Dear Friends,

By standing together as a united UCD community committed to research progress, we have begun to unlock the mysteries of the effects of urea cycle disorders and catalyze the development of new interventions and therapies to improve the lives of patients with UCD. Research for UCDs has increased over 400% in the last five years and continues to grow as data from the NIH-funded Urea Cycle Disorders Consortium Longitudinal Study reveals more details and patterns about how the disorders are affecting patients as a whole and from disorder to disorder.

The Longitudinal Study is an observational study that allows researchers to monitor UCD patients and their treatment over time to understand the effects of the disorder, how well treatments are working, and why patients may have different outcomes. Our UCD researchers have been analyzing this study data and have produced nine research articles of their findings. The articles, published in medical journals, provide information about UCD to medical professionals and raise awareness of the disorder. The data is leading to new studies that are important to our patients and families.

Other critical projects include using neuroimaging to understand the effects of UCD on the brain, and clinical trials for new drugs and interventions. In this issue of NUCDF News, we will focus on providing you with updates, along with information on new and ongoing studies that are open for participation.

Thank you again to all our families, medical professionals and supporters for your commitment to accelerating this critical research. Together, we can conquer UCD!

Warm regards,

Cindy Le Mons
Executive Director, NUCDF
Working Wonders...

ASA Research Leads to Transformational Scientific Discovery

NUCDF is proud to announce that the work of Dr. Brendan Lee’s research team at Baylor has resulted in a major discovery in AsA deficiency that also transforms basic human science. The research has been published in *Nature Medicine*, a preeminent scientific journal, and changes long-held theories about the role of nitric oxide in the human body as a regulator of cardiovascular function. The discovery is the result of research spanning several years conducted by the team, including three consecutive NUCDF Fellowship awardees, Ayelet Erez, MD, PhD, Oleg Shchelochkov, MD, and Sandesh Nagamani, MD. Dr. Stephen Cederbaum says of Dr. Lee’s work, “He has transformed treatment of this rare condition and illustrates what one creative mind in the hands of an excellent and persistent scientist can do.” NUCDF and our families are delighted beyond words that our investment in these three promising young scientists and Dr. Lee’s work has resulted in this life-changing discovery.

Thirteen years ago, Dr. Brendan Lee’s interest was sparked when he began treating children with argininosuccinate lyase deficiency (AsA), one of the six urea cycle disorders. One of Dr. Lee’s young patients developed high blood pressure (essential hypertension) at age 3. Over the next few months, two other families reported to the National Urea Cycle Disorders Foundation that their children had developed essential hypertension. Coincidentally, those children also had AsA deficiency.

Or was it a coincidence? AsA is a rare disorder and few children, probably less than 70, had been identified at that time. Essential hypertension in preschool-aged children is uncommon. What were the chances of three children in this very tiny AsA disorder population all developing high blood pressure?

“It was unresponsive to any drugs usually used to treat high blood pressure – ACE inhibitors, calcium channel blockers, etc.,” said Dr. Lee. One potential explanation for this was a central deficiency of nitric oxide in the body.

Nearly 20 years ago, the journal *Science* tagged nitric oxide as the “molecule of the year.” Since that time, researchers have tried to study and target this simple molecule that is involved in virtually every process of the body. However, focusing on the nitric oxide molecule and the enzyme, argininosuccinate lyase (AsL), that is directly involved in its production has proven difficult and futile.

The paradox

“Arginine is the single amino acid in the body that makes nitric oxide,” said Dr. Brendan Lee, professor of molecular and human genetics and a Howard Hughes Medical Institute investigator at Baylor College of Medicine in Houston, Texas. Even though there may be sufficient arginine in the cell to produce enough nitric oxide for the cell’s needs, giving more arginine results in the production of more nitric oxide. That is the “arginine paradox.”

Now, Dr. Lee and his research team (including three NUCDF Fellowship awardees) have not only found a way to change the production of nitric oxide in the cell, along the way they may have solved the mystery of the arginine paradox. Their work was recently published in the prestigious journal, *Nature Medicine* (http://www.nature.com/nm/index.html).

“Think of it as though you were baking a cake,” said Dr. Lee. “You have tons of eggs in the bakery but you can bake only so many cakes each day. You should be saturated in terms of your requirement for eggs. For some reason, though, when a truck brings in an extra 10 cases of eggs, you make more cakes.”

*Argininosuccinate lyase unlocks the mystery*

The answer rests with argininosuccinate lyase (ASL), an enzyme critical to making arginine – the precursor to nitric oxide. When a person is lacking in the ASL enzyme, they cannot make enough nitric oxide, often causing damage to the liver and other organs. Studies in mice show that without this ASL enzyme, they cannot make or use arginine. When the ASL-deficient mice were given extra arginine, it did not solve the problem with nitric oxide.

Patients with AsA have a deficiency in the ASL enzyme that can cause high ammonia levels, resulting in damage to the brain and other organs. Thankfully, there are effective urea cycle disorder treatments that help prevent the deadly build-up...
of ammonia. However, even without episodes of elevated ammonia, patients with ASA often have other complex, long-term health problems – many of which could be due to a deficiency in nitric oxide.

“To carry our bakery story further, this enzyme not only delivers the eggs to the bakery, it also transfers the eggs in the bakery into the blender for use in baking the cakes,” said Dr. Lee. “This enzyme has two separate functions. The first is to make arginine and the second is to hold together a complex of proteins that transfers arginine inside the cell, or into the ‘oven,’ that makes nitric oxide.”

“What our work suggests is that this enzyme is the central way of regulating all of nitric oxide production in the body.” These findings open a door into ways to explore the effect of nitric oxide on a host of disorders that occur in the general population and impact overall health.

