PhD, Houston, TX) will determine the maximal tolerated dose of citrulline as a potential therapy for patients with mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS). The Mitochondrial Sequencing Data Resource (MSeqDR) initiated by Dr. Marni Falk, has been supported by a NAMDC pilot award. A NAMDC fellowship program (PI, Richard Haas, MD, San Diego, CA) has been actively training the next generation of mitochondrial disease clinical investigators. This fellowship program has trained 3 clinicians: Dr. Zaruzuela Zolkipli-Cunningham (currently Assistant Professor of Neurology, Children's Hospital of Philadelphia), Dr. Samantha Marin (currently Assistant Professor of Neurology, University of Manitoba), and Dr. Austin Larson (currently Medical Biochemical Genetics Fellow, University of Colorado, Aurora).

1. NAMDC Overall Structure and Interactions:

UMDF has generously continued funding for a full-time NAMDC Project Manager, who works in the SAC under Drs. Michio Hirano and Seamus Thompson. The Project Manager's numerous responsibilities include management of: IRB protocols, the NAMDC Clinical Registry, NAMDC conference calls, and interactions with UMDF. Johnston Grier was the first NAMDC Project Manager (2010-15) and was replaced by Dr. Xiomara Rosales. The UMDF has also provided the venue for the annual NAMDC site investigator face-to-face meetings, which is held at the UMDF Annual Meeting. The most recent NAMDC face-to-face meeting was held on June 14, 2016 and lasted over five hours. In addition, at the UMDF Meeting, NAMDC has recruited patients for the NAMDC clinical registry and obtained blood samples for the NAMDC biorepository.

The NIH Program and Scientific Officials, Drs. Katrina Gwinn, Danuta Krotoski, and Katherine Camp 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, participated in the Data Safety Monitoring Board (DSMB) meetings of Project 1 (MNGIE AHSCT (Allogeneic Hematopoietic Stem Cell Transplantation) Safety Study), reviewed pilot study grant applications (DK), and monitored all interactions with the DMCC.

The DMCC representative for NAMDC, Amy Roberts Holbert, has meticulously followed NAMDC activities: processing of NAMDC protocols through administrative approvals, NAMDC study protocol progress, and participation in NAMDC conference calls and site investigator meetings. Ms. Holbert monitors NAMDC registry enrollment data provided by Richard Buchsbaum, SAC Data Manager and the NAMDC Project Manager.

2. NAMDC Central IRB: To facilitate implementation of study protocols, NAMDC is establishing a Central Institutional Review Board (CIRB) at Columbia University Medical Center under the guidance of Brenda Ruotolo (Executive Director, Human Protection Office/IRBs, CUMC) and Alan Teller (IRB Associate Director, Operations, Human Protection Office/IRBs, CUMC). The CIRB will improve protocol review efficiency, communication, standard operating procedures, and generate single IRBs for NIH and industry sponsors. The CIRB has conducted reviews of research requirements and regulations at each of the 16 NAMDC sites and has drafted Reliance Agreements for each site after approval of Columbia University Legal Counsel and the Executive Director of Clinical Research at CUMC. Four NAMDC sites have signed the Reliance Agreement, 2 are expected to sign soon, 1 has requested minor revisions, and 6 have not yet responded. Once finalized, the NAMDC Clinical Registry and Biorepository Protocol (RDCRN Protocol NAMDC 7401) will be submitted to the CIRB for approval.

3. “NAMDC Clinical Registry and Biorepository” [Protocol 7401]: NAMDC received NIH approval of the NAMDC Clinical Registry and Biorepository protocol on April 20, 2011. The NIH watermarked protocol (20Apr11) has been approved by IRBs at 12 NAMDC sites. An amended version of the protocol was submitted NIH on June 10, 2012. The Registry collects information on 127 data items including: clinical manifestations (73 items), family history, neurological tests (23 items), blood and urine tests (11 items), histological studies (10), biochemical analyses (7), molecular genetics (6), and other. Richard Buchsbaum, SAC, has transferred anonymized data files to the DMCC at 1-2 month intervals since 3/21/12.

Enrollment of mitochondrial disease patients is progressing steadily and has exceeded the 15 per month rate required to reach the targeted goal of 1000 patients by the end of the current U54 grant (August 31, 2019). As of June 1, 2016, 906 patients had been enrolled; this number surpassed our target by 91 patients. Nevertheless, in the past year, NAMDC Registry recruitment has declined below our target (118 new patients enrolled between May 1, 2015-June, 2016 ~9.8 patients/month). To enhance recruitment, we are trying to develop a remote patient recruitment system.

As described below, Drs. Jaya Ganesh and Georgirene Vladutiu have developed NAMDC Diagnostic Criteria for mitochondrial disease to be used for research purposes. We are currently testing the Diagnostic Criteria on NAMDC Registry patients. These Criteria will require 39 new data items in the NAMDC Registry (18 required for all patients and 21 contingent items based on other data). Richard Buchsbaum will update the NAMDC Registry to incorporate the new data items.

There have been six data use requests for the NAMDC Registry: 1) endocrinopathies in primary mitochondrial disorders (Dr. Shana E. McCormack, Children’s Hospital of Philadelphia); 2) association of abnormal acylcarnitine profiles with mtDNA mutations (Dr. Austin Larson, Children’s Hospital of Colorado); 3) algorithm assistance and data mining project (Stealth BioTherapeutics); 4) development of a predictive model to identify patients with CPEO (Astellas Pharma); 5) demographic and patient diagnosis information of NAMDC Biorepository specimen (Drs. Jeejabai Radhakrishnan and Raul Gazmuri, Rosalind Franklin University of Medicine and Science); 6) identify adult patients with primary mitochondrial disease and mitochondrial myopathy for clinical trial recruitment (Dr. Amel Karaa, Massachusetts General Hospital); and 6) demographic details of the NAMDC registry population for a PCORI grant application (Dr. Amel Karaa). In addition, Robert Schoenaker (Medical Student, Radboud University Nijmegen, The Netherlands), under the supervision of Dr. Hirano, is analyzing data in the NAMDC Registry. This analysis will be submitted as Mr. Schoenaker’s medical school research project and will be submitted to a peer-reviewed journal for potential publication.

The NAMDC Biorepository for blood, DNA, skin biopsies, and cultured skin fibroblasts has been established at the Mayo Clinic. A Material Transfer Agreement (MTA) has been implemented and covers all 16 active NAMDC sites. As of June 1, 2016, samples from 205 patients had been shipped to the NAMDC Biorepository, which is directed by Dr. Edward Highsmith.

In addition, NAMDC has established a NAMDC Virtual Fibroblast Biorepository with a centralized web-based database designed by Dr. Richard Buchsbaum. This database allows web-based data entry on human fibroblast lines available at each NAMDC site (patients must be participants in the NAMDC Registry and sign consent to allow sharing of their fibroblast lines). To date, 75 fibroblast lines from 7 NAMDC sites have been entered into this Virtual Fibroblast Biorepository, which allow access to any scientific investigator, who submits a brief study protocol that is approved by the NAMDC Biorepository Committee.

