

**Autonomic Disorders Consortium (ADC)**  
**PI: David Robertson, MD – Vanderbilt University**

Major Goals	Diseases Studied
<ul style="list-style-type: none"> <li>To develop novel therapies for improving quality of life and altering course of disease</li> <li>To standardize the evaluation of autonomic function</li> <li>To learn more about the long-term prognosis of the disorders</li> <li>To develop patient registries</li> <li>To develop data / specimen banks</li> </ul>	<ul style="list-style-type: none"> <li>Postural Tachycardia Syndrome (POTS)</li> <li>Pure Autonomic Failure (PAF)</li> <li>Multiple System Atrophy / Shy-Drager Syndrome (MSA)</li> <li>Autoimmune Autonomic Ganglionopathy (AAG)</li> <li>Parkinsonism with Autonomic Failure</li> <li>Lewy Body Disease</li> <li>Dopamine <math>\beta</math>-Hydroxylase Deficiency</li> <li>Norepinephrine Transporter Dysfunction</li> <li>Familial Dysautonomia</li> <li>Baroreflex Failure</li> <li>Neurally Mediated Syncope</li> <li>Pheochromocytoma</li> <li>Mastocytosis</li> <li>Takotsubo Syndrome</li> </ul>

Study Title	Goals	Status
Peripheral Dopamine in Postural Tachycardia Syndrome	To determine how changes in kidney dopamine (DA) activity influence urinary sodium excretion.	<b>At NINDS Committee</b>
Randomized, Double-blind, Placebo-controlled Clinical Trial to Assess the Efficacy, Safety, and Tolerability of Rifampicin in Patients with Multiple System Atrophy	To evaluate the efficacy of rifampicin compared to placebo in patients with MSA.	<b>DSMB Committee Meeting Sept 2010</b>
Norepinephrine Transporter Blockade in Neurogenic Orthostatic Hypotension	To determine if the pressor response of atomoxetine can distinguish between patients with pre-ganglionic lesions versus with those with post-ganglionic lesions.	<b>At NINDS Committee</b>
Prosthetic Baroreceptor System for Orthostatic Hypotension	To develop a prosthetic baroreceptor system and to test hemodynamic effects of epidural spinal cord stimulation.	<b>At NINDS Committee</b>
The phenotype and natural history of primary autonomic disorders	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 clinical phenotype of a number of rare autonomic disorders.	<b>Draft version at consortium sites</b>
Randomized, Placebo-Controlled Trial to Evaluate the Efficacy of IVIG in Autoimmune Autonomic Ganglionopathy	To determine the effect of intravenous immunoglobulin (IVIG) treatment on orthostatic hypotension, autonomic symptoms and quality of life scores in patients with AAG. To determine the effect of targeted immunomodulatory treatment on orthostatic hypotension, autonomic symptoms and quality of life scores in patients with AAG.	<b>At RDCRN for 1<sup>st</sup> Review</b>

### 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. Trainees participating in the Consortium educational experiences at Vanderbilt this year included Hossam Mustafa MD, Luis Okamoto MD, and Amy Arnold, PhD. In subsequent years education and training support will be extended to other consortium sites. Two trainees from the Consortium will attend the Fall Conference on Rare Diseases in Bethesda.

### 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. The following is an incomplete list of advocacy groups that share our vision, as new advocacy groups arise constantly. (Dysautonomia Foundation, National Dysautonomia Research Foundation, Shy-Drager MSA Support Group, Dysautonomia Information Network, OI Resources, Syncope Trust and Reflex Anoxic Seizures Support Group)

**Angelman, Rett, & Prader-Willi Syndromes Consortium (ARPWSC)**

**PI:** Alan K. Percy, MD; **Co-PI:** Arthur L. Beaudet, MD

**Major goals:** The major goals of this consortium are to develop robust natural history data for specific aspects as prospects for effective interventions emerge, training to increase the pool of rare diseases investigators, and address specific clinical features with targeted pilot studies.

**Disorders under study:** Angelman syndrome, Rett syndrome and other *MECP2*-related phenotypes, Prader-Willi syndrome and Early-onset Morbid Obesity (EMO)

**Longitudinal studies:**

**5201:** Rett Syndrome Natural History  
Current enrollment: 920/1000; Status: Actively enrolling

**5202:** Prader-Willi Syndrome/Early-onset Morbid Obesity Natural History  
Current enrollment: 190/300; Status: Actively enrolling

**5203:** Angelman Syndrome Natural History  
Current enrollment: 196/300; Status: Actively enrolling

**Clinical trials:**

**5204:** Efficacy of a Therapeutic Treatment Trial in Angelman Syndrome  
Closed to accrual: 91 participants; Status: Data under analysis

**Pilot studies:**

**5207:** Sleep disorders in Angelman, Rett, and Prader-Willi syndromes  
Goals: Evaluate prevalence and natural history of sleep dysfunction  
Status: Protocol development and IRB approval in progress

**Number of persons trained:** Current: 3; Previous: 16

**Patient Advocacy Groups:**

Prader-Willi Syndrome Association  
International Rett Syndrome Foundation  
Angelman Syndrome Foundation  
Foundation for Angelman Syndrome Therapeutics

Patient Advocacy Groups are actively involved maintaining vibrant links with families, promoting study participation, funding consortia training and pilot studies, and participating in CPAG activities.

## Brain Vascular Malformation Consortium (BVMC)

**William L. Young, MD, Program Director, (PI); and Douglas A. Marchuk, PhD, Co-Director**

**Diseases Being Studied include (a)** Familial Cavernous Malformations (CCM)— Common Hispanic Mutation; **(b)** Sturge-Weber Syndrome (SWS)—Leptomeningeal Angiomatosis; and Hereditary Hemorrhagic Telangiectasia (HHT) associated Brain Arteriovenous Malformation (BAVM)

The major goals are:

**CCM:** To establish a CCM database at the University of New Mexico and recruit 500 CCM1 patients with the Common Hispanic Mutation (CHM) to investigate additional genetic and non-genetic factors that influence CCM lesion burden. We will also evaluate CCM lesion progression (both number and size) in 100 patients over the study period.

**SWS:** To develop a national standardized database of patients with Sturge-Weber Syndrome, determine the usefulness of urine tests and to investigate whether this test can demonstrate progression of brain involvement caused by SWS, and perform genetic testing of SWS patients and their family members to find the causative genes of SWS. Targeted sample is 800.

**HHT:** To construct an HHT clinical research database; we will determine clinical risk factors for hemorrhage in HHT patients with BAVM and use genotype as potential marker for increased intracranial hemorrhage risk. This is a longitudinal study of 875 HHT patients with BAVMs and 2625 HHT patients without BAVMs.

The BVMC will provide a much-needed and valuable resource for the clinical neurovascular community for the study of these disorders. Brain vascular malformations are resource-intensive to manage effectively, and have a high probability of serious neurological morbidity. Specific medical therapies for these diseases are lacking. The identification of markers for progression would improve patient surveillance and optimize management, and treatment trials will require risk stratification for selection and surrogate outcomes for trial development. Pilot projects will evaluate novel treatment strategies for the diseases, including the use of aspirin in SWS and tetracycline-class agents in hemorrhagic vascular malformations. The BVMC will provide a detailed program for training new investigators in clinical research on rare diseases.

Training program has had one trainee to date for the CCM project. Another is currently recruited for the HHT project.

There are three advocacy groups: **Angioma Alliance** (Amy Akers); **The Sturge-Weber Foundation** (Karen L. Ball), **HHT Foundation International Inc.** (Marianne S. Clancy). The groups are involved in all aspects of BVMC functions and governance.

Recruitment has just begun for all three projects.

There are no specific tools available to the RDCRN, but special expertise in molecular genetics, epidemiology and biostatistics, and clinical database management are strengths.

### 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*

**Douglas A. Marchuk, PhD, Leader**

Duke University

**Anne Comi, MD, Co-Leader**

Kennedy Krieger Institute

##### *Project 3: Cerebral Hemorrhage Risk in Hereditary Hemorrhagic Telangiectasia*

**Marie E. Faughnan, MD, Leader**

University of Toronto

**William L. Young, MD, Co-Leader**

University of California, San Francisco

***Genetic and Statistical Analysis Core***

**Charles E. McCulloch, PhD, Leader**

**Ludmila Pawlikowska, PhD, Co-Leader**

University of California, San Francisco

***Pilot/Demonstration Project Core***

**William L. Young, MD, Director**

University of California, San Francisco

***Training (Career Development) Core***

**Charles E. McCulloch, PhD, Director**

**William L. Young, MD, Co-Director**

University of California, San Francisco

**Participating Clinical Sites**

United States:

- University of California, San Francisco, CA
- University of New Mexico, Health Sciences Center, Albuquerque, NM
- Duke University, Durham, NC
- Hugo W. Moser Research Institute at Kennedy Krieger, Baltimore, MD
- Children's Hospital, Boston, MA
- Washington University, St. Louis, MO
- Oregon Health & Sciences University, Portland, OR
- Medical College of Georgia, Augusta, GA
- University of Utah, Salt Lake City, UT
- University of Pennsylvania School of Medicine, Philadelphia, PA
- Mayo Clinic, Rochester, MN
- Yale University School of Medicine, New Haven, CT
- Baylor College of Medicine, Houston, TX
- Wayne State University, Detroit, MI
- Barrow Neurological Institute, Phoenix, AZ
- Nationwide Children's Hospital, Columbus, OH
- Laser and Skin Surgery Center, New York, NY
- Emory University, Atlanta, GA
- Johns Hopkins University, Baltimore, MD

Canada:

- St. Michael's Hospital/University of Toronto, Toronto, ON
- Sick Kids, The Hospital for Sick Children, Toronto, ON
- Centre Hospitalier de l'Université de Montréal, Montreal, QC
- University of Alberta, Edmonton, AB
- St. Paul's Hospital/University of British Columbia, Vancouver, BC

**Advocacy**

**Angioma Alliance**

Amy Akers

(757) 818-0403

[Amy.Akers@angioma.org](mailto:Amy.Akers@angioma.org)

**The Sturge-Weber Foundation**

Karen L. Ball

(973) 895-4445

[kball@sturge-weber.org](mailto:kball@sturge-weber.org)

**HHT Foundation International Inc.**

Marianne S. Clancy, MD

(800) 448-6389

[mariannes.clancy@hht.org](mailto:mariannes.clancy@hht.org)

## Clinical Investigation of Neurological Channelopathies (CINCH)

Principal Investigator: Robert C. Griggs, M.D.