Transformative for ASA

Until now, patients with ASA were treated with a restricted protein diet and very high amounts of arginine which served to keep ammonia within, or near, the normal range. The expectation was that these patients would do very well, better than in those urea cycle disorders in which ammonia was harder to control.

Surprisingly, the outcome was the opposite. Despite normal ammonia levels, ASA patients often still have deficits in intellectual function and worse liver disease. The cause of the liver disease is now understood to be due to excessive accumulation of argininosuccinate. The detrimental effects of excessive argininosuccinate on the brain are suspected, but remain unproven. With his studies, Dr. Lee has established a lower arginine dose to treat ASA patients, a dose already shown to lessen the liver problems. Studies to show that neurological outcome can be improved have been formally proposed and are clearly necessary. NUCDF’s research priorities include supporting this neurological research.

Dr. Lee’s research has shown that agents that produce nitric oxide and which are already approved can improve hypertension and other potential complications in certain forms of ASA deficiency. Less arginine leads to less argininosuccinate accumulation and better health. Providing the normal products of the missing reaction will be the next major step forward. This will be the focus of Dr. Lee’s next project.

“We hope it transforms the field,” said Dr. Lee.
High-dose arginine may increase liver inflammation in ASA deficiency

In addition to its role in the urea cycle, argininosuccinate lyase (ASL) is also essential for endogenous (produced within the body) synthesis of arginine. Patients affected by ASA deficiency can have liver involvement ranging from liver enlargement (hepatomegaly) with elevations of liver enzymes to severe liver fibrosis. The standard of care for patients with ASA deficiency has historically included arginine supplementation that compensates for the decreased endogenous synthesis in addition to promoting the excretion of nitrogen (ammonia) as argininosuccinic acid. Results of a recent study suggest a lower dose of arginine combined with sodium phenylbutyrate may help reduce liver dysfunction in ASA deficiency.

Researchers hypothesized that if increased levels of argininosuccinic acid were the predominant cause for liver dysfunction, a high dose of therapeutic arginine (500mg/kg/day) would be associated with worsening of liver functions as compared to a low dose of arginine (100mg/kg/day) combined with sodium phenylbutyrate, which would result in lower levels of argininosuccinic acid levels. To evaluate the effects of these two treatments on liver function in patients with ASA, a randomized double-blind placebo controlled cross-over trial was carried out by Dr. Brendan Lee and his team at Baylor as part of the Urea Cycle Disease Consortium research. Eleven patients completed both arms of the trial and were included in the analysis.

As expected, patients had significantly increased levels of phenylacetylglutamine and phenylacetic acid while on low-dose arginine with sodium phenylbutyrate, and higher plasma arginine and citrulline levels while on high-dose arginine. Ammonia control was comparable between the two arms of the trial. Patients had statistically significant increases in plasma ASA levels while on high-dose arginine. AST levels were also increased in the high-dose arginine arm. Patients with abnormal liver transaminases seemed to have the most increase in liver enzymes while on high-dose arginine. The function of the liver as assessed by PT, INR, Factors VII, IX and fibrinogen were comparable between the two arms of the study.

These results reveal that high dose arginine may lead to higher liver inflammation in patients with ASA, especially in patients with existing liver dysfunction. The results have therapeutic implications, as they suggest it may be optimal to treat ASA patients who have liver dysfunction with lower doses of arginine combined with sodium phenylbutyrate.

©National Urea Cycle Disorders Foundation
The Two Faces of Executive Function

Metacognitive Problems
- Getting started/initiation
- Organizing Materials
- Working Memory
- Planning approach to tasks
- Difficulty monitoring one’s work
- Problems completing tasks

Behavioral Regulation Problems
- Inflexibility
- Impulsivity
- Emotional Control
- Difficulty monitoring one’s own behavior

Outcomes for UCD vary widely and are related to many factors including severity of disorder, age of onset, day-to-day metabolic stability, response to treatment, and frequency and severity of hyperammonemic episodes.

Children with UCD often experience difficulty with attention and focusing on tasks. Sometimes they do not perform well on neuropsychological tests because of these characteristics. Upcoming research will include studying each disorder separately to determine if there are differences in intellectual, adaptive and behavioral functioning depending on disorder. Adaptive testing methods may be necessary to adequately capture this information.

EFFECTS OF UCD ON THE BRAIN

Intellectual, Adaptive and Behavioral Functioning in Children with UCD

Summary of paper published in Pediatric Research 2009 authored by LS Krivitzky, T Babkian, HS Lee, NH Thomas, KL Burke Paul, ML Batshaw

UCD can lead to an accumulation of ammonia in the blood and brain that may result in neurodevelopmental disabilities. This study analyzed data from the Longitudinal Study of UCD to attempt to describe the intellectual, adaptive, and emotional/behavioral functioning of children with UCD. Intellectual functioning refers to the ability to learn, think, solve problems and make sense of the world. Adaptive behavior includes the age-appropriate behaviors necessary for people to live independently and to function safely and appropriately in daily life. Adaptive behaviors include real life skills such as grooming, dressing, safety, safe food handling, school rules, ability to work, money management, cleaning, making friends, social skills, and personal responsibility expected based on age. Measures of emotional/behavioral functioning assess one’s ability to learn, build and maintain interpersonal relationships, and regulate behavior, feelings, mood, and fears.

