

# UCDC Update

## Newsletter of the Urea Cycle Disorders Consortium

### Greetings from the UCDC Leadership

Since our last issue of the *UCDC Update* newsletter in April 2013, the UCDC has been busy on multiple fronts, thus, we have a lot to share with you in this issue.

- With our research and patient advocacy partners, we organized the 4th International Symposium on Urea Cycle Disorders. The proceedings have since been published and are summarized in this newsletter.
- Our long-time esteemed leader and UCD research pioneer, Dr. Mark Batshaw, stepped down from his role as the principal investigator of the UCDC in the summer of 2015. We are grateful to Mark for his many years of leadership and for assembling our group of investigators to form the UCDC. The UCDC Leadership since 2015 has included Mendel Tuchman, Shawn McCandless, Sandesh Nagamani and Cynthia Le Mons. In August 2017 Mendel Tuchman will step down as Director of the UCDC and Andrea Gropman will assume this role.
- The UCDC has continued to grow with the support of the NUCDF by adding two new sites in Northern California: Stanford University and University of California San Francisco.
- In 2014, the National Institutes of Health (NIH) funding for the UCDC was extended for another 5 years (through 2019). Current studies are described in this newsletter.
- We are grateful for the commitments from the Kettering Fund and the O'Malley Foundation for their continued financial support of the UCDC.

We hope that you will find this newsletter informative and encouraging. Thank you for your contribution to UCD research and for helping us meet the UCDC's goal of improving the outcome for all individuals with UCDs and their families.

Mendel Tuchman, MD, Andrea Gropman, MD,  
Shawn McCandless, MD, Sandesh Nagamani, MD, and Cynthia Le Mons  
Urea Cycle Disorders Consortium Leadership

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**Mendel Tuchman, MD  
and  
Andrea Gropman, MD**

The UCDC is funded by the National Institutes of Health (NIH), the O'Malley Foundation, the Dietmar-Hopp Foundation, the Rotenberg Family Fund, the Kettering Family Fund, and the National Urea Cycle Disorders Foundation



## Proceedings from the 4<sup>th</sup> International Symposium of Urea Cycle Disorders

In September 2013, the UCDC co-hosted the 4th International Symposium on Urea Cycle Disorders in Barcelona, Spain. The 2-day symposium focusing on UCD was attended by 322 researchers and physicians, which included a scientific poster session and 14 presentations divided into 4 main categories: pathophysiology, early detection, new treatments, and longitudinal (long-term natural history) studies around the world. Proceedings were published in *The Journal of Molecular Genetics and Metabolism* and are summarized here on pages 2 - 4.

### Pre-Clinical

#### A Zebrafish Model of Hyperammonemia

Hyperammonemia is the principal consequence of UCD. The exposure of the brain to high ammonia levels can lead to a wide range of neurocognitive deficits, intellectual disabilities, coma and even death.

Drs. Feldman, Tuchman and Caldovic developed a zebrafish model to screen and discover drugs for treatment of hyperammonemia. Zebrafish are small transparent fish that breed rapidly. It is easy to observe the developing organs in the fish and their biological response to drugs and toxins is similar to those of mammals. The zebrafish are sensitive to ammonia and can absorb ammonia that is added to the water they live in. If successful, drugs discovered using this screening model could lead to more treatment options for patients with UCD.

Feldman B, Tuchman M, Caldovic L (2014) *Molecular Genetics & Metabolism*, vol. 113, p. 142-147.

(DWI), fluid-attenuated inversion recovery (FLAIR) and magnetic resonance spectroscopy (MRS).

The imaging studies provided evidence that there are alterations in brain biochemistry, changes to the white matter in the brain, and changes in cognitive function; even in patients with late onset (partial) OTC deficiency. Possible causes for the differences can be seen with the imaging and include alterations in glutamine and brain chemicals myoinositol and choline. A reduction in white matter in the brain may affect executive function, attention, and cognitive control. These changes can be observed even in participants who have a normal IQ. This brings attention to the need for further imaging studies to investigate these brain effects which can be subtle, especially in people with partial OTC deficiency, and to investigate these effects in people with other urea cycle enzyme deficiencies.

Pacheco-Colon, Fricke S, VanMeter J, Gropman AL (2014) *Molecular Genetics & Metabolism*, vol. 113, p. 118-126.

#### Investigating Neurological Deficits in Carriers and Affected Patients with Ornithine Transcarbamylase Deficiency

Even “asymptomatic carrier” females with OTC deficiency (OTCD), those who do not have symptoms typically associated with OTCD, show differences in cognitive function when they were challenged with fine motor tasks, measures of executive function, and measures of cognitive flexibility.