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) and Geogirene Vladutiu (SUNY Buffalo) have developed NAMDC Diagnostic Criteria, which are being applied on a research basis to the NAMDC Registry. The Criteria uses clinical, biochemical, histological, and molecular genetic criteria to classify patients with suspected mitochondrial diseases into specific syndromes or non-syndromic diagnoses with levels of certainty: definite, probable, possible, and unlikely. The Diagnostic Criteria revisions will require 39 new data items in the NAMDC Registry (18 required for all patients and 21 contingent items based on other data).

5. “Natural History of MNGIE (NAHIM)” [Protocol 7402] A natural history study of MNGIE has been initiated by Dr. Michio Hirano. The protocol was reviewed and approved by the NIH and subsequently approved by the CUMC Institutional Review Board (IRB) on September 24, 2012. We have enrolled five 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. The five Secondary Aims include collecting supporting safety and preliminary clinical outcome data through 2 years post-implantation, and identifying any possible refinements to the recruitment and follow-up procedures, and the data management systems, which will be used in a subsequent phase II biological allocation trial. The protocol is NIH approved and has been approved at all study sites. No patients have been enrolled yet. Three candidate patients have been identified; one fulfills enrollment criteria and has 39 10/10 HLA-matched potential donors (awaiting confirmation from 2nd HLA assessment and National Marrow Donor Program screening as well as HLA-typing of unaffected sibling).

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. Data collected as part of the Registry are included in this study. Further data are collected through patient diaries and electronic case report forms (eCRFs). 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. Eight patients have been enrolled.

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. There are 7 patients enrolled. 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. To enhance enrollment, Dr. Claudio Bruno (University of Genoa, Italy) has been recruited as an international study investigator.

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 will 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. The goal is to develop a more comprehensive and detailed background for future specific clinical trials related to the type of PDC deficiency. The study protocol has been approved and seven patients have been enrolled.

NAMDC Pilot Study Program

10. NMR Observation of Brain Oxidative Metabolism” [Protocol 7409] The first pilot study recipient, Dr Juan Pascual (University of Texas at Southwestern) aimed to apply ultra high-field (7T) nuclear magnetic resonance (NMR) spectroscopy to quantitate alterations of metabolites in muscle and brain of patients with mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS). If this technique fulfills expectations, it will be applicable to a wide-range of neurological disorders. An IRB protocol was approved, but no patients were enrolled during the initial 3 year NAMDC U54 grant; therefore, NAMDC support for this project was terminated.

11. **“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). The protocol was approved by the NIH on 4/11/13. NAMDC has provided \$25,000 pilot study funding to this project.
12. **“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.
13. **“Citrulline for MELAS Dose Finding Study [RDCRN Protocol pending]**. Dr. Fernando Scaglia (Baylor College of Medicine) is PI of this pilot project which aims to determine 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). Once established, this dose will be used in a future clinical trial. This protocol is currently under development. In collaboration with Drs. Seamus Thompson, Ken Chung, Xiomara Rosales, and Michio Hirano, Dr. Scaglia has drafted a dose-escalation study design. Together with Dr. Kathy Camp (ODS) and Dr. Rosales, Dr. Scaglia is identifying a supplier of USP grade citrulline and is planning to draft an IND.

NAMDC Survey Studies

14. **“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. This survey was conducted by Dr. Hirano, Kris Engelstad, MS, and Dr. Mark Sauer (Department of Obstetrics and Gynecology, CUMC). Ninety-two women carriers, representing 13 distinct mtDNA mutations, completed the “ONGT carrier survey”. All patients surveyed were aware that they could transmit the mutation to their offspring, with 78% (35/45) of women who were of child bearing age indicating that the risk was sufficient to consider not having children, and 95% (87/92) of all carriers indicating that the development of this technique was important and worthwhile. Of the twenty-one patients surveyed considering childbearing, having their own biological offspring was very important to 11 (52%) women and somewhat important to 9 (43%) women. Fourteen of these women (78%) were willing to donate oocytes for research and development. Of 112 healthy oocyte donors who completed the “ONGT donor survey”, 97 (87%) indicated that they would donate for a viable embryo using ONGT. Thus, our surveys indicate that the majority of mtDNA carriers and oocyte donors support the development of ONGT techniques to prevent transmission of mtDNA-diseases. The results have been published (Engelstad K, Sklerov M, Kriger J, Sanford A, Grier J, Ash D, Egli D, DiMauro S, Thompson JL, Sauer MV, Hirano M. Attitudes toward prevention of mtDNA-related diseases through oocyte mitochondrial replacement therapy. *Hum Reprod*. 2016;31(5):1058-65. PubMed PMID: 26936885; PMCID: PMC4840023).
15. **“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.
16. **“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 survey was disseminated through NAMDC and the RDCRN registries. The study ascertained each patient’s specific mitochondrial disease diagnosis, specific dietary supplements used, adjunct therapy, and the effects of the supplements on symptoms and health. The survey is complete and enrollment is closed (N=162; 125 completed and 37 incomplete surveys). Preliminary results were presented at the NIH Dietary supplement use in Mitochondrial Disease Workshop in December 2014 and at the 2015 UMDF meeting. The manuscript has been accepted by Molecular Medicine and Metabolism.

17. ***“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 was disseminated through the NAMDC and the RDCRN registries. The survey is complete and enrollment is closed. Preliminary results were presented at the NIH Dietary supplement use in Mitochondrial Disease Workshop in December 2014. An abstract was presented at the 2015 UMDF meeting and the final paper for publication is being written.
18. ***“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 and enrollment is closed. 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. The data are being analyzed by Joshua Krieger and Dr. Seamus Thompson at the SAC, CUMC.
19. ***“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 enrollment is closed (N=144 patients). Data analysis is ongoing.
20. ***NAMDC Clinical Investigator Training Program.*** Dr. Richard Haas (University of California at San Diego) is the PI of the NAMDC training program, which will train clinical mitochondrial disease investigators. 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 have been presented. The first fellow, Dr. Zarazuela Zolpikli (pediatric neurologist and metabolic disorders specialist) has already completed the training program and is currently an Assistant Professor at the University of Pennsylvania. Dr. Samantha Marin was the second NAMDC fellow and completed her training on June 30, 2015. She is currently a Pediatric Neurologist and Assistant Professor at the University of Manitoba, Winnipeg, Canada. Dr. Austin Larson is the third NAMDC fellow and will complete the fellowship at the end of June, 2016 and then resume his Clinical Genetics training at the University of Colorado.