These domains were measured through testing and parent questionnaires in 92 children with UCD (33 neonatal onset, 59 late onset). Approximately 50% of children with neonatal onset UCD performed in the range of intellectual disability (ID), including about 30% who were severely impaired. In comparison, only 25% of the late onset group were in the range of ID. There is also evidence that children with UCD have difficulties with some emotional/behavioral and executive function skills (difficulties with behavior regulation, organization, and goal directed behaviors). In conclusion, the study reveals that children with UCD present with a wide spectrum of intellectual and behavioral outcomes. Children with neonatal onset UCDs (presenting in the first 4 weeks of life) have a much higher likelihood of having an intellectual disability, which becomes more evident with increasing age. However, even children with late onset UCDs demonstrate evidence of a wide spectrum of neurocognitive and behavioral impairment, particularly in aspects of attention and executive functioning (intellectual processes).
The Longitudinal Study of Urea Cycle Disorders is an observational study of the natural history of UCD in affected patients being conducted at 11 US and 3 international centers. The study aims are to learn how well current treatments are working, find better ways to treat UCD, and try to predict and prevent symptoms that occur with UCD.

The Longitudinal Study has been enrolling participants since February 2006 and currently has 521 participants. The following are summaries of selected published papers resulting from the study.

Cross-Sectional Multi-center Study of Patients with Urea Cycle Disorders in the United States Molecular Genetics and Metabolism 2008: This study reports the clinical and laboratory characteristics of patients with UCD in the United States using data collected from the Longitudinal Study. The analysis was limited to data collected at the time of the patient’s first study visit. The Longitudinal Study patient statistics revealed:

- 55% of patients had OTC deficiency, 16% had argininosuccinic aciduria (ASA), 14% had citrullinemia.
- 79% of the participants were white, 15% Latino, 7% Asian, 5% African American, 9% reported no race or more than one race.
- 39% of participants reported intellectual/developmental disabilities, 35% learning disabilities, and 50% had abnormal neurological examinations including reflex abnormalities, tone changes or abnormal movements.
- Plasma levels of branched-chain amino acids (valine, leucine, isoleucine) were reduced in patients treated with ammonia scavenging drugs (sodium phenylbutyrate and sodium benzoate).
- Plasma glutamine levels were higher in proximal UCDs (CPs1, OTCD) and in neonatal-onset disease.

Hepatocellular Carcinoma in a Research Subject with Ornithine Transcarbamylase Deficiency Molecular Genetics and Metabolism in press: Fourteen years after participating in a phase 1 OTC gene therapy study using an adenoviral vector to deliver a normal OTC gene to her liver cells, a 66-year-old woman with symptomatic OTC deficiency presented with hepatocellular carcinoma (HCC) (liver cancer). The vector that was used in the gene therapy study is not thought to cause cancer.

A recent review of data collected by the Longitudinal Study found three patients that are being treated for HCC, which is higher than would be expected in this population. This suggests that individuals with UCD may be at increased risk for developing liver cancer, as has been observed in other inborn errors of metabolism. Researchers will be studying this further to determine if there is, in fact, an increased risk of liver cancer in UCD and whether this is related to chronic liver inflammation. If this is found to be the case, recommendations may be made for annual abdominal ultrasounds for early detection, as is recommended for other disorders that have an increased risk of liver cancer. Additional studies are needed to determine whether there will be a need to establish these recommendations in the future.

WHAT STUDY FINDINGS MAY MEAN FOR YOU OR YOUR FAMILY

If you have questions or would like to discuss any study findings, implications, participation or other information contained in the NUCDF Newsletter, please don’t hesitate to contact NUCDF at:

CureUCD@nucdf.org | Phone (626)578-0833
New Videos Online

NUCDF Conference Presentation Series

UNI Study: Urea Cycle Disorders, Nutrition and Immunity, presented by Peter J. McGuire, MS, MBBCCh, Physician-Scientist, NHGRI, Urea Cycle Disorders Research Section

- Learn what research is revealing about the activation of the immune system during viral illness or infection and the deleterious effects on the urea cycle.
- Learn why nutritional status may affect the immune system.
- Learn about the UNI Study, what we hope to learn, and how to participate.

www.nucdf.org/resources_videos.html
What is Oxidative Stress?

The understanding of UCDs has increased and new treatments and optimal management are improving the outcomes of children and adults with UCD. While we have been largely focused on preventing high ammonia levels, we also have to be aware of the effects of the disorder on long-term health. By recognizing these factors, we may be able to improve the overall and long-term health of those affected by UCD. Researchers are now turning attention to the role of nutrition, oxidative stress and cytokine response in UCD.

The war against free radicals

Oxidative stress is the damage caused to a cell through a normal oxidation process happening all the time in our bodies. However, when something disturbs the balance of this process, the result is often toxic.

Free oxygen radicals are created during the normal oxidation process. Free radicals are missing a simple electron and are in search of another molecule that they can combine with to become “whole.” In their quest, they fire charges that damage other cells and structures around them. Imagine an iron pipe lying on the ground. After years of exposure to the environment, rain and sun, it begins to rust. The rust is caused by oxidation and free radicals.

In our bodies, this “rusting” is the aging process. The more free radicals your body contains, the more damage potentially occurs. Compare the skin of a 5-year-old to that of a 90-year-old. The difference you can see is the destructive effect of free radicals on skin cells.

But oxidative stress doesn’t just happen on the outside. Even though our bodies do an amazing job of neutralizing them in a normal, low-toxin setting, increased and prolonged exposure to free radicals causes a faster build-up of “rust” or disease in our bodies. In fact, it is the cause of many diseases, including heart disease, cancer, arthritis, diabetes, autoimmune and neurodegenerative diseases like Alzheimer’s.

Common triggers for increased free radicals in the body are environmental/air pollution, cigarette smoking, excess stress, medications, excessive exercise and increased exposure to sunlight. In UCD, metabolic imbalances as well as nutritional deficiencies increase oxidative stress, triggering a cascade of free radicals and potential for cell damage.

