

57.

CPAG: THE POWER OF COALITION

Coalition of Patient Advocacy Groups

Successful rare disease research relies on a number of critical factors, including dedicated investigators and adequate funding. However, one such factor trumps all the rest: *Patients*. With no patients, there can be no research. Recognizing the critical role patient advocacy groups (PAGs) play in organizing patient support, identifying patient community needs and funding research, the Rare Diseases Clinical Research Network (RDCRN) engages PAGs as full partners in RDCRN supported research.

The Coalition of Patient Advocacy Groups (CPAG) is the patient advocacy arm of the Rare Diseases Clinical Research Network (RDCRN). In this role, patients groups serve as liaisons to their patient communities, ensuring two-way communication between consortium investigators and patient representatives and advising on issues of concern to the patient group, including study design, informed consent and research priorities.

Who We Are

CPAG is composed of representatives from more than 80 rare disease patient advocacy groups participating in current RDCRN research consortia.

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.

What We Do

In addition to working closely with investigators and staff within our own consortia, CPAG members work collectively to advance the goals of the RDCRN. Through monthly calls and annual face-to-face meetings, CPAG members discuss topics of interest to our patient communities, 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 in order to be better research partners.

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.

In addition to working towards stronger research consortia within the network, CPAG member groups educate policy makers and the general public about the 'power of coalition,' as embodied in the RDCRN model, to successfully and cost-effectively advance research in rare diseases.

58. Data Management and Coordinating Center Summary
Principal Investigator: Jeffrey Krischer, PhD

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

- a. A public website that serves as a portal for the rare diseases community, including public and health care professionals, to provide information on research on rare diseases, consortium activities, RDCRN-approved protocols and practice guidelines. This portal had over 600,000 visits in the last year.
- b. A patient contact registry to permit the registration of individuals who self-select for their interest in participating in clinical research. The Contact Registry also provides ongoing contact with over 9,800 individuals, alerting them when new studies are opened in the Network or approved studies open at new sites. New enhancements to the contact registry include registration for multiple diseases, collection of diagnostic criteria, and options to participate in online protocols and/or share information with Consortium PIs and PAGs.
- c. A secure, password-protected members' website for 2,290 Consortium members from 488 institutions that includes announcements, calendars, protocol management tools and electronic case report forms. Among the functions supported include systems for adverse event reporting and monitoring, research pharmacy drug management, biospecimen tracking, image processing, desktop videoconferencing, and automated reporting.
- d. Collaboration on study design and implementation for 77 actively accruing studies from 167 sites that now have over 11,600 enrolled patients.
- e. Ensured appropriate regulatory compliance with regard to adverse event reporting, HIPPA and DSMB oversight.
- f. Conducted and distributed reports for 317 audit site visits (Review 10% of cases and select data points conducted within 18 months of first accrual, then annually thereafter for interventional studies and within 3 years thereafter for observational studies) and 75 monitoring visits (Review all subjects accrued and all data points every 3 months).
- g. Collaborated in preparation and co-authored 45 scientific presentations and publications.
- h. Conducted in-person and web-based training for consortia investigators and clinical research associates to ensure the high quality and completeness of submitted data and protocol compliance.
- i. Promulgation of data standards that provide consistency across research protocols and diseases to enhance the value of the research data collected.
- j. Established a data base of clinical and laboratory findings that permits a close linkage between biological specimens and a well-characterized clinically followed population encoding 22,542,917 data points, photographs, CT scans, PET scans, x-ray images and videos.

Network focused publications:

- Richesson RL, Krischer J. **Data standards in clinical research: gaps, overlaps, challenges and future directions.** *J. Am. Med. Inform. Assoc.* Nov-Dec 2007;14(6):687-696.
- Richesson RL, Malloy JF, Paulus K, Cuthbertson D, Krischer JP. **An automated standardized system for managing adverse events in clinical research networks.** *Drug Saf.* 2008;31(10):807-822.
- Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, Nguyen T, Paulus K, Merkel PA. **Clinical research for rare disease: opportunities, challenges, and solutions.** *Mol. Genet. Metab.* Jan 2009;96(1):20-26.
- Richesson RL, Lee HS, Cuthbertson D, Lloyd J, Young K, Krischer JP. **An automated communication system in a contact registry for persons with rare diseases: scalable tools for identifying and recruiting clinical research participants.** *Contemp. Clin. Trials.* Jan 2009;30(1):55-62.
- Richesson RL, Nadkarni P. **Data standards for clinical research data collection forms: current status and challenges.** *J. Am. Med. Inform. Assoc.* May 1 2011;18(3):341-346.
- Richesson RL, Sutphen R, Shereff D, Krischer JP. **The Rare Diseases Clinical Research Network Contact Registry update: Features and functionality.** *Contemp. Clin. Trials.* Mar 2 2012.

59. Angelman, Rett, and Prader-Willi Syndromes Consortium
Principal Investigator: Alan Percy, MD – University of Alabama at Birmingham;
Co-PI: Arthur Beaudet, MD – Baylor College of Medicine

Disorders Under Study:

Angelman syndrome: PI – Lynne Bird, MD, UCSD

Rett syndrome: PI – Alan Percy, MD, UAB

Non Rett syndrome, *MECP2* positive females and males

MECP2 Duplication disorder

Prader-Willi syndrome: PI – Daniel Driscoll, MD, PhD, Univ. of Florida

Early Morbid Obesity lacking PWS mutations

Major goals: Conduct longitudinal studies, promote clinical trials, and train young investigators (graduate students, postdoctoral fellows and junior faculty) in translational research in rare diseases as an integral part of this project

Angelman syndrome:

Longitudinal assessment of individuals with AS

Establish genotype-phenotype correlations

Examine efficacy of symptomatic treatments

Rett syndrome:

Establish phenotype/genotype correlation across a broad spectrum of RTT

Perform longitudinal studies across a broad sample of individuals with RTT

Continue survival surveillance study across a broad spectrum of individuals with RTT

Prader-Willi syndrome:

Determine the natural history of Prader-Willi syndrome

Genotype-phenotype comparisons among the 3 main molecular classes of PWS (deletion, uniparental disomy and imprinting defect)

Determine the natural history of non-PWS Early-onset Morbid Obesity (EMO)

Compare and contrast the PWS to the EMO group and EMO subgroups

Longitudinal Studies:

Longitudinal studies have progressed well in all three disorders

Current enrollments: AS (5203): 265 of 300 proposed

RTT (5201): 1104 of 1350 proposed

PWS (5202): 352 of 450 proposed

Pilot Studies:

Rare Disease Sleep Pilot Research Plan: Current enrollment 458 (5207)

Principal objectives:

1) Assess prevalence and type of sleep problems in AS, RTT, and PWS

2) Correlate effect of sleep problems with the behaviors in these individuals

3) Assess whether these problems improve or worsen with age

4) Correlate genotypes with various sleep problems and their severity

5) Assess treatment outcome of sleep disorders in these individuals with respect to improvement in quality of life and course of the disease

Clinical Trials:

Angelman Syndrome

1) Folate-betaine trial completed: no benefit shown

2) Extension of folate-betaine trial (5204): Metafolin, betaine, creatine, and B12; no benefit shown

3) FDA/OPD phase II clinical trial of levodopa in Angelman syndrome; not part of RDCRC

Rett syndrome

IGF-1 clinical trial: performed at Children's Hospital Boston; not part of RDCRC

Prader-Willi syndrome

- 1) Evaluation of tolerance, behavior, anxiety, and food intake after nasal administration of Oxytocin in children with PWS

Training Program Summary:

Training has progressed well in all three consortia with both MD and PhD participating. Presently, more than two dozen have participated.

Role and Involvement of Patient Advocacy Groups:

Angelman Syndrome Foundation: Eileen Braun

Foundation for Angelman Syndrome Therapeutics: Paula M. Evans, Chair; Sharon Claridge, Board member and attends monthly conference calls

International Rett Syndrome Foundation (formerly International Rett Syndrome Association): Stephen Bajardi, Executive Director; Steven Kaminski, Chief Scientific Officer

Prader-Willi Syndrome Association: Janalee Heinemann, Director of Research and Medical Affairs

The Patient Advocacy Groups have provided exceptional support both in terms of participant recruitment and in direct grants for training and pilot projects. In addition, IRSF (and its predecessor IRSA) has been instrumental in funding the remote travel clinics (Oakland, Chicago, New Brunswick, Miami, and Tampa) that account for about 40% of enrollment in RTT.

60.

Autonomic Disorders Consortium (ARD)
Principal Investigator: David Robertson, MD – Vanderbilt University

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

Study Title	Goals	Status
6101 Peripheral Dopamine in Postural Tachycardia Syndrome	To determine how changes in kidney dopamine (DA) activity influence urinary sodium excretion.	Completed dose escalation phase. Continue to enroll in main study.
6102 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.	Enrollment is complete. Many patients are still on study.
6103 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.	Enrollment continues
6104 Safety and Efficacy of Intravenous Norepinephrine for Orthostatic Hypotension.	To develop a prosthetic baroreceptor system and to test hemodynamic effects of epidural spinal cord stimulation.	Closed to accrual due to early stopping rules.
6105 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.	Recently opened to enrollment.

RDCRN Summaries

Study Title	Goals	Status
6106 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.	Enrollment continues.

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. Trainees at the Mayo Clinic Rochester, MN include Adam Loavenbruck, MD and Ajay Barsaik, MBBS. In subsequent years education and training support will be extended to other consortium sites.

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).

61. Brain Vascular Malformations Consortium (BVMC)
PI: William L. Young, MD, Co-PI: Douglas A. Marchuk, PhD

Major Goals:

CCM: To establish a CCM database at the University of New Mexico and recruit 500 CCM1 patients with 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 300.

HHT: To construct an HHT clinical research database; we will determined clinical risk factors for hemorrhage In HHT patients with BAVM and use genotype as potential marker for increased intracranial hemorrhage risk. This is longitudinal study of 875 HHT patient 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 marker for progression 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.

Diseases under Study:

Familial Cavernous Malformations (CCM)-Common Hispanic Mutation
Sturge-Weber Syndrome (SWS)-Leptomeningeal Angiomatosis
Hereditary Hemorrhagic Telangiectasia (HHT) associated Brain Arteriovenous Malformation (BAVM)

Longitudinal Studies

Project 1

6201: Modifiers of disease severity in cerebral malformations
Current Enrollment: 233/500

Project 2

6202: Innovative approaches to gauge progression of Sturge-Weber Syndrome
Current Enrollment: 200/300

6204: Establishing reliability for Quantitative EEG, Transcranial Doppler, behavioral outcomes and Optical Coherence Tomography in SWS: The next step toward biomarker
Current Enrollment: 40/60

Project 3

6203: Cerebral Hemorrhage Risk in Hereditary Hemorrhagic Telangiectasia
Current Enrollment: 519/875

Pilot Studies:

Project 1: Permeability MRI in Cerebral Cavernous Malformations Type 1 in New Mexico: Effects of Statins

Project 2: Establishing reliability for Quantitative EEG, Transcranial Doppler, behavioral outcomes and Optical Coherence Tomography in SWS: A first step toward biomarker development.

