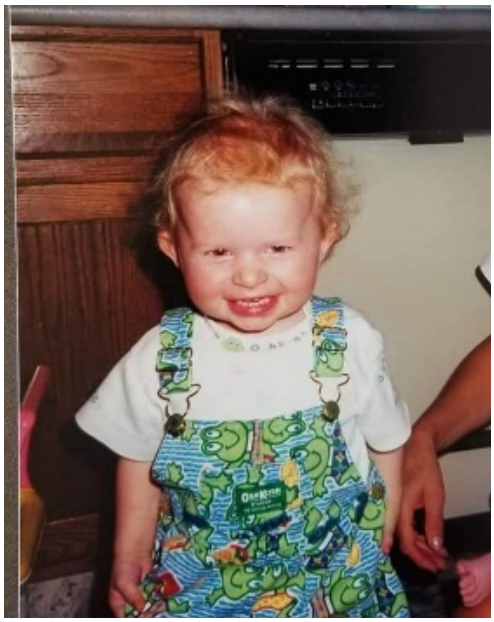
The HCU *Herald*

More HCU News Inside

HCU HERO: SAMANTHA FROM CANADA

My name is Samantha and I was not diagnosed through newborn screening. I was breastfed as a baby. My childhood genetic doctor, Dr. Greenberg at the Health Sciences Center in Winnipeg, Manitoba said this was probably one of the reasons why I didn't get sick until foods got introduced into my diet.



In my first few years I was one of those cranky babies; little did anyone know this was because I was actually a sick little girl. I was diagnosed with CBS deficient HCU around the age of 2 years old. I was seen by Dr. Paul Chapman who noticed my lenses were dislocated and had referred me to a childhood eye doctor. In November 2013 I underwent outpatient eye surgery to correct my bad lazy eye syndrome, which I had in both eyes.

I was put in the hospital around the age of 2 for several week at the Children's Health Sciences Center in Winnipeg after I had multiple seizures per day (no knows exactly knows when the seizures started.) I also had started to lose muscle tone to the point where I was unable to sit up on my own. I don't remember exactly how I was diagnosed; however, I was put through multiple different tests.

Homocystinuria has affected me growing up and currently in adulthood primarily with eye problems. (On my last exam my left eye was -9 and my right eye was -10). At some point in the next year or two I will have to undergo outpatient surgery once again to correct my lazy eye syndrome, and to correct my double vision. I was told at my last eye appointment with a specialist in September 2019 that I don't look straight at people and that my head is slightly tilted out of alignment. (I was shocked to hear this, but always had a feeling I never looked totally straight at people, with comments here and there growing up.)

It was predicted by my doctors at the time when I was first diagnosed that I would not make it through my first year - I proved them wrong. Later on my doctors thought I would not be able to walk or talk - I knocked their socks off once again proving them wrong. Growing up, I did have speech

therapy as I did not talk till a later age in development. Once I figured out how to talk, I never stopped. I do have some speech problems with stuttering and I believe this is from consuming too much protein. My limit is 40 grams per day. However, under doctor's supervision, I have cut that in half to 20 grams of protein per day to see it the stuttering decreases. I have always found it annoying when I stutter to the point where I will change wording just to complete a sentence, or stop all together because people don't have the time to listen to me trip over my sentences. Growing up I found myself to be unbalanced and sometimes still feel this way.

I feel I have overcome a lot of my challenges by showing people I could do what they thought I was never capable of doing – I proved them wrong. Adults thought I was dumb, but it turns out I was smarter than they thought. I graduated from High School in 2016 and graduated from Confederation College in Kenora, Ontario (my hometown) in 2019. Istudied Early Childhood Education and I am now a Full Time Preschool Teacher. I teach children ages 2.5 years to 4 years in age. I teach children about colors, numbers, patterns, ABC's, nursery rhymes, songs, and much more. I love every minute.

I have recently found that I love to travel. In September 2019 I traveled to multiple places in Australia for a month and absolutely loved every minute! My next trip is coming up in October 2020 and will be travelling with my good friend Paige to different parts of Egypt. I cannot wait, I'm so excited!