The heroic role of antioxidants

One of the keys to reducing the amount of free radicals in your system is antioxidants. Antioxidants give up the missing electron to the free radicals. Antioxidants neutralize the free radicals and enable the body to excrete them safely before they can cause harm.

Our bodies already make several different types of antioxidants all on their own. In UCDs, we may need to provide the body with supplemental antioxidants as increased protection in the war against free radicals. Antioxidants may provide a preventive and therapeutic advantage in reducing the effects of free radicals.

Eat your colors

Many healthy foods provide a natural source of antioxidants. Getting these foods into UCD kids – notoriously picky eaters – may be a challenge, but there are many foods to choose from.

According to Debra Hook, R.D., M.P.H., in her presentation at the 2010 NUCDF Family Conference on nutritional management of UCDs, natural foods containing both phytochemicals and antioxidants should be part of the UCD diet. One of her slides said, “Eat your Colors.”

As a rule, dark-colored fruits and vegetables have more antioxidants than other fruits and vegetables. Most can be eaten raw, pureed, or blended separately or together for a healthy shake.

An important first step in adding antioxidants to the diet is to meet with your metabolic dietitian to develop a plan to help you incorporate them into your UCD diet plan.

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<tr>
<th>Powerful Antioxidants</th>
<th>Phytochemicals</th>
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<td>Blueberries</td>
<td>Allicin - found in garlic and onions</td>
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<td>Pomegranate (juice)</td>
<td>Anthocyanins – deep colored berries</td>
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<tr>
<td>Cranberries</td>
<td>Lycopene - tomatoes</td>
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<td>Artichokes (cooked)</td>
<td>Lutein – dark green leafy vegetables like spinach and kale</td>
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<td>Blackberries, Prunes</td>
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<td>Raspberries</td>
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New research is scheduled to begin investigating the role of nitric oxide in citrullinemia and the effects of inflammation as a trigger for decompensation in UCD. As soon as the studies open for enrollment of participants, we will post the info on our NUCDF website.

1 Nitric Oxide Flux and Ureagenesis in ASS deficiency

Patients with argininosuccinic aciduria (ASA) also called argininosuccinic lyase deficiency, are deficient in the urea cycle enzyme argininosuccinic acid lyase (ASL). Another urea cycle disorder, citrullinemia (ASS), is due to a deficiency in the enzyme argininosuccinic synthetase (ASS). These two enzymes are expressed in many tissues in the body for generation of arginine. The role of ASL in the production of arginine and the subsequent deficiency of nitric oxide has been shown to cause long-term complications such as high blood pressure and liver dysfunction. If decreased nitric oxide is the reason for complex clinical findings in some forms of ASA, it could be expected that citrullinemia would also cause similar problems. However, these problems have not been seen in citrullinemia patients. This study seeks to answer two questions: 1) Do citrullinemia patients also have decreased nitric oxide production and 2) Is there a difference between the importance of ASL vs ASS in the generation of nitric oxide?

2 Oxidative Stress, Inflammation and Acute Metabolic Decompensation in UCD

There are markers for oxidative stress that measure physiologic stress on the body. Inflammatory cytokines are a type of protein secreted by cells during inflammation. This study will help to answer whether measuring these in individuals with UCD can reveal the state of metabolic control. Will the oxidative stress markers and inflammatory cytokines change as ammonia changes? This could help predict if a hyperammonemic episode is going to occur so that early intervention or treatment might prevent it.

Save the Date!

2012 NUCDF CONFERENCE
July 13-15, 2012
Grand Hyatt, Washington DC

- Stay in the loop - Hear about the new studies and latest research.
- Learn about new treatments and improved approaches to managing UCD.
- Meet other UCD families, researchers and experts in the field.

Watch for details at www.nucdf.org
Registration Packets will be mailed to NUCDF members in mid-April.
For more information, contact:
NUCDF
Email: 2012conference@nucdf.org
Phone: (626)578-0833

“We thought we knew a lot about our daughter’s disorder until we went to our first conference. We were welcomed like family and learned more in 1 day than we had in 3 years on our own. It changed our lives...we won’t miss another one!”

See the story in this issue about oxidative stress and how we might be able to prevent some of its effects.
Uncovering the Mysteries of the Brain

How does the brain respond to elevated ammonia? Are the effects of UCD on the brain preventable or reversible? New UCD research using specialized neuroimaging techniques may provide the answers and lead the way to developing new interventions to protect the brain.

Up to now, how hyperammonemia disrupts brain function has not been well understood. What exactly causes the brain to be injured? How much injury occurs and precisely what areas of the brain are involved? Why is there often variation in the recovery of patients after a hyperammonemic event?

Dr. Andrea Gropman is a rare breed. Dr. Gropman is a neurologist and a geneticist (how smart can one person be?). She is leading critical UCD brain research that uses specialized brain imaging techniques to study how UCDs affect the brain. This special neuroimaging can be used to obtain information about the timing, extent, and reversibility of these effects, as well as the mechanism of brain injury.

Finding brain biomarkers for UCD

Can we then use these technologies to track or prevent injury? Gaining an understanding of how and why the brain is being affected in UCD adults and children is critical to improving outcomes. A crucial step is the identification of “biomarkers” in the brain. Biomarkers are biochemical features or characteristics that can be used to measure the progress of disease or the effects of treatment. Brain biomarkers for UCD could help predict the severity of a hyperammonemic event, and be useful for clinical monitoring (effects and timing of treatment) and interventional studies. These biomarkers are critical to advancing the development of new interventions and treatments to protect the brain in UCD.