Co-Principal Investigator: Richard Barohn, M.D.

### Study Sites:

University of Rochester, Robert C. Griggs, MD; Brigham and Women's Hospital, Anthony Amato, MD; University of California Los Angeles, Robert Baloh, MD, Joanna Jen, MD, PhD; Institute of Neurology, London, UK, Michael Hanna, MD; London Health Sciences Ctr., London, ON, Shannon Venance, MD, PhD; Univ. of Texas Southwestern Dallas, Stephen Cannon, MD, PhD; University of Kansas Medical Center, Richard Barohn, MD; Univ. of California San Francisco, Louis Ptacek, MD; University of Milan, Valeria Sansone, MD

### CINCH Goals:

(1) Characterize the natural history of the diseases, (2) Devise clinical outcome measures and biomarkers for clinical trials in the diseases, (3) Identify or discover putative therapeutic agents for Phase 1 and 2 trials, (4) Expand the pool of patient-oriented researchers committed to research on rare diseases, (5) Develop informational resources to foster investigator/patient participation in research on channelopathies. Three natural history studies and two therapeutic trials are in progress to help to achieve these aims.

### CINCH Diseases:

**Episodic ataxia (EA)** affects the central nervous system and causes incoordination of movement.

**Andersen-Tawil syndrome (ATS)** is a rare form of periodic paralysis that affects skeletal and heart muscle.

**Non-dystrophic myotonia (NDM)** is a rare condition that causes disabling weakness and stiffness.

CINCH investigators have identified now 3 distinct non-dystrophic myotonias, variants of ATS syndrome, and 7 episodic ataxias.

### Protocols:

**5301 Andersen-Tawil Syndrome (ATS): Genotype-Phenotype Correlation and Longitudinal Study (currently 25 subjects).**

This prospective study includes gene mutation analysis, clinical endpoints of attack frequency, severity, and duration, and laboratory endpoints such as QTc interval and severity and frequency of ventricular arrhythmias.

**5302 Episodic Ataxia Syndrome: Genotype-phenotype correlation and longitudinal study (currently 131 subjects).**

**Enrollment completed (study ongoing).** This prospective study includes gene mutation analysis, and clinical endpoints of attack frequency, severity, and duration.

**5303 Nondystrophic Myotonias: Genotype-Phenotype Correlation and Longitudinal Study (currently 95 subjects).**

**Enrollment completed (study ongoing).** This study includes: Characterization of the clinical features of NDM; Delineation of the natural history of NDM; Determination of whether physical exam and/or electrophysiologic findings can reliably distinguish genotypes.

**5306 Phase II Therapeutic Trial of Mexiletine in Non-Dystrophic Myotonia (IND #77,021) (currently 54 of 60 targeted subjects).**

This FDA Orphan Drug-funded phase II trial is a randomized, double-blind, placebo-controlled cross-over study to assess whether mexiletine improves both quantitative and qualitative measures of myotonia in patients with non-dystrophic myotonia. Enrollment is ahead of target, and the study will conclude early in 2011.

### Pilot Studies:

**5304 A pilot study on the safety and tolerability of 4-aminopyridine (4AP) in Episodic Ataxia Type 2** was funded by the RDN (2006) but withdrawn because of unavailability of the drug or a partner industry. The drug and partner are now available. Dr. Jen has been notified that the FDA Orphan Drug Grant will be awarded as soon as IRB approval is final.

**Genetic Analysis of Hypokalemic Periodic Paralysis and Paramyotonia Congenita (Michael Hanna, PI, funded by a supplemental award from the RDCRN).** This pilot study genotyped a cohort of patients with a clinical diagnosis of hypokalemic periodic paralysis or paramyotonia congenita who did not have any of the known genetic mutations associated with the disease. A number of novel mutations were defined (point mutations in arginine residues) and are now being characterized in terms of their physiologic mechanisms.

### Training Program:

CINCH has trained twenty-two fellows, all of whom have remained involved in rare diseases research. 21 of 22 are in full time academic work. Fellows received partial support -- to maximize the number of trainees with the limited funding. This partial support incentivized trainees and preceptors to secure supplemental/additional support.

**Trainees (current positions): Ronan Walsh MD**, Honorary Lecturer at Royal College of Physicians; Consultant neurologist, Hermitage Medical Clinic; **Hannah Briemberg MD** Clinical Assistant Professor, University of British Columbia; **Mohammad Salajegheh MD** Current trainee, Brigham; **Doreen Fialho MRCP, PhD** Specialist Registrar Neurophysiology, Kings College Hospital; **Tracey Graves MRCP, PhD** Specialist Registrar Neurology, John Radcliffe Hospital; **Emma Matthews MD** Specialist Registrar in Neurology, Royal Free Hospital; **Goran Rakocevic MD**; Assistant Professor, Thomas Jefferson University Hospital;

**Kevin Kerber MD** Assistant Professor, University of Michigan; **Kevin Brennan MD** Clinical Instructor, UCLA; **Joanna Jen MD PhD** Professor, UCLA; **Araya Puwnant, MD** Current Trainee University of Rochester; **Yoon-Hee Cha MD** Current trainee, UCLA; **Junko Nakayama MD, PhD** Assistant Professor, University of Tsukuba; **Magnus Dias da Silva MD, PhD** Postdoctoral Fellow, UCSF; **Hsien-Yang Lee PhD** Current Trainee, UCSF; **David Saperstein MD** Clinical Associate Professor, University of Arizona; **Yunxia Wang MD** Assistant Professor, University of Kansas; **Jaya Trivedi MD** Associate Professor, Univ. of Texas Southwestern at Dallas; **Shannon Venance MD, PhD** Assistant Professor, London Health Sciences Center; **James Cleland MBChB** Consultant Neurologist, Waikato District Health Board; **Paul Twydell DO** Assistant Professor, University of Rochester; **Dipa Raja Rayan, MD** Current trainee, Institute of Neurology, London

**Patient Advocacy Groups:**

Patient Advocacy Groups (PAG's) including work in collaboration with CINCH researcher investigators toward fuller understanding of the causes of and potential treatments and cures for these diseases:

The Muscular Dystrophy Association (MDA) provides support for the treatment and cure of ATS and the NDM.

<http://www.mda.org/>.

The National Ataxia Foundation provides support for the treatment and cure of the EA's. <http://www.ataxia.org/>.

The Periodic Paralysis Association provides support for the treatment and cure of ATS. <http://www.periodicparalysis.org/>.

### Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA)

CRC-SCA: University of Florida (Ashizawa T (PI), Subramony SH), Emory University (Wilmot G), Johns Hopkins University (Ying S), Massachusetts General Hospital (Schmahmann J), UCLA (Perlman S), University of Chicago (Gomez C), University of Michigan (Paulson H), University of Minnesota (Bushara K), University of South Florida (Zesiewicz T), University of Utah (Pulst S), DMCC (Roberts Holbert A), NINDS (Galpern W), ORDR (Ferguson J), National Ataxia Foundation (Hagen S)

- **Longitudinal studies, clinical trials and pilot studies (goals, status and results):**

- **Longitudinal studies:** Natural History Database for spinocerebellar ataxia (SCA) 1, 2, 3 and 6.
  - Since our RC1 (ARRA) grant was awarded on September 28, 2009, the IRB approval of 9 of 10 sites have been obtained to date and these 9 sites have successfully undergone the DMCC training.
  - We have enrolled 44 participants. More are scheduled to be enrolled. The table below shows the enrollment status
- **Patient Registry**
  - The DMCC Contact Registry has registered 176 subjects, including 38 SCA1, 36 SCA2, 55 SCA3, and 33 SCA6 subjects.
  - The National Ataxia Registry has had contacts with 640 participants.
- **Clinical Trials**
  - We have no clinical trials proposed in the original application. However, a phase-I, randomized, double-blind, placebo-controlled multi-center study for safety and tolerability of Coenzyme Q10 is ongoing at University of Florida, Johns Hopkins University, and UCLA. We plan to enroll 20 subjects and 7 have been enrolled.
- **Genetic Modifier – a Pilot Project**
  - Since IRB approval at University of Utah was delayed, only 20 samples have been sent to University of Utah where genetic modifier analyses will be conducted. We will “catch up” with the DNA collection.

- **Training program summary including number of persons trained:**

After a national search, Vikram Shakkottai, M.D., Ph.D. was selected as a trainee. He has successfully obtained a K08 grant, which will start in January 2011. To fill the vacated trainee’s position, we are conducting a search of candidates. We are an ARRA-grant (RC1) supported site and funding is enough only for one trainee at a time.

- **Role and involvement of patient advocates group(s) in consortia including names of organizations**

The National Ataxia Foundation (NAF) is our patient advocate group. Ms. Sue Hagen has been extremely instrumental for establishing the National Ataxia Registry and for the recruitment of subjects for the Natural History Database. NAF is providing funding for a part of the SCA-CRC operation, and this is a vital cost share for the SCA-CRC.

**Dystonia Coalition**  
**PI: H. A. Jinnah, MD, PhD**

**Primary diseases under study:** Focal Dystonias, including,

1. Cranial dystonia (blepharospasm with or without lower facial grimacing)
2. Oromandibular dystonia (jaw or tongue dystonia)
3. Laryngeal dystonia (including spasmodic dysphonia)
4. Cervical dystonia
5. Limb dystonia

**Major Goals:**

1. Developing a more complete understanding of the natural history of focal dystonias
2. Establishing instruments appropriate for monitoring disease severity
3. Assembling proper diagnostic criteria for the various focal dystonias
4. Creating a resource for exploring potential biomarkers

**Projects:**

Project 1: Natural History & Biospecimen Repository for Focal Dystonia

(Perlmutter – Washington University in St. Louis) - NINDS approved, Final IRB approval pending

The overall goal is to develop a better understanding of focal dystonias so that we may improve the treatment of affected patients by collecting clinical data and creating a biospecimen repository.

Project 2: Comprehensive Rating Tools for Cervical Dystonia

(Comella - Rush University) - NINDS approved, Final IRB approval pending

The overall goal is 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.

Project 3: Validity & Reliability of Diagnostic Methods & Measures of Spasmodic Dysphonia

(Ludlow - James Madison University) - NINDS approved, Final IRB approval pending

The overall goal is to demonstrate validity of a novel diagnostic instrument for spasmodic dysphonia and to determine validity/reliability of two measures for detecting change in symptoms and quality of life.

**Pilot Project Program:** All results are pending. One study is nearing completion and the rest are completing regulatory documentation prior to beginning.