### Neuroimaging

#### Advances in Urea Cycle Neuroimaging

Using neuroimaging, Dr. Gropman has identified specific biomarkers of brain injury (chemicals in the brain that can be used to measure brain injury) in people with OTC deficiency. People with and without OTC deficiency had multiple types of testing done, such as magnetic resonance imaging (MRI), diffusion weighted imaging

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Measures of cognitive function (executive function, verbal memory, simple attention, non-verbal memory, motor function, and language) were tested in individuals with OTCD who do exhibit symptoms (symptomatic) and then the scores were compared to those from asymptomatic female carriers of OTCD and a healthy control group. A total of 81 people participated in the neuropsychological testing. No differences were found in measures of simple attention, language skills or verbal memory between asymptomatic OTC patients and controls. However, when they were cognitively challenged with tests measuring executive function, fine motor ability, cognitive flexibility and inhibition ability, both the symptomatic patients and the asymptomatic OTC carriers scored lower than the healthy control group. The results of this study suggest that asymptomatic carriers of OTC may harbor deficits in executive function and motor tasks that may not become apparent until they are challenged to perform difficult tasks.

Sprouse C, King J, Helman G, Pacheco-Colon I, Shattuck K, Breeden A, Seltzer R, VanMeter, JW, Gropman AL (2014) *Molecular Genetics & Metabolism*, vol. 113, p. 136-141.

## Longitudinal Study

### A Longitudinal Study of Urea Cycle Disorders

Information learned in an analysis of data from the first 614 study patients in the UCDC Longitudinal study was published in August 2014. This is a summary of some of the findings:

- The estimated average birth prevalence of UCDs is 1 in every 35,000 births. This would predict that approximately 114 babies with a UCD will be born in the U.S. each year.
- Elevated glutamine levels were associated with worse performance on neuropsychological tests.
- Protein intake for all age groups is higher than recommended. Pediatric growth based on weight was within the expected range but height velocity was lower than the general population.

- As of January 2013, 66 patients participating in the study had received a liver transplant. Of those, 42 were under 2 years of age. Since 2010 there has been a trend toward performing transplants in patients at a younger age.
- Data on liver failure suggests that risk of acute and chronic liver failure may be under recognized in urea cycle disorders.
- We are conducting further studies to look at liver disease, such as Dr. Burrage's pilot study described on page 10.

Batshaw ML, Tuchman M, Summar M, Seminara J, members of the Urea Cycle Disorders Consortium (2014) *Molecular Genetics & Metabolism*, vol. 113, p. 127-130.

### Sodium Phenylbutyrate Decreases Plasma Branched-Chain Amino Acids in Patients with Urea Cycle Disorders

Analysis of Longitudinal Study data showed that use of sodium phenylbutyrate is associated with a decrease in levels of plasma branched-chain amino acids and suggest that this should be monitored in patients with UCDs.

Sodium phenylbutyrate (NaPBA), trade name Buphenyl®, is a medication that helps eliminate waste nitrogen in the body. This study looked at laboratory results including amino acid and ammonia levels, and dietary intake from 553 people with UCDs. A total of 38% of the study participants were taking NaPBA. It was found that plasma levels of leucine, valine and isoleucine (i.e., the branched-chain amino acids) were significantly lower in subjects taking NaPBA but other amino acid levels were not affected. The risk for branched-chain amino acid deficiency was significantly higher with the use of NaPBA. Reduced levels of the branched-chain amino acids may increase the risk of catabolism. Reduced levels of branched-chain amino acids were not associated with an increase in number of hyperammonemia episodes in the study patients.

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However, branched chain amino acids should be monitored in urea cycle disorder patients closely, to prevent levels from getting too low. a.

Burrage LC, Mahim J, Gandolfo L, Lee BH, members of the Urea Cycle Disorders Consortium, Nagamani SC (2014) *Molecular Genetics & Metabolism*, vol. 113, p. 131-135.

### Studies from Our International Partners

#### Pathophysiology of Brain Dysfunction in Hyperammonemic Syndromes: The Many Faces of Glutamine

Dr. Butterworth looked at possible causes of brain dysfunction in people with hyperammonemic syndromes, which include patients with urea cycle disorders and patients with acute liver failure.

With hyperammonemia, there is an increase in blood and tissue concentrations of the amino acid, glutamine. Increased levels of glutamine in the brain have been correlated with encephalopathy (abnormal brain function) and brain edema (swelling) but there is no direct evidence that glutamine is the cause of those problems. Although potential mechanisms for brain dysfunction are discussed in this article, further

research is needed to determine direct causes and possible methods of prevention or treatment.