Is the brain compensating?

Neuropsychological testing is also being used to measure the secondary effects of UCD on the brain. Dr. Gropman’s cutting-edge research combines special neuroimaging techniques that characterize alterations in the brain chemistry and neural structure, with special neuropsychological tests. For example, while the patient is in the scanner, they perform tasks, like pressing a button when they see certain letters on a video screen. This allows Dr. Gropman to simultaneously “see” and monitor changes as the brain activates in reaction to performing tasks. (continued next page)
Mysteries - cont’d

The more complex the task, the more the brain activates; Dr. Gropman can then identify abnormalities or deficits in the activation patterns. She is finding that in OTC patients, the brain may be compensating for damage in one area by activating other parts of the brain. Their brains are actually working harder compared to an unaffected person to accomplish the same tasks.

Previous neuropsychological studies in OTC carriers reported by Gyato, et al, indicated that despite average IQ scores, OTC carriers displayed specific neurocognitive deficits in nonverbal intelligence, fine motor/dexterity/speed, visual memory, attention and executive function skills, and math. These findings are typically associated with white matter or subcortical dysfunction. By using special imaging techniques (1H MRS, DTI and fMRI) Dr. Gropman has been able to confirm white matter injury in OTC patients and carriers affecting the frontal lobe that involves working memory and executive function.

Glutamine - a biomarker?

Over the last few years, Dr. Gropman’s work has revealed that even in the absence of hyperammonemia, there are subtle or even significant alterations in the biochemistry of patients with OTC deficiency and OTC carriers. This raises an important question about the role of glutamine in OTC and CPS1 deficiencies. In animal and human studies, accumulations of ammonia, glutamine and glutamate have been shown to exert toxic effects on the brain. Clinical signs of hyperammonemia can begin at 60 micromol/L, including anorexia, irritability, lethargy, disorientation, vomiting and somnolence, eventually progressing to brain swelling and coma. A rise in glutamine levels in the blood has long been theorized to be a predictor of impending hyperammonemia. For the first time, Dr. Gropman’s studies using 1H MRS revealed elevated brain glutamine in OTC patients with hyperammonemic encephalopathy (HE - an alteration of brain function or structure caused by high levels of ammonia). The results provide evidence that HE is related to elevated concentration of glutamine in the brain and a disruption of cerebral metabolism.

Dr. Gropman used the same 1H MRS technique to investigate cerebral metabolism in stable patients with partial OTC deficiency. The results showed that both symptomatic and asymptomatic patients had significant increases in glutamine and decreased concentrations of myoinositol compared to normal controls. This observation in women with OTC who were asymptomatic suggests the possibility of unrecognized biochemical disturbances and may explain some of the neurocognitive deficits observed in these patients.

It’s all about the brain

The studies provide details about the pattern and type of injury in UCD and characterize several important brain biomarkers. Biomarkers in OTC deficiency include increased brain glutamine levels and possibly depletions of myoinositol – indicators of disturbed osmotic balance in brain chemistry. Markers of white matter injury reveal alterations that may impair learning and memory.

These studies need to be expanded to better understand when these alterations may be occurring, their relationship to age, early metabolic changes and progression. Most importantly, can there be recovery? The studies will help address whether even “asymptomatic” OTC patients or carriers should receive treatment to avoid long term effects on cognition.

New studies have been proposed using these techniques to identify brain biomarkers in citrullinemia and ASL – which may be different than those found in OTC deficiency. These biomarkers can then be used to access and monitor effectiveness of treatment and help evaluate current and novel therapies to improve neurological outcome.

How You Can Participate

Eligibility:

- OTC females and late onset males, confirmed biochemically or by genetic mutation
- Ages 7-60 years of age, with stable health
- Able to comply with testing, not claustrophobic

Washington, DC Study:

- Travel to Washington, D.C. for 2-3 days (travel expenses paid)
- Provide a 3-day diet history
- Have blood and urine drawn for ammonia, glutamine, orotic acid, liver functions and chemistries
- Undergo 1 ½-2 hours of cognitive testing
- Undergo 4 hours of scanning, split over 2-3 sessions

Or for All OTC patients

Release the films from any previous MRIs performed before or after diagnosis (at any age)
- Simply sign a consent to have raw data from the scan released to Dr. Gropman for reinterpretation by new software and comparison

Contact Study Coordinator: Ileana Pacheco-Colon, ip126@georgetown.edu
Phone 202-657-4671
Did you know...

Orphan diseases like UCD rarely have even one FDA-approved drug treatment. Our UCD community is an exception. Buphenyl was approved in 1996 after a small number of our UCD families participated in the clinical trials and a battle for approval that included congressional support.

Currently less than 500 patients are being treated with Buphenyl. Carbaglu was approved in 2009 for NAGs deficiency and is being used in less than 10 NAGs patients (clinical trials are being conducted to evaluate its potential use as an acute treatment for hyperammonemia in OTC, CPS1, and two organic acidemias).

The development of HPN-100 has taken over 8 years and ultimately involved a model cooperative effort between Hyperion Therapeutics, the National Urea Cycle Disorders Foundation and UCD Research Consortium, and many dedicated medical professionals at the clinical trial sites.

The approval of HPN-100 would mark another major milestone for our UCD community and NuCDF's unwavering commitment to saving lives. We have every hope that the result will be a life-changing improvement for adults and children with UCD.

New Drug Alternative for UCD Awaits FDA Approval

UCD patients often struggle to tolerate the terrible taste of drugs used for treatment. Parents struggle to “get the medicine” into their children. HPN-100, a nearly tasteless, odorless liquid awaiting FDA approval, may change all that...