THE PORPHYRIAS CONSORTIUM

82. Porphyrias Consortium

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

For the past seven years our Consortium 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)

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. All sites are actively enrolling; over 700 subjects to date.
- 7203 A double-blind, randomized, placebo-controlled, parallel group trial on the efficacy and safety of Panhematin™ in the treatment of acute attacks of porphyria:** a single site Phase II interventional study to evaluate the clinical efficacy and safety of Panhematin™ compared to glucose treatment started early for acute attacks of porphyria. Actively enrolling at UTMB, 19 subjects enrolled to date.
- 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. All sites are actively enrolling, 114 enrolled to date.
- 7206 Hydroxychloroquine (HCQ) vs. phlebotomy for porphyria cutanea tarda:** a Phase II randomized, open-label, 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. Three sites actively enrolling, 30 subjects enrolled to date.
- 7207 Erythropoietic Protoporphyrias: Natural History, Genotype-Phenotype Correlations, and Psychosocial Impact:** an observational longitudinal investigation of the natural history, complications, and therapeutic outcomes in people with erythropoietic protoporphyria, to systematically investigate the psychological effects of the erythropoietic protoporphyrias on children and adults, and to investigate the correlation between the identified genotypes and the resulting clinical presentation, also determining the possible interaction of other genetic markers. All sites actively enrolling, 120 subjects enrolled to date.

New and Upcoming Studies

- 7208 Evidence-Based Assessment of Medication Sensitivity in Acute Hepatic Porphyrias:** an innovative online protocol where a web-based tool will be developed to collect reports from physicians who are managing patients with one of the acute porphyrias, in which an acute attack is 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.
- 7209 Effect of Oral Iron Therapy on Erythrocyte Protoporphyrin Levels in the Erythropoietic Protoporphyrias:** a pilot clinical trial and the overall objectives of this study are 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.
- 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

- 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.
- 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 Porphyrias.

Recent Publications

1. Yasuda M, et al. Liver Transplantation for Acute Intermittent Porphyria: Biochemical and Pathologic Studies of the Explanted Liver. Mol Med 2015. In Press
2. Gou E, Balwani M, Bissell DM, Bloomer JR, Bonkovsky HL, Desnick RJ, Naik H, Phillips JD, Singal AK, Wang B, Keel S, Anderson KE. Pitfalls in Erythrocyte Protoporphyrin Measurement for Diagnosis and Monitoring of Protoporphyrins. Clin Chem. 2015;61(12):1453-6.
3. Farrell CP, Overbey JR, Naik H, Nance D, McLaren GD, McLaren CE, Zhou L, Desnick RJ, Parker CJ, Phillips JD. The D519G Polymorphism of Glyceronephosphate O-Acyltransferase Is a Risk Factor for Familial Porphyria Cutanea Tarda. PLoS One. 2016. Epub ahead of print
4. Naik H, Stoecker M, Sanderson SC, Balwani M, Desnick RJ. Experiences and concerns of patients with recurrent attacks of acute hepatic porphyria: A qualitative study. Mol Genet Metab. 2016. Epub ahead of print
5. Chen B, Solis-Villa C, Hakenberg J, Qiao W, Srinivasan RR, Yasuda M, Balwani M, Doheny D, Peter I, Chen R, Desnick RJ. Acute Intermittent Porphyria: Predicted Pathogenicity of HMBS Variants Indicates Extremely Low Penetrance of the Autosomal Dominant Disease. Hum Mutat. 2016. Epub ahead of print
6. Sachar M, Anderson KE, Ma X. Protoporphyrin IX: the Good, the Bad, and the Ugly. J Pharmacol Exp Ther. 2016;356(2):267-75. Review.

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. 19 Trainees are currently in place affiliated with a PC site, 11 of which are supported by the PC's advocacy group, The American Porphyria Foundation's, "Protect the Future" Program.
2. Each Trainee has an active role in the diagnosis and management of porphyria patients, clinical and basic research, publication and education.
3. Establishment of 3 Satellite Sites of the Porphyrias Consortium supported by the APF as part of the "Protect the Future" program. These sites include Dr. Angelika Erwin, MD, PhD, Cleveland Clinic; Dr. Cynthia Levy, MD, University of Miami; and Dr. Sioban Keel, MD, University of Washington, and they participate in the main Longitudinal Study of the Consortium.

Coordination with the American Porphyria Foundation (APF)

The Consortium remains closely aligned with the APF:

- The PC Steering Committee, which includes the APF Executive Director, Mrs. Desiree Lyon Howe, meets monthly by phone to discuss Consortium progress, plans, and issues;
- The APF monthly Newsletter and their Website have announced our Consortium and 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.

DMCC

1. Utilization of the RDCRN-PC Contact Registry: as of 10/1/16, over 1700 individuals from the US, Canada, and several foreign countries have enrolled in the PC Contact Registry; of these, over 1350 requested and were referred to their nearest PC site.
2. Secondary Questions: a set of optional questions, specific for each porphyria to provide additional information for a large number of patients or family members was developed in 2014 and has been completed by ~900 participants. Responses are currently being analyzed for publication.
3. Together with the DMCC we have completely revised the content of our website as well as the layout to be more user-friendly and provide patients and health care providers with the most up to date information about the Porphyrias.
4. RDCRN Committee Memberships: PC PIs maintain membership in several RDCRN Steering Committees, including the Strategic Planning Committee, Operations Committee, and Training Committee



83. Primary Immune Deficiency Treatment Consortium (PIDTC) **Principal Investigator: Morton J Cowan, M.D.**

Major Goals and Diseases:

- To create an inclusive consortium of North American centers that treat children with Primary Immune Deficiency (PID), including Severe Combined Immune Deficiency (SCID), Wiskott-Aldrich Syndrome (WAS) and Chronic Granulomatous Disease (CGD).
- To define the critical factors and biologic markers that predict survival and other outcomes of children with SCID, WAS, and CGD following hematopoietic stem cell transplantation (HCT) or medical therapies.
- To characterize the long-term outcomes and late effects in children with SCID, WAS and CGD who undergo HCT and other therapies.
 - To develop hypotheses as to the optimal approach to HCT for children with various types of SCID, WAS and CGD that will utilize the least amount of conditioning therapy while optimizing a successful outcome.
 - To test these hypotheses in prospective randomized clinical trials.
 - To use this information to define which children with WAS and CGD are most likely to benefit from HCT and how different forms of SCID should best be treated.
- To prove the feasibility of newborn screening for SCID, starting with a pilot trial in Athabascan-speaking Native Americans.
- To train junior investigators in PID clinical research.
- To disseminate information to clinicians, scientists, patients and parents regarding the most up-to-date approaches to diagnosis and treatment of PIDs.