Butterworth RF (2014) *Molecular Genetics & Metabolism*, vol. 113, p. 113-117.

#### Dietary Protein in Urea Cycle Defects: How Much? Which? How?

It is a challenge to provide just the right amount of protein to children with urea cycle disorders, in order to support normal growth and function without triggering metabolic decompensation. In this article, Dr. Boneh presented findings from Australia (note: treatment & management of UCDs may differ from the experience of U.S. patients). Their highlights include:

- 1) Most patients with urea cycle disorders tolerate a natural protein intake that is compatible with metabolic stability and good growth
- 2) Protein aversion may lead to risk of chronic protein deficiency
- 3) Further protein restriction may lead to metabolic decompensation and hyperammonemia
- 4) Essential amino acid (EAA) supplementation should be considered at times of metabolic decompensation
- 5) Enteral feeding (by mouth or by tube into the GI tract) is advantageous over parenteral nutrition (nutrition is supplied directly into the veins)

Boneh A (2014) *Molecular Genetics & Metabolism*, vol. 113, p. 109-112.

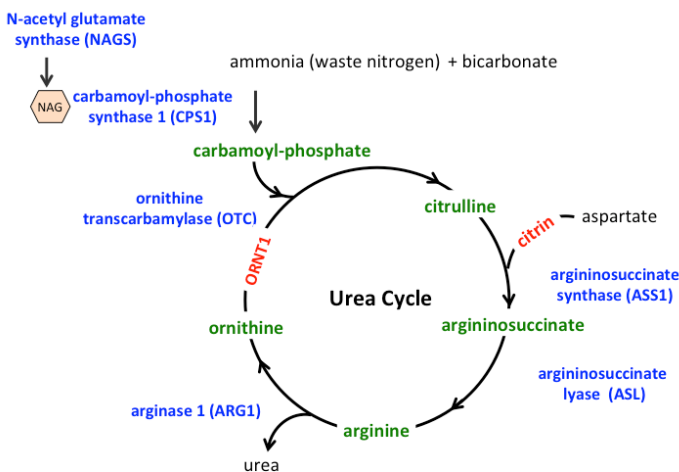


Figure 1: The urea cycle



Dr. Peter McGuire  
Physician Scientist, NIH

## What Factors Lead to Elevations in Ammonia in Patients with Urea Cycle Disorders?

Dr. Peter McGuire, a UCDC collaborator and physician scientist at the National Institutes of Health with a translational research program concentrating on immunometabolism, examined the Longitudinal Study of Urea Cycle Disorders dataset in order to identify factors that triggered Hyperammonemia.

McGuire and colleagues report that infection is the most common precipitating event for acute hyperammonemia in patients with UCD and is associated increased hospitalization rate, length of stay, and use of intravenous ammonia scavengers. Their findings suggest that the catabolic and immune effects of infection may be targets for clinical intervention.

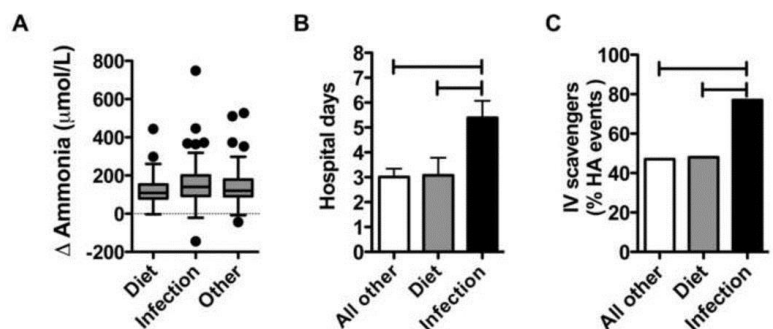
Episodes of elevated blood ammonia levels from the first 562 patients enrolled in the UCDC longitudinal study were reviewed through April 2012. Ammonia levels were considered elevated if they were greater than 100  $\mu\text{mol/L}$ . Highlights of their analyses include:

- 128 UCD patients had a total of 413 hyperammonemia episodes between 2006-2012
- Study participants had, on average, less than 1 episode per year during this time
- For patients who had hyperammonemic events, 65% experienced 1-3 events, while 23% has 4-6 events during this time
- Common factors precipitating hyperammonemic events include infection (33%), dietary non-compliance (11%), change in medication (9%), stress (5%), menstruation (2%), pregnancy (0.5%), unknown factors (3%) and “other” (31%) factors that did not fit into current reporting categories
- Hospital stays were ~2 days longer if infection was the cause for hyperammonemia
- Patients hospitalized for infection also had increased need for IV medication (77%), compared to 48% of those hospitalized for diet non-compliance and 47% for other causes

Collectively, these data suggest that activation of the immune system during an infection may cause UCD patients with hyperammonemia to have a more extended period of illness.