THAP1 Sequence Variants in Primary Dystonia (LeDoux – University of Tennessee)

Development and Validation of Clinical Diagnostic Guidelines and A Novel Severity Rating Scale for Primary Blepharospasm

(DeFazio – University of Bari, Italy)

A Multi-Center, Exploratory, Double Blind, Placebo Controlled, Dose Escalation Study of Sodium Oxybate as a Symptomatic Treatment for Idiopathic Cervical Dystonia (Frucht – Columbia University)

Cerebellum and Cortical Plasticity: The Case of Focal Dystonia (Roze – Pierre & Marie Curie University, Paris, France)

DYT6 Dystonia – A Window to the Mechanisms of Primary Dystonia (Bhatia – University College London, England)

**Training Program Summary:** 2 junior investigators and 1 senior investigator currently funded

Maren Carbon-Correll, MD, The Feinstein Institute for Medical Research, Neurologist, Mentor-Dr. David Eidelberg

Alberto Espay, MD, MSc, University of Cincinnati, Neurologist, Mentors-Dr. Jerzy Szaflarski & Dr. Robert Chen

Mateusz Zurowski, MD, MSc, University of Toronto, Psychiatrist, Mentors-Dr. Susan Fox & Dr. Cynthia Comella

**Patient Advocacy Groups:**

- Have helped to financially support the Dystonia Coalition pilot projects program, training program, primary projects, and annual meeting
- DMRF provides effort to help coordinate the DC annual meeting and pay our clinical sites
- In charge of determining what contact registry we will use within the dystonia community

American Dystonia Society

Bachmann-Strauss Dystonia and Parkinson Foundation

Benign Essential Blepharospasm Research Foundation

Dystonia Medical Research Foundation

European Dystonia Foundation

National Spasmodic Dysphonia Association

The National Spasmodic Torticollis Association

ST/Dystonia

Tyler's Hope

WE MOVE



**Genetic Disorders of Mucociliary Clearance Consortium (GDMCC)****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; Pseudohypoaldosteronism; Bronchiectasis.

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

**Protocol 5901 - Longitudinal Study of Primary Ciliary Dyskinesia: Participants 5-18 Years of Age.** This protocol involves 120 participants who are followed at yearly intervals for 5 years. The study began in 2006 and enrollment was completed in September, 2009. As of August, 2010, 1 patient has completed 5 visits, 28 have completed 4 visits, 43 have completed 3 visits, 32 have completed 2 visits and 16 have completed 1 visit. 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.

**Protocol 5902- Rare Genetic Disorders of the Airways: Cross-sectional Comparison of Clinical Features, and Development of Novel Screening and Genetic Tests.** 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 emphasizes a complete assessment of phenotypic, physiologic, ciliary ultrastructural, and genetic characterization of patients. We can correlate the phenotype of our PCD patients with the genotype and phenotype of specific ciliary defects. 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.

**Protocol 5903- Early Onset and Progression of Primary Ciliary Dyskinesia Lung Disease Prior to 10 Years of Age.** This protocol has enrolled 48 participants (17 weeks to 5 years of age) who are followed at yearly intervals for 5 years. This observational study is evaluating imaging, physiologic, microbiologic and clinical symptomatology data in subjects with PCD. The study started in 2008, and enrollment is currently concluding. As of August, 2010, 2 patients have completed 3 visits, 16 have completed 2 visits and 30 have completed 1 visit.

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

This protocol involves 260 adult participants who have bronchiectasis, and enrollment will be stratified by gender and presence (or absence) of non-tuberculous mycobacteria (NTM). The goal will be to test for body morphotype differences in those with and without NTM, and test for underlying genetic etiologies. The protocol has been approved, and will start in Sept-Oct, 2010.

**Training Section:** The goal is to provide trainees with professional and research skills needed to be productive academic leaders in rare lung diseases. We currently have 8 active trainees, including fellows and postdoctoral students. Four trainees presented abstracts at the May, 2010 American Thoracic Society and another trainee has a first-authored paper in review. Trainees participate in bi-monthly conference calls and are involved in helping to establish a clinical (treatment) trial network.

**Role of Advocacy Groups:** The PCD Foundation and NTMir Organization are involved in bi-monthly conference calls, and contribute to planning and execution of studies and educational programs. The founder of the PCD Foundation, Michele Manion, serves on the CPAG for the RDCRN Steering Committee.

## **Immune Mediated Disorders after Allogeneic Hematopoietic Cell Transplantation (cGVHD)**

PI: Stephanie J. Lee, MD, MPH  
Co-PI: Paul J. Martin, MD  
NIH Institute: NIAID, Dr. Jonah Odum

**Major Consortium Goals and Diseases Under Study:** Recipients of allogeneic hematopoietic cell transplants (HCT) suffer from unique immune mediated disorders. Although components of these disorders resemble known autoimmune syndromes or solid organ allograft rejection, the underlying immunology is poorly characterized. The two most common immune mediated complications are heterogeneous syndromes collectively called "acute graft-versus-host disease (GVHD)" and "chronic GVHD." Chronic GVHD is the leading cause of non-relapse death more than 2 years after allogeneic HCT. The different syndromes within GVHD are likely to have different pathogenic mechanisms. The goal of this Consortium is to advance our understanding and treatment of these disorders.

**Project Status:** All studies collect biologic specimens and have corollary laboratory studies. Project 1 is an observational study. After enrollment, patients will be followed prospectively for the development of immune mediated disorders. This project is undergoing IRB review at the sites. Project 2 will test two treatments, imatinib and rituximab, for cutaneous sclerosis. Skin biopsies will be analyzed for markers for severity and response. This study is undergoing NIH signoff and then will be released to the sites. Pilot 1 will test triple therapy (fluticasone, azithromycin, and montelukast, "FAM") for bronchiolitis obliterans syndrome. This protocol is undergoing NIH signoff and then will be released to sites.

**Training Program:** The Consortium's first trainee is Dr. Joseph Pidala of Moffitt Cancer Center. Dr. Pidala will be using data generated by the U54 studies to conduct studies of the quality of life associated with immune mediated disorders. He will also be studying biomarkers predictive of the onset, severity or response to treatment of these disorders.

### **Patient Advocacy Organizations:**

National Marrow Donor Program, Elizabeth Murphy, Ed. D, RN;  
National Bone Marrow Transplant Link, Myra Jacobs, M.A.;  
Blood & Marrow Transplant Information Network, Sue Stewart

### **Clinical sites:**

1. Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Seattle, WA
2. Dana-Farber Cancer Institute, Boston, MA
3. Stanford University, Palo Alto, CA
4. University of Minnesota, Minneapolis, MN
5. Vanderbilt University, Nashville, TN
6. Medical College of Wisconsin, Milwaukee, WI
7. Washington University, St. Louis, MO
8. Moffitt Cancer Center, Tampa, FL
9. University of Michigan, Ann Arbor, MI (pending)
10. Memorial Sloan Kettering Cancer Center, New York, NY (pending)

### **Additional laboratory site (not clinical site):**

11. University of North Carolina, Durham, NC

## Inherited Neuropathies Consortium (INC)

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 [1, 2]. CMT affects ~1 in 2500 people (approximately 120,000 Americans) [3] and is among the most common inherited neurological disorders. The majority of patients with CMT have autosomal dominant inheritance, although X-linked dominant and autosomal recessive forms also exist. Apparent sporadic cases occur, since dominantly inherited disorders may begin as a new mutation in a given patient. The majority of CMT neuropathies are demyelinating, although up to one third appear to be primary axonal disorders [4, 5]. Most patients have a “typical” CMT phenotype characterized by onset by early adulthood, distal weakness, sensory loss, foot deformities (pes cavus and hammer toes), and absent ankle reflexes. However, many patients develop severe disability in infancy or early childhood (congenital hypomyelinating neuropathy and Dejerine-Sottas neuropathy), while others develop few if any symptoms of neuropathy until adulthood.

Despite the clinical similarities among patients with CMT, it has long been realized that the group is genetically heterogeneous. At present, mutations in more than 30 genes have been identified that cause inherited neuropathies, and more than 44 distinct loci have been identified. A summary of the genes associated with CMT neuropathies can be found online at <http://www.molgen.ua.ac.be/CMTMutations/Mutations/MutByGene.cfm>. Although > 30 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 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.

To develop our Inherited Neuropathy Consortium (INC) RDCRC we are proposing three Clinical Research Projects, one of which will be to develop and maintain a inherited neuropathy Website. We are also proposing three Pilot Projects. **Clinical Research Project 1** will perform natural history studies on CMT1B, CMT2A, and CMT4A. CMT1B, caused by mutations in the major PNS myelin protein gene, *MPZ*, is the most frequent form of CMT 1 for which there is no natural history data available; CMT2A, caused by mutations in the nuclear encoded mitochondrial gene, *MFN2*, is the most common form of CMT2; and CMT4A, caused by mutations in the nuclear encoded mitochondrial gene, *GDAP1*, is the most common form of CMT4. **Clinical Research Project 2** is to identify genetic factors that cause and modify CMT1A, the most common inherited neuropathy. In this project we will also utilize genome-wide convergence of linkage analyses, expression data, and exome resequencing of small axonal CMT pedigrees to identify novel CMT2 genes. **Clinical Research Project 3** will establish a Website Resource for the inherited neuropathies, based on OMIM, for patients, families and investigators. We will also have 3 Pilot Projects. **Pilot Project 1** will establish a scoring system for quantifying impairment in young children with various forms of CMT; **Pilot Project 2** will test the pediatric scoring system created in Pilot Project 1 in a two year natural history study of children with various types of CMT1, CMT2 and CMT4. **Pilot Project 3** will develop a Phase I trial using curcumin to treat selected patients with early onset CMT1B.