What is HPN-100?

HPN-100 or glycerol phenylbutyrate (GPB), is an ammonia scavenging agent currently in development as a treatment for urea cycle disorders. Clinical trials using HPN-100 in adults and children have been conducted and long-term studies are ongoing. NuCDF has been supportive of the development of GPB as an answer to our call for a drug that was more easily tolerated and administered than the burdensome UCD drugs available over the last 20 years.

How does it work?

GPB creates an “alternative pathway” for ammonia to be excreted from the body in patients who have urea cycle disorders. Two current treatments for UCD, sodium phenylbutyrate (NaPBA, trade name Buphenyl) and sodium benzoate also work by creating other pathways to remove ammonia.

Sodium phenylbutyrate and glycerol phenylbutyrate (GPB) both contain phenylbutyric acid (PBA) as the active ingredient. GPB works similarly to sodium phenylbutyrate by combining phenylacetic acid (PAA) with glutamine, an amino acid in the body created by the conversion of ammonia and glutamate in the liver. This conjugation results in phenylacetylglutamine (PAGN). PAGN is then excreted in the urine.

GPB differs from sodium phenylbutyrate in that GPB is a short chain triglyceride – a liquid oil which contains no sodium. GPB is administered orally as a liquid and is almost tasteless and odorless. Approximately three teaspoons of GPB liquid is equivalent to 40 tablets (20 grams) of sodium phenylbutyrate. This represents a major improvement for children and adults who currently have difficulty taking sodium phenylbutyrate tablets or powder.

Three clinical trials

A total of 65 UCD patients (54 adults and 11 pediatric UCD patients aged 6-17 years) participated in short-term (2-4 week) comparison studies using what is called a switchover – switching from sodium phenylbutyrate to GPB under clinical supervision in a hospital research center.

At the conclusion of the short-term study, 51 adult patients and 26 pediatric patients were then enrolled in one of two 12-month long treatment protocols using GPB (one for adult patients, one for pediatric patients ages 6-17).

UCD patients often exhibit deficits in executive function, which is defined as difficulty in goal setting, planning, monitoring progress and purposeful problem solving (Krivitsky L. 2009). To help measure these deficits, neuropsychological evaluations were performed at baseline (when patients were taking sodium phenylbutyrate) and at the conclusion of the 12-month study (after being on GPB).
Future Potential
Obtaining FDA Approval

Following FDA (Food and Drug Administration) guidelines, Hyperion Therapeutics – developer of HPN-100 – has submitted the study findings and data to the FDA regularly during the course of the clinical trials.

Subsequently, Hyperion filed an application for New Drug Approval (NDA) with the FDA on December 23, 2011. The application was accepted on February 23, 2012. The FDA will now review all clinical trial data and decide whether it will approve HPN-100 for use in urea cycle disorders. If approved, the hope is that HPN-100 may be available to urea cycle disorder patients by Spring 2013.

New Treatment - cont’d

New observations
In a report on the Phase II study in children published in Molecular Genetics and Metabolism, the authors report:

“The present study underscores the difficulty clinicians face in making decisions regarding drug dosing based on blood ammonia [levels]. Even under the controlled conditions of the present trial, including excellent compliance with diet and study drug in patients whose ammonia values were viewed as well controlled by their physicians prior to enrollment, ammonia values on average varied more than 10-fold over the course of the day. This observation suggests that random values for blood ammonia are of limited utility and that ammonia levels should be drawn at a constant time in relation to meals and medication for monitoring of treatment.

Urinary output of PAGN, in contrast to blood levels or drug metabolites, shows promise as a biomarker of dose selection and compliance monitoring in pediatric UCD patients and is practical to perform in routine clinical practice.”

Peds under 6 trial
Another clinical trial evaluating gPB in pediatric patients under 6 years old was completed in late 2011. Patients were offered enrollment in a 12-month extension trial, which is currently ongoing.

HPN-100 Trial Results at a Glance

1. A total of 65 patients completed the switchover study, and 69 patients completed the long-term study.
2. Two subjects who normally received sodium phenylbutyrate via an NG tube were able to receive gPB orally during the study.
3. A pooled analysis of data from all three studies was performed. Ammonia levels of patients in the switch-over study were significantly lower on gPB than sodium phenylbutyrate. In the 12-month long-term study, the average monthly ammonia level was normal while on gPB (17.8-32.7 µmol/L for adults and 17.1-23.3 µmol/L for pediatric patients).
4. The number of hyperammonemic crises and number of patients experiencing crises was lower during extended gPB treatment.
5. In adult patients, all neuropsychological test scores remained unchanged compared to baseline scores.
6. Executive function testing in pediatric patients was significantly improved on gPB, including goal setting, monitoring progress and purposeful problem solving.
7. Ammonia levels fluctuate widely during the day and rise after meals (postprandially).
8. Measurement of urinary PAGN may prove to be a new biomarker for evaluating compliance and calculating dosing.

Supporters Rock the Challenge!

Our Cure the Cycle Challenge in late October was a great success, raising over $125,000 in donations and sponsorships for NUCDF’s Brain Project research. Awareness of UCDs reached thousands of people across the country through the media and social networking sites like Facebook. We’re already gearing up for 2012 and an exciting event! Our supporters make it possible for NUCDF to fund critical brain research projects in our pursuit of ways to protect the brain from UCD.

The Challenge was held in memory of Jim Stavas, a strapping healthy Napa Valley fire captain for 30 years who fell into a coma due to undiagnosed CP1 deficiency after a simple sinus surgery. Jim fought valiantly through 18 months of rehabilitation for stroke-like symptoms and a series of hospital-borne infections. On October 1, 2007, Jim lost his battle with UCD.