The data provided by the UCDC Longitudinal Study allows for further investigation into factors that trigger hyperammonemia by collecting data on patients with these rare disorders from multiple medical centers. Treatment of hyperammonemia is also being recorded and analyzed. The authors of this study hope to further explore the role of immune activation and to identify new targets for intervention in the management of acute hyperammonemia.

McGuire PJ, Lee HS, members of the Urea Cycle Disorders Consortium, Summar ML (2013) Pediatrics, vol. 163, p. 1705-1710.



A) Change in baseline plasma ammonia during acute hyperammonemia in patients with UCD is greater when infection is present before hyperammonemia. B) Length of stay for hospitalization due to various acute hyperammonemia precipitants in patients with UCD. C) Use of intravenous (IV) ammonia scavengers for the treatment of acute hyperammonemia due to various precipitants in patients with UCD. *Other* – indicates cause not due to diet or infection.

## Improving Long-Term Outcomes in Urea Cycle Disorders

This recent publication from the UCDC was led by Drs. Waisbren, Gropman and Batshaw, and focused primarily on analyses of neuroimaging & neuropsychological testing. The neuroimaging findings are similar to those summarized on p. 2-4 from the 4<sup>th</sup> International Symposium on UDC's.

Highlights from the Neuropsychological analyses:

- When neuropsychological deficits occurred in UCD patients, they tended to be more prominent in motor/performance & memory areas
- When behavioral difficulties occurred in UCD patients, they were primarily noted in the areas of attention, hyperactivity, and aggression
  - ❖ Boys with OTC were the exception, they tended to be withdrawn
- Individuals with OTCD, CPS1D, NAGSD & HHH tended to have increased intelligence scores over time, while patients with ARGD, ASLD & ASSD tended to have typical early development followed by declines in functioning
  - ❖ This finding may reflect earlier detection through newborn screening & better treatments now than in earlier years → continued evaluation of the data collected in the Longitudinal Study will help to determine the effect of newborn screening and/or novel therapies available to younger patients on long-term outcomes for patients with UCDs
- Age at initial onset of symptoms & number of hyperammonemic events fail to explain the variability noted between UCD groups.



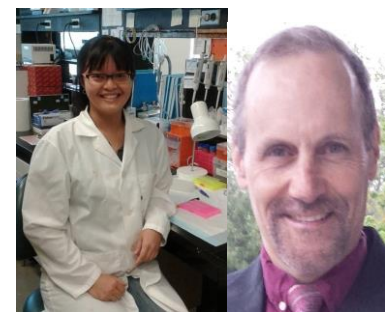
*Dr. Susan Waisbren & patient  
Boston Children's Hospital,  
Harvard Medical School*

Large collaborative, longitudinal studies like this one present challenges due to diversity of study populations, treatments prescribed & clinics providing services. This variability also provides an opportunity, however, for identifying sensitive outcome measures & impact of diverse treatments. Data obtained from the UCDC will be valuable for establishing evidence-based guidelines for the treatment of UCD in the future.

Waisbren SE, Gropman AL, Batshaw ML (2016) Inherited Metabolic Diseases, vol. 39, p. 573-584

## Animal Model of Arginase-1 Deficiency Highlights Potential for Future Success and Challenges in Restoring Urea Cycle Function for Patients with UCDs

UCDC trainee, Yuan Yan (Angie) Sin and her mentor, Colin Funk, have created a mouse model of ARGD that has essentially no Arg1 enzyme and a severe clinical presentation. In their recent publication, they have used new genetic technology (called CRISPR/Cas9) to fix the Arg1 mutations in cells derived from their mouse model. Testing of these cells in test tubes has provided mixed results in terms of their ability to make Arg1 enzyme at a level that would lead to full function of the urea cycle. Further studies of these cells, both in cell culture and after implantation into the ARGD mouse model, will be the next step in these efforts to find new ways to treat patients with ARGD.