The following sites comprise the INC RDCRC: (1) Wayne State University, Department of Neurology, Detroit MI; (2) Miami Institute of Human Genomics, University of Miami, Miami FL; (3) University of Rochester, Department of Neurology, Rochester NY; (4) the University of Pennsylvania, Department of Neurology and (5) Childrens’ Hospital of Philadelphia, Philadelphia Pa; (6) the National Hospital of Neurology and Neurosurgery, London England; the (7) C. Besta Neurological Institute, Milan, Italy; and (8) the Children’s Hospital of Westmead, Sydney, Australia. The lead personnel are as follows: Dr. Michael Shy, PI of the RDCRC. And Dr. Gyula Acsadi, Co-PI, are from the Departments of Neurology and Pediatrics at Wayne State University School of Medicine. Drs Stephan Zuchner and Jeffery Vance, from the University of Miami Institute of Human Genomics, will lead the investigations of Clinical Research Project 2. Dr. David Herrmann from the University of Rochester will direct one of the Pilot Projects and also be involved with training fellows of the INC in clinical trial design. He will be aided in this by Dr. Michael McDermott, also from the University of Rochester who will also function as the Chief Biostatistician for our RDCRC. Dr. Steven Scherer from the Department of Neurology at the University of Pennsylvania will be responsible for developing the Web-site for the INC RDCRC. Dr. Richard Finkel, from the Children’s Hospital of Philadelphia (CHOP) will direct the development of our Pediatric CMT evaluation form. Dr. Finkel will be assisted with this project by Dr. Acsadi from Wayne State University and Dr. Francesco Muntoni from the Dubowitz Neuromuscular Centre in the University College of London Institute of Child Health. Dr. Mary Reilly, from the Department of Neurology of the National Hospital for Neurology and Neurosurgery, London England, will lead the training component of the INC RDCRC.

We are very pleased to have several outstanding Patient Advocacy Groups (PAG) associated with the INC RDCRC. These groups include the Charcot Marie Tooth Association (CMTA) and CMT United Kingdom (CMTUK). Patrick Livney, Chair of the CMTA will serve on the Internal Advisory Board of the INC RDCRC as will Ms. Alex Williamson of CMTUK. We believe that both the CMTA and CMTUK will become excellent members of the Coalition of PAG (CPAG). We are also very pleased to have

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## RDCRN Summaries

two additional organizations, TREAT-NMD and the Muscular Dystrophy Association (MDA) associated with the INC RDCRC. TREAT-NMD is a network of excellence for rare neuromuscular diseases with a combination of investigators and patient advocates. TREAT-NMD is funded by the European Commission. Our TREAT-NMD representative is Dr. Francesco Muntoni, a member of our IAB, who is an active member of TREAT-NMD in addition to his role at the Dubowicz Center. The MDA is a nonprofit health agency dedicated to developing treatments and cures for neuromuscular diseases including CMT. Dr. Valerie Cwik, Senior Vice President and Research and Medical Director of the MDA has also agreed to serve on the Internal Advisory Board of the INC RDCRC.

In summary we are all excited to be a member of the RDCRN and look forward to working together to advance the care of patients with inherited peripheral neuropathies.

## Lysosomal Disease Network (LDN)

**PI:** Chester Whitley, MD, PhD;   **Co-PI:** Elsa Shapiro, PhD

### Major goals:

Although individually rare “orphan” conditions, the Lysosomal diseases collectively affect 1 in 6,000 individuals and are responsible for a significant disability and disease burden. These diseases have become a test bed for some of the most innovative and advanced experimental treatments. The rarity of each Lysosomal disease means that no single medical research center has an opportunity to see the entire spectrum, or to acquire sufficient numbers to adequately test new therapies. The combined and integrated efforts of the Lysosomal Disease Network will focus limited resources toward creating a network of centers with expertise in one or more of these diseases in order to solve major challenges in diagnosis, disease management, and therapy. Solutions to these problems will have direct impact on patients suffering from Lysosomal disease, and important implications for medical practice.

### Disorders under study:

Aspartylglucosaminuria; Batten disease; Cholesteryl Ester Storage Disease; Fabry Disease; Fucosidosis; Galactosialidosis types I/II; Krabbe Disease; Neuronal Ceroid Lipofuscinosis (Infantile, Late Infantile, Juvenile); Mucopolipidosis Type II; Mucopolipidosis Type III (alpha/beta); Mucopolipidosis Type IV; Mucopolysaccharidosis type I (Hurler, Hurler-Scheie, and Scheie); Mucopolysaccharidosis Type II (Hunter Syndrome); Mucopolysaccharidosis Type III (Sanfilippo Syndrome A, B, C, and D); Mucopolysaccharidosis Type VI ( Maroteaux-Lamy Syndrome); Niemann-Pick Disease (Type C); Pompe Disease; Sandhoff Disease; Schindler Disease; Sialidosis types I/II; Tay-Sachs Disease; Wolman Disease; Alpha-Mannosidosis Types I/II; Beta-Mannosidosis

### Longitudinal studies:

- 6702:** Natural History and Structural-Functional Relationships in Fabry Renal Disease
- 6703:** Longitudinal Studies of Brain Structure and Function in MPS Disorders (Pending Implementation by RDCRN/DMCC)
- 6704:** The Natural History of Mucopolipidosis Type IV (Open to Enrollment)
- 6705:** Longitudinal Study of Bone Disease and the Impact of Growth Hormone Treatment in MPS I, II, and VI
- 6706:** Epidemiology and Natural History of Wolman and Cholesteryl Ester Storage Disorders
- 6707:** Characterizing the Neurobehavioral Phenotype(s) in MPS III
- 6708:** Pulmonary Disease and Exercise Tolerance in Boys with Fabry Disease
- 6709:** CRIM Responses in Pompe Disease
- 6710:** LSD: Health, Development, and Functional Outcomes in Preschool Children
- 6711:** Fabry Disease Identification
- 6712:** Clinical Laboratory Investigations of Glycoprotein Storage Disorders
- 6713:** A Natural History Study of Hexosaminidase Deficiency
- 6715:** Longitudinal Study of Cognition in Subjects with Niemann-Pick Disease, Type C
- 6716:** Assessment of Neurological Deterioration in Subjects with LINCL
- 6717:** Longitudinal Studies in Batten Disease
- 6718:** Gene Therapy for Tay-Sachs Disease
- 6719:** Immune Response to Intrathecal Enzyme Therapy in Mucopolysaccharidosis I Patients

### Interventional Studies:

- 6701:** Phase I Trial of Pyrimethamine to Treat LOTS
- 6714:** Intrathecal ERT for Cognitive Decline in MPS I

### Participating Centers:

Baylor College of Medicine; Baylor Research Institute; Cedars-Sinai Medical Center; Children’s Hospital Boston, Children’s Hospital Medical Center, Cincinnati; Children’s Hospital and Research Center, Oakland; Children’s Hospital of Buffalo; Coriell Institute for Medical Research; Duke University; Emory University; ExSAR Corporation; Greenwood Genetic Center; Joan and Sanford Weill Medical College of Cornell University; Kennedy Krieger Institute; Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center; Massachusetts General Hospital/Harvard Medical School; Mayo Clinic; National Institute of Child Health and Human Development; New York University; Oregon Health and Sciences University; The Hospital for Sick Children, University of Toronto; University of British Columbia; University of California, Los Angeles; University of Chicago; University of Minnesota; University of Rochester; University of Utah

### Patient Advocacy Groups:

National Tay-Sachs & Allied Diseases Association; International Society for Mannosidosis & Related Diseases; Cystinosis Research Network; Cystinosis Research Network; Association for Glycogen Storage Disease; Fabry Support and Information Group; The Fabry Disease Foundation; Children’s Gaucher Disease Research Fund; National Gaucher Foundation; Hide and Seek

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RDCRN Summaries

Foundation for LDN Research; Hunter's Hope Foundation; The Project- The Children's Rare Disease Network; National Mucopolysaccharidoses (MPS) Society; Mucopolipidosis IV Foundation; Adrenoleukodystrophy Foundation; MLD Foundation; United Leukodystrophy Foundation; National Niemann-Pick Disease Foundation; The Ara Parseghian Medical Research Foundation; Batten Disease Support and Research Association; Nathan's Battle Foundation; Acid Maltase Deficiency Association; Madisons Foundation

## North American Mitochondrial Disease Consortium (NAMDC) September 21, 2010

Mitochondrial diseases are clinically and genetically heterogeneous disorders. The complexity of mitochondrial diseases is due to the ancestral autonomy of this organelle, which is still under dual genetic control, namely mitochondrial DNA (mtDNA) and nuclear DNA (nDNA). The mitochondrial genome encodes 13 subunits of the mitochondrial respiratory chain whereas the nuclear genome encodes over 1400 genes required for a variety of mitochondrial functions. Mitochondrial diseases are baffling to general practitioners, frightening to patients and families, and generally misunderstood. Together with their rarity, the clinical and genetic heterogeneity of mitochondrial diseases has hindered natural history studies and rigorous clinical trials.

The North American Mitochondrial Disease Consortium (NAMDC) was created to provide critical infrastructure for clinical mitochondrial disease research and education. Comprised of 11 centers of excellence in the United States and Canada, NAMDC is directed by Drs. Salvatore DiMauro, Principal Investigator and Michio Hirano, Co-Principal Investigator, at Columbia University Medical Center. NAMDC is currently funded by a two-year ARRA grant.

More than 20 distinct mitochondrial diseases are included in NAMDC. In close collaboration with Dr. J.L.P. (Seamus) Thompson and Richard Buchsbaum of the Statistical Analysis Center (SAC) at the Columbia University Mailman School of Public Health, we have made substantial progress in the following areas:

1. Establishing the NAMDC network. We have enrolled 11 centers of excellence in the US and Canada. We have met with the PIs or their representatives at the June, 2010 United Mitochondrial Disease Foundation (UMDF) meeting in Scottsdale, AZ and we have held five conference calls. There is general agreement and enthusiasm on this collaborative effort.
2. The patient registry. This crucial NAMDC instrument, has been drafted and is being vetted by the NAMDC members. Richard Buchsbaum has created a user-friendly web-based interface for data entry. We have submitted a revised IRB protocol for the registry and submission of biological samples to a biorepository based at the Mayo Clinic, Rochester, MN. Once approved by the Columbia IRB Office, we will distribute the protocol to all sites for local IRB approval. This would guarantee relative uniformity among sites. Importantly, the UMDF (the major mitochondrial patient advocacy group) is committed to recruit patients for NAMDC.
3. Diagnostic guidelines. For the registry to be effective, well-defined diagnostic criteria are needed. Given the heterogeneity of mitochondrial diseases, this is no easy task. Starting from published diagnostic criteria, we are developing NAMDC's own guidelines for diagnosing mitochondrial diseases and for classifying them into specific syndromes whenever possible. We will validate the data submitted to the registry and diagnoses will be reviewed by a specific committee. This process will generate NAMDC-certified diagnoses to clinicians and patients and will insure that a reliable database is available for clinical studies.
4. The biorepository has been established under the directorship of Dr. Devin Oglesbee and is ready to accept samples from sites. A manual for the appropriate submission and retrieval of samples is being drafted and a special committee will oversee the operation of the biorepository.
5. Statistical design and trial proposals. Dr. Thompson Principal Investigator for Statistical and Data Management for NAMDC and Dr. Hirano have designed a randomized clinical trial of allogeneic bone marrow transplant for patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) and plan to submit a grant application. With NAMDC support, Dr. Peter Stacpoole (University of Florida, Gainesville) will also apply for support of a randomized double-blind study of DCA in children with pyruvate dehydrogenase (PDH) deficiency.
6. Education. We envision an education program aimed at training young clinicians both in the complexity of the diagnostic process and in research.