Studies:

- **Protocol 6901. A Prospective Natural History Study of Diagnosis, Treatment and Outcomes of Children with SCID Disorders:** The goal is to identify pre-HCT and early post HCT biologic factors that best predict successful engraftment, immune reconstitution, survival and other outcomes with minimal toxicity. We have enrolled over 200 patients in this study and are preparing an analysis of the 1st 100 patients.
- **Protocol 6902. A Retrospective and Cross-Sectional Analysis of Patients Treated for Severe Combined Immunodeficiency (1968-2010):** The goal is to identify the late effects of treatment on children with SCID as well as to identify pre-HCT and early post HCT biologic factors that best predict successful engraftment, immune reconstitution, and survival and other outcomes with minimal toxicity. We have enrolled over 700 patients to date and are completing a study of over 500 patients diagnosed with typical SCID and treated with hematopoietic cell transplant from 1980 through 2010. We are also completing the analysis of datasets on patients with SCID-related disorders and those undergoing gene therapy and enzyme-replacement therapy.
- **Protocol 6903. A Natural History, Retrospective and Cross-Sectional Study to Evaluate the Outcomes of Hematopoietic Cell Transplantation (HCT) in Chronic Granulomatous Disease (CGD) Treated Since 1995:** The goal is to define the critical clinical factors and biologic markers that predict survival and other outcomes of children with CGD following HCT or medical therapies and to characterize the long term outcomes and late effects. Recipients of HCT will be compared to a control group of patients with CGD who were not transplanted. We have enrolled 50% of the patients and are initiating a preliminary analysis.
- **Protocol 6904. A Natural History, Retrospective and Cross-Sectional Study to Evaluate the Outcomes of Hematopoietic Cell Transplantation (HCT) in Wiskott-Aldridge Syndrome (WAS) Treated since 1998.** The goal is 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 and late effects. We have enrolled 50% of the patients and are initiating a preliminary analysis.
- **Protocol 6905. Randomized study of very low versus low dose busulfan in transplant for severe combined immunodeficiency.** This is a multicenter clinical trial aimed at identifying the optimal dose of busulfan for achieving B cell reconstitution in newly diagnosed babies with SCID. An application for funding is pending.

Pilot Project: T cell exhaustion in SCID patients with poor T cell reconstitution. Preliminary results suggest that SCID patients with poor T cell reconstitution present a T cell differentiation program skewed towards T cell exhaustion. This differentiation profile is known to be associated with poor cytotoxic functions and viral control, reduced antigen-driven proliferation and impaired renewal capacity. We thus postulated that T cell exhaustion contributes to poor T cell functions in SCID patients with limited T cell reconstitution after HSCT. The aims of this study are to: 1) demonstrate that inhibitory receptor expression correlates with an exhausted transcriptional signature in SCID patients with low CD4 T cell counts and 2) establish if the absence of conditioning regimen predisposes to T cell exhaustion.

Pilot Project: Investigation of CARD11 PRD mutations and function in primary immune deficiencies. The adapter protein, CARD11, plays a critical role in NF- κ B activation after B and T cell antigen receptor engagement. Despite a growing spectrum of human immunodeficiency diseases linked to mutations in CARD11, standard immune testing typically fails to discern between activating or inhibitory CARD11 mutations, as both cause impaired *ex vivo* T cell proliferative responses. The decision to transplant and the choice for optimal conditioning for these patients depends upon the polarity of the variant effect, thus new data and novel diagnostic tools are needed to solve this dilemma. In this proposal, we will extensively characterize novel variants identified within the CARD11 PKC-regulatory domain (PRD) in two unrelated patients with immune dysregulation phenotypes and, in parallel, directly compare their functional activities with additional activating and inactivating mutant CARD11 proteins.

Training Program: We have funded 14 fellows to date. The fellows have all participated in our annual PIDTC Scientific Workshop by presenting abstracts of their work and all have remained in academic medicine.

Patient Advocacy Groups: The PIDTC has worked with the *Immune Deficiency Foundation (IDF)* to develop their biannual workshops and the *IDF*, *WAS*, *CGD* and *Jeffrey Modell* Foundations have been participating in our annual PIDTC Scientific Workshops. There has been a session on PAGs at each meeting. We have also completed a quality of life online survey of patients and parents with WAS and a manuscript is in preparation. A survey on supportive care for families of PID patients undergoing transplantation is ongoing.

DMCC: The PIDTC has been working closely with the DMCC on protocol and case report forms (CRFs) development. Rosalie Holland, on behalf of the DMCC, participates in the weekly conference calls of the PIDTC Steering and Protocol Working Committees to help facilitate implementation of the many forms created to support the protocols.

Summary of progress to date (see specific protocols above for details): The PIDTC has successfully implemented major components of the consortium including regular meetings of the PIDTC Steering Committee and Protocol Working Teams (PWT), development of the Scientific Planning Committee (SPC), establishment of a Fellowship Committee and process for awarding fellowship grants, creation of a PIDTC Website and development of content for the website, and development of a Publication Policy. The PIDTC PWT is a strong core group of investigators dedicated to protocol development, that includes the Steering Committee, statistician, junior investigators, protocol PI's and NIAID and DMCC representation. The PWT holds a weekly 2 hour conference call. The SPC includes PI's from all of the participating centers as well as junior investigators and other key scientists, ORD, NIAID and DMCC representation. The SPC meets monthly. The PIDTC is actively working with the Patient Advocacy Groups (conference call every 3 months) both with respect to their parent meetings as well as to gain their help in recruiting patients. We initiated an annual PIDTC Scientific Workshop in 2011. We were awarded an R13 grant (renewed once with second renewal pending) for support and have obtained outside funding and will have the 7th workshop in May 2017. We have included European speakers in each of our workshops. In addition, the PIDTC is represented at the European Blood and Marrow Transplant Inborn Errors Working Party annual meeting. This collaborative effort has led to several collaborative studies and publications. The PIDTC has also initiated the development of a prospective intervention trial in newborn SCID patients evaluating the optimal dose of busulfan. We received R34 funding for planning this project and funding for the trial is pending.



84. 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 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 is used to support 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 will expand our study potential and ability to assess the inflammatory biosignature of the cohorts. The Consortium also supports a vigorous Pilot Project and Clinical Training program for new investigators.

Protocols

Hereditary Causes of Nephrolithiasis and Kidney Failure (RDCRN 6401)

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

Cystine Capacity Clinical Study (CysCap) (RDCRN 6402)

To evaluate current methodologies of monitoring urine lithogenicity and predicting clinical outcomes in patients with cystinuria. The overall goal is to correlate urinary parameters with the likelihood of stone formation to better guide therapy and to reduce morbidity. Status: Active

Screening for Dent Disease Mutations in Patients with Proteinuria or Hypercalciuria and Calcium Urolithiasis (RDCRN 6403)

Targeted genetic screening (*CLCN5* and *ORCL1* genes) in patients with clinical suspicion of Dent Disease and in first degree relatives of probands with confirmed *CLCN5* or *ORCL1* variants when necessary for segregation analysis. Status: Active

Biobank Protocol (RDCRN 6404)

To obtain high quality biological samples from well characterized patients with primary hyperoxaluria, cystinuria, APRT deficiency, and Dent disease, and from their family members, for use in research. Status: Active

Influence of Hydroxyproline Plasma Concentration on its Metabolism to Oxalate (RDCRN 6405)

To determine the mean percent conversion of hydroxyproline to urinary oxalate and the contribution of hydroxyproline metabolism to the amount of oxalate excreted in urine. Status: Recruitment completed

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

To demonstrate that certain mutations predispose individuals with hyperoxaluria to more severe disease. Status: Active

Assessment of Health-Related Quality of Life in Rare Kidney Stone Formers in the Rare Kidney Stone Consortium (RDCRN 6408)