*Drs. Angie Sin & Colin Funk  
Queen's University,  
Ontario, CA*

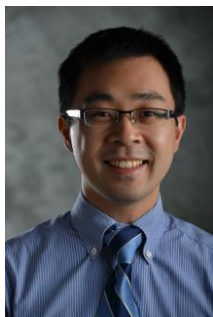
Sin YY, Price PR, Ballantyne LL, Funk CD (2017) Scientific Reports, vol. 7, p. 2585-2597

## N-Carbamyl-L-Glutamate Research in Patients with Partial CPS1D

In an article published in *Journal of Pediatrics*, Dr. Nicholas Ah Mew and colleagues highlight the effects of treatment of patients with carbamyl phosphate synthetase 1 (CPS1) with a medication called N-carbamyl-L-glutamate. Their preliminary results show that this medication could potentially increase urea production and decrease ammonia levels. To give some background, the first step in the urea cycle is catalyzed by the enzyme carbamoyl-phosphate synthase 1. The enzyme is only active in the presence of N-acetyl-L-glutamate. A stable analog of N-acetyl-L-glutamate, called N-carbamyl-L-glutamate (NCG, also called Carbaglu) has been studied in another urea cycle disorder (NAGS deficiency) with success. Carbaglu was able to improve urea production and normalize blood ammonia levels in NAGS patients.

In this research study, Carbaglu was given to 5 patients with CPS1 deficiency and similar outcome measures were tested. Four patients demonstrated increased ureagenesis (urea production) and a decrease in the overall median ammonia levels with Carbaglu treatment (115 vs 82  $\mu\text{mol/L}$ ). One patient was given a longer-term trial of Carbaglu and had long-term stabilization of ammonia levels and was slowly weaned off of sodium phenylbutyrate. Future research will include identifying CPS1 mutations that may be responsive to NCG and a clinical trial of NCG in patients who experience acute hyperammonemia (high blood ammonia levels).

Ah Mew N, McCarter R, Daikhin Y, Lichter-Konecki U, Nissim I, Yudkoff M, Tuchman M (2014) *Pediatrics* vol. 165, p. 401-403.



*Dr. Nicholas Ah Mew  
Children's National  
Medical Center*



## PCORI Awards \$2.1 Million for UCD Research

A research team from the UCDC has been approved for a \$2.1 million study by the Patient-Centered Outcomes Research Institute (PCORI) to evaluate treatment options and impacts of care delivery for patients with urea cycle disorders.

Mendel Tuchman, MD, principal investigator for the UCDC, is also the principal investigator of this study: "Comparative effectiveness of treatment in rare diseases: Liver transplantation vs. medical treatment in urea cycle disorders". He is leading a team of investigators from Children's National, the George Washington University, the National Urea Cycle Disease Foundation and the Studies in Pediatric Liver Transplantation research group.

"This project was selected for PCORI funding not only for its scientific merit and commitment to engaging patients and other stakeholders, but also for its potential to fill an important gap in our health knowledge and give people information to help them weigh the effectiveness of their care options," said PCORI Executive Director Joe Selby, MD, MPH. "We look forward to following the study's progress and working with Children's National Health System to share the results".

Specifically, the team will focus on the currently available major treatment options to help families make decisions about management alternatives in care. The options include whether to seek conservative treatment (medical diet, amino acid supplementation, and drugs that could help metabolize ammonia) or choose liver transplantation, to reduce or normalize blood ammonia in UCD patients.

An increasing number of patients with UCD are undergoing liver transplants instead of conservative treatment, but both options are considered effective in reducing or normalizing blood ammonia levels, Dr. Tuchman said. Although liver transplantation eliminates the ammonia problem, transplant carries post-surgical risks. Conservative management may normalize ammonia levels, but the risk of elevated ammonia increases during infection, viral illness or other triggers.

## Research Into Rare Diseases of Childhood

Dr. Mark Batshaw, former Director of the UCDC, Dr. Steven Groft, Director of the National Center for Advancing Translational Sciences' Office of Rare Diseases Research (ORDR), and Dr. Jeffrey Krischer, Director for the Pediatric Epidemiology Center at the University of South Florida co-authored an opinion article in the *Journal of the American Medical Association* about the history and importance of rare disease research. The manuscript highlights the limited research in rare diseases prior to the Orphan Drug Act, the importance of rare disease research, the challenges faced while conducting such research, and the enormous impact of such research in understanding rare diseases and its implications on patient care.