**NEPTUNE**  
**Nephrotic Syndrome Study Network**  
**Matthias Kretzler, MD, Principal Investigator**

The Nephrotic Syndrome Study Network (NEPTUNE) is a multicenter, translational study of nephrotic syndrome studying Focal and Segmental Glomerular Sclerosis (FSGS) - Minimal Change Disease (MCD), and Membranous Nephropathy (MN). The goals of the study is to establish a collaborative, integrated, cost-effective, investigational infrastructure to conduct clinical and translational research in these disease areas, specifically to: a) perform longitudinal observational cohort studies on patients with incipient biopsy proven FSGS/MCD and MN, b) institute a pilot and ancillary projects program using the unique resources, clinical data, or specimens in NEPTUNE, c) administer a training program for post-doctoral / junior faculty trainees preparing for clinical and translational research in glomerular diseases, d) collaborate with the Office of Rare Diseases Research (ORDR) Data Management Coordinating Center (DMCC) and NephCure to develop a web-based exchange platform for lay people, physicians, and scientists.

To implement the above goals, NEPTUNE will use a multicenter, prospective cohort study with un-blinded standardized evaluation of clinical and molecular outcomes in two, defined separate and parallel cohorts of study participants. Four hundred and fifty participants will be enrolled into two main FSGS/MCD and MN cohorts over 30 months and these cohorts will serve as central resources of NEPTUNE. High resolution clinical phenotypes of the cohort patients will be related to genome wide analyses using a comprehensive biorepository of renal tissue, blood and urine specimen to molecularly define disease categories, outcome predictors and therapeutic targets. NEPTUNE is dedicated to serving as a resource to the community of science and lay persons interested in studying FSGS/MCD/MN, and with pilot and ancillary study investigators, will use the clinical information, pathological analysis, and the molecular data generated by NEPTUNE. The NEPTUNE protocol was activated and the first patient enrolled into NEPTUNE on April 21, 2010. NEPTUNE currently has nine sites activated.

An essential part of NEPTUNE is the establishment of a pilot and ancillary project program. Pilot and ancillary study policies have been established by respective committees and approved by the Steering Committee. The first pilot study has been initiated by the Mayo Clinic (PI's Drs. Hogan and Lieske) and is currently evaluating a series of biobanking procedures to develop an optimal protocol for urine sample processing for molecular analysis for NEPTUNE and the scientific community at large. Three ancillary studies are currently under review and will go before the Steering Committee for final approval. The NEPTUNE Training program policies are in place and a first request for applications has been released.

NEPTUNE currently works with two patient advocacy groups, the NephCure Foundation and the Halpin Foundation. With NephCure and the DMCC, a series of community outreach tools are currently developed that can be reviewed at the NEPTUNE website. A patient contact registry has been established at the DMCC (<http://rarediseasesnetwork.epi.usf.edu/registry/>) for patients with nephrotic syndrome. As a consequence of outstanding outreach efforts by NephCure, 674 patients have already self-registered at the RDCRN registry in the Nephrotic Syndrome category. The registry will provide information to registered patients via the DMCC as an honest broker on translational and clinical research efforts emerging in the field of nephrotic syndrome research. The NephCure Foundation and the Halpin Foundation are two well-established disease-specific foundations and their representatives are active members of various NEPTUNE Committees, including the Steering Committee and the Recruitment and Retention Committees. With the NephCure Foundation's assistance, a series of patient education brochures have been developed, in addition to a video, which will both serve as outreach tools. NEPTUNE researchers are dedicated to improving understanding and identifying promising treatments for FSGS, MCD and MN.



**Porphyrias Consortium**  
**Rare Diseases Clinical Research Network – 1U54 DK083909-1**  
**PI: Robert J. Desnick, PhD, MD**

The mission of the Porphyrias Consortium of the Rare Diseases Clinical Research Network (PC) is to improve the diagnosis, treatment, and quality of life for patients suffering from the inborn errors of heme biosynthesis, the Porphyrias. The consortium includes six regional sites, each with a PI expert in the porphyrias. These include: The Mount Sinai School of Medicine (R.J. Desnick, PhD, MD), University of California at San Francisco (D.M. Bissel, MD), University of Texas Medical Branch, Galveston (K.E. Anderson, MD), University of Utah (J.P. Kushner, MD), University of Alabama at Birmingham (J.R. Bloomer, MD), and the recently added site, Carolinas Medical Center (H. Bonkowsky, MD). The American Porphyria Foundation (APF), the patient support and advocacy organization for the Porphyrias, is directly involved in all the activities of the PC. The most frequent Porphyrias include the following diseases: Acute Intermittent Porphyria, ALAD-Deficiency Porphyria, Congenital Erythropoietic Porphyria, Erythropoietic Protoporphyrria, Hereditary Coproporphyrria, Porphyria Cutanea Tarda, and Variegate Porphyria.

**Year '01 Goals and Accomplishments:** Initial efforts have focused on developing: 1) the PC Website content; 2) the major clinical study, the Longitudinal Observational Study, for each porphyria; 3) Investigator-Initiated Clinical Trials; 4) a Sample Repository; and 5) our Trainee Program. Four face-to-face meetings of the site PIs, their trainees, and NIH, DMCC, and APF staff have been held during the past year. A fifth meeting will be held October 30<sup>th</sup> in Boston. Conference calls have been held monthly. Accomplishments during the '01 year include: 1) development and implementation of The Porphyrias Consortium Website; 2) development of our first and most important study for all seven porphyrias, the Longitudinal Study; 3) development of The Porphyrias Repository, which has been approved by the DMCC and submitted to the Mount Sinai IRB. IRB approval is expected by October 1<sup>st</sup> when the Repository will begin accepting samples; 4) coordination of our biochemical and molecular diagnostic laboratories so that each enrolled patient is diagnostically confirmed and the specific causative mutation identified; 5) successful recruitment of ten young clinical faculty trainees. Also, graduates, post-doctoral, and young faculty researchers are now in our training program; 6) coordination with the APF which has been directly involved in all of our efforts.

**Status of Protocols:**

**Longitudinal Study of the Porphyrias:** This is an observational study to determine the natural history of each porphyria; expected enrollment of 600+ patients. The Study Protocol and Case Report Forms have been approved by the investigators, NIH, and the DMCC. Each site has submitted the protocol to their respective IRB's, and is awaiting approval to begin recruiting patients. Expected enrollment October 1.

**Hematin Clinical Trial:** This is a clinical trial of Hematin v. glucose in the treatment of acute porphyric attacks. A grant to Dr. Anderson has been funded by the Office of Orphan Drug Development, and FDA approval has been obtained. This trial will begin in 2011.

**Clinical Trial of Afamelanotide:** This is a Phase 2 clinical trial of subcutaneous bioresorbable Afamelanotide (a melanocyte-stimulating hormone analogue) to treat Erythropoietic Protoporphyrria (EEP).

**Training Program:** We are now training ten young faculty members, at least one at each site, to become an expert in the clinical diagnosis/management of Porphyria patients. They are also involved in our clinical trials, from IRB submission to data analysis. They have attended all PC meetings, as well as the Gordon Research Conference on Porphyria this past summer. Also, we are training graduate students, post-doctoral fellows, and young faculty in porphyria-related basic and clinical research at our sites.

**Interaction with the American Porphyria Foundation (APF):** We continue to have close interactions with the APF. The APF's Executive Director, Desiree Lyon Howe is a member of the RDCRN Steering Committee and has attended all of our meetings. The APF has raised funds to support our trainees and provided travel expenses for our young faculty trainees to attend our meetings and the recent Gordon Research Conference on the Porphyrias. Finally, the APF will refer patients to our sites for the Longitudinal Studies and other clinical studies via their newsletter, website, and emails to their patient members.

## Primary Immune Deficiency Treatment Consortium (PIDTC)

PI: 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 develop a “virtual sample repository” of cell, serum, and DNA samples from patients enrolled prospectively, for use in future studies of biomarkers and genetic etiology.
- 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:

1. **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 begun to enroll patients in this study. Several participating centers have obtained IRB approval and others are in process of submission. Investigators are using the DMCC website for training, and the certification process is underway. The CRFs and other forms have been completed and have been submitted to the DMCC for conversion to electronic format.
2. **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 are in process of completing the protocol and anticipate this will be finalized by the end of September.
3. **A Natural History and Cross-Sectional Study to Evaluate the Outcomes of Hematopoietic Cell Transplantation (HCT) in Wiskott Aldrich Syndrome (WAS) and Chronic Granulomatous Disease (CGD):** The goal is to define the critical clinical factors and biologic markers that predict survival and other outcomes of children with WAS and CGD following HCT or medical therapies and to characterize the long term outcomes and late effects. We anticipate completing the protocol during the fall of 2010.
4. **Population-based newborn screening for SCID.** The goal of this pilot study is to show that newborn screening for SCID, consisting of TREC analysis of dried blood spots, can successfully identify SCID in time for optimal treatment. Navajo Indians having a high incidence of SCID due to a founder mutation will participate in the pilot project. It is well underway and is enrolling subjects for newborn screening for SCID among Indians on the Navajo Reservation.

**Training Program:** We have funded 4 fellows (two in year 1 and two for year 2). We have implemented procedures for increasing the number of applicants including advertising and revision of the eligibility criteria which have been successful.

**Patient Advocacy Groups:** The PIDTC has worked with the *Immune Deficiency Foundation (IDF)* to develop their biannual workshops, including one in NYC and one in SF this year; also with the *WAS Foundation* for their first workshop in Chicago this year. The IDF, WAS, CGD and Jeffrey Modell Foundations will all be participating in our first annual PIDTC Scientific Workshop to be held in SF in April 2011. They are all planning to provide information about our protocols to their membership.

**DMCC:** The PIDTC has been working closely with the DMCC to develop our protocol case report forms (CRFs) and PIDTC website. Lisa Harewood, 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. The updated modules on the DMCC website will be used by all of the participating centers to complete training for protocols. The PIDTC website committee and Lisa Harewood, on behalf of the DMCC, meet for weekly conference calls to facilitate development of the PIDTC website.