Assessment of quality of life in patients with rare causes of kidney stones. Status: Active

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

This pilot investigation uses 24 hr. urine aliquots from PHI patients & healthy sibling controls; and longitudinally collected 24 hr. urine from patients with PHI to determine unique proteomic markers of PHI vs. healthy (intra-familial) controls. Status: Approved

Systematic Review of Clinical Biopsies of Dent Disease Patients (RDCRN 6410)

To determine the frequency and nature of glomerular changes in Dent disease patients. Status: Active

Novel Assay for the Determination of Urinary 2, 8 Dihydroxyadenine and other Key Urinary Purine Metabolites (RDCRN 6412)

To study the applicability of a newly developed UPLC-MS/MS method in clinical management of patients with APRT deficiency and dihydroxyadeninuria. Status: Active/Closed to Accrual

Effect of Increasing Doses of Cystine Binding Thiol Drugs on Cystine Capacity in Patients with Cystinuria (RDCRN 6413)

To evaluate the effect of escalating doses of cystine binding thiol drugs on the cystine capacity of the urine to help guide the therapy and minimize unnecessary side effects. Status: Active

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. Status: Active

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

To characterize the microbiome in 4 groups of participants. Status: Active

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

To establish a prospective longitudinal cohorts of patients with primary hyperoxaluria, enteric hyperoxaluria, cystinuria, Dent disease, Lowe syndrome, and APRT deficiency and identify biomarkers associated with disease progression. Status: Active

Pilot Studies

1. Establishment of primary cultures from PHI hepatocytes, Hari Koul
2. New drugs for cystinuria, Amrik Sahota
3. Post kidney transplant nephrocalcinosis: Incidence, risk factors and graft, E. Tosetto
4. Genotype-phenotype correlation in Dent's disease: The role of modifying factors, H. Amer
5. Genotype-phenotype correlation in Dent's disease: The role of modifying factors, F. Anglani
6. Novel assay for the determination of urinary 2,8-dihydroxyadenin and other key urinary purine metabolites, V. Edvardsson
7. Descriptive and functional analyses of gut microbiome alterations in hyperoxaluria, L. Nazzari
8. Proteomics of crystalline nephropathy, C. Langman and E. Brooks
9. Screening of monogenic stone formers and recurrent stone formers for disease causing mutations, P. Harris
10. Characterization of specific renal cellular activation or injury in primary hyperoxaluria. M. Jayachandran

Training Program

1. Dr. Lada Beara Lasic, Role of phosphorus and FGF 23 in patients with Dent disease
2. Dr. Hatem Amer, Transplant nephrocalcinosis: Incidence, risk factors and graft function
3. Dr. Larissa Kovacevic, Urine proteomic analysis in cystinuric patients with renal stones
4. Dr. Whittamore, Acid-base regulation of intestinal oxalate transport in primary hyperoxaluria
5. Dr. Lama Nazzal, Descriptive analysis of gut microbiome alterations in hyperoxaluric conditions
6. Dr. David Sas, Characterization of urinary microbiome in primary hyperoxaluria and cystinuria
7. Dr. Min-Hwang Chang, Mechanistic studies of CLCN5 point mutations to understand genotype-phenotype correlations in Dent disease

Patient Advocacy Groups

Goals of the RKSC are achieved through close collaboration with our PAG partners: The OHF (PH), International Cystinuria Foundation (ICF), Cystinuria Support Network (CSN), Lowe Syndrome Association (Dent 2), the Dent Disease Foundation (Dent disease), and the APRTd Support Network (APRT deficiency). 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 directions.



85. Rare Lung Diseases Consortium

Principal Investigator: Bruce C. Trapnell, MD
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 145/300

RLD 5710: A Longitudinal Study of Hermansky-Pudlak Syndrome Pulmonary Fibrosis, *actively enrolling*, current enrollment 46/80

RLD 5712: Longitudinal Evaluation of Pulmonary Alveolar Proteinosis; protocol under development

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), *protocol under development*, anticipated enrollment February 2017

RLD 5717: Evaluation of the Safety, Pharmacokinetics and Pharmacodynamics of Inhaled Sargramostim in Patients with Autoimmune Pulmonary Alveolar Proteinosis, *protocol under development*, anticipated enrollment November 2016

Observational Studies

RLD 5714: Assessment of Safety of Air Travel in Patients with Diffuse Cystic Lung Disease, *actively enrolling*, current enrollment 147/300

RLD 5715: Retrospective Review of CT Images in Rare Lung Diseases, *actively enrolling*, current enrollment 53/250

RLD 5716: Use of Hyperpolarized ¹²⁹Xe MR Lung Imaging in Children and Adults, *actively enrolling*, current enrollment 4/28

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 89/500

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: 4

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.

2016 International Rare Lung Diseases Conference:

On September 22-25, 2016, more than 450 individuals attended the 2016 International Rare Lung Diseases Conference in Cincinnati, Ohio. Dr. David Fajgenbaum, co-founder and Executive Director of the Castleman Disease Collaborative Network welcomed everyone with his presentation "Overtime: A Physician-Scientist-Patient Fighting to Cure Castleman Disease". The next day RLD experts presented cutting-edge data about 17 different rare lung diseases. At the RLDC Celebration Banquet, awards were given to the Researchers who have dedicated their lives to finding cures for rare lung diseases. The following day, RLD researchers and clinicians gathered in workshops to discuss the development of diagnostics and therapeutics for some of the rarest of lung diseases. The conference closed with Rare Lung Diseases Clinic Director's Congress where researchers and clinicians discussed challenges and successes in RLD research.

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.





86. Rett Syndrome, MECP2 Duplication Disorder, and Rett-related Disorder Consortium

Principal Investigator: Alan Percy, MD – University of Alabama at Birmingham

Study Administrator and Co-PI: Jeffrey Neul, MD, PhD – University of California San Diego

Project Manager: Jane Lane, RN BSN – University of Alabama at Birmingham

Disorders Under Study

Rett Syndrome: PI – Alan Percy, MD, UAB

MECP2 Duplication Disorder: PI – Jeffrey Neul, MD, PhD, UCSD

Rett-related Disorders: PI – Jeffrey Neul, MD, PhD, UCSD

Study sites:

1. Baylor College of Medicine – site PI: Daniel Glaze, MD
2. Boston Children's Hospital – site PI: Mustafa Sahin, MD, PhD
3. Children's Hospital of Philadelphia – site PI: Eric Marsh, MD, PhD
4. Cincinnati Children's Hospital – site PI, Shannon Standridge, DO
5. Cleveland Clinic – site PI: Sumit Parikh, MD
6. Gillette Children's Hospital – site PI: Art Beisang, MD
7. Greenwood Genetic Center – site PI: Steve Skinner, MD
8. Oakland Children's Hospital – site PI: Mary Jones, MD
9. Rush Medical Center – site PI: Peter Heydemann, MD
10. University of Alabama at Birmingham – site PI: Alan Percy, MD
11. University of California San Diego – site PI: Jeffrey Neul, MD, PhD
12. University of Colorado – site PI: Tim Benke, MD, PhD
13. University of Rochester – site PI: Alexander Paciorkowski, MD
14. Vanderbilt University – site PI: Sarika Peters, PhD
15. Washington University St. Louis – site PI: Robin Ryther, MD