The authors credit the Orphan Drug Act for playing a large role in facilitating research into rare diseases, which are defined as diseases affecting fewer than 200,000 residents in the United States. Since the act went into effect in 1983, the U.S. Food and Drug Administration (FDA) has approved more than 450 products to treat approximately 250 rare disorders. The National Institute of Health (NIH) has also supported clinical research into rare diseases by creating the Rare Diseases Clinical Research Network (RDCRN). At the time of publication, there were 17 consortia that made up the RDCRN whereas now, there are 22, including the UCDC. The RDCRN functions to promote collaborative clinical research in rare diseases, to train clinical investigators in rare disease research, to promote quality proof-of-concept research projects, and to create access to information related to rare diseases for physicians, researchers, health care professionals, and patients.

The importance of conducting research in rare diseases in children is highlighted. For many disorders, early treatment can result in significantly improved outcomes and quality of life. With the advances in research and understanding of rare genetic disorders, many of these rare disorders are being diagnosed and treated at an early stage. More importantly, research of rare genetic conditions can lead to a better understanding, and even treatments, for more common disorders. For example, research on familial hypercholesterolemia, a rare genetic condition with high cholesterol, led to the development of statin medications that are now used to treat high cholesterol in a large number of people who are at risk for heart disease. Consortia like the UCDC are critical to advancing clinical research into rare diseases because single institutions do not have enough patients with specific rare disorders to perform clinical studies effectively. Before the UCDC, longitudinal studies (observational studies in which data is gathered from the same participants repeatedly over a period of time) in urea cycle disorders had fewer than 50 patients. Currently, the UCDC is following over 700 patients at 14 sites in the United States, Canada, and Europe and continues to enroll new patients.

Another point stressed in the article is that for rare disease research to be successful, the support and involvement of patient advocacy groups is critical. These types of groups initially advocated for the Orphan Drug Act and the creation of the RDCRN and they are instrumental in providing investigators with information and patient perspectives on research studies that would be of interest to the families.

Batshaw ML, Groft SC, Krischer JP (2014) *Journal of the American Medical Association*, vol. 311, p. 1729-1730.



DMCC Director Dr. Jeff Krischer with the Health Informatics Institute servers at USF

The Data Management and Coordinating Center (DMCC), located at the Health Informatics Institute at the University of South Florida houses data for the RDCRN centrally via electronic data capture systems. The DMCC also provides administrative support to the RDCRN, RDCRN protocol monitoring, and a user-friendly resource site for the public, research scientists, and clinicians.



## Academic Research, Patient Advocacy and Industry Collaborate to Bring New Drug to Market



An Editorial was published in the June 2013 issue of the journal *Hepatology* accompanying the article reporting the medication glycerol phenylbutyrate (Ravicti®) for the treatment of urea cycle disorders (UCDs). In this Editorial, Dr. Pramod Mistry from the Yale University School of Medicine highlights the history of development and approval of therapeutic agents for urea cycle disorders, the challenges in conducting robust clinical trials in ultra-orphan diseases, and the importance of collaborative clinical research networks like the UCDC in advancing such trials.

In the Editorial, the historical evolution of treatment of urea cycle disorders was reviewed, starting with the pioneering efforts of Drs. Saul Brusilow and Mark Batshaw, who developed the scientific rationale for the first therapy consisting of oral sodium benzoate and sodium phenylacetate combined with dietary protein restriction. This treatment, while effective, resulted in offensive body odor. Hence, Dr. Brusilow developed a more tolerable form, sodium phenylbutyrate, which was a prodrug that could be converted to phenylacetate. However, FDA regulations at the time prevented immediate approval of the new medication because of the lack of efficacy and safety data. There was no funding available to conduct the required clinical studies. The gridlock was finally resolved through philanthropy and patient advocacy, and the FDA approved sodium phenylbutyrate (Buphenyl®) for treatment of UCDs in 1996.

Sodium phenylbutyrate (Buphenyl®) became the standard-of-care for maintenance therapy in the treatment of UCDs, even though randomized clinical trials were never conducted. Although Buphenyl® was a significant improvement in the treatment of UCDs, many patients were required to take up to 40 large capsules per day. Moreover, many patients also reported side effects such as a bad taste and gastrointestinal symptoms. Dr. Brusilow then proposed another modification to the treatment, glycerol phenylbutyrate, which is a liquid prodrug of sodium phenylbutyrate with the benefit of being a nearly odorless, tasteless oil that does not contain sodium.

Dr. Mistry outlines the critical collaboration between academia under the UCDC leadership, patient advocacy (NUCDF), and industry (Hyperion Therapeutics Inc.) that lead to the successful FDA approval of the medication. The studies involved a total of 91 patients, when there are fewer than 500 known patients with UCDs in the United States who were being treated with Buphenyl®. This remarkable collaboration has led to the approval of a new treatment for UCDs that may improve the quality of life of some UCD patients.