**Summary of Year 1:** During the first year, 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, selection of a

PIDTC Website Committee and development of content for the website, and development of a Publication Policy and selection of a Publication Committee Chair. 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 PWT of the PIDTC has established a collaborative relationship with the Lysosomal Storage Disease Consortium of the RDCRN to validate and use a phone-based neurodevelopmental assessment protocol for evaluating patients in our prospective longitudinal natural history study of SCID and to use parent and nurse-administered questionnaires for assessing neurodevelopment as part of our cross-sectional studies of SCID, WAS and CGD. 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 will meet monthly; we had our first call in early August. The PIDTC is actively working with the Patient Advocacy Groups both with respect to their parent meetings as well as to gain their help in recruiting patients. We anticipate holding an annual PIDTC Scientific Workshop; the first will be in San Francisco in April 2011. We have developed an agenda and submitted an R13 application to help with funding of the April 2011 PIDTC Scientific Workshop. To facilitate study of these rare diseases, one of the goals of the PIDTC is to promote collaboration with our European colleagues. The PI and co-PI of the PIDTC have been invited to speak at the European Group for Blood and Marrow Transplantation (EBMT) Inborn Errors Working Party (IEWP) meeting in Venice, Italy in November 2010. The PIDTC has invited several representatives from this group to participate at our PIDTC Scientific Workshop in April 2011.

**Rare Kidney Stone Consortium (RKSC)**  
**Principal Investigator: Dr. Dawn Milliner**

The Rare Kidney Stone Consortium (RKSC) received funding in October 2009. During the months since that time the, program directors and key personnel have been actively engaged in organizational work for the consortium. The goals of RKSC are to: (1) establish and expand registries and collaborate with patient organizations for the rapid dissemination of knowledge (2) stimulate generation of testable hypotheses regarding mechanisms of renal injury in these diseases through registry findings, tissue resources, and pilot projects. (3) develop cohorts of well-characterized patients for future clinical studies, (4) support small scale clinical studies in these cohorts and (5) attract and train investigators to rare diseases research in nephrology. We are pursuing these goals through 4 interlinked projects, each centered around a disease process – primary hyperoxaluria (PH), cystinuria, Dent disease, and APRT deficiency, with the overall goal of developing new treatments directed at protecting renal function and reducing nephrocalcinosis and stone formation.

### Longitudinal Studies

1. Patient Registries for PH, cystinuria, Dent disease, and APRT deficiency: REDCap has been selected as the web based application to house each of the four registries. REDCap was selected since this program is supported through a joint effort of all NIH funded CTSA's and provides an adaptable vehicle for our studies. Registries for cystinuria, Dent and APRT deficiency have been fully developed within REDCap. Active PH registry enrollment continues with enrollment to date of 249 PH patients. The PH registry will remain in Quickbase until the end of 2010, then if REDCap is performing well, will be migrated to REDCap.
2. Tissue Banks: A tissue bank is in place for PH with tissue samples provided this year to several investigators. Tissue banks are in development for the three other diseases.
3. The PH registry (IPHR) was examined for outcomes of transplantation in PH patients. A manuscript with our findings is currently in press in the American Journal of Transplantation.
4. A quality of life study of patients with cystinuria was recently completed and a manuscript submitted.

### Pilot Studies

1. Dr. Holmes study of metabolism of hydroxyproline in patients with primary hyperoxaluria is under way with ongoing development of a tracer for the studies. This project has taken on new relevance with the recent description of a third genetic defect causing PH (PH, type III) that appears to modify the metabolic pathway for hydroxyproline.
2. Dr. Monico's study of the genetic modifiers of gene expression in PH is in the specimen gathering stage.
3. Dr. Koul's has established protocols for culture of hepatocytes from PH-1 patients. He is working to establish serum free media for primary culture of these hepatocytes and to generate cell lines from PH-1 patients using immortalization with hTert. These studies will continue to the second year of support.
4. Following a competitive application process the following were selected for new pilot studies for the coming year. Dr. Sahota – *New Drugs for Cystinuria* and Dr. Amer – *Post Kidney Transplant Nephrocalcinosis: Incidence, Risks Factors, and Graft Function*

### Training Program

Dr Lada Beara-Lasic is our current and initial trainee, under the mentorship of Drs. David Goldfarb and John Lieske. Her project centers around the Dent Disease registry. She has actively participated in design of the registry program on REDCap. She has made contacts worldwide with Dent researchers to recruit their participation with our consortium. She has designed a clinical trial to screen and identify Dent patients amongst a nephrotic syndrome cohort.

### Role and involvement of Patient Advocates Group(s) in Consortia

1. There is ongoing work with our partner Patient Advisory Groups (PAGs) which include the Oxalosis and Hyperoxaluria Foundation (OHF), Cystinuria Support Network (CSN), International Cystinuria Foundation (ICF), and the Lowe Syndrome Association (LSA). Representatives of each are members of the RKSC Steering Committee.
2. Two patient and family workshops were held in 2010, in collaboration with the ICF and CSN for patients with cystinuria in NYC in July (<http://www.cysinturia.org/index.php/news/409-2010-icf-cystinuria-symposium-announced>) and in collaboration with the OHF for patients with primary hyperoxaluria in NYC in August in conjunction with the 9th International PH workshop and the International Pediatric Nephrology Association meeting ([http://www.ipna2010.org/secondary.php?section=program&content=non-Profit\\_Foundation\\_Symposia](http://www.ipna2010.org/secondary.php?section=program&content=non-Profit_Foundation_Symposia)).

## **Salivary Gland Carcinomas Consortium (SGCC)**

PI: Adel K. El-Naggar, MD, PhD

### **Diseases Being Studied**

Mucoepidermoid Carcinoma, Adenoid cystic carcinoma, Adenocarcinoma (Salivary Duct Carcinoma)

### **Goals of the SGCC**

- 1) Investigate molecular and genomic events associated with the development, progression and heterogeneity of salivary gland malignancies.
- 2) Identify and validate molecular markers for biological assessment and therapeutic purposes.
- 3) Develop and conduct novel targeted clinical trials for patients with these cancers.

### **Salivary Gland Carcinomas Consortium Overview**

Molecular epidemiologic analysis of patients and controls has been initiated to determine if a polymorphism exists at certain repair genes in the constitutional DNA. Pilot studies to identify the genomic differences between myoepithelial and epithelial cells in different salivary tumors are being conducted. The results indicate biological differences that may need to be considered in assessing these tumors.

### **Training Program Summary**

Career Development Program- Dr. Diana Bell

Postdoctoral Fellow- Dr. Yoshitsugu Mitani

A career development candidate has completed a full year of training that resulted in her commitment to the field and assuming a leadership position in salivary research. A postdoctoral fellow from Japan has also been a part of the program and actively involved in the genomic characterization of these cancers. Efforts of both candidates have led to two in press publications:

Diana Bell, Dianna Roberts, Merrill Kies, Randal S Weber and A K El-Naggar. Cell-type dependent biomarkers expression in adenoid cystic carcinoma (ACC): biological and therapeutic implications. Cancer, in press.

Yoshitsugu Mitani, Jie Li, Pulivarthi H Rao, Yi-Jue Zhao, Diana Bell, Scott M Lippman, Randal S Weber, Carlos Cautin and A K El-Naggar. Comprehensive Analysis of the MYB-NFIB Gene Fusion in Salivary Adenoid Cystic Carcinoma: Incidence, Variability and Clinicopathological Significance. Clinical Cancer Research, in press.

### **Participating Clinical Sites**

- The University of Texas M. D. Anderson Cancer Center, Houston, TX
- University of California San Francisco, San Francisco, CA
- University of Florida, Gainesville, FL
- Johns Hopkins Medical Institute, Baltimore, MD

### **Advocacy**

Adenoid Cystic Carcinoma Research Foundation

The patient advocacy group is intimately involved in the recruitment of subjects for control and donating tumor materials by patients. The ACCRF is updated on the progress of the program.

## Sterol and Isoprenoid Diseases Consortium (STAIR)

*Principal Investigator: Robert Steiner, M.D.*

### 1) Major goals, and diseases under study

The overall goal of the Sterol and Isoprenoid Research consortium or STAIR with PI Robert D. Steiner is to study a group of diseases bound by common biochemistry, impact on health, and rarity, caused by inborn errors in sterol and isoprenoid metabolism including Smith-Lemli-Opitz syndrome (SLOS), Niemann-Pick type C (NPC), Sjögren-Larsson syndrome (SLS), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), mevalonic aciduria, sitosterolemia and cerebrotendinous xanthomatosis (CTX). STAIR specific goals are: 1) to conduct 2 major clinical studies (a longitudinal clinical study of patients with SLOS and a therapeutic trial to evaluate the efficacy of antioxidant therapy in SLOS), 2) to conduct at least 2 pilot research studies involving patients with SLS or HIDS, 3) train investigators in rare disease clinical research, 4) work with patient advocacy groups involved in the diseases, and 5) actively participate in RDCRN activities.

### 2) Longitudinal studies, clinical trials and pilot studies (goals, status and results)

*“Smith-Lemli-Opitz Syndrome: A Longitudinal Clinical Study of Patients Receiving Cholesterol Supplementation (Steiner, #7001):*

The primary objective is to determine clinical and biochemical outcomes in patients with Smith Lemli-Opitz syndrome receiving dietary cholesterol supplementation. Secondary objectives include: 1) to correlate biochemical and clinical phenotypes in SLOS subjects given dietary cholesterol with changes in whole body cholesterol pool size, and with its major determinants (cholesterol synthesis, absorption and intake); 2) to identify and refine clinical or biochemical markers that can be used as outcome measures in a future therapeutic trial; 3) to identify a biomarkers that can be used for diagnostic testing or screening; 4) to develop a registry of well characterized SLOS patients and to maintain a repository of biomaterials corresponding to these patients. The study has been reviewed and approved by the DMCC and DSMB. STAIR sites are in the process of submitting to their IRBs.

*Sjögren-Larsson Syndrome longitudinal biomarker study (Rizzo):* This is an observational, longitudinal study with SLS patients to identify novel biomarkers that correlate with disease progression. The study is under development.

*SC4MOL deficiency (Vockley):* This is a pilot study to characterize the biological and immunological aspects of methylsterol oxidase deficiency. The study has been approved by the UPMC IRB and will soon be submitted to DMCC.