Major Goals:

- 1: Longitudinal studies of disorders including genotype-phenotype correlations, survival surveillance, clinical severity assessments, and quality of life measures
- 2: Neurophysiologic studies of visual and auditory evoked potentials
- 3: Biobanking of blood for plasma, DNA, and RNA and skin biopsy samples

Longitudinal Studies

Longitudinal studies have built on the prior study involving more than 1200 participants including more than 1120 with Rett syndrome. Current enrollment is now more than 220 in this expanded study including individuals with Rett syndrome, those with MECP2 mutations not meeting the criteria for Rett syndrome, MECP2 duplication, and FOXP1 and CDKL5 mutations

Pilot Studies

- 1: Development of a Rett-specific behavioral outcome measure
- 2: Metabolomics assessment to identify potential biomarkers

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

1. **IGF-1 Trial:** Boston Children's Hospital, Rush Medical Center, and Greenwood Genetic Center
2. **Trofinetide Trial (Neuren Pharmaceuticals):** Baylor College of Medicine, Boston Children's Hospital, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Gillette Children's Hospital, Greenwood Genetic Center, Oakland Children's Hospital, Rush Medical Center, University of Alabama at Birmingham, University of California San Diego, University of Colorado, Vanderbilt University
3. **Sarizotan Trial (Newron Pharmaceuticals):** Baylor College of Medicine, Rush Medical Center, University of Alabama at Birmingham, University of California San Diego

Training Program

Training is progressing well with two trainees now participating, each in two year programs, and two in research-related studies

Role and Involvement of Patient Advocacy Groups

Rettsyndrome.org – Consortium support: Steve Kaminsky and Janice Ascano;

Patient advocacy: Paige Nues

Rett Syndrome Research Trust – Monica Coenraads

MECP2 Duplication – Dick Sobsey, Dyna and Joseph Mendoza, Katie Moe

International Foundation for CDKL5 Research – Kathryn Frame, Karen Utey

International FOXP1 Foundation – Ileana Giordani, Jennifer Leonard

The Patient Advocacy Groups are integral to the functioning of the consortium providing encouragement for participant enrollment and participation in on-going activities of the consortium.

Rettsyndrome.org is a direct partner in the consortium participating in funding for the three major goals, the pilot projects, and training and supporting 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:

1. Neul JL, Fang P, Barrish J, Lane J, Caeg E, Smith EO'B, Zoghbi HY, Percy A, Glaze DG. Specific Mutations in Methyl-CpG-Binding Protein 2 Confer Different Severity in Rett Syndrome. **Neurology** 70:1313-1321,2008
2. Kirby RS, Percy AK, Lane JB, Glaze DG, Skinner SA, MacLeod P, Barrish J, Annese F. Longevity in Rett Syndrome: Probing the North American Database. **J Peds** 159:135-138, 2010. PMC2794941
3. Percy AK, Lee HS, Neul JL, Lane JB, Skinner SA, Geerts SP, Annese F, Graham J, McNair L, Motil KJ, Barrish JO, Glaze DG. Profiling Scoliosis in Rett Syndrome. **Pediatr Res** 67:435-439, 2010. PMC2852102
4. Glaze DG, Percy AK, Skinner S, Motil KJ, Neul JL, Barrish JO, Lane JB, Geerts SP, Annese F, Graham J, McNair L, Lee H-S. Epilepsy and the natural history of Rett syndrome. **Neurology** 74:909-912,2010. PMC2836870
5. Percy A, Neul J, Glaze D, Motil K, Skinner S, Khwaja O, Lee H, Lane J, Barrish J, Annese F, McNair L, Graham J, Barnes K. Rett Syndrome Diagnostic Criteria: Lessons from the Natural History Study. **Ann Neurol** 68:PMC33021984
6. Lane JB, Lee H-S, Smith LB, Cheng P, Percy AK, Glaze DG, Neul JL, Motil KJ, Barrish JO, Skinner SA, Annese F, McNair L, Graham J, Khwaja O, Barnes K, Krischer JP. Clinical severity and quality of life in children and adolescents with Rett Syndrome. **Neurology** 77:1812-1818, 2011. PMC3233210
7. Tarquinio D, Motil K, Hou W, Lee H, Glaze DG, Skinner SA, Neul JL, Annese F, McNair L, Barrish JO, Geerts SP, Lane JB, Percy AK. Growth Failure in Rett Syndrome: Specific Growth References. **Neurology** 79:1653-1661, 2012.
8. Cuddapah VA, Pillai RB, Shekar KV, Lane JB, Motil KJ, Skinner SA, Tarquinio DC, Glaze DG, McGwin G, Kaufmann WE, Percy AK, Neul JL, Olsen ML. *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
9. Neul J, Lane J, Lee H, Geerts S, Barrish J, Annese F, Baggett L, Barnes K, Skinner S, Motil K, Glaze D, Kaufmann W, Percy A. Developmental delay in Rett syndrome: data from the natural history study. **J Neurodev Disord** 2014, 6:20
10. Killian J, Lane J, Cutter G, Skinner S, Kaufmann W, Tarquinio D, Glaze D, Motil K, Neul J, Percy A. Pubertal Development in Rett Syndrome Deviates from Typical Females. **Pediatr Neurol** 51:769-775, 2015. PMC4254166
11. Tarquinio D, Hou, W, Neul JL, Lane JB, Barnes KV, O'Leary HM, Bruck NM, Kaufmann WE, Motil KJ, Glaze DG, Skinner SA, Annese F, Baggett L, Barrish JO, Geerts SP, Percy AK. Age of diagnosis in Rett syndrome: patterns of recognition among diagnosticians and risk factors for late diagnosis. **Pediatr Neurol** 52:585-591,2015 doi:10.1016/j.pediatrneurol.2015.02.007. [PMID: PMC4442062]
12. Tarquinio DC, Hou W, Neul JL, Kaufmann WE, Glaze DG, Motil KJ, Skinner SA, Lee H-S, Percy AK. The changing face of survival in Rett syndrome and *MECP2*-related Disorders. **Pediatr Neurol** 53:402-411,2015. NIHMS 705517.
13. Killian, Jr. JT, Lane JB, Lee H, Pelham J, Skinner S, Kaufmann WE, Glaze D, Neul JL, Percy AK. Caretaker Quality of Life in Rett Syndrome: Disorder Features and Psychological Predictors. **Pediatr Neurol** 58:67-74, 2016. NIHMS 771109
14. Sajan, SA, Jhangiani SN, Muzny DM, Gibbs RA, Lupski JR, Glaze DG, Kaufmann WE, Skinner SA, Friez MJ, Percy AK, Neul JL. Rett Syndrome that is not caused by mutations in *MECP2*, *CDKL5*, and *FOXP1* is genetically complex, heterogeneous, and enriched in mutations in chromatin regulators. **Genet in Med**. DOI: GIM.2016.42, 2016.