Project 3: Topical Anti-angiogenic Therapy for Telangiectasia in HHT: Proof of Concept [HHT Topical Pilot]

Project 4: Small pilot study test the feasibility of the use of Avastin for treating AVM patients. Currently working with Genentech and UCSF neuro-oncologists to judge feasibility of getting Genentech to fund the cost of the study drug.

Training Program Summary

We have had had four trainees to date:

1. Yasir Khan, Project 1, Modifier Genes in Cerebral Cavernous Malformations

RDCRN Summaries

2. Takeo Nishida, Project 3, Cerebral hemorrhage risk in Hereditary Hemorrhagic-Telangiectasia.
3. Eboni Lance, Project 2, Innovative Approaches to gauge progression of Sturge-Weber Syndrome.
4. Helene Choquet is our current trainee and is associated with Project 1. Dr. Choquet received her PhD in Human Genetics with Honors from Lille North of France University in October 2010. Her research is to identify genetic risk factors that contribute to rare vascular malformations to improve understanding of the biological mechanisms that underlie these diseases.

Contract 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

William Young, MD, Director

University of California, San Francisco

Pilot/Demonstration Project Core

Charles McCulloch, PhD, Leader

Ludmila Pawlikowska, PhD, Co-Leader

University of California, San Francisco

Training (Career Development) Core

Charles McCulloch, PhD, Director

William Young, MD, Co-Director

University of California, San Fran.

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
- Mayo Clinic, Rochester, MN
- Yale University School of Medicine, New Haven, CT
- University of California Los Angeles
- 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

Patient Advocacy Groups

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, specifically partnering with our CCM and HHT studies to help with the overall recruitment.

62. Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA)

CRC-SCA: University of Florida (Ashizawa T (PI), Subramony SH, Xia G (trainee)), 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, Shakkottai V (trainee)), University of Minnesota (Bushara K), University of South Florida (Zesiewicz T), University of Utah (Pulst S), Columbia University (Kuo S-H), UCSF (Geschwind M), Baylor College of Medicine (Jimenez-Shahed J), DMCC (Roberts Holbert A, Cuthbertson D), NINDS (Galpern W), ORDR (Ferguson J), National Ataxia Foundation (Hagen S)

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

- **Expansion of the CRC-SCA sites**

Since our RC1 (ARRA) grant was awarded on September 28, 2009, the number of our CRC-SCA sites increased from 8 to 13 with three new sites (Additional sites: Massachusetts General Hospital, Johns Hopkins University, Columbia University, UCSF and Baylor College of Medicine). The IRB approval was obtained from all participating institutions. We have also received applications for joining the CRC-SCA from the Barrow Neurological Institute (Fife T), UTSW (Khemani P) and Stanford University (Chuang RS).

- **Preparation for international collaborations**

We have been collaborating with Drs. Thomas Klockgether, Alexandra Dürr and Ludger Schöls of the European Ataxia Study Group (ASG; previously known as EUROSCA). Additionally, we have been working on establishing a Chinese SCA consortium for the past two years. We have made trips to Shanghai (Fudan University), Beijing (Beijing University) and Changsha (Central China University) to organize the consortium. The key organizer of the consortium is Dr. Beisha Tang of the Central China University in Changsha, and the consortium will include six major sites including Changsha, Shanghai, Beijing, Hong Kong, Zhengzhou, and Guanzhou. We provided outcome measure instruments to Dr. Tang who has translated them into Chinese. We have given training sessions for the scale for ataxia rating and assessment (SARA) scoring to them to ensure the uniformity of SARA data acquisition. We have also started our collaborations with a Brazilian site (Dr. Helio Teive, Federal University of Parana, Curitiba) and a government-funded Japanese SCA consortium (Dr. Hidehiro Mizusawa). All these international collaborators will use essentially identical protocols and outcome measures, allowing for direct comparisons of data between countries. In the future, these collaborations will enable us to conduct international large-scale clinical trials of SCAs, and develop valuable opportunities to study ethnic and cultural impact on the natural course of SCAs.

- **Longitudinal studies:**

Natural History Database for SCAs 1, 2, 3 and 6.

- We have enrolled 347 subjects consisting of 61 subjects with SCA1, 75 with SCA2, 137 with SCA3, and 74 with SCA6.
- The proportion of SCA3 subjects in the CRC-SCA cohort is larger and that of SCA2 subjects are smaller than those in a European study ($p < 0.01$ chi-square).
- SCA6 subjects had significantly later onset of the disease than subjects with SCA's 1, 2 or 3 ($p < 0.0001$).
- The mode of onset was most commonly an unstable gait in all SCAs.
- Subjects with SCA2 have greater difficulties with sitting than SCA6 subjects ($p = 0.0041$), with speech than SCA3 subjects ($p = 0.0271$) and with 9HPT than SCAs 1, 3 and 6 ($p = 0.0015$), suggesting that SCA2 subjects have more prominent upper body ataxia.
- The annual increase of the SARA score was the greatest in SCA1, which was 16% greater than SCA2, 32% greater than SCA3, and 46% greater than SCA6.
- Six-month longitudinal data showed the actual progression rate of SCA1 subjects twice fast than those of SCAs 2 and 3, while the progression was negligible in subjects with SCA6. However, the standard deviations of the data were large. Longer follow-up data are currently being analyzed.

RDCRN Summaries

- **Patient Registry**
 - The DMCC Contact Registry has registered 363 subjects, including 57 SCA1, 49 SCA2, 78 SCA3 and 54 SCA6 subjects and 125 subjects with other ataxias.
 - The National Ataxia Registry has had contacts with 1408 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 has been completed at the University of Florida, Johns Hopkins University, and UCLA. Dr. Guangbin Xia has been awarded an investigator-initiated grant from Acorda to conduct a trial of dalfampridine for treatment of patients with SCA1, 2, 3 and 6.

- **Genetic Modifier – a Pilot Project**
 - Of the 347 subjects, DNA samples from 245 subjects, including 52 SCA1, 46 SCA2, 93 SCA3 and 54 SCA6 subjects, were re-genotyped with size controls of known CAG repeat numbers. Re-genotyped alleles differed from the reported repeat size by 1 CAG in 38%, 2 CAGs in 10%, 3 or more in 6% of these samples. Unexpectedly, no mutation was found in 4 (1.6%), contrary to positive results of commercial testing. Sequence analysis showed 98.8% concordance with repeat number determined by fragment sizing in our laboratory.
 - The age at onset of these patients from the natural history database showed a significant inverse correlation with the size of CAG repeat in each SCA type (Figure 2). The inverse correlations were weaker in each SCA than those reported in a Duch-French Cohort. Possible explanations include: (1) the age at onset determined in a multi-center study, (2) geographic distribution, (3) ethnic diversity, and (4) exclusion of 1st and 2nd degree relatives.
 - Part of the variability in the age at onset is accounted for by the long-normal allele of SCA1 alone and in interaction with the pathological allele in SCA1 patients ($p=0.005$). Long-normal SCA6 alleles showed highly significant association with premature age at onset ($p<0.002$). Furthermore, the long-normal allele of SCA2 affects the age at onset in SCA3 patients ($p<0.0001$) as does the long-normal allele of SCA3 in SCA6 patients ($p=0.001$). As with all allelic association studies, independent confirmation of this finding is necessary.

Training program summary including number of persons trained:

After a national search, Vikram Shakkottai, M.D., Ph.D. was selected as the first trainee. He has successfully obtained a K08 grant, which started in January 2011. The second trainee was Guangbin Xia, M.D., Ph.D. who has started a project to establish induced pluripotent stem cell lines from SCA patients. He also completed his Master's degree training in clinical investigation while he was a RDCRN trainee. He plans to submit his K08 grant application this fall. We were an ARRA-grant (RC1) supported site and funding was for two trainees for the entire funding period.

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

The National Ataxia Foundation (NAF) was 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 was providing funding for a part of the SCA-CRC operation, and this was a vital cost share for the SCA-CRC.

63. **Dystonia Coalition Principal Investigator: H. A. Jinnah, MD, PhD**

Primary diseases under study: Primary Dystonias, including,

1. Facial dystonias (blepharospasm or lower facial grimacing)
2. Oromandibular dystonia (jaw or tongue)
3. Laryngeal dystonia (including spasmodic dysphonia)
4. Cervical dystonia (neck)
5. Limb dystonia (arm or leg)
6. Segmental dystonia (any combination of two of the above in contiguous body areas)
7. Multi-focal dystonia (any combination of two of the above in non-contiguous body areas)
8. Generalized dystonia (multiple body regions affected)

Major Goals:

1. Develop a more complete understanding of the natural history of focal dystonias
2. Establish instruments appropriate for monitoring disease severity
3. Assemble proper diagnostic criteria for the various focal dystonias
4. Create a resource for exploring potential biomarkers

Major Clinical Studies:

Project 1a: Natural History of Primary Dystonia

(Perlmutter – Washington University in St. Louis) – 135 subjects enrolled; 19 clinical sites enrolling, 15 more completing regulatory paperwork for participation

The overall goal is to develop a better understanding of the clinical features and progression of primary dystonias so that we may improve the treatment of affected patients by collecting clinical data longitudinally.

Project 1b: Biospecimen Repository for Primary Dystonia

(Perlmutter – Washington University in St. Louis) – 756 subjects enrolled; 19 clinical sites enrolling, 15 more completing paperwork

The overall goal is to create a biospecimen repository linked to valuable clinical data, so that we may begin to explore potential biomarkers and diagnostic measures.

Project 2: Comprehensive Rating Tools for Cervical Dystonia

(Comella - Rush University) – 164 out of 200 subjects enrolled; 10 clinical sites enrolling

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) – 99 out of 200 subjects enrolled; 3 clinical sites enrolling

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:

9 funded to date; results pending unless noted otherwise.

1. Gene sequence variants in primary dystonia (LeDoux – University of Tennessee)
Results: Showed the c.-237_236GA>TT THAP1 sequence variant does not increase risk for primary dystonia which has immediate clinical implications with regards to genetic counseling. Identified 3 additional THAP1 missense mutations. Started genetic characterization of an African-American kindred with adult-onset dystonia & have found several variants in THAP1. Extended work on the first known risk factor for late-onset focal dystonia.
2. Development of a diagnostic & rating scale for blepharospasm (DeFazio – University of Bari, Italy)
3. Cortical plasticity and the cerebellum in focal dystonias (Roze – Pierre & Marie Curie University, Paris, France)
4. DYT6 dystonia – a window to the mechanisms of primary dystonia (Bhatia – University College London, England)
5. Characterization of endophenotypes in focal task-specific dystonia (Klein – University of Lübeck, Germany)
6. Increasing CERTainty in blepharospasm rating scales (Peterson, University of California, San Diego)
7. An investigation of the neuropathology, clinical phenotype and expression characteristics of brain tissue with THAP1 and TOR1A mutations (Houlden – University College London, England)

RDCRN Summaries

8. Item Response Theory: An Individualized Approach to Evaluating a Comprehensive Cervical Dystonia Rating Scale (Eichenseer – Rush University)
9. A new rating scale for focal task-specific dystonia of the musician's hand (Frucht – Mt. Sinai School of Medicine)

Development (Training) Program Summary:

6 junior investigators and 1 senior investigator funded

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

Primary project: Sensorimotor network activity as a functional imaging marker for dystonia

Results: Training complete, project results: Acquired f-MRI and DTI data in six subjects with DYT6 mutations and five subjects with sporadic dystonia. The data suggest that the topography of symptoms in hereditary dystonia may relate to the individual microstructural factors affecting the cortico-striatal projections. Further confirmation of these observations is needed.