Over the years I have gotten better at telling my friends and co-workers about my genetic disease. They do not understand fully what Homocystinuria is, but they do understand that I cannot have a lot of foods that they normally eat. They are great in accommodating my needs when it comes to outings and asking what I am able to have.

If I ever get the chance to tell another HCU patient or parents of a child newly diagnosed, I would tell them, "things will get worse before they get better, but not to worry as there's always a light at the end of every tunnel". I would tell them to never give up on yourself or your child and to always believe you or they are capable of doing anything, and to not look at Homocystinuria as a disability but as a gift of love for the person they or their child is now and will become in the future.

RECIPES FROM THE KITCHEN:

Lemon Bars

Makes 9 servings

Ingredients:

Crust

- 1 1/4 c Cambrooke Baking Mix
- 1/2 tsp Salt
- 2 tsp Lemon Zest
- 4 TBSP Butter, unsalted melted

Filling

- 13 1/2 fl.oz. Canned Coconut Milk
- 3 fl.oz. Sweetened Condensed Coconut Milk
- 1/4 c Sugar
- 30 g Lemon Pudding, dry mix only, Instant
- 1 tsp Lemon Zest
- 1 1/2 tsp Agar Agar powder
- 1/4 c Lemon Juice

Nutritional Information

- Serving size: 1 bar
- Protein per serving: 0.8 g
- Calories per serving: 241

Directions:

1. Preheat oven to 350 degrees. Line a 9x9 or 8x8 square pan with parchment, allowing some to trail over the edge. This will help with easy removal of the bars.
2. In a small bowl combine the baking mix, salt, and lemon zest. Gently mix to combine. Add the melted butter and gently mix until moistened. Pour into the prepared square pan. Gently press mixture around bottom of pan until it reaches all sides. Make sure the crust is even across the bottom. Bake for 12 minutes. Remove from oven and allow to cool.

1. While the crust is cooling, prepare the filling. In a small bowl add the pudding mix, agar agar powder, and lemon zest. Set aside. In a medium saucepan, add the coconut milk, sweetened condensed milk, and sugar. Place on stove on medium heat. Bring to a slow simmer, stirring occasionally. Combine the pudding mixture and lemon juice. Mix together. It will get thick. Add to the heated coconut milk mixture. Continue to cook over medium heat, whisking frequently, until thickened enough to coat the back of a spoon. Pour filling onto cooled crust. Refrigerate, uncovered, until firm. Once firm and cold it can be covered. Remove bars from pan to cut. Serve cold with a sprinkle of powdered sugar.

THANK YOU, CHEF AMBER GIBSON

RECIPES FROM THE KITCHEN:

Biscuits

Makes 7 servings

Ingredients:

- 2 c Cook for Love Baking Mix
- 1/4 c Better Than Milk, Rice Milk Powder
  - Pictured below
- 2 tsp Baking Powder
- 1/2 tsp Baking Soda
- 3/4 tsp Salt
- 4 TBSP Butter, cold, cut into cubes
- 1/4 c Sour Cream
- 1/4 c Rice milk

Nutritional Information

- Serving size: 1 biscuit
- Protein per serving: 0.8 g
- Calories per serving: 205

Directions:

1. Preheat oven to 375 degrees. Line a baking sheet with parchment and set aside.
2. Combine all dry ingredients in a medium bowl and gently whisk to combine. Using a pastry blender or your fingers, cut the butter cubes into the dry ingredients until mixture resembles corn meal. Using a fork, mix the sour cream into the butter mixture. Add the rice milk (or other nondairy milk of choice) and mix until the dough can hold together.
3. Lightly dust counter with baking mix and dump the dough onto the counter. Knead until dough is smooth, but do not over mix. Gently pat dough into a disc that is one inch thick. Using a round biscuit cutter, cut rounds of biscuits out of the dough and place onto the prepared baking sheet. Bake for 12 to 14 minutes until lightly browned. Do not over bake.