87. Sterol and Isoprenoid Diseases Consortium (STAIR)

Principal Investigator: William B. Rizzo, MD – University of Nebraska Medical Center

Major STAIR Goals	Diseases Studied	STAIR Sites
STAIR investigates a group of rare genetic diseases bound by common biochemistry caused by inborn errors affecting sterol and isoprenoid metabolism. Goals are: • To conduct clinical (interventional and natural history) and pilot research studies • To train investigators in rare disease clinical research • To support research efforts of patient advocacy groups involved in the diseases • To actively participate in RDCRN	• Smith-Lemli-Opitz Syndrome (SLOS) • Mevalonate Kinase Deficiency (MKD) / Hyper-IgD Syndrome (HIDS) • Sjögren-Larsson Syndrome (SLS) • Sitosterolemia • Methylsterol Oxidase Deficiency (SC4MOL) • Cerebrotendinous Xanthomatosis (CTX) • Peroxisome Biogenesis Disorders (PBD) • Disorders of Dolichol Metabolism	• University of Nebraska Med Ctr • Washington State University • Cincinnati Children's Hosp • University of Pittsburgh • University of Manitoba • Colorado Children's Hosp • National Human Genome Res Institute, NIH • Oregon Health & Science Univ • Radboud University • University of South Florida
Study Title	Goals	Status
Sjögren-Larsson Syndrome: A Longitudinal Study of Natural History, Clinical Variation and Evaluation of Biochemical Markers (STAIR 7004) • PI: William B. Rizzo, MD	• Observational, longitudinal study to characterize the natural history of SLS • Identify novel biomarkers that correlate with disease progression • Maintain a Biorepository of biospecimens	Active. recruitment ongoing
Effects of Fish Oil, Colesevelam, and Combination Therapy on Sterol Metabolism in Sitosterolemia (STAIR 7007) • PI: Peter Jones, PhD, and Semone Myrie, PhD	• Interventional study on the optimal therapy of sitosterolemia in patients currently taking ezetimibe	Recently approved by NICHD. Beginning recruitment, 2016
Clinical and Basic Investigation into Known and Suspected Disorders of Dolichol Synthesis and Utilization • PI: William A. Gahl, MD, PhD, and Lynne Wolfe, MS, CRNP	• Observational, longitudinal study to characterize the natural history of Dolichol disorders • Identify novel biomarkers that correlate with disease progression • Maintain a Biorepository of biospecimens	Study is currently in development stage.
Smith-Lemli-Opitz Syndrome: A Longitudinal Clinical Study of Patients Receiving Cholesterol Supplementation (STAIR 7001) • PI: Robert Steiner, MD, Jean-Baptiste Roullet, PhD	• Observational, longitudinal study to determine clinical and biochemical outcomes in patients with SLOS receiving dietary cholesterol supplementation • Correlate biochemical and clinical phenotypes in study participants with whole body cholesterol pool size and major determinants of cholesterol synthesis, absorption and intake • Identify or refine clinical or biochemical markers for use as outcome measures • Develop a national SLOS patient registry • Maintain a Biorepository of	Study in data analysis phase. No longer recruiting

	biospecimens	
Assessment of Sterol Metabolism in Sitosterolemia: A Pilot Study of Patients Treated with Ezetimibe (STAIR 7002) • PI: Peter Jones, PhD	• Pilot Study to determine if treatment with ezetimibe decreases plant sterol pool size in patients with sitosterolemia	Study completed.
Trainee	Clinical Site/Mentor	Research Project
Andrea DeBarber, PhD	Oregon Health & Science University Primary Mentor: Robert Steiner, MD Training Start/End date: 2010 – 2011	Improving diagnostic and therapeutic monitoring for techniques in CTX
Miao He, PhD	Emory University ^[1] Primary Mentor: Gerard Vockley, MD Training Start/End date: 2010 – 2012	Developing new methods to characterize methylsterol abnormalities in patients with SC4MOL and characterizing the immune response and inflammatory pathways
Shibani Kanungo, MD	University of Pittsburgh Medical Center Primary Mentor: Gerard Vockley, MD Training Start/End date: 2011- 2012	Feasibility of newborn screening for SC4MOL deficiency and developing a clinical treatment protocol for SC4MOL deficiency
Semone Myrie, PhD	University of Manitoba Primary Mentor: Peter Jones, PhD Training Start/End date: 2014-2016	Therapeutic studies of sitosterolemia and investigations of sterol pool size, turnover and nutrition in SLOS
Mousumi Bose, PhD	University of Nebraska Medical Center Primary Mentor: William Rizzo, MD Training Start/End date: 2016-2018	Characterize patient quality of life and nutritional/growth aspects of STAIR diseases
Patient Advocacy Groups	Mission	Role in STAIR
Smith-Lemli-Opitz/RSH Foundation ^[1] (SLO/RSH) Founded: 1988 • www.smithlempiopitz.org	Supporting families, individuals and professionals dealing with SLOS by providing a network of ongoing communication, funding research, and raising awareness to enhance the quality of life, improve current treatments and strive towards a cure.	Provides support to STAIR by advertising clinical research studies on SLOS, providing financial resources, and sponsoring scientific and family conferences.
United Leukodystrophy Foundation (ULF) Founded: 1982 • www.ulf.org	Dedicated to providing patients and their families with information about their disease and assistance in identifying sources of medical care, social services, and genetic counseling; establish a communication network among families; provide information to health care providers; promote research into causes, treatments, and prevention of the leukodystrophies.	Supports STAIR by advertising clinical research studies on CTX, providing financial resources for scientific meetings and family conferences.
Foundation for ^[1] Ichthyosis & Related Skin types (FIRST) ^[1] Founded: 1981 • www.firstskinfoundation.org	Educate, inspire, and connect those touched by ichthyosis and related disorders through emotional support, information, advocacy, and research funding for better treatments and eventual cures	Publicizes STAIR studies and patient referrals for STAIR SLS studies.
Autoinflammatory Alliance Founded: 2006 (as NOMID Alliance) • www.autoinflammatory.org	Dedicated to promoting awareness, proper diagnosis and treatment, and improved care for people with autoinflammatory diseases.	Provides publicity about STAIR studies and refers patients for STAIR HIDS studies.

Global Foundation for Peroxisomal Disorders (GFPD) • www.Thegfpd.org	The mission of the GFPD is to fund and promote peroxisome disorder research and to assist families and professionals through educational programs and support services related to Zellweger spectrum disorders.	Works with STAIR to develop natural history data on peroxisomal disorders and other STAIR diseases
Patient Advocacy Groups	Mission	Role in STAIR
Sitosterolemia Foundation Founded: 2015 • www.Sitosterolemiafoundation.org	Sitosterolema Foundation is dedicated to supporting families, individuals and professionals dealing with Sitosterolemia; provide a network of ongoing communication, funding research and raising awareness; enhance the quality of life while improving on current treatment methods.	Provides publicity about STAIR studies and conferences. Refers patients to studies on sitosterolemia.