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

Primary project: Sensory and emotional processing in psychogenic dystonia: A functional MRI study

Results: Ongoing, project results pending

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

Primary project: Psychiatric assessments of patients with cervical dystonia

Results: Ongoing, project results pending

Morvarid Karimi, MD, Washington University in St Louis, Neurologist, Mentors: Dr. Joel Perlmutter

Primary project: GPI induced plasticity in primary cervical dystonia

Results: Ongoing, project results pending

Teresa Kimberley, PhD, PT, University of Minnesota, Physical therapist, Mentor: Dr. Cathrin Buetefisch

Primary project: Determining the efficacy of synergistic intervention in focal hand dystonia with rTMS and sensorimotor retraining

Results: Ongoing, project results pending

Brian Berman, MD, MS, University of Colorado, Denver, Neurologist, Mentor: Dr. Mark Hallett & Dr. Tor Wager

Primary project: Functional connectivity of the basal ganglia in primary focal dystonia: a pilot study

Results: Ongoing, project results pending

Aparna Wagle-Shukla, MD, University of Florida, Neurologist, Mentor: Dr. Michael Okun

Primary project: Pathophysiological insights into STN DBS for primary cervical dystonia

Results: Ongoing, project results pending

Patient Advocacy Groups:

- Have helped to financially support the Dystonia Coalition pilot projects program, development program, travel stipend program, primary projects, and annual meeting.
- DMRF provides effort to help coordinate the DC annual meeting and pay our clinical sites.
- Created patient registry in collaboration with Dystonia Coalition Executive committee and support this registry.
- Advertise the registry in newsletters/e-blasts. Over 2,300 people with dystonia have registered.
- Organized a dystonia brain bank

Action for Dystonia, Diagnosis, Education, & Research

American Dystonia Society

Bachmann-Strauss Dystonia and Parkinson Foundation

BeatDystonia

Benign Essential Blepharospasm Research Foundation

Dystonia, Inc

Dystonia Ireland

Dystonia Medical Research Foundation

Dystonia Medical Research Foundation – Canada

The Dystonia Society

Dystonie-Qc

European Dystonia Foundation

Foundation for Dystonia Research

National Spasmodic Dysphonia Association

National Spasmodic Torticollis Association

Tyler's Hope

WE MOVE



64. Genetic Disorders of Mucociliary Clearance Consortium Principal Investigator: Michael R Knowles, MD

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

Diseases - Primary Ciliary Dyskinesia (PCD); variant CF; 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, 2012, 65 patients have completed 5 visits, 95 have completed 4 visits, 105 have completed 3 visits, 111 have completed 2 visits and 120 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 now have nearly 300 patients with confirmed PCD with hallmark ultrastructural ciliary defects and/or biallelic PCD-causing genetic mutations. 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. In addition, we have now identified nearly 20 PCD-causing genes (several being written up for publication), and we can now identify ~65% of PCD patients by genetic testing; plus, additional exome sequencing for additional discovery is underway in 70 more PCD patients.

Protocol 5903- Early Onset and Progression of Primary Ciliary Dyskinesia Lung Disease Prior to 10 Years of Age. This protocol involves 56 participants (17 weeks to 5 years of age) who are followed at yearly intervals for 5 years. Of these 56 participants, 33 have a confirmed diagnosis of PCD. This observational study is evaluating imaging, physiologic, microbiologic and clinical symptomatology data in subjects with PCD and probable PCD. The study started in 2008, and enrollment has concluded. As of August, 2012, 2 patients have completed Visit 4, 16 patients have completed Visit 3, 34 have completed Visit 2, 45 have completed Visit 1 and 55 have completed a baseline Visit. Preliminary findings have demonstrated that among children with a confirmed PCD diagnosis, all had chronic, daily cough, nasal congestion and recurrent otitis media, usually starting before 1 year of age, as well as abnormal chest CTs; > 80% had neonatal respiratory distress. These findings demonstrate significant disease burden in children with PCD <5 years old and emphasize the need for further study to determine risk factors for disease progression and optimal disease management.

Protocol 5904- Cross-sectional Characterization of Idiopathic Bronchiectasis

The protocol was approved, and started in September, 2010. This protocol was designed to characterize clinical features, body morphometrics, and respiratory microbiology in 260 patients with non-PCD/non-CF (“idiopathic”) bronchiectasis, stratified by gender and presence/absence of non-tuberculous mycobacterial (NTM) respiratory tract infection. We have enrolled 101 patients to date and are on track with enrollment goals.

Training Section: The goal is to provide trainees with the professional research skills needed to be productive academic leaders in rare lung diseases. The Consortium currently has 12 active trainees, including fellows and post-

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doctoral students. To promote this goal, the trainees successfully presented 2 (Noone and Horani) abstracts at the 2012 ATS conference, and another trainee submitted a first-authored paper for peer reviewed publication on the diagnostic yield of nasal scrape biopsies). Trainees participate in bi-monthly conference calls and are involved in helping to establish a clinical (treatment) trial network.

Role of Advocacy Groups: Genetic disorders of mucociliary clearance can lead to a host of clinical problems, the most serious being severe lung disease. GDMCC research has helped redefine the genetic picture of these disorders, enabling faster, more accurate diagnosis, improving ability to identify individuals at risk for developing difficult to treat lung infections, and promising that in the future these disorders will be in line to potentially benefit from a new generation of therapies that target genetic mutations. Because of natural history studies done by the GDMCC, we are now able to distinguish PCD from other disorders using phenotypic features and a novel, non-invasive screening test (nasal nitric oxide). This monumental advancement in diagnostic capability addresses a serious problem with delayed and/or missed diagnosis that has plagued the PCD community for decades and has resulted in increased, preventable morbidity. With this improved understanding of the disorder and diagnosis, the PCD Foundation is now able to establish a network of PCD clinical care and research centers throughout North America, and develop a registry to aid in future research efforts.

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

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

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

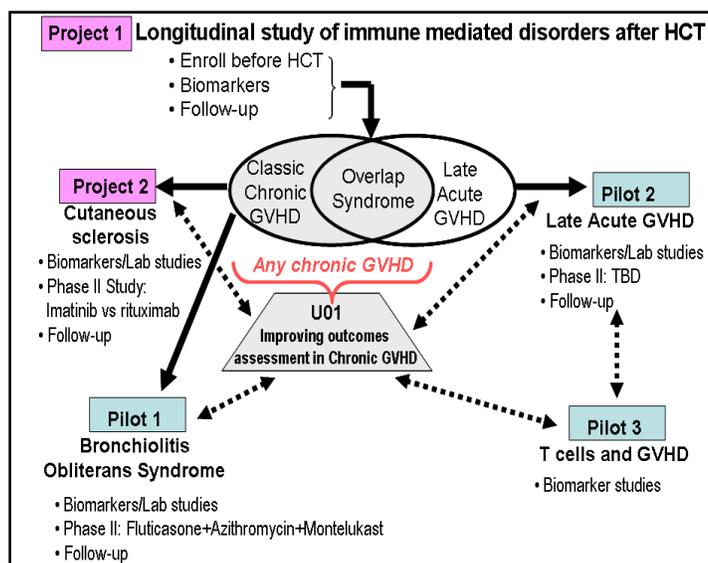
65. Immune Mediated Disorders after Allogeneic Hematopoietic Cell Transplantation
(aka Chronic GVHD Consortium) (GVHD = graft-vs.-host disease)
PI: Stephanie J. Lee, M.D., M.P.H.; Co-PI: Paul J. Martin, M.D.

NIH Project Officer: Bill Merritt (NCI)
Grant number: CA163438

Diseases under study: Late, persistent or recurrent acute GVHD; Chronic GVHD; Cutaneous sclerosis; Bronchiolitis obliterans syndrome

Background: 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. In 2011, approximately 7,000 allogeneic HCTs were performed in the United States, primarily for the treatment of rare diseases such as leukemia, lymphoma, multiple myeloma and other hematologic diseases. Approximately 30-50% of allogeneic HCT recipients develop immune-mediated disorders, resulting in high treatment-related morbidity and mortality, lower functional status and worse quality of life. The two most common immune-mediated complications are heterogenous syndromes collectively called “acute graft-vs.-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 our Consortium is to advance our understanding and treatment of these disorders.

Projects: Project 1 is an observational study with integrated biologic investigations. Patients will be enrolled prior to HCT and followed prospectively for the development of immune mediated disorders. Samples will be collected at enrollment and then serially after the onset of an immune mediated disorder. These research samples will be used by our laboratory collaborators to discover and validate biologic correlates. Project 2 and Pilot 1 are clinical trials targeting well-recognized but poorly understood syndromes with particularly high morbidity/mortality: cutaneous sclerosis, bronchiolitis obliterans syndrome and late acute GVHD. Novel targeted therapies and extensive biologic analysis will help us better understand and treat these disorders.



Study #	Name	Current Enrollment	Target Enrollment
Project 1	Longitudinal observational study	424	1118
Project 2	Cutaneous sclerosis	18	74
Pilot 1	Bronchiolitis obliterans syndrome	10	42

Training: Our first trainee, Dr. Joseph Pidala, finished his 2 years of support and remains actively engaged with the Consortium. Two new trainees, Dr. Yoshi Inamoto and Dr. Aleksandr Lazarian started their funding on September 1, 2012.

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Patient Advocacy: We collaborate with three patient advocacy organizations to reach out to patients, families and physicians: Office of Patient Advocacy, National Marrow Donor Program (Elizabeth Murphy); National Bone Marrow Transplant Link (nbmtLINK, Myra Jacobs); and Blood and Marrow Transplant Information Network (BMTInfoNet, Sue Stewart). In October, our patient advocacy organizations will help spread the word about our ongoing clinical trials.

Clinical Sites (n=15):

- Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Seattle, WA
- Dana-Farber Cancer Institute, Boston, MA
- Stanford University, Palo Alto, CA
- University of Minnesota, Minneapolis, MN
- Vanderbilt University, Nashville, TN
- Medical College of Wisconsin, Milwaukee, WI
- Washington University, St. Louis, MO
- Moffitt Cancer Center, Tampa, FL
- Memorial Sloan Kettering Cancer Center, New York, NY
- Weill Cornell Medical College, New York, NY
- Roswell Park Cancer Institute, Buffalo, NY
- Cleveland Clinic, Cleveland, OH
- Mayo Clinics, Scottsdale, AZ and Rochester, MN
- University of North Carolina, Chapel Hill, NC
- National Cancer Institute, Bethesda, MD



66.