RECIPES FROM THE KITCHEN:

Breakfast Gravy

Makes 3 servings

Ingredients:

- 1/2 c Rice milk
- 1/2 tsp Cambrooke Chicken-Flavored Consommé & Seasoning, dry
- 1 TBSP Cambrooke Sausage Patty Mix
- 1 tsp Butter
- 15 g Small diced white button mushrooms

Nutritional Information

- Serving size: 42.6g
- Protein per serving: 0.4g
- Calories per serving: 42

Directions:

1. In a one cup measuring cup add the rice milk, consommé powder, and sausage patty mix. Gently mix to combine and set aside.

2. In a small skillet over medium heat add the butter. Once melted, add the mushrooms and sauté for two minutes. Pour in the milk mixture. Cook over medium heat, continuously whisking until thickened. Remove from heat immediately as you do not want it to thicken too much. Season with salt and pepper if desired. Serve warm

Dear Methia,

Does More Betaine, Mean More Protein Allowance?

I've been taking Betaine for as long as I can remember, and the only thing I know is that it's supposed to decrease my homocysteine levels. I take it twice daily without any problems. What I don't understand, though, is why this low protein diet is really necessary if I'm the right dose of my medications? My friend with homocystinuria from camp told me that she stopped counting her protein, doubled her Betaine dose and that this should "even out" her levels. Is this true? I don't think anyone from her metabolic clinic advised her to do that.

Sincerely,
Medication Maniac

Dear *Med Maniac,*

Whoa! This is a pretty complicated question, with an equally complicated answer. I'm going to start this lesson with a firm statement: With classic homocystinuria (HCU), you cannot achieve good metabolic control without both protein restriction and your prescribed medications - most importantly, Betaine. In fact, not restricting your protein while taking Betaine can be dangerous. The reason for this goes back to the methylation cycle (have you ever looked at that? What a headache!) which I'll attempt to simplify for you in a few steps here:

1. **Methionine is an essential amino acid.** Amino acids are the building blocks of proteins that are found in every cell in the human body. Your body can make some of these amino acids on your own. However, methionine is one of the eight amino acids that all bodies cannot make and therefore have to obtain from food, making it an essential amino acid. This is why, with HCU, you cannot completely eliminate methionine from your diet – it's vital to your health, but not too much of it! (I like to call this the "Goldilocks Rule").
2. **Methionine is converted to homocysteine in the methylation cycle.** When you eat foods with protein, multiple reactions take place to make this conversion. In classical HCU, this step in the breakdown of methionine is not "broken."
3. **Homocysteine is supposed to be converted to another amino acid, cysteine, with the help of an enzyme called cystathionine beta synthase (CBS).** Homocysteine is what we call an "amino acid bridge" to cysteine, meaning its intended fate is to be properly converted. In classic HCU, THIS is the step that is "broken," because the CBS enzyme does not work properly. Homocysteine then builds up in the bloodstream, placing you at risk for blood clots.
4. **Trimethylglycine (Betaine, or brand name Cystadane) is a compound that is prescribed in HCU to convert homocysteine back to methionine to reduce homocysteine levels.** Betaine is a low toxicity compound and prescribed by doctors at patient-specific doses to treat HCU. While it is very effective and essential for management, it is not a cure.
5. **Because Betaine converts homocysteine back to methionine, it would make sense for methionine levels to be higher than normal in patients with HCU – even with good control.** When your geneticists see you for follow-up, they will probably order both homocysteine levels and plasma amino acids to check your methionine for routine monitoring. Because you have HCU, methionine levels will be a little higher than for someone without HCU.
   When you eat more protein than you should, your methionine levels will be higher – but add Betaine to the mix, and you could see a critically high value. A high methionine intake combined with a medication that causes your body to essentially produce MORE methionine can result in levels as high as 1,000 micromoles/L. This is a critically high value that has been linked to brain edema (https://onlinelibrary.wiley.com/doi/full/10.1002/jmd2.12092) and could be the result of too much protein, too much Betaine, or both!