In memory of Jim, firefighters and first responders from 3 Napa County fire departments, police and emergency personnel came out to bike and volunteer for the event. Cyclists also included NUCDF families (shout out to Amanda Sonntag and the Stavas family), friends and medical professionals. UCD expert Dr. George Diaz came from NY and joined his friend, Dr. Freedhand from Napa, to ride in support of NUCDF and our UCD families. Dr. Diaz flew in with his family and then flew all the way back to NY the next day. That’s commitment!

We started our Challenge event with an emotional balloon release in tribute to all our angels lost to UCDs and a commitment to keep fighting to improve the lives of all those living with UCD. Cyclists then rode 50 or 100 mile routes through the beautiful vineyards and hill country of Napa over the course of 8 hours. They were joined in spirit by over 30 NUCDF families participating as “Virtual Riders.” Our Virtual Riders set up fundraising pages on the Cure the Cycle website to raise funds in support without having to leave home! NUCDF mom Jamie Oliphint biked an amazing 50 miles with a friend in her own Texas community. Jamie plans to have more friends join her for the 2012 Challenge. All our riders and volunteers (volunteers pictured right) were AWESOME!

Thank you to all our participants, volunteers, donors and organizing committee for your support! Heartfelt thanks to Toni Martinez for her efforts and unerring commitment, and our deep appreciation to the Stavas Family for courageously allowing us to share their story, and giving us the privilege of holding the Challenge in memory of Jim.

Big thanks to our Top Fundraisers & Sponsors

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Challenge Team Manager
Larry Nolan and Team Specialized

Top Teams
HyperCycles AC Napa Fire & Police Riders Team Avery Team Mariscal

Top Fundraisers
Klara Dickinson Bruce Scharschmidt Toni Martinez Melissa Von Rohr
Let's Rock the 2012 Challenge!

To participate as a cyclist, virtual rider or volunteer for the 2012 Cure the Cycle Challenge

Contact: CureUCD@nucdf.org
Dear Friends,

I am 32 years old and have OTC. I was one of the first females to be diagnosed with OTC. My mother was a carrier. Prior to me, she lost a son from OTC at 8 days old. Today, I live with my loving husband Michael in Canton, Ohio.

We both enjoy the NUCDF family conferences and opportunities that come with being members of our NUCDF family. The Denver conference was our 3rd conference together. Every year we manage to learn something new. We really enjoyed the breakout sessions and I was privileged to be asked to help moderate one. Michael and I attended Adults with UCDs, Low Protein Diet for Life, and Clinical Trials.

Meeting with other adults and carriers of UCDs was very beneficial for us both. We discussed some commonalities that some of us share ranging from migraine headaches, difficulty staying awake while driving longer than 30 minutes, and getting tired easily. During the adult session, Dr. Gropman made note of these issues and perhaps we will learn more in the future. The topic of pregnancy was also of interest. The doctors and professionals there informed us of the risks that come with deciding to have a child. In short, it is possible to have a baby, but the chances of the child having OTC still remain 50/50 and the uncertainty of the potential complications is still a big concern. It is a personal choice that each family must make. I do know that some people have been blessed to have a healthy pregnancy and child while others have had to face a rougher road. We also talked about managing a full-time job and/or school while dealing with UCD. I work full-time and go to school part-time, but it has been a long and difficult road to get to a place where I am fulfilled and able to stay healthy. Some tips that were shared by several UCD adults included informing your employer of your illness in case of an emergency, keeping a standing order for a blood ammonia level with you, wearing a medical alert bracelet, taking your meds to work with you, and keeping sugar packets/candy in your purse or desk drawer in case of times of fatigue or nausea.

The Low Protein Diet for Life session gave insight on how to handle issues about compliance with diet, school inclusion issues that UCD children are bound to face, as well as low protein recipes tips. It was suggested that families make low protein meals that everyone can eat. There are many companies that make low protein foods now and you can find recipes online as well (NUCDF also has a Recipe Book). When I was younger we did not have these resources and my mother would commonly make me a “butter boo” sandwich -- two pieces of very thin Pepperidge Farm bread with butter. I am glad that UCD children have more options today and hope to see more in the future. Thanks to NUCDF, we’ve come a long way.

The Clinical Trials Workshop was very informative for those seeking ways to get involved with testing new medications (HPN-100 Trials), as well as other research that will accelerate development down the road. These opportunities include the Longitudinal Study, neuroimaging studies study being conducted by Dr. Andrea Gropman and many more. I am a participant in the HPN-100 trials, Longitudinal, and OTC neuroimaging study. I have found all three to be relatively easy to participate in and beneficial for myself and my family.

I am so glad that I was able to attend the Denver conference and make new friends and reconnect with old ones. Michael and I both enjoy the conferences and it is cathartic for us to talk with families who understand the struggles we face. Both of us will hold the memories of Denver with us for a lifetime. I am proud to be a member of the NUCDF and am very excited about the developments to come. I frequent NUCDF’s online ReachUCD community often. It is a great place to get to know others in our community, learn more from the resources and videos, ask questions or voice concerns. Cindy Le Mons has asked me to be involved as a mentor for our UCD teens. Years ago many of our pioneer UCD families did not have these resources and today it helps us to connect and not feel so alone in our battles. My husband has even joined and finds it beneficial as a spouse to have as an outlet. I hope to see many of you at the 2012 conference in Washington, DC!