The Inherited Neuropathy Consortium **Principal Investigator: Michael Shy, MD**

Charcot-Marie-Tooth disease (CMT) is the eponym for heritable peripheral neuropathy and is named for three investigators who described it in the late 1800s. CMT affects ~1 in 2500 people (approximately 120,000 Americans) and is among the most common inherited neurological disorders. 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. 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 50 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 > 50 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.

Overview

To develop our Inherited Neuropathy Consortium (INC) RDCRC we are conducting 5 Clinical Research Projects, and have developed and maintained an inherited neuropathy Website. We are also performing three Pilot Projects. **Clinical Research Project 1** is a natural history study for all forms of CMT with a particular emphasis on CMT1B, CMT2A, and CMT4A and CMT4C. 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*, and CMT4C, caused by mutations in the SH3TC2 gene, are the most common forms of CMT4. We have currently enrolled **1347** patients into this protocol. We have developed and published new clinical outcome instruments for adults (CMTBSv2, in the Journal of the Peripheral Nervous System) and children (CMTPedS, in the Annals of Neurology) with CMT. Both these instruments are already in use internationally and will be the standard outcome measures for upcoming clinical trials in CMT. **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. We have currently enrolled over 500 patients into this study. We are analyzing data from the first GWAS study performed for CMT1A and have identified a number of novel genes from our exome study. **Clinical Research Project 3** has established a Website Resource for the inherited neuropathies, based on OMIM, for patients, families and investigators. We have approximately 1000 patients in our patient contact registry and are conducting two research protocols based on interactions with the contact registry. We also have clinical information for physicians on almost all forms of inherited neuropathy on the website. We have 3 Pilot Projects. **Pilot Project 1** has already established a scoring system for quantifying impairment in young children with various forms of CMT (CMTPedS) (Ann Neurol 2012); **Pilot Project 2** is currently testing CMTPedS in a two year natural history study of children with various types of CMT1, CMT2 and CMT4. **Pilot Project 3** is currently developing a Phase I trial using curcumin to treat selected patients with early onset CMT1B.

Composition of INC RDCRC

The following sites comprise the INC RDCRC: (1) The University of Iowa, Department of Neurology, Iowa City, IA; (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; (7) the C. Besta Neurological Institute, Milan, Italy; (8) the Children's Hospital of Westmead, Sydney, Australia; (9) the Johns Hopkins University, Baltimore, Md; (10)The University of Washington, Seattle, WA; (11) Stanford University, Palo Alto, CA, (12), Vanderbilt University, Nashville TN, and (13) The Dubowitz Neuromuscular Centre (London). Sites from Harvard University and the intramural Neurogenetics program at the NIH will be joining the consortium when their IRB applications have been approved. The lead personnel are as follows: Dr. Michael Shy, University of Iowa, PI of the RDCRC. Dr. Mary Reilly from the National Hospital in London is Co-PI and heads our training program. Drs Stephan Zuchner from the University of Miami Institute of Human Genomics, leads the investigations of Clinical Research Project 2. Dr. David Herrmann from the University of Rochester directs one of the Pilot Projects and also is also involved with training fellows of the INC in clinical trial design. He is aided in this by Dr. Michael McDermott, also from the University of Rochester who also functions as the Chief Biostatistician for our RDCRC. Dr. Steven Scherer from the Department of Neurology at the University of Pennsylvania is responsible for developing the Web-site for the INC RDCRC. Dr. Joshua Burns from Sydney Australia, Richard Finkel, from the Nemours Childrens' Hospital Orlando, and Michael Shy from the University of Iowa have directed the development of our Pediatric CMT evaluation form. Dr. Francesco Muntoni from the Dubowitz Neuromuscular Centre in the University College of London Institute of Child Health has assisted them in this project. Other site PIs include Tom Bird from the University of Washington, John Day from Stanford University, Jun Li from Vanderbilt, Charlotte Sumner and Tom Lloyd from Johns Hopkins, and Sabrina Yum from CHOP. Bill David and Florian Eichner will lead the Harvard site. Kenneth Fishbeck will lead the NIH site.

Trainees:

The INC has supported 100% of the salaries for four outstanding young trainees; two in our clinical trial design track and two in our basic translational research track. Dr. Mario Saporta has just finished his two year training program in which he learned iPSC technology and now has a number of neuronal lines developed from skin biopsies of patients with assorted forms of inherited neuropathies. Dr. Saporta, mentored by Dr. Shy, has just joined a stem cell institute in Rio de Janeiro in which he will continue his studies and continue to collaborate with the INC. Dr. Sinead Murphy, mentored by Dr. Reilly, now heads up the peripheral neuropathy program at Dublin University in Ireland. She is developing the Irish national registry for CMT-ID and also continues to collaborate with the INC. Dr. Alex Resor is mentored by Dr. Reilly at the National Hospital in London and beginning the second year of a two year translational fellowship. He is investigating molecular mechanisms of motor neuropathies caused by mutations in distal heat shock proteins. Dr. Vera Fridman, mentored by Dr. Shy is beginning the one year clinical trial design fellowship. She has been promised a junior faculty position at Harvard Medical School at the end of her fellowship where she will establish their neuropathy clinic. We are proud of the accomplishments of all of these trainees and are confident that they will remain leaders in the field of genetic neuropathy research for years to come.

PAGS, External Advisory Board, and the DMCC

We are very pleased to have several outstanding Patient Advocacy Groups (PAG) associated with the INC RDCRC. These groups include the Muscular Dystrophy Association (MDA), the Charcot Marie Tooth Association (CMTA) and CMT United Kingdom (CMTUK). Annie Kennedy from the MDA, Elizabeth Ouellette (CMTA) and Ms. Alex Williamson of CMTUK are our representatives on the PAGS. We have been ably assisted by our External Advisory Board that consists of Merit Cukowicz from Harvard University, Dr. Larry Wrabetz, from the University of Buffalo, Dr. Robert Griggs, from the University of Rochester, Dr. Garth Nicholson, from the University of Sydney, and both Dr. Vincent Timmerman and Peter DeJonghe, from the University of Antwerp. The EAB has formally critiqued the INC RDCRC in February 2012 and we are utilizing this critique to help design our future goals. Finally, we are extremely grateful to the staff of the DMCC who has helped our consortium in every project we have undertaken.

In summary we all remain excited to be members of the RDCRN and look forward to working together to advance the care of patients with inherited peripheral neuropathies. We have published over 20 manuscripts during the past year that we believe advance the field of inherited neuropathies. It is our expectation that within the next year we will be conducting multicenter clinical trials for different genetic types of CMT; trials that would not have been possible without the establishment of the INC RDCRC.

67.

The Lysosomal Disease Network (LDN)

PI: Chester B. Whitley, PhD, MD; Co-PI: Elsa G. Shapiro PhD

Mission:

The Lysosomal diseases is a collection of approximately 40 syndromes with incidence rates ranging from 1 in 20,000 (Gaucher disease) to 1 in 300,000 (Wolman disease) live births; taken together these conditions are responsible for a significant amount of disability and disease burden. The rarity of each Lysosomal disease means that no single medical research center has an opportunity to see sufficient numbers of patients with any one disease to effectively describe the full spectrum of each disease or adequately test any new therapies. The combined and integrated efforts of the LDN will focus on 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 a direct impact on patients suffering from Lysosomal disease and important implications for medical practice.

Lysosomal Conditions:

Aspartylglucosaminuria; Batten disease; Cholesteryl Ester Storage disease; Fabry disease; Fucosidosis; Galactosialidosis types I&II; Krabbe disease; Neuronal Ceroid Lipofuscinosis (infantile, late infantile, juvenile); Mucopolysaccharidosis type II, III, & IV; Mucopolysaccharidosis types I, II, III, IV, VI (Hurler, Hurler-Scheie, and Scheie; Hunter, Sanfilippo, Morquio, and Maroteaux-Lamy syndromes, respectively); Niemann-Pick disease; Pompe disease; Sandhoff disease; Schindler disease; Sialidosis types I & II; Tay-Sachs disease; Wolman disease; Alpha-Mannosidosis types I & II; Beta-Mannosidosis.

Longitudinal Studies:

LDN 6701” Phase I Trial of Pyrimethamine to treat Late Onset Tay-Sachs Disease.

LDN 6702 “Natural History and Structural Functional Relationships in Fabry Renal Disease (Drs. Michael Mauer and Behzad Najafian PIs). Active, enrolling subjects.

LDN 6703 “Longitudinal Studies of Brain Structure and Function in MPS Disorders” (Dr. Elsa G. Shapiro PI). Active, enrolling subjects.

LDN 6704 “The Natural History of Mucopolysaccharidosis type IV” (Dr. Raphael Schiffmann PI). Active, enrolling subjects.

LDN 6705 “Longitudinal Study of bone and Endocrine Disease in Children with MPS I, II, and VI: A Multicenter Study of the Lysosomal Disease Network” (Dr. Lynda Polgreen PI). Active, enrolling subjects.

LDN 6706 “Epidemiology and Natural History of Wolman and Cholesteryl Ester Storage Diseases” (Dr. Gregory Grabowski PI). Active, enrolling subjects.

LDN 6709 “Determination of Cross-Reactive Immunological Material (CRIM) Status and Longitudinal Follow-Up in Individuals with Pompe Disease” (Dr. Pryia Kishnani PI). Active, enrolling subjects.

LDN 6711 “Expanded Screening for the Fabry Trait” (Drs. Katherine Sims, Michael Mauer, Raphael Schiffmann, PIs).

LDN 6712 “A Project to Investigate Clinical and Laboratory Features of Glycoprotein Storage Disorders (Dr. Sara Cathey PI). Active, enrolling subjects.

LDN 6713 “A Natural History of Hexosaminidase Deficiency” (Dr. Chet Whitley PI)

LDN 6715 “Longitudinal Study of Cognition in Subjects with Niemann-Pick Disease, Type C” (Dr. Marc Patterson PI).

LDN 6716 “Genotype-Phenotype Correlations of Late Infantile Neuronal Ceroid Lipofuscinosis” (Drs. Douglas Ballon and Jonathan Dyke PIs). Active, enrolling subjects.

LDN 6717 “Longitudinal Studies in Batten Disease” (Dr. Jonathan Mink PI). Active, enrolling subjects

Pilot Projects:

LDN 6710 “Lysosomal Storage Disease: Health, Development, and Functional Outcomes in Preschool Children” (Dr. Michael Msall PI).

LDN 6714 “A Study of Intrathecal Enzyme Replacement for Cognitive Decline in Mucopolysaccharidosis Type I (Drs. Patricia Dickson and Agnes Chen PIs). Active, enrolling subjects

LDN 6720 “Carotid Structure and Function in MPS Syndrome: A Multicenter Study of the Lysosomal Disease Network” (Drs. Aaron Kelly and Raymond Wang PIs). Active, enrolling subjects

LDN 6721 “Intravenous N-acetylcysteine for the Treatment of Gaucher’s Disease and Parkinson’s Diseases” (Drs. Paul Tuite and James Cloyd PIs). Active, enrolling subjects.