*Smith-Lemli-Opitz Syndrome and antioxidant (Steiner/Porter):* this is a clinical trial to determine if antioxidants or a combination of antioxidants and statin improve IQ and DQ in SLOS patients receiving cholesterol supplementation. The protocol is finalized, we are preparing submission to DMCC.

*Sitosterolemia: ezetimibe and whole body plant sterol pool size (Jones):* this is a pilot study that will determine if treatment with ezetimibe decreases plant sterol pool size in patients with sitosterolemia. The design of the study is being finalized and expect to submit to DMCC by end of year.

*Cerebrotendinous xanthomatosis (CTX) natural history protocol (Steiner):* The design of the study is being finalized.

### 3) Training/Career development program

We currently have two RDCRN funded trainees, Andrea DeBarber, Ph.D. (OHSU) and Miao He, Ph.D. (Emory). Dr. DeBarber is focusing her work on improving diagnostic and therapeutic monitoring techniques for cerebrotendinous xanthomatosis (CTX), and on developing a biomarker assay for SLS. She is also being trained in Clinical Research, having enrolled in the OHSU Human Investigation Program, and actively participating in SLOS-related clinical and laboratory research activities. Dr. DeBarber started her training on March 1<sup>st</sup>, 2010. Dr. He, is a Clinical Biochemical Geneticist at Emory University. Her primary mentor is STAIR Site Principal Investigator Gerard Vockley, M.D. Ph.D. She will also be trained by David Ledbetter, Ph.D. and Rani Singh, Ph.D. at Emory University, her academic home. Dr. He started her training on August 1<sup>st</sup>, 2010. She has planned rotations in several of STAIR labs (Drs. Gibson, Vockley, Steiner, Porter) and will focus her work on developing new methods to characterize methylsterol abnormalities in patients with SC4MOL deficiency and new methylsterol disorders, and characterizing the immune response and inflammatory pathways in patients with methylsterol disorders.

### 4) Role and involvement of PAGS

Four PAGs have been actively working with STAIR: SLO/RSH (Cynthia Gold), NNPFD (Cate Walsh-Vockley), FIRST (Jean Pickford) and ULF (Paula Brazeal). Cate Walsh-Vockley stepped down from her position at NNPFD and we are working to find a replacement who would be willing/interested in working with us. Cross-linking the STAIR website with their foundation's website, STAIR participation in their newsletter, planning combined conferences, supporting STAIR trainees have been discussed. SLOS/RSH, FIRST and ULF have been invited to participate in the upcoming CPAG Face to Face Meeting (September 20, 2010) and the 2<sup>nd</sup> Conference on Clinical Research for Rare Diseases(September 21, 2010).

**Urea Cycle Disorders Consortium (UCDC)**  
**PI: Mark L Batshaw, M.D., Co-PI: Mendel Tuchman, M.D.**

**Disorders Studied**

N-acetylglutamate synthetase (NAGS) deficiency, carbamyl phosphate synthetase I (CPSI) deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinate synthetase (AS) deficiency (citrullinemia), argininosuccinate lyase (AL) deficiency (argininosuccinic aciduria), arginase (ARG) deficiency (argininemia), citrulline (CITR) deficiency (citrullinemia type II), and hyperornithinemia, hyperammonemia, homocitrullinuria (HHH) syndrome

**Major Goals**

1. Conduct clinical research as described in the studies section
2. Maintain a contact registry and a nation-wide network of regional centers for the diagnosis, treatment and clinical research in UCD
3. Train a new generation of investigators and clinicians who will dedicate their careers to the study and treatment of rare diseases
4. Expand our already extensive UCDC website content for education and research in UCD that: (a) provides best practice guidelines for health care professionals for diagnosis and treatment; (b) promotes heightened public awareness about UCD; and (c) links investigators in the field to relevant scientific literature and technologies
5. Continue our close collaboration with the National Urea Cycle Disorders Foundation (NUCDF), the patient advocacy group for UCD
6. Continue to work with the pharmaceutical/biotech industry to develop and test novel medications and treatments that improve survival and outcome (cognitive function and quality-of-life) in UCD
7. Further our close liaison with public authorities to advocate for expansion of newborn screening programs

**Studies****Longitudinal Study of Urea Cycle Disorders (RDCRN 5101)**

Enrollment goal: 550 subjects                      Current enrollment: 430 subjects (as of 8/3/2010)

Status: Active

Objective: The objective of this protocol is to conduct a longitudinal multidisciplinary investigation of the natural history, morbidity, and mortality of people with UCD.

Preliminary Data: We have published several papers including an interim cross-sectional analysis of the first 183 patients enrolled during the initial 22 months of this study (9,16) and an update in 2009 (14) and an investigation of an association between vaccines and hyperammonemia in children with UCD (10).

**A Randomized, Double-Blind, Crossover Study of Sodium Phenylbutyrate (Buphenyl™) and Low- Dose Arginine (100 mg/kg/day) Compared to High-Dose Arginine (500 mg/kg/day) Alone on Liver Function, Ureagenesis and Subsequent Nitric Oxide Production in Patients with Argininosuccinate Lyase (AL) deficiency (RDCRN 5102)**

Enrollment goal: 12 subjects                      Current enrollment: 11 subjects (as of 8/3/2010)

Status: Active

Objective: To determine if the treatment of argininosuccinic aciduria (ASA) patients with sodium phenylbutyrate (Buphenyl™) in conjunction with lowered doses of arginine improves liver function as measured by short-term assessment of synthetic activity and the use of stable isotope tracers to assess ureagenesis and nitric oxide production.

**Assessing Neural Mechanisms of Injury in Inborn Errors of Urea Metabolism Using Structural MRI, Functional MRI, and Magnetic Resonance Spectroscopy (RDCRN 5104)**

Enrollment goal: 46 subjects                      Current enrollment: 46

Status: Closed to accrual/ data Analysis

Objective: To investigate the neural mechanisms underlying cognitive and motor dysfunction in OTCD by utilizing a multidisciplinary approach with cognitive testing and neuroimaging platforms.

Preliminary Results: Findings demonstrate that females with OTCD who were previously considered asymptomatic harbor subtle yet significant neurocognitive deficits that correlate with a known underlying pathology in white matter. Data shows that low myoinositol is a biomarker of a prior HA episode and represents a compensatory mechanism to correct astrocytic swelling due to high glutamine. fMRI data confirms previous neuropsychological testing results demonstrating deficits in executive function and fine motor skills of OTCD subjects. Results have been published (3-8). Protocols 5107 and 5108 expand on findings from 5104.

**Investigation of Brain Nitrogen Metabolism in Partial Ornithine Transcarbamylase Deficiency (OTCD) Using 1H MRS, DTI, and fMRI (RDCRN 5107)**

Status: Protocol approved; MOO and eCRF development

Objective: 1) To estimate white matter damage (macroscopic and microscopic) in participants with OTCD versus controls. 2) To determine a profile of brain biochemical abnormalities in participants with OTCD versus controls. 3) Assess cognitive and motor systems abnormalities in the participant cohort as compared to age matched typically developing non-disease controls.

**N-carbamylglutamate (NCG, Carbaglu) in the Treatment of Hyperammonemia**

Enrollment goal: 84 subjects                      Current enrolment: 22 subjects (as of 9/1/2010)

Status: Active (RDCRN “branded” study; to be submitted for approval through RDCRN review process)

Objective: To investigate the use of N-carbamylglutamate (NCG), a new therapeutic agent for a subset of hyperammonemic conditions which are caused by a deficiency of NAG, including NAGS deficiency, propionic acidemia (PA), methylmalonic acidemia (MMA), and partial CPSI deficiency.

Preliminary Results: Oral NCG improves urea cycle function and decreases plasma ammonia levels in patients with NAGS deficiency, partial CPSI deficiency, PA and MMA (1,2,15).

**Oxidative Stress, Inflammation and Acute Decompensation in Urea Cycle Disorders Pilot Project**

Enrollment goal: 50 subjects

Status: Protocol under review

Objective: The primary purpose of the proposed study is to characterize the oxidative stress and inflammatory cytokine status in UCD during baseline and decompensated states.

**Training Program Summary**

We provided funding from RDCRC NIH grant and two related foundation grants to provide at least 50% effort support for 1-2 year training periods of 1 graduate student, 8 clinical genetics/ metabolism fellows and 2 junior faculty members in rare disease research, focusing on UCD.

**Role of Patient Advocacy Group**

The National Urea Cycle Disorders Foundation (NUCDF) has been an integral partner and collaborator in the UCDC since its inception. The executive director of NUCDF serves as a voting member of the executive committee of the consortium. One of her key roles has been to continually challenge the existing paradigms and barriers to advancing research in UCD. NUCDF has been very involved in the patient registry and Longitudinal Study enrollment. In terms of study design, NUCDF had a direct involvement in the development of protocols, consents, content evaluations, and progress reporting. NUCDF has also contributed to website content and the UCDC training program.