Warmly,
Emily Rohrer
Commitment to Saving Lives

A Newborn Screening Test for OTC Deficiency

Dr. Piero Rinaldo, a pioneer in NBS at Mayo Clinic in Minnesota, has developed an analytical tool to detect OTC from newborn blood spots. Similar tests are already available for ASA and citrullinemia and have been part of the state newborn screening panels for several years. NUCDF has been supporting the validation of the OTC analytical tool by asking OTC families to release their child’s newborn screening test to the study. Dr. Rinaldo utilizes the screens to fine-tune the specificity of the OTC analytical tool. He has been successful in detecting OTC from NBS results.

NUCDF has convened a Task Force to ensure addition of OTC deficiency to the Health and Human Services uniform newborn screening panel. The Task Force will be responsible for compiling the information necessary to nominate OTC to the recommended panel and promote its approval by the HHS Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children. The SACHD is responsible for evaluating evidence-based and peer-reviewed recommendations regarding conditions for which all newborns should be screened, including inborn disorders like OTC.

For a disorder to be considered for formal review, the following conditions must be met:

1. The nominated condition is medically serious.
2. Prospective pilot data (U.S. and/or international) from population-based assessment are available for the disorder.
3. The spectrum of the disorder is well described, to help predict the phenotypic range of those children who will be identified on population-based NBS.
4. There is a screening test that is capable of identifying the condition.
5. If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky.
6. There are defined treatment protocols, FDA approval/clearance (if applicable) and availability of treatment.

Coverage for Nutritional Treatments

Medical Foods Equity Act

NUCDF has been participating in efforts led by NPKU Alliance to support the passage of the Medical Foods Equity Act. Senate Bill S.311 was introduced by Senator John Kerry. House Bill HR 1311 was introduced by Representative Baldwin of Wisconsin. The Medical Foods Equity Act would require:

- Insurance companies to cover the cost of medical foods, and pharmacologic doses of vitamins and amino acids.
- Insurers cover the cost of medical equipment and supplies needed to administer medical foods.
- Secretary of Health and Human Services to determines the minimum yearly coverage for all health insurance plans.
- New federal standards would not preempt state standards that require a higher minimum standard.

NUCDF families have helped by contacting their legislators and asking them to sign on as sponsors of the bill. The bill is now in committee.

Please take a few moments to make a difference for all those who are struggling with access to treatment. Contact your legislators and ask them to support the Medical Foods Equity Act.

NUCDF signs onto NPKU Alliance letter to HHS Secretary Sebelius advocating for coverage of medical foods and formulas under the new Essential Health Benefits

In December 2011, Department of Health and Human Services (HHS) issued a “pre-rule bulletin” announcing its decision to offer “flexibility” to states in selecting essential health benefits. There will be no national set of essential health benefits; each state will be able to choose its essential health benefits from four specific categories. This flexibility does not guarantee coverage for medical formulas or modified low-protein foods — the cornerstone of treatment for UCD and many other inborn errors of metabolism. UCD families have helped by sending emails and letters to HHS educating the agency that failure to ensure coverage could lead to severe disability or death in patients with UCD, and that the cost of coverage is far less expensive than the enormous cost of hospitalization to care for sick UCD infants, children and adults.

TAKE ACTION - Sign a consent to release your OTC child’s state newborn screen to Dr. Rinaldo’s study. For details and to obtain a consent form, contact: CureUCD@nucdf
**2012 NUCDF CALENDAR**

**February**
- **UCD Families all over the world participate in Rare Disease Day.** NUCDF participates in special activities in Washington, DC as part of the National Institutes of Health Rare Disease Clinical Research Network’s Coalition of Patient Advocacy Groups (CPAG). NUCDF’s executive director is co-chair of CPAG, a coalition of over 90 rare disease advocacy organizations working to accelerate research for rare diseases

**March**
- **NUCDF will attend National Organization for Rare Disorders Workshop in San Francisco**
- **NUCDF executive director will participate in Urea Cycle Disorders Consortium strategic planning meeting**
- **NUCDF exhibits at the Society for Inborn Errors of Metabolism meeting in Charlotte, NC. (SIMD is an organization for medical professionals dedicated to research and treatment for inborn errors of metabolism)**

**April**
- **NUCDF executive director will participate in an invitation-only National Institutes of Health meeting, “Charting a New Course for Intellectual and Developmental Disabilities (IDD) Research”**
- **2012 NUCDF Family Conference Registration packets will be mailed out**

**May**
- **NUCDF sponsors 1st UCD Nutritional Management Guidelines Consensus Meeting in Washington DC**

**July**
- **NUCDF Annual Family Conference and Urea Cycle Disorders Consortium Joint Meeting, Washington DC**

**September**
- **NUCDF co-chairs Coalition of Patient Advocacy Groups Annual Meeting**

**November**
- **3rd Annual Cure the Cycle Challenge awareness and fundraising event, Napa Valley, CA**
- **Inaugural Rare and Precious Benefit Dinner and Auction, Culinary Institute of America, St. Helena, CA**

Together we can conquer UCD.

**Don’t miss a thing! Update your contact information!** We UCD families are so busy we often forget to keep our contact information updated so we can receive important news and alerts from NUCDF. If you haven’t updated your member information in awhile, you can use the Membership Form online to do so. Membership is free! Update your Member info at www.nucdf.org/membership.asp

**Need help or support? We’re here to help.** Have questions about research participation? Would you like to network with other UCD families or just stay in the loop? **NUCDF is all of us standing together to fight UCD.** Just send us an email to ucdsupport@nucdf.org or call us at (626)578-0833 (Pacific Standard time zone)

**Send in your story!** Every story is powerful and helps raise awareness of UCD. Your story can even help educate policymakers about the needs and concerns of our UCD families or be part of our new series of awareness videos.

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