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Completed Pilot Projects:

LDN 6707 “Characterizing the Neurobehavioral Phenotype(s) in MPS III (Dr. Michael Potegal PI). DMCC data entry only; patient enrollment complete.

LDN 6708 “Pulmonary Disease and Exercise Tolerance in Boys with Fabry Disease (Dr. William Wilcox PI). DMCC data enrollment only; patient enrollment complete.

LDN6718 “Gene Therapy for Tay-Sachs Disease (Phase 1-Natural History Data Gather) (Dr. Chet Whitley, PI). DMCC data transfer in place.

Trainee Projects:

“Immune Response to Intrathecal Enzyme Therapy in Mucopolysaccharidosis I Patients” (Dr. Moin Vera, Fellow, PI LDN 6719).

“Discovery of genetic modifier(s) linking Gaucher disease & hematologic malignancy” (Sara Lo, Fellow, PI)

“MPS Longitudinal Study of Brain Structure and Function” (Dr. Julie Eisengardt, Fellow, PI)

1.)”Urinary GAG and Its Role as an Outcome Measure in Mucopolysaccharidoses; 2) Classifying and Managing Infusion Reactions to Enzyme Replacement Therapy; 3) Combination Therapy for MPS VI; 4) Medication Therapy Management for Patients with Inherited Metabolic Disorders; 5) Combination Oral Therapies for the Gangliosidoses.” (Dr. Jeanine Utz, Fellow, PI)

1.)“Urinary GAG and Its Role as an Outcome Measure in Mucopolysaccharidoses; 2) Assessing and Managing Fabry Disease Pain: The role of gabapentin. (Jonica Hazert, Fellow, PI)

“Novel Transporters for MPS I and MPS III A Enzyme Replacement Therapy” (Wenyong Tong, Fellow, PI)

1)”Longitudinal Studies of Brain Structure and function in MPS Disorders; current project is to evaluate phenotype and genotype relationship in Mucopolysaccharidosis Type I” (Alia Ahmed, Fellow, PI).

Participating Centers:

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; 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; New York University; Oregon Health 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; Children’s Hospital of Orange County; University of Washington; University of California, San Diego

Patient Advocacy Groups:

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

68. North American Mitochondrial Disease Consortium (NAMDC)
Principal Investigator: Dr. Michio Hirano
Co-Principal Investigators: Dr. John LP (Seamus) Thompson and Salvatore DiMauro

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 16 centers of excellence in the United States and Canada, NAMDC is directed by Drs. Michio Hirano, Principal Investigator, John LP (Seamus) Thompson and Salvatore DiMauro, Co-Principal Investigators, at Columbia University Medical Center.

More than 20 distinct mitochondrial diseases are included in NAMDC. In close collaboration with the United Mitochondrial Disease Foundation (UMDF), we have made substantial progress in the following areas:

1. Established the NAMDC network. We have enrolled 14 centers of excellence in the US and Canada plus two more that will be activated soon. We have met with the PIs or their representatives at the annual United Mitochondrial Disease Foundation (UMDF) meetings since 2010 with conference calls every 1-2 months.
2. The NAMDC Clinical Registry (RDCRN Protocol 7401). This crucial NAMDC instrument, collects patient information via a user-friendly web-based interface for data entry. The NIH-watermarked version of the IRB protocol allow clinical information input into the registry and submission of biological samples to a biorepository based at the Mayo Clinic, Rochester, MN. To date, more than 270 patients have enrolled in the NAMDC registry.
3. NAMDC Research Diagnoses. 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. Controversial diagnoses will be reviewed by a specific committee. This process will generate NAMDC Research Diagnoses, which will be sent to NAMDC site principal investigator, who, in turn, may communicate the information to patients. These NAMDC Research Diagnoses will insure that a reliable database is available for clinical studies.
4. The NAMDC biorepository has been established under the directorship of Dr. Devin Oglesbee and is ready to accept samples from sites.
5. Education. Dr. Richard Haas is the PI of the NAMDC Clinical Fellowship program which seeks to train future mitochondrial disease clinical investigators. The program requires 6 months training at the University of California San Diego plus two 3 month rotations at other NAMDC sites. The first fellow, Dr. Zuela Zolkipli has already started the program.
6. NAMDC includes a clinical trial of allogeneic hematopoietic stem cell transplantation (AHSCT) for MNGIE and two natural history studies: Alpers disease and MNGIE. In addition, a survey study on attitudes towards oocyte nuclear transfer as a technique to prevent transmission of mitochondrial DNA mutations is in progress.
7. A NAMDC pilot study program has been initiated.

69.

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

Overview.

The Nephrotic Syndrome Study Network (NEPTUNE) is a multicenter, translational effort studying Focal and Segmental Glomerular Sclerosis (FSGS) - Minimal Change Disease (MCD), and Membranous Nephropathy (MN). The goal of the study is to establish a collaborative, integrated, cost-effective, investigational infrastructure to conduct clinical and translational research in these disease areas. The specific aims of the network are: 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.

Studies and Results.

To implement the overall goal and specific aims listed above, NEPTUNE is using a multicenter, prospective cohort study with un-blinded standardized evaluation of clinical and molecular outcomes in two, defined separate and parallel cohorts of study participants. Four hundred and fifty participants will be enrolled into two main FSGS/MCD and MN cohorts and will serve as central resources of NEPTUNE. As of August 30, 2012, enrollment stands at 321 enrolled participants.

High resolution clinical phenotypes of the cohort patients are being utilized, patient self reported outcomes are captured and a digital histopathology archive is generated. Genome wide molecular analyses using a comprehensive biorepository of renal tissue, blood and urine specimen will allow 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, is using the clinical information, pathological analysis, and the molecular data generated by NEPTUNE. NEPTUNE currently has 18 clinical sites activated and two additional sites are in progress for activation.

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 was initiated by the Mayo Clinic (PI's Drs. Hogan and Lieske) and evaluated 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 additional pilot projects that have been approved and funded include: 2. Validation of the NEPTUNE Virtual Microscopy-based Histopathology Protocol Tool (PI, Dr. Laura Barisoni). The aim of this pilot project is to validate a NEPTUNE histopathology scoring system based on a virtual microscopy protocol that includes annotators and readers. 3. Renal Morphometry in a Large, Clinical Study (PI, Dr. Kevin Lemley). This pilot project aims to determine if practical methods of morphometric analysis of biopsies can be used in a large clinical study based on routine clinical biopsies. A second aim of this study will determine if the addition of selected morphometric parameters enhances the predictive power of models based on standard clinical variables and glomerular gene expression. 4. A Pilot Study to Assess the Efficacy of Rituximab Therapy in Patients with Treatment Resistant Idiopathic FSGS: An Assessment of the Relevance of suPAR and Activation of Podocyte $\beta 3$ Integrin. (PI's, Dr. Daniel Cattran, Dr. Michelle Hladunewich, Dr. Jochen Reiser). This study is a pilot trial to assess the safety, feasibility, and efficacy of utilizing Rituximab in 20 adult and pediatric patients with high activity of suPAR and treatment resistant FSGS or with a significant intolerance or contraindications to these therapies. Two additional pilot studies are currently in review by NEPTUNE's Scientific Advisory Board.

NEPTUNE has an active ancillary study program; 20 ancillary studies have been approved as ancillary study and eight have been funded either externally or internally.

Training Program Summary.

The NEPTUNE Training Program is designed to support advanced post-doctoral and junior faculty trainees, or established investigators interested in redirecting their investigative focus, who are preparing to become independent investigators in clinical and translational research in human glomerular disease. Successful applicants to the NEPTUNE Training Program design and carry out an individually tailored program that combines a clearly defined training component with a mentored research experience that employs the resources of NEPTUNE or that addresses a question relevant to glomerular disease. Key components of the NEPTUNE training program include: a) a mentored research project, b) an individualized training program with formal didactic training, c) associated career development activities, d) training in responsible conduct of research, e) subsequent research experiences. NEPTUNE has created a unique training environment and culture in Nephrology. There are five officially funded NEPTUNE trainees and at least six other trainees that are closely affiliated with NEPTUNE. The five funded trainees are:

1. Vimal Derebail, UNC, A novel mechanism for venous thromboembolism in nephrotic syndrome.
2. Tanya Pereira, U. Miami, Role of soluble urokinase (suPAR) in early onset Nephrotic Syndrome.
3. Rivka Ayalon, Boston University, The value of anti-PLA2R for diagnosis and monitoring of membranous nephropathy.
4. Pietro Canetta, Columbia University, Genetic risks for common mechanisms of injury among distinct nephrotic diseases.
5. Larysa Wickman, University of Michigan, Urinary podocyte-specific mRNA ratio as a marker of glomerular disease.

NEPTUNE trainees are actively engaged in focused working groups and committees within NEPTUNE. Trainees present at NEPTUNE steering committee meetings, Conferences on Clinical Research for Rare Diseases and national and international meetings.

Patient Advocacy Groups in NEPTUNE.

NEPTUNE currently includes 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, 1419 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, which will serve as outreach tools. NEPTUNE researchers are dedicated to improving understanding and identifying promising treatments for FSGS, MCD and MN.

Significant international outreach includes establishment of a network of nephrotic syndrome research centers. A sister network in Europe (Eurenomics) is using a shared systems biology core with NEPTUNE; NEPTUNE-China (Nanjing) has been trained and received federal funding and an H3 Africa network funded by NIH is currently starting outreach into sub-Saharan Africa.

70. Porphyrrias Consortium
Principal Investigator: Robert J. Desnick, PhD, MD, Mount Sinai School of Medicine, NY, NY

Disorders under study: acute and cutaneous porphyrias, including:

- Acute Intermittent Porphyria (AIP)
- Hereditary Coproporphyrria (HCP)
- Variegate Porphyria (VP)
- Aminolevulinic Acid Dehydratase Deficiency Porphyria (ADP)
- Porphyria Cutanea Tarda (PCT)
- Congenital Erythropoietic Porphyria (CEP)
- Erythropoietic Protoporphyrria (EPP)
- X-Linked Protoporphyrria (XLP)

Studies:

7201 Longitudinal Study of the Porphyrrias: a longitudinal observational study investigating the clinical presentation, biochemical findings, genetic status, complications, and therapeutic outcomes of diagnostically confirmed individuals with any of the acute or cutaneous porphyrias. All sites are actively enrolling; 310 subjects to date.

7202 Mitoferrin-1 Expression in Patients with Erythropoietic Protoporphyrria: an observational study to determine if abnormal *mitoferrin-1* (*MFRN1*) expression contributes to the phenotype in some patients with the genetic/metabolic disorder erythropoietic protoporphyria (EPP). Four sites actively enrolling; 7 subjects to date.

7203 A double-blind, randomized, placebo-controlled, parallel group trial on the efficacy and safety of Panhematin™ in the treatment of acute attacks of porphyria: a Phase II interventional study to evaluate the clinical efficacy and safety of Panhematin™ compared to glucose treatment started early for acute attacks of porphyria. All sites pending IRB approval.