**Publications**

1. N. Ah Mew, R. McCarter, Y. Daikhin, M. Yudkoff, M. Tuchman. N-carbamylglutamate augments ureagenesis and reduces ammonia and glutamine levels in patients with propionic acidemia, *Pediatrics*. 2010 Jul;126(1):e208-14. PMID: 20566609
2. Caldovic L, Morizono H, Daikhin Y, Nissim I, **McCarter RJ, Yudkoff M, Tuchman M**. Restoration of ureagenesis in N-acetylglutamate synthase deficiency by N-carbamylglutamate. *J Pediatr*. 2004 Oct;145(4):552-4.
3. **Gropman A**. Brain imaging in urea cycle disorders. *Mol Genet Metab*. 2010;100 Suppl 1:S20-30. PMID: 20207564
4. **Gropman AL, Fricke ST, Seltzer RR**, Hailu A, Adeyemo A, Sawyer A, **van Meter J**, Gaillard WD, **McCarter R, Tuchman M, Batshaw M**; Urea Cycle Disorders Consortium. 1H MRS identifies symptomatic and asymptomatic subjects with partial ornithine transcarbamylase deficiency. *Mol Genet Metab*. 2008;95(1-2):21-30. PMID: 18662894
5. **Gropman AL**, Gertz B, Shattuck K, Kahn IL, Seltzer R, **Krivitzky L**, Van Meter J. Diffusion Tensor Imaging Detects areas of abnormal white matter microstructure in patients with partial Ornithine Transcarbamylase Deficiency (OTCD). *AJNR Am J Neuroradiol*. 2010 May 20. [Epub ahead of print]. PMID: 20488904
6. **Gropman AL, Seltzer RR, Yudkoff M**, Sawyer A, **VanMeter J, Fricke ST**. 1H MRS allows brain phenotype differentiation in sisters with late onset ornithine transcarbamylase deficiency (OTCD) and discordant clinical presentations. *Mol Genet Metab*. 2008 94(1):52-60. PMID: 18262815
7. **Gropman AL, Summar M**, Leonard JV. Neurological implications of urea cycle disorders. *J Inherit Metab Dis*. 2007 30(6):865-79. PMID: 18038189
8. **Gropman AL & Rigas A**. Neurometabolic disorders: urea-cycle disorder, outcomes, development and treatment. *Pediatric Health* 2008, 2 (6): 701-713
9. **Krivitzky LS, Babikian T, Lee HS, Thomas NH, Burke-Paull KL, Batshaw ML**. Intellectual, Adaptive, and Behavioral Functioning in Children with Urea Cycle Disorders, *Pediatric Research*. 2009 Jul;66(1):96-101. PMID: 19287347
10. Mitchell S, Ellingson C, Coyne T, Hall L, Neill M, Christian N, Higham C, Dobrowolski Urea Cycle Disorder Consortium, **Summar M**. Genetic variation in the urea cycle: investigating key candidate genes for common diseases. *Hum Mutat*. 2009 Jan;30(1):56-60. PMID: 18666241
11. Patrick TB, Rachel **Richesson R**, Andrews JE, Folk LC. SNOMED CT Coding Variation and Grouping for “other findings” in a Longitudinal Study on Urea Cycle Disorders. *AMIA Annu Symp Proc*. 2008 Nov 6:11-5. PMID: 18998949
12. **Richesson RL, Lee HS**, Cuthbertson D, Lloyd J, Young K, Krischner 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*. 2009 Jan;30(1):55-62. Epub 2008 Sep 7. PMID: 18804556
13. Schlegel, C; Edwards, KM; Morgan, T; **Welch-Burke, T; Lee, Hye-Seung; Urea Cycle Consortium; Summar, M**. No association of Vaccines and Hyperammonemic Events in Children With Urea Cycle Disorders (UCD) (In press)
14. **Seminara J, Tuchman M, Krivitzky L, Krischer J, Lee HS, LeMons C, Baumgartner M, Cederbaum S, Diaz GA, Feigenbaum A, Gallagher RC, Harding CO, Kerr DS, Lanpher B, Lee B, Lichter-Konecki U, McCandless SE, Merritt JL, Oster-Granite ML, Seashore MR, Stricker T, Summar M, Waisbren S, Yudkoff M, Batshaw ML**. Establishing a Consortium for the Study of Rare Diseases: The Urea Cycle Disorders Consortium. *Mol Genet Metab* 2010;100 Suppl 1:S97-S105. Epub 2010 Feb 10. PMID: 20188616
15. **Tuchman M**, Caldovic L, Daikhin Y, Horyn O, Nissim I, Nissim I, Korson M, Burton B, **Yudkoff M**. N-carbamylglutamate markedly enhances ureagenesis in N-acetylglutamate deficiency and propionic acidemia as measured by isotopic incorporation and blood biomarkers. *Pediatr Res*. 2008 Aug;64(2):213-7.
16. **Tuchman M, Lee B, Lichter-Konecki U, Summar ML, Yudkoff M, Cederbaum SD, Kerr DS, Diaz GA, Seashore MR, Lee HS, Krischer JP, Batshaw ML and the Urea Cycle Disorders Consortium of the Rare Diseases Clinical Research Network**. Cross-sectional multi-center study of patients with urea cycle disorders in the United States. *Mol Genet Metab* 2008; 94:397-402.

**Vasculitis Clinical Research Consortium**

PI: Peter A. Merkel, MD, MPH

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

The Vasculitis Clinical Research Consortium (VCRC) is an international, multi-center, clinical research infrastructure for the study of vasculitis. The VCRC is the major multi-center clinical research program in North America and one of the two major vasculitis research networks in the world. The VCRC was one of the founding Consortia within the Rare Diseases Clinical Research Network (RDCRN) [U54 RR019497] and was granted funding for a second 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) [9U54AR057319].

The VCRC includes 11 sites in the United States and Canada many additional international collaborating centers.

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

1. Maintain and expand the administrative and scientific infrastructure of the VCRC
2. Continue the five VCRC Longitudinal Studies and associated Biomarker Discovery Projects and maintain and expand the VCRC Data and Specimen Repository
3. Conduct a multicenter, randomized, double-blind, placebo-controlled trial of abatacept for the treatment of Takayasu's arteritis and giant cell arteritis
4. Conduct a series of projects to develop and validate new outcome measures for vasculitis for use in clinical research Takayasu's arteritis
5. Continue the VCRC Pilot Project Program to support the efficient conduct of Phase I and II studies of promising new therapeutics for vasculitis
6. Continue and expand the VCRC Fellowship Program to train young investigators in methodology for clinical and translational research in vasculitis
7. 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:** Giant Cell Arteritis, Takayasu's Arteritis, Polyarteritis Nodosa, Wegener's Granulomatosis, Microscopic Polyangiitis, and Churg-Strauss Syndrome

**Longitudinal Studies:**

**5502:** Giant Cell Arteritis, *actively enrolling*, current enrollment 150/300

**5503:** Takayasu's Arteritis, *actively enrolling*, current enrollment 114/250

**5504:** Polyarteritis Nodosa, *actively enrolling*, current enrollment 61/150

**5505:** Wegener's Granulomatosis & Microscopic Polyangiitis, *actively enrolling*, enrollment 332/600

**5506:** Churg-Strauss Syndrome, *actively enrolling*, current enrollment 104/250

*Multiple biomarker discover projects are linked to Longitudinal Studies and >10 projects are currently underway in data analysis phases; several more projects are schedule to start this year*

**5510:** Genetic Repository One Time DNA protocol; all six diseases; *IRB approval pending*

*Several candidate gene and microarray studies using stored DNA samples linked to comprehensive clinical phenotyping are under way.*

**Pilot Studies:**

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

*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 *actively enrolling*, current enrollment 24/60

**5524:** Plasma exchange and glucocorticoid dosing for ANCA-Associated Vasculitis, *actively enrolling*, current enrollment 5/500

**Observational Studies:**

**5515:** Imaging study of MRI and PET/CT scans in TAK, *actively enrolling*, current enrollment 12/36

**5531:** Vasculitis Reproductive Health Survey, *IRB approval pending*

*The VCRC is also directed and coordinating a large program directed at development and validation of outcome measures for use in clinical trials in vasculitis.*

**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 persons trained:** Current: 3, Previous: 4

**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. Additional support for VCRC projects comes from grants from the NIAMS (1RC1 AR058303; P60 AR047785; U01 AR51874; HHSN2682007000036C), the FDA (R01 FD003516), the Vasculitis Foundation, and industry partners.

**Data Management and Coordinating Center Summary**  
**Jeffrey Krischer, Principal Investigator**

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

- a. A 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 has over 2.2 million hits per 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 5,600 individuals, alerting them when new studies are opened in the Network or approved studies open at new sites.
- c. A secure, password-protected members' website for 2,042 Consortium members from 330 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 28 actively accruing studies from 59 sites that now have over 4,200 enrolled patients.
- e. Ensured appropriate regulatory compliance with regard to adverse event reporting, HIPPA and DSMB oversight.
- f. Collaborated in preparation and co-authored 42 scientific presentations and publications.
- g. 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.
- h. Promulgated data standards that provide consistency across research protocols and diseases to enhance the value of the research data collected.
- i. 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 12,920,064 data points, photographs, CT scans, PET scans, x-ray images and videos.

Network focused publications:

- Richesson RL, Krischer JP: **Data Standards in Clinical Research: Gaps, Overlaps, Challenges and Future Directions.** In Press: *JAMIA* 2007; 14(6):687-696.
- Richesson RL, Malloy JF, Paulus K, Krischer JP: **An Automated Standardized System for Managing Adverse Events in Clinical Research Networks.** Under Review: *Drug Safety*, February 2008.
- Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, Nguyen T, Paulus K, Merkel PA; **Rare Diseases Clinical Research Network.: Clinical research for rare disease: opportunities, challenges, and solutions.** *Mol Genet Metab* 96(1):20-6, 2009.
- 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* 30(1):55-62,

## **CPAG: THE POWER OF COALITION**

### *Coalition of Patient Advocacy Groups*

CPAG is the patient advocacy arm of the Rare Diseases Clinical Research Network (RDCRN). In this role, we enthusiastically partner with rare disease researchers, government organizations and national advocacy organizations to advance the cause of research for individuals with rare disorders.

#### **CPAG's Vision**

Through broad collaboration between research professionals and advocacy groups, rare disorders will make better and faster progress towards treatment options and cures.

#### **CPAG's Mission**

The Coalition for Patient Advocacy Groups (CPAG) will promote collaboration between participating rare disease advocacy organizations and the Rare Diseases Clinical Research Network (RDCRN) to facilitate better access to and earlier benefit from research undertaken in rare diseases. As the patient advocacy arm of the RDCRN, CPAG members will use their position to advance the cause of rare disease research through the RDCRN.

#### **CPAG and RDCRN-2**

With the growth of the RDCRN program in the second round of funding (RDCRN-2), the CPAG group grew substantially and currently consists of 81 separate rare disease patient advocacy organizations affiliated with 19 RDCRN consortia\*.

CPAG monthly meetings are held by phone. Additionally, there are two face-to-face meetings a year, held in conjunction with other RDCRN activities. Meetings are led by three CPAG co-chairs with the assistance and support of staff from the Office of Rare Diseases Research (ORDR). Meetings, both phone and face-to-face, are opportunities to discuss topics of interest to members, address issues related to patient group interaction within individual consortia, provide expert guest speakers for critical topics and to help each other build stronger individual organizations.

#### **CPAG Goals and Initiatives**

CPAG is dedicated to encouraging continuous advancement in communication and cooperation between researchers and patient groups and to facilitate patient recruitment for successful research outcomes. Working with the DMCC, we've established a public website for individuals interested in learning more about CPAG and RDCRN research opportunities (<http://rarediseasesnetwork.epi.usf.edu/CPAG/>). We have initiated surveys of CPAG members and consortia personnel to help identify areas of strength or weakness in working within our individual consortia to improve patient group/researcher relationships. We solicit feedback from members and strive to provide targeted information on calls and in meetings to advance the 'Power of Coalition' for CPAG members and for the RDCRN!

\*Data from the RDCRN website: <http://rarediseasesnetwork.epi.usf.edu/>