Mistry PK (2013) *Hepatology*, vol. 57, p. 2100-2102.

## UCDC Projects in the 3<sup>rd</sup> Funding Cycle

As in the previous 2 funding cycles, there are 3 major studies in this funding cycle, which is 2014-2019. The major projects will be funded for the full 5-year period. The grant also allows us to continue training the next generation of UCD researchers by providing training grants and to try new ideas through smaller pilot study grants. There is a competitive process each year to select at least one pilot project and at least one trainee project. Pilot and trainee projects are 1-2 year studies.

### Major Projects

The **Longitudinal Study of Urea Cycle Disorders** is a research study to learn more about the natural history of UCDs, find out how well current treatments are working, find better ways to treat UCDs, and prevent and predict symptoms that occur with UCDs. In the third cycle of funding, we will focus on learning more about pregnancy and pregnancy outcomes, long-term morbidities, cancers, and liver disease. We will also work with our European and Japanese partners to examine differences in treatments and outcomes and to analyze data together, which will increase the strength of our data and allow us to look at the more rare disorder types. This study is conducted at all UCDC sites, has been enrolling since 2006, and has more than 700 participants across all of the UCD subtypes.

The **Biomarkers of Neurological Injury and Recovery Study** uses neuroimaging techniques to develop novel biomarkers (a measurable substance whose presence in the body is indicative of some phenomenon such as disease, infection, etc.), which will enable us to more precisely define how UCDs affect the brain and neuropsychological performance. We hope that this will help to predict outcomes and to monitor how treatment is working. This study will initially be conducted at Children's National Health System in Washington, DC (Dr. Andrea Gropman) and Boston Children's Hospital (Dr. Susan Waisbren & Dr. Gerard Berry).

Dr. Sandesh Nagamani and Dr. Brendan Lee at Baylor College of Medicine are conducting a study titled **The Efficacy of Nitric Oxide (NO) Supplementation as a Treatment for the Long-Term Complications in Argininosuccinate Lyase Deficiency (ASLD)**, as clinical trial of new treatments for patients with argininosuccinic aciduria (ASLD) using inorganic nitrites to restore otherwise deficient levels of nitric oxide.

### Pilot and Demonstration Project Program

Pilot studies are small-scale studies to test a concept and determine if a larger scale study is warranted. The UCDC is currently conducting 4 pilot studies: 1) NextGen newborn screening panel to permit early identification of proximal UCDs; 2) a drug (novel urease inhibitor) which reduces the effect of ammonia release by the microbiome; 3) use of the contact registry to test the feasibility of collecting data via on-line surveys and determine whether self-reported data aligns with Longitudinal Study data; 4) a study that uses a type of ultrasound and blood biomarkers to assess liver stiffness and injury.

### Trainee Projects

Investigators within 10 years of earning the MD or PhD degrees are eligible for trainee grants and are mentored by UCD experts during their project. The work of Dr. Angie Sin and her mentor, Dr. Colin Funk, is summarized on page 7. Dr. Omar Ayyub is working with his mentor Dr. Marshall Summar at Children's National to develop and market a hand-held ammonia monitor for home use.

To read the full articles summarized in this newsletter (coming soon) and to learn more about UCDC research, visit the UCDC website at <https://www.rarediseasesnetwork.org/ucdc/>

## Longitudinal Study of Urea Cycle Disorders Enrollment

Data current as of April 30, 2017

Subtype and Onset			
Subtype	Neo-natal Onset	Late Onset	Total
<b>OTCD</b> Ornithine transcarbamylase deficiency	50	363	413
<b>ASLD</b> Arginosuccinate lyase deficiency or argininosuccinic aciduria (ASA)	54	64	118
<b>ASSD</b> Argininosuccinate synthetase deficiency, argininosuccinic acid synthetase deficiency or citrullinemia	67	36	103
<b>ARGD</b> Arginase deficiency	1	26	27
<b>CPSID</b> Carbamylphosphate synthetase I deficiency	14	8	22
<b>HHH/ORNTD</b> Hyperornithinemia, hyperammonemia, homocitrullinuria syndrome or ornithine deficiency	1	10	11
<b>CITRD</b> Citrin deficiency, citrullinemia type II	1	4	5
<b>NAGSD</b> N-acetylglutamate synthetase deficiency	2	3	5
<b>Diagnosis Pending</b>	2	7	9
<b>Total</b>			713