7204 Clinical Diagnosis of Acute Porphyrrias: an observational study to determine the prevalence of abnormal lab tests and porphyria-like symptoms in adult family members of index cases of acute porphyrias, to devise a clinical index for the likelihood of acute porphyria genetic carrier state, and, to test the validity of an elevated urinary porphyrins and porphyrin precursors as a diagnostic tool for acute porphyria. Two sites actively enrolling.

7205 Quantification of the Effects of Isoniazid Treatment on Erythrocyte and Plasma Protoporphyrin IX Concentration and Plasma Aminolevulinic Acid in Patients with Erythropoietic Protoporphyrria: an interventional pilot study of 9-12 subjects to determine whether INH lowers the plasma concentration of protoporphyrin IX in patients with EPP and XLP. Four sites actively enrolling.

7206 Hydroxychloroquine (HCQ) vs. phlebotomy for porphyria cutanea tarda: a Phase II randomized, open-label, noninferiority study comparing two standard treatments for PCT, low-dose hydroxychloroquine or repeated phlebotomy, to compare the efficacy and safety of these two treatments by comparing the rates of recurrence of symptoms and assessing the effects of susceptibility factors. One site actively enrolling.

7207 Erythropoietic Protoporphyrrias: Natural History, Genotype-Phenotype Correlations, and Psychosocial Impact: an observational longitudinal investigation of the natural history, complications, and therapeutic outcomes in people with erythropoietic protoporphyria, to systematically investigate the psychological effects of the erythropoietic protoporphyrias on children and adults, and to investigate the correlation between the identified genotypes and the resulting clinical presentation, also determining the possible interaction of other genetic markers. One site actively enrolling.

Publications:

- Gene Reviews (an NIH-sponsored, expert-authored, peer-reviewed disease descriptions that apply genetic testing to the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions; published exclusively on-line): submission of updated disorder descriptions, pending final review
- Balwani M, Desnick RJ, **The porphyrias: advances in diagnosis and treatment.** *Blood*, 7/12/2012 [Epub]
- Singal A K, Kormos-Hallberg C, Lee C, Ramanujam VMS, Grady, JJ, Freeman DJ, Anderson, KE, **Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda.** *Clinical Gastroenterology and Hepatology*, in press.
- Manisha Balwani, Dana Doheny, David F. Bishop, Irina Nazarenko, Makiko Yasuda, Harry A. Dailey, Karl Anderson, D. Montgomery Bissell, Joseph Bloomer, Herbert Bonkovsky, John Phillips, Lawrence Liu, Robert J. Desnick, **Frequency of Novel and Known Ferrochelatase and Erythroid-Specific 5'-Aminolevulinatase Synthase Mutations Causing Erythropoietic Protoporphyrria and X-Linked Protoporphyrria in North America**, to be submitted to *Blood*.

Other Consortium Activities:

- **Porphyrias Repository:** a repository has been established at MSSM for blood, urine, DNA, saliva, tissue, and cultured cell specimens from biochemically and molecularly diagnosed porphyria patients and family members.
- **Coordination of the Consortium's Biochemical and Molecular Diagnostic Laboratories:** Laboratories at two sites, specifically UTMB's Porphyria Biochemical Laboratory and MSSM's Genetic Testing Laboratory, have coordinated efforts to provide appropriate testing for the diagnosis of each porphyria, thus, facilitating a confirmed diagnosis of all study participants, providing testing of over 125 patients for the consortium in the past year.
- **Porphyria Outreach and Education Module (POEM)** has been established to provide outreach education for healthcare providers about the diagnosis and treatment of the porphyrias.
- **Scheduled meetings and conference calls**, including
 1. Monthly conference calls with all the PIs, the president of our advocacy group, The American Porphyria Foundation, and invitations extended to the NIH, ORG, NIDDK, and DMCC.
 2. Quarterly face-to-face meetings with PIs, Trainees, representatives from the NIH, NIDDK, ORD, DMCC, & APF
 3. Bi-weekly conference calls with all the site coordinators, hosted by the Project Manager

Training Program

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

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

Accomplishments:

1. A comprehensive Training Plan has been developed
2. 20 Trainees are in place, including 17 affiliated with a PC site and 3 international Trainees, 11 of which are supported by the PC's advocacy group, The American Porphyria Foundation's, "Protect the Future" Program.
3. Each Trainee has an active role in the diagnosis and management of porphyria patients, clinical and basic research, publication and education.

DMCC

Utilization of the RDCRN-PC Contact Registry:

1. Tracking of Registrants: as of 9/12/12, over 930 individuals from the US, Canada, and several foreign countries have enrolled in the PC Contact Registry; of these, over 690 requested and were referred to their nearest PC site.
2. Referral Process: Referred Registrants are contacted by site coordinators, provided information about the Consortium and its studies, scheduled for confirmatory diagnostic testing, if needed, and then for a clinic appointment, if desired.
3. Development of Secondary Questions: set of optional questions, specific for each porphyria to provide additional information for a large number of patients or family members, to be sent to all individuals who previously enrolled in the Contact Registry. Responses will be analyzed, providing important information for publication.
4. RDCRN Committee Memberships: PC PIs maintain membership in several RDCRN Steering Committees, including Strategic Planning Committee and Education Committee, and our Project Manager is on the Registry Committee.

Coordinated efforts with the DMCC: the DMCC has played a pertinent role in the coordination of PC activities by:

1. assisting study PIs in protocol development and implementation,
2. tracking and maintenance of all data, providing access to PIs and RCs,
3. maintaining the Contact Registry, facilitation of the enhancement program & development of the secondary questions,
4. providing updates on protocol approvals, and
5. maintaining accessibility with the Project Manager as well as site RCs.

Coordination with the American Porphyria Foundation (APF): The Consortium remains closely aligned with the APF:

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

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

Major Goals and Diseases:

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

Studies:

- **Protocol 6901. A Prospective Natural History Study of Diagnosis, Treatment and Outcomes of Children with SCID Disorders:** The goal is to identify pre-HCT and early post HCT biologic factors that best predict successful engraftment, immune reconstitution, survival and other outcomes with minimal toxicity. We have enrolled over 60 patients in this study and are preparing an analysis of the 1st 50 patients.
- **Protocol 6902. A Retrospective and Cross-Sectional Analysis of Patients Treated for Severe Combined Immunodeficiency (1968-2010):** The goal is to identify the late effects of treatment on children with SCID as well as to identify pre-HCT and early post HCT biologic factors that best predict successful engraftment, immune reconstitution, and survival and other outcomes with minimal toxicity. We have enrolled over 400 patients to date and are completing a study of over 200 patients diagnosed with classic SCID and treated with hematopoietic cell transplant from 2000 through 2009.
- **Protocol 6903. A Natural History, Retrospective and Cross-Sectional Study to Evaluate the Outcomes of Hematopoietic Cell Transplantation (HCT) in Chronic Granulomatous Disease (CGD) Treated Since 1995:** The goal is to define the critical clinical factors and biologic markers that predict survival and other outcomes of children with CGD following HCT or medical therapies and to characterize the long term outcomes and late effects. Recipients of HCT will be compared to a control group of patients with CGD who were not transplanted. The protocol and consent have been completed and we are currently generating the data report forms. We anticipate activating this protocol for patient enrollment early in 2013.
- **Protocol 6904. A Natural History, Retrospective and Cross-Sectional Study to Evaluate the Outcomes of Hematopoietic Cell Transplantation (HCT) in Wiskott-Aldridge Syndrome (WAS) Treated since 1998.** The goal is to define the critical clinical factors and biologic markers that predict survival and other outcomes of children with WAS following HCT or medical therapies and to characterize the long term outcomes and late effects. The protocol and consent have been completed and we are currently generating the data report forms. We anticipate activating this protocol for patient enrollment early in 2013.

- **Pilot Project: Population-based newborn screening for SCID.** The goal of this pilot study was 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 participated in this pilot project. The study is complete and a manuscript is in preparation. Based on this study, newborn screening has been formally instituted on the Navajo Reservation.
- **Pilot Project: Investigation of B cell reconstitution, function and dysregulation after hematopoietic cell transplantation for severe combined immunodeficiency.** The goals of this study are: To explore whether B cell phenotype and *in vitro* functional responses correlate with *in vivo* functional B cell reconstitution in SCID patients post-HCT, and therefore may predict which patients can become independent of exogenous Ig. To explore the relationship of B cell maturation, BAFF levels and skewed BCR diversity with development of autoimmune manifestations after HCT for SCID. To achieve these aims we will perform longitudinal analysis of B cell phenotype, *in vitro* function, BAFF levels, and BCR diversity in relation to relevant HCT and post-HCT factors, making use of clinical data and blood collected prospectively from SCID patients enrolled on PIDTC Protocol 6901. Patients are currently being entered into this study and data collected.

Training Program: We have funded 8 fellows (two each in years 1-4). The fellows have all participated in our annual PIDTC Scientific Workshop by presenting abstracts of their work.

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, and one in Palo Alto that is coming up. We have also worked with the *WAS Foundation* for their first workshop in Chicago in 2012. The *IDF*, *WAS*, *CGD* and *Jeffrey Modell* Foundations have been participating in our annual PIDTC Scientific Workshops that were held in San Francisco and Boston in 2011 and 2012, respectively. There has been a session on PAGs at each meeting and this will continue for our 3rd Workshop in Houston in May 2013.

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

Summary of progress to date (see specific protocols above for details): The PIDTC has successfully implemented major components of the consortium including regular meetings of the PIDTC Steering Committee and Protocol Working Teams (PWT), development of the Scientific Planning Committee (SPC), establishment of a Fellowship Committee and process for awarding fellowship grants, creation of a PIDTC Website and development of content for the website, and development of a Publication Policy. The PIDTC PWT is a strong core group of investigators dedicated to protocol development, that includes the Steering Committee, statistician, junior investigators, protocol PI's and NIAID and DMCC representation. The PWT holds a weekly 2 hour conference call. The SPC includes PI's from all of the participating centers as well as junior investigators and other key scientists, ORD, NIAID and DMCC representation. The SPC meets monthly. The PIDTC is actively working with the Patient Advocacy Groups both with respect to their parent meetings as well as to gain their help in recruiting patients. We initiated an annual PIDTC Scientific Workshop in 2011. We were awarded an R13 grant for support and have obtained outside funding and will have the 3rd workshop in May 2013. We have included European speakers in each of our 1st two workshops and will continue this activity for the 3rd workshop. In addition, the PIDTC is represented at the European Blood and Marrow Transplant Inborn Errors Working Party annual meeting. This collaborative effort has led to a collaborative study of non-conditioned unrelated donor transplants for SCID and discussions about a collaborative study comparing busulfan to treosulfan conditioning. The PIDTC has also initiated the development of a prospective intervention trial in newborn SCID patients evaluating the optimal dose of busulfan. We will be applying for an R34 planning grant from NIAID for the December deadline. We are presenting this to our European colleagues in October and this may become a joint study.

72.