88. Urea Cycle Disorders Consortium

PI: Mendel Tuchman

OVERVIEW	
Major Goals:	1) To advance our understanding of the pathophysiology of urea cycle disorders (UCD) by performing collaborative clinical research. 2) To nurture development of the next generation of orphan disease researchers by training this still-nascent cadre to become expert in the clinical investigation of rare disorders, especially UCD. 3) To identify promising new approaches to UCD care by performing pilot/demonstration (proof of concept) clinical research projects which will deploy state-of-the-art methodologies. 4) To disseminate knowledge 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.
Disorders Studied:	1. N-acetylglutamate synthetase (NAGS) deficiency 2. Carbamyl phosphate synthetase I (CPSI) deficiency 3. Ornithine transcarbamylase (OTC) deficiency 4. Argininosuccinate synthetase (AS) deficiency (citrullinemia) 5. Argininosuccinate lyase (AL) deficiency (argininosuccinic aciduria) 6. Arginase (ARG) deficiency (argininemia) 7. Citrulline (CITR) deficiency (citrullinemia type II) 8. Hyperornithinemia, hyperammonemia, homocitrullinuria (HHH) syndrome
STUDIES	
Introduction:	The UCDC is now in its third 5-year funding cycle. In addition to numerous pilot and trainee projects, 9 major studies have been conducted resulting in more than 30 publications. The following is a summary of studies funded in this grant cycle. In addition, the UCDC continues two studies initiated in the previous grant cycle: the N-carbamylglutamate in the Treatment of Hyperammonemia (RDCRN 5105) and Carbaglu Surveillance Protocol (RDCRN 5111).
Major Protocol 1:	Longitudinal Study of Urea Cycle Disorders (UCDC 5101) PI: Mendel Tuchman, MD, Children's National Health System
Objective(s):	To conduct a longitudinal multidisciplinary investigation of the natural history, morbidity, and mortality of people with UCD.
Status:	Active, recruiting Enrolled: 764 participants as of 9/30/16 Target: 550 Limit: 1,100
Results:	This study has allowed the UCDC to publish fifteen papers on UCD (and several other related papers using 5101 data) including cross sectional analysis, liver dysfunction and hepatocellular injury, neuropsychological outcomes, hyperammonemic event triggers, vaccines and association with metabolic events, incidence of UCD, and improving long term outcomes.
Major Protocol 2:	Biomarkers of Neurological Injury and Recovery in Urea Cycle Disorders PI: Andrea Gropman, MD, Children's National Health System
Objective(s):	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.
Status:	Protocol approved and activated on 8/16/16. Study team is working on initiating enrollment.
Major Protocol 3:	Nitric Oxide Supplementation as a Therapeutic Intervention in Argininosuccinate Lyase Deficiency PI: Sandesh Nagamani, MD, Baylor College of Medicine

Objective(s):	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.
Status:	This protocol has been approved by NICHD and will be reviewed by the DSMB on 10/31/16.
Pilot Studies:	Manipulating the Microbiome in UCDs , PI: Nicholas Ah Mew, MD, Children's National Health System Targeted Massively Parallel DNA Sequencing for Newborn Screening for Proximal UCDs , PI: Shawn McCandless, University Hospitals Cleveland Medical Center UCD Practice Patterns and Outcomes Assessment , PI: Jeffrey Krischer, DMCC, University of South Florida Prospective Cross-sectional Non-invasive Assessment of Chronic Liver Disease in UCD , PI: Lindsay Burrage, Baylor College of Medicine
Trainee Studies:	Enzyme Replacement Therapy in Mouse Models of Arginase Deficiency , PI: Lindsay Burrage, Baylor College of Medicine Development and Evaluation of Handheld Blood Ammonia Meter , PI: Omar Ayuub, PhD, Children's National Health System Pre-clinical Gene Editing for Arginase-1 Deficiency , PI: Yuan Yan Sin, MBBS, PhD, Hospital for Sick Children
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 for 19 graduate students, clinical genetics/ metabolism fellows and junior faculty members in rare disease research.	



Principal Investigator: Peter A. Merkel, MD, MPH

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 two 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].

The VCRC includes 20 sites in the United States and Canada >70 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 disease, cryoglobulinemic vasculitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), giant cell arteritis, granulomatosis with polyangiitis (Wegener's), 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 352

5503: Takayasu's Arteritis; *actively enrolling*, current enrollment 201

5504: Polyarteritis Nodosa; *actively enrolling*, current enrollment 102

5505: Granulomatosis with Polyangiitis & Microscopic Polyangiitis; *actively enrolling*, enrollment 863

5506: Eosinophilic granulomatosis with polyangiitis; *actively enrolling*, current enrollment 233

5507: Aortitis; study activation expected in December 2016

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 670 [in addition to the 1751 cases from the VCRC Longitudinal Studies for a total of 2421 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.*

Pilot Studies:

- 5522:** Abatacept for mild relapsing Wegener's granulomatosis, *recruitment complete*, 20/20
5562: A randomized multicenter study for isolated skin vasculitis, study activation expected in November 2016
5563: Clinical transcriptomics in systemic vasculitis, study activation expected in November 2016
Several new pilot studies of promising new agents for the treatment of vasculitis are under consideration by the VCRC Steering Committee.

Clinical Trials:

- 5523:** Abatacept for GCA and TAK; *recruitment complete*, 80
5524: Plasma exchange and glucocorticoid dosing for ANCA-Associated Vasculitis; *recruitment complete*, 704
5525: Randomized controlled trial comparing rituximab and azathioprine for AAV; *actively enrolling*, current enrollment 185
5526: Randomized controlled trial of prednisone in GPA; *actively enrolling*, current enrollment 62
5527: Randomized, placebo controlled trial of abatacept in GPA; *actively enrolling*, current enrollment 19

Observational Studies:

- 5511:** VCRC Tissue Repository; study activation expected in November 2016
5515: Imaging study of MRI and PET/CT scans in TAK; *actively enrolling*, current enrollment 26
5531: Vasculitis Reproductive Health Survey; *recruitment complete*, 467
5532: Vasculitis pregnancy registry; *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; *actively enrolling*, current enrollment 177
5536: Impact of Vasculitis on Employment and Income Study; *recruitment complete*, 426
5599: Second layer diagnostic questions for VCRC Contact Registry; 2,968 questionnaires completed to date

Outcome Measures

- 5540:** Development of Disease-Specific Outcomes in Vasculitis
5541: Validation of PROMIS for use in Vasculitis
 OMERACT Vasculitis Working Group

Training Program:

The VCRC 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.

Number of VCRC Fellows trained: Current: 1, Previous: 10

Patient Advocacy Groups: The Churg-Strauss Syndrome Association, the PAN Support Network, and the Vasculitis Foundation. Patient Advocacy Groups are 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, TerumoBCT].