By UCDC Sites	
Site/Institution	On Study
<b>Children's National</b> (Washington, DC)	114
<b>U of California Los Angeles</b>	64
<b>Baylor</b> (Houston, TX)	76
<b>Children's Hosp Heidelberg</b> (Germany)	54
<b>University Hospital Zurich</b> (Switzerland)	46
<b>Rainbow Babies and Children's</b> (Cleveland, OH)	58
<b>Mount Sinai</b> (New York, NY)	52
<b>Boston Children's Hospital</b> (MA)	49
<b>Children's Hosp of Philadelphia</b> (PA)	39
<b>Hospital for Sick Children</b> (Toronto, Canada)	37
<b>Children's Hospital of Colorado</b> (Aurora/Denver)	33
<b>Seattle Children's Hospital</b> (WA)	36
<b>University of Minnesota</b> (Minneapolis)	25
<b>Oregon Health and Science</b> (Portland)	18
<b>Closed Sites (Yale, Vanderbilt)</b>	12
<b>Total</b>	713

### Take Action

Take an active role in urea cycle research...

If you haven't registered with the Rare Diseases Clinical Research Network Contact Registry\*, consider doing so, so that you can **receive the most current information** on:

- Open recruitment for clinical studies of your disorder
- Opening of new UCDC clinical sites
- Awareness and advocacy group activities
- Information about future opportunities to participate in UCD research
- Receive information and publications from the UCDC, such as this newsletter

Click [here for the Contact Registry link](https://www.rarediseasesnetwork.org/cms/ucdc/Get-Involved/ContactRegistry). (<https://www.rarediseasesnetwork.org/cms/ucdc/Get-Involved/ContactRegistry>)

\*The Contact Registry is a way for you to provide your contact information so that the UCDC can contact you to keep you informed about UCDC research. It does not facilitate contact between individuals with UCD.

\*713 participants have enrolled in the Longitudinal Study. 106 of these are "off study" due to death, being lost to follow up, or being withdrawn for other reasons. 607 participants are currently "on study".

*Striving to improve the lives of individuals and families affected by urea cycle disorders*



The **Urea Cycle Disorders Consortium (UCDC)** is a team of doctors, researchers, and patient advocates, working together to improve the lives of individuals and families affected by urea cycle disorders through research and education. The consortium provides a way for patients to join doctors and researchers in developing new and better treatments for urea cycle disorders by participating in research studies. The greater the collaboration between doctors and patients, the more we can learn about urea cycle disorders. This important first step is necessary if we are to find new and better treatments.

## Participating Institutions and Principal Investigators (PIs)

### **Children's National Health System** (lead institution)

Washington, District of Columbia  
PIs: Mendel Tuchman, MD, Andrea Gropman, MD and Nicholas Ah Mew, MD

### **Baylor College of Medicine** Houston, Texas

PIs: Sandesh Nagamani, MD and Brendan Lee, MD, PhD

### **Children's Hospital of Colorado** Aurora, Colorado

PIs: James Weisfeld-Adams, MB, ChB and Curtis Coughlin II, MS, CGC

### **Children's Hospital of Philadelphia** Philadelphia, Pennsylvania

PI: Marc Yudkoff, MD

### **The David Geffen School of Medicine at UCLA**

Los Angeles, California  
PI: Derek Wong, MD

### **The Hospital for Sick Children**

Toronto, Ontario, Canada  
PI: Andreas Schulze, MD, PhD

### **Icahn School of Medicine at Mount Sinai**

New York, New York  
PI: George Diaz, MD, PhD

### **Boston Children's Hospital**

Boston, Massachusetts  
PIs: Susan Waisbren, PhD and Gerard Berry, MD

### **Oregon Health and Science University**

Portland, Oregon  
PI: Cary Harding, MD

### **Rainbow Babies and Children's Hospital**

Cleveland, Ohio  
PI: Shawn McCandless, MD

### **Seattle Children's Hospital**

Seattle, Washington  
PI: J. Lawrence Merritt III, MD

### **University Children's Hospital**

Zurich, Switzerland  
PI: Matthias Baumgartner, MD

### **University of Heidelberg**

Heidelberg, Germany  
PI: Georg Hoffmann, MD

### **University of Minnesota Masonic Children's Hospital**

Minneapolis, Minnesota  
PI: Susan Berry, MD

### **University of California San Francisco**

San Francisco, California  
PI: Renata Gallagher, MD, PhD

### **Stanford University**

Stanford, California  
PI: Gregory Enns, MD



### Contact the UCDC:

Jennifer Seminar  
UCDC Program Manager  
Phone: 202-306-6489

E-mail: [jseminar@childrensnational.org](mailto:jseminar@childrensnational.org)