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

Our work over the past year has been highly responsive to the objectives of the RDCRN to improve availability of rare disease information, treatment, clinical studies and general awareness for both patients and the medical community. We have accomplished this by advancing understanding of disease expression and renal injury in 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. Through a coordinated and integrated approach we have provided research diagnostic testing, pooled data from patient experience, and established a consortium for cooperative exchange of information among investigators, clinicians, patient advocacy groups, and patients and their families. This sharing of knowledge and resources among all is contributing to the care and well being of patients while advancing the science.

The goals of the Rare Kidney Stone Consortium (RKSC) are: (1) establish and expand patient registries and collaborate with patient organizations for 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 disease research.

Diseases Studied: We are pursuing these goals through 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. Establishing registries for longitudinal study of these diseases is foundational for our work.

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

Status: Active, 12/13/2010, 434 /730 enrolled as of 09/17/2012

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

Cystine Capacity Clinical Study (CysCap) (RDCRN 6402)

Status: Active, 05/22/2012

Goal: To evaluate current methodologies of monitoring urine lithogenicity and predicting clinical outcomes in patients with cystinuria. The overall goal will be to correlate urinary parameters with the likelihood of stone formation with the hopes of guiding therapy and thereby reducing morbidity in cystinurics.

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

Status: Active, 05/24/2012

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

Biobank Protocol (RDCRN 6404)

Status: Active, 08/02/2012

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

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

Status: Protocol under review

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

RDCRN Summaries

Correlation of Disease Expression with Specific Mutations in Primary Hyperoxaluria (RDCRN 6406)

Status: Protocol under review

Goal: To demonstrate that certain mutations predispose individuals with hyperoxaluria to move severe disease.

PH III Carrier Registry (RDCRN 6407)

Status: Protocol under review.

Goal: To advance understanding of gene expression and the factors potentially associated with stones and renal injury in PH III carriers.

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

Status: Protocol under review

Goal: Assessment of quality of life in patients with rare causes of kidney stones and linkage to relevant clinical data in disease registry.

Pilot Studies:

1. Establishment of Primary Cultures From PH 1 Hepatocytes, Dr. Hari Koul (funded by grant)
2. New Drugs for Cystinuria, Dr. Amrik Sahota (funded by Mayo Clinic cost share)
3. Post Kidney Transplant Nephrocalcinosis: Incidence, Risks Factors, and Graft Function, Dr. Hatem Amer (funded by Mayo Clinic cost share)
4. Novel Assays For The Determination of Urinary 2,8-Dihydroxyadenine Excretion, Drs. Edvardsson and Palsson (funded by grant, July 2012)

Training: Dr. Lada Beara-Lasic received an initial 2 years of funding for study of Dent disease, under the mentorship of Drs. David Goldfarb and John Lieske. She participated in design of the registry in REDCap, and developed content for the RKSC web pages. She made contacts worldwide with Dent researchers to recruit their participation with our consortium. She designed a clinical trial to screen and identify Dent patients amongst a nephrotic syndrome cohort. Dr. Beara-Lasic has been active as a member of the RDCRN Registry Committee. She successfully completed a Masters of Clinical Science Program at NYU in clinical research. Dr. Beara-Lasic was then successful in setting up social media sites for people with Dent Disease while serving as an informal consultant for affected people on the Internet. She was first author on a review paper for Clinical Reviews in Bone and Mineral Metabolism.

Due to promising progress, Dr. Lada Beara-Lasic was given an additional 2 years of funding to solidify her research in the field of Rare Kidney Stone disease. She will study “The role of phosphorus and FGF 23 in patients with Dent disease”; testing the hypothesis that patients with Dent disease have decreased phosphorus absorption in the proximal tubule and suppressed FGF 23, which in turn causes the elevation of 1,25(OH)₂-vitamin D₃.

Patient Advocacy Groups: Representatives of the Oxalosis and Hyperoxaluria Foundation (OHF), the Cystinuria Support Network (CSN), the International Cystinuria Foundation (ICF) and the Lowe Syndrome Association (LSA) are members of our Steering Committee and participate in monthly Steering Committee calls. Our PAG members provided input to the development of the RDCRN patient contact registry and policies. A new PAG, the APRT Deficiency Patient Support Network has continued its path toward a more structured organization with the assistance of Drs. Vidar Edvardsson and Runolfur Palsson. The RKSC in collaboration with the International Cystinuria Foundation will be hosting the Rare Kidney Stone Consortium Symposium in London in December 15, 2012. Discussions have begun with the OHF for a patient meeting in the U.S. in 2013 as well as hosting of the next International PH Workshop in 2014 or 2015.

73. **Salivary Gland Carcinomas Consortium (SGCC)** **Principal Investigator: 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- Drs. Akli Said and Diana Bell

Postdoctoral Fellows- Drs. Yoshitsugu Mitani and Li Xu

Efforts of the candidates have led to the following recent press publications:

Bell D, Holsinger CF, El-Naggar AK. CRTCl/MAML2 fusion transcript in central mucoepidermoid carcinoma of mandible--diagnostic and histogenetic implications. *Ann Diagn Pathol* 14(6):396-401, 12/2010.

Bell A, Bell D, Weber RS, El-Naggar AK. CpG Island Methylation Profiling in Human Salivary Gland Adenoid Cystic Carcinoma. *Cancer*. e-Pub 1/2011

Bell D, Bell A, Roberts D, Weber RS, El-Naggar AK. Developmental transcription factor EN1-a novel biomarker in human salivary gland adenoid cystic carcinoma*. *Cancer*. E-Pub 7/2011.

Mitani Y, Li J, Weber RS, Lippman SL, Flores ER, Caulin C, El-Naggar AK. Expression and Regulation of the β N and TAp63 Isoforms in Salivary Gland Tumorigenesis Clinical and Experimental Findings. *Am J Pathol* 179(1):391-9, 7/2011.

Mitani Y, Rao PH, Futreal PA, Roberts DB, Stephens PJ, Zhao YJ, Zhang L, Mitani M, Weber RS, Lippman SM, Caulin C, El-Naggar AK. Novel Chromosomal Rearrangements and breakpoints at the t(6;9) in Salivary Adenoid Cystic Carcinoma: association with MYB-NFIB chimeric fusion, MYB expression, and clinical outcome. *Clin Cancer Res*. 2011 November 15; 17(22): 7003-7014.

Li N, Xu L, Zhao H, El-Naggar AK, Sturgis EM. A comparison of the demographics, clinical features, and survival of patients with adenoid cystic carcinoma of major and minor salivary glands versus less common sites within the Surveillance, Epidemiology, and End Results registry. *Cancer* 118(16):3945-53, 8/2012.

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.

74. Sterol and Isoprenoid Diseases Consortium (STAIR)
Principal Investigator: Robert D. Steiner, MD – Oregon Health & Science University

Major Goals	Diseases Studied
<ul style="list-style-type: none"> To study impact on health in a group of rare diseases bound by common biochemistry caused by inborn errors in sterol and isoprenoid metabolism To conduct at least 2 major clinical studies (intervention and natural history) To conduct at least 2 pilot research studies To train investigators in rare disease clinical research To work with patient advocacy groups involved in the diseases To actively participate in RDCRN activities 	<ul style="list-style-type: none"> Smith-Lemli-Opitz Syndrome (SLOS) - Mevalonate Kinase Deficiency (MKD/HIDS) Sjögren-Larsson Syndrome (SLS) – Natural History Sitosterolemia Methylsterol Oxidase Deficiency (SC4MOL) Cerebrotendinous Xanthomatosis (CTX) Niemann-Pick Disease – Type C (NPC)

Study Title	Goals	Status
Smith-Lemli-Opitz Syndrome: A Longitudinal Clinical Study of Patients Receiving Cholesterol Supplementation (STAIR 7001) CTG ID# NCT01356420	<ul style="list-style-type: none"> Observational, longitudinal study to determine clinical and biochemical outcomes in patients with SLOS receiving dietary cholesterol supplementation. Correlate biochemical and clinical phenotypes in study participants with changes in whole body cholesterol pool size with the major determinants of cholesterol synthesis, absorption and intake. Identify or refine clinical or biochemical markers for use as outcome measure for future clinical trials. Identify a biomarker that can be used for diagnostic testing or screening. Develop a national registry of well-characterized SLOS patients. Maintain a biorepository of biomaterials. 	Active Recruitment Current accrual of 23 participants in 3 of 5 clinical sites.
Assessment of Sterol Metabolism in Sitosterolemia: A Pilot Study of Patients Treated with Ezetimibe (STAIR 7002) CTG ID# NCT01584206	<ul style="list-style-type: none"> Pilot Study to determine if treatment with ezetimibe decreases plant sterol pool size in patients with sitosterolemia 	Completed enrollment of 8 participants – completing last study procedures
B7 Coreceptor Molecules as Clinically-Relevant Surrogate Biomarkers in the Hyper IgD syndrome (HIDS) form of Mevalonate Kinase Deficiency (MKD) (STAIR 7003) CTG ID# NCT01568736	<ul style="list-style-type: none"> Pilot study to determine if costimulatory B7 glycoprotein abnormalities identified in the murine MKD model will be recapitulated in sera obtained from humans with HIDS either before, during or after febrile episodes. Determine if B7 glycoprotein molecule levels will correlate to a clinical symptomatic severity score and several biomarkers. Gain new insight into underlying pathophysiology 	One site activated 8/23/12, open for enrollment; second international site local IRB submission phase almost completed
Sjögren-Larsson Syndrome: A Longitudinal Study of Natural History, Clinical Variation and Evaluation of Biochemical Markers (STAIR 7004)	<ul style="list-style-type: none"> Observational, longitudinal study to identify novel biomarkers that correlate with disease progression. 	Protocol approved by NICHD 8/3/12. Submitted to local IRB; soon to be open to recruitment
Sterol-C4 Methyl Oxidase Deficiency (SC4MOL)	<ul style="list-style-type: none"> Natural history study to characterize the biological and immunological aspects of methylsterol oxidase 	Finalizing study design; then submit to NICHD & DMCC
Cerebrotendinous Xanthomatosis (CTX)	<ul style="list-style-type: none"> Natural history study 	Study design being finalized

RDCRN Summaries

Training

STAIR has supported 3 trainees. 1-2 Trainee positions available .

Andrea DeBarber, Ph.D	Oregon Health & Science University Primary Mentor: Robert Steiner, M.D. Training Start/End date: 4/1/10 - 8/31/11	<ul style="list-style-type: none"> ▪ Improving diagnostic and therapeutic monitoring for techniques in CTX ▪ Developing a biomarker assay for SLS ▪ Being trained in clinical and laboratory research
Miao He, Ph.D	Emory University Primary Mentor: Gerard Vockley, M.D. Training Start/End date: 8/1/10 - 07/31/12	<ul style="list-style-type: none"> ▪ Developing new methods to characterize methylsterol abnormalities in patients with SC4MOL ▪ Characterize the immune response and inflammatory pathways in SC4MOL
Shibani Kanungo, M.D.	UPMC Primary Mentor: Gerard Vockley, M.D. Training Start/End date: 9/1/11- 06/30/12	<ul style="list-style-type: none"> ▪ Feasibility of newborn screening for SC4MOL deficiency ▪ Develop/coordinate a clinical treatment protocol for patients with SC4MOL deficiency

Smith-Lemli-Opitz/RSH Foundation (SLO/RSH) Founded: 1988 www.smithlempiopitz.org	The Smith-Lemli-Opitz RSH Foundation is a non-profit organization dedicated to supporting families, individuals and professionals dealing with Smith-Lemli-Opitz syndrome. By providing a network of ongoing communication, funding related research, and raising awareness, we are committed to enhancing the quality of life of affected individuals while improving on current treatment methods and striving towards a cure.	<ul style="list-style-type: none"> ○ Working with this group to sponsor a Parent Scientific conference in Pittsburg, PA June 26-30 2013 – have good scores on R13 grant for funding ○ Wrote newsletter article with latest expert opinion in cholesterol supplementation ○ Working with group to reorganize website for a more prominent link to STAIR clinical trials ○ SLO/RSH leadership participates in monthly STAIR PI conference calls.
United Leukodystrophy Foundation (ULF) Founded: 1982 www.ulf.org	This group is dedicated to providing patients and their families with information about their disease and assistance in identifying sources of medical care, social services, and genetic counseling; establishing a communication network among families; increasing public awareness and acting as an information source for health care providers; and promoting and supporting research into causes, treatments, and prevention of the leukodystrophies.	<ul style="list-style-type: none"> ○ Fully supported the STAIR-organized 2nd Cerebrotendinous Xanthomatosis (CTX) Scientific Conference (July 2012, DeKalb, IL) ○ Leadership participates in monthly PI conference calls
Foundation for Ichthyosis & Related Skin types (FIRST) Founded: 1981 www.firstskinfoundation.org/	FIRST's mission is to educate, inspire, and connect those touched by ichthyosis and related disorders through emotional support, information, advocacy, and research funding for better treatments and eventual cures	<ul style="list-style-type: none"> ○ Leadership participates in monthly PI conference calls
National Niemann-Pick Disease Foundation Founded: 1992 www.nnpdf.org/	NNPDF supports and promotes research to find treatments and a cure for all types of Niemann-Pick Disease, and we provide support services for individuals and families affected by NPD.	<ul style="list-style-type: none"> ▪ Active participation of NNPDF representative during STAIR Year 1 of funding. ▪ STAIR is now actively seeking a NNPDF representative to work on future studies
Contact/Support from: <ul style="list-style-type: none"> ▪ NOMID Alliance www.nomidalliance.org ▪ Sitosterolemia (Canadian Hutterite) 	<ul style="list-style-type: none"> ▪ NOMID Alliance is dedicated to support patients/families with autoinflammatory diseases (including HIDS) ▪ Not a formal PAG 	<ul style="list-style-type: none"> ▪ Integration with STAIR pending ▪ Support STAIR HIDS project ▪ Actively participate in STAIR 7002

75. **Urea Cycle Disorders Consortium**
PI: Mark Batshaw, MD; Co-PIs: Mendel Tuchman, MD and Marshall Summar, MD

MAJOR GOALS	DISEASES STUDIED
<ol style="list-style-type: none"> 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, 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 in UCD 7. Further our close liaison with public authorities to advocate for expansion of newborn screening programs 	<ol style="list-style-type: none"> 1. N-acetylglutamate synthetase (NAGS) deficiency 2. Carbamyl phosphate synthetase I (CPSI) deficiency 3. Ornithine transcarbamylase (OTC) deficiency 4. Argininosuccinate synthetase (AS) deficiency (citrullinemia) 5. Argininosuccinate lyase (AL) deficiency (argininosuccinic aciduria) 6. Arginase (ARG) deficiency (argininemia) 7. Citrulline (CITR) deficiency (citrullinemia type II) Hyperornithinemia, hyperammonemia, homocitrullinuria (HHH) syndrome

STUDIES	
Study:	Longitudinal Study of Urea Cycle Disorders (RDCRN 5101)
Objective(s):	Conduct a longitudinal investigation of the natural history, morbidity, and mortality of people with UCD.
Status:	Active, recruiting (578 subjects enrolled as of August 30, 2012)
Results:	Three descriptive papers and two preliminary analysis papers have been published. Data has contributed to at least four other papers. 5 manuscripts resulting from Longitudinal Study data are currently in development.
Study:	A Randomized, Double-Blind, Crossover Study of Sodium Phenylbutyrate 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 deficiency (RDCRN 5102)
Objective(s):	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 & the use of stable isotope tracers to assess ureagenesis & nitric oxide production
Status:	Closed to accrual; analysis phase (12 subjects enrolled)
Results:	Patients had significantly increased levels of argininosuccinate, and aspartate aminotransferase (AST) levels while on the high-dose arginine arm. Subjects with elevated AST or alanine aminotransferase (ALT) treatment with high-dose of arginine resulted in increases in both aminotransferase levels. Our results suggest administering higher doses of arginine in subjects with argininosuccinic aciduria results in increases hepatic aminotransferase levels especially in a subset of patients with elevated baseline aminotransferases. Low-dose arginine combined with nitrogen scavenging therapy should be considered as a therapeutic option for treatment of ASA in patients with elevations of hepatic aminotransferases. This will be published in the J.of Molecular and Genetic Metabolism.
Study:	Assessing Neural Mechanisms of Injury in Inborn Errors of Urea Metabolism Using Structural MRI, Functional MRI, and Magnetic Resonance Spectroscopy (RDCRN 5104)
Objective(s):	To investigate the neural mechanisms underlying cognitive and motor dysfunction in OTCD by utilizing a multidisciplinary approach with cognitive testing and neuroimaging platforms.
Status:	Closed to accrual/ data Analysis (46 subjects enrolled)
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 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

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Study:	N-carbamylglutamate (NCG, Carbaglu) in the Treatment of Hyperammonemia (RDCRN 5105)
Objective(s):	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.
Status:	Active, recruiting
Results:	Oral NCG improves urea cycle function and decreases plasma ammonia levels in patients with NAGS deficiency, partial CPSI deficiency, PA and MMA. Preliminary results have been published (see publications).
Study:	Investigation of Brain Nitrogen Metabolism in Partial Ornithine Transcarbamylase Deficiency (OTCD) Using 1H MRS, DTI, and fMRI (RDCRN 5107)
Objective(s):	1) To estimate white matter damage 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.
Status:	Active, recruiting
Results:	Preliminary results have been published.
Study:	Oxidative Stress, Inflammation & Acute Decompensation in UCD Pilot Project (RDCRN 5109)
Objective(s):	The primary purpose of this study is to characterize the oxidative stress and inflammatory cytokine status in UCD during baseline and decompensated states.
Status:	Active, recruiting
Results:	Too soon for results
Study:	Carbaglu Surveillance Protocol (RDCRN 5111)
Objective(s):	The UCDC is conducting a post-marketing surveillance study of N-carbamyl glutamate for Orphan Europe.
Status:	Active, recruiting

TRAINING

Summary:	We provided funding from the RDCRN NIH grant & 2 related foundation grants to provide at least 50% effort support for 1-2 year training periods. To date this funding has provided training for 1 graduate student, 9 clinical genetics metabolism fellows & 2 junior faculty members in rare disease research, focusing on UCD.
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PATIENT ADVOCACY GROUP INVOLVEMENT

Summary:	The National Urea Cycle Disorders Foundation has been an integral partner & 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 & barriers to advancing research in UCD. NUCDF has made contributions to the patient registry & 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.
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PUBLICATIONS

Longitudinal Study – RDCRN 5101
9 publications.
ASA Study – 5102
One manuscript in press.
Imaging Studies – 5104 and 5107
9 publications.
N-Carbamylglutamate Study – 5105
5 publications and one submitted manuscript.

76.

Vasculitis Clinical Research Consortium
Principal Investigator: Peter A. Merkel, MD, MPH
www.RareDiseasesNetwork.org/VCRC

The Vasculitis Clinical Research Consortium (VCRC) is an international, multi-center, clinical research infrastructure for the study of vasculitis. The VCRC is the major multi-center clinical research program in North America and one of the two major 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 12 sites in the United States and Canada and 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: Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss), Giant Cell Arteritis, Granulomatosis with Polyangiitis (Wegener's), Microscopic Polyangiitis, Polyarteritis Nodosa, and Takayasu's Arteritis

Longitudinal/Cohort Studies:

VCRC 5502: Giant Cell Arteritis, *actively enrolling*, current enrollment 227/300

VCRC 5503: Takayasu's Arteritis, *actively enrolling*, current enrollment 150/250

VCRC 5504: Polyarteritis Nodosa, *actively enrolling*, current enrollment 77/150

VCRC 5505: Granulomatosis with Polyangiitis & Microscopic Polyangiitis, *actively enrolling*, enrollment 546/600

VCRC 5506: Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss), *actively enrolling*, current enrollment 154/250

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

VCRC 5510: Genetic Repository One Time DNA protocol; all six diseases; current enrollment 289/1300 (in addition to >1100 DNA samples from the Longitudinal Studies)

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

RDCRN Summaries

Clinical Trials:

- VCRC 5522:** Abatacept for mild relapsing Wegener's granulomatosis, recruitment complete, 20/20
- VCRC 5523:** Abatacept for Giant cell arteritis and Takayasu's arteritis *actively enrolling*, current enrollment 42/66
- VCRC 5524:** Plasma exchange and glucocorticoid dosing for ANCA-Associated Vasculitis, *actively enrolling*, current enrollment 5/500
- VCRC 5525:** Randomized controlled trial comparing rituximab and azathioprine for ANCA-associated vasculitis, *open for enrollment November 2012*
- VCRC 5526:** Randomized controlled trial of varying prednisone tapering schedules in granulomatosis with polyangiitis (Wegener's), protocol under development

Observational Studies:

- VCRC 5515:** Imaging study of MRI and PET/CT scans in TAK, *actively enrolling*, current enrollment 12/36
- VCRC 5531:** Vasculitis Reproductive Health Survey, *recruitment complete*, 467 subjects
- VCRC 5532:** Vasculitis pregnancy registry; protocol under development
- VCRC 5533:** Vasculitis illness perception study; *recruitment complete*, 707 subjects
- VCRC 5534:** Vasculitis educational needs study; *recruitment complete*, 386 subjects

Outcome Measure Studies:

- VCRC 5540:** Development of a Disease-Specific Outcome Measure for Vasculitis
- VCRC 5541:** Validation of PROMIS 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 VCRC Fellows: Current: 3, Previous: 6

Patient Advocacy Groups:

The Churg-Strauss Syndrome Association, the PAN Support Network, and the Vasculitis Foundation. Our Patient Advocacy Groups are actively involved in the VCRC, promoting study participation and recruitment, advising on study design and implementation, 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 (RC1 AR058303; P60 AR047785; U01 AR51874; HHSN2682007000036C; R01 AR064153), the FDA (R01 FD003516), the NHLBI (R01 HL115041), the PCORI, the Vasculitis Foundation, industry partners, and other sources.