Dosing your medications and determining the right amount of protein for you is a delicate balance – both of which are incredibly important for your management. You should not make these changes on your own. But don't forget that you are the most important member of your care team, and asking these questions and communicating with your clinic is the best way to advocate for your best care.

Sincerely,
Methia

HCU NETWORK AMERICA

IS LOOKING FOR STATE AMBASSADORS

Looking for active and outgoing members of the HCU community

What does an ambassador do?

Ambassadors...

- *Connect with local HCU families*
- *Share their story*
- *Advocate and raise awareness for HCU*
- *Amplify and support our mission*
- *Help fund-raise*

Get involved today! Contact Danae'
dbartke@hcunetworkamerica.org

BECOME A STATE AMBASSADOR FOR HCU NETWORK AMERICA

HCU Network America

Focused on the Few™...

At Recordati, we focus on the few - those affected by rare diseases. They are our top priority and at the core of everything we do. Our mission is to reduce the impact of extremely rare and devastating diseases by providing urgently needed therapies. We work side-by-side with rare disease communities to increase awareness, improve diagnosis and expand availability of treatments for people with rare diseases.

Recordati Rare Diseases is proud to support HCU Network America in their commitment to people living with HCU.

RECORDATI RARE DISEASES GROUP
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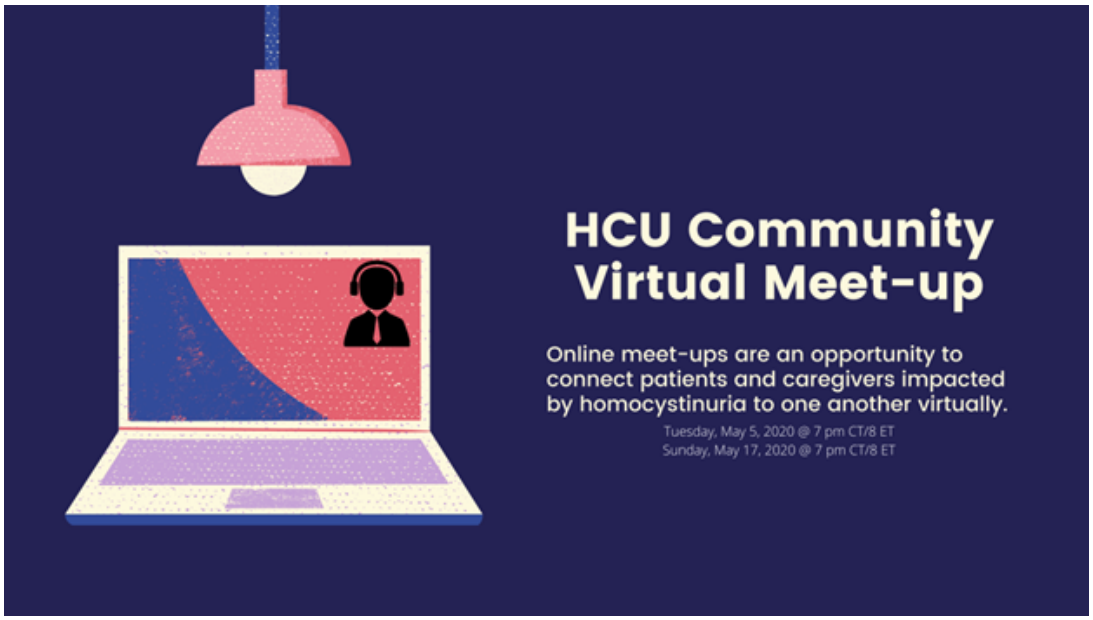
NP-RRD-US-0162

EVENTS



Come check out our Virtual Homocystinuria Meet-up!

Join our virtual meet-up for a chance to meet, connect, and learn from other patients and caregivers who are facing similar challenges. Whether it's navigating diet adherence issues, insurance, clinic visit, or life transitions, you are not alone.

Space is limited, so make sure to register early! Once registering, you will receive additional details about accessing the meet-up. Register now at:
https://www.eventbrite.com/o/hcu-network-america-30163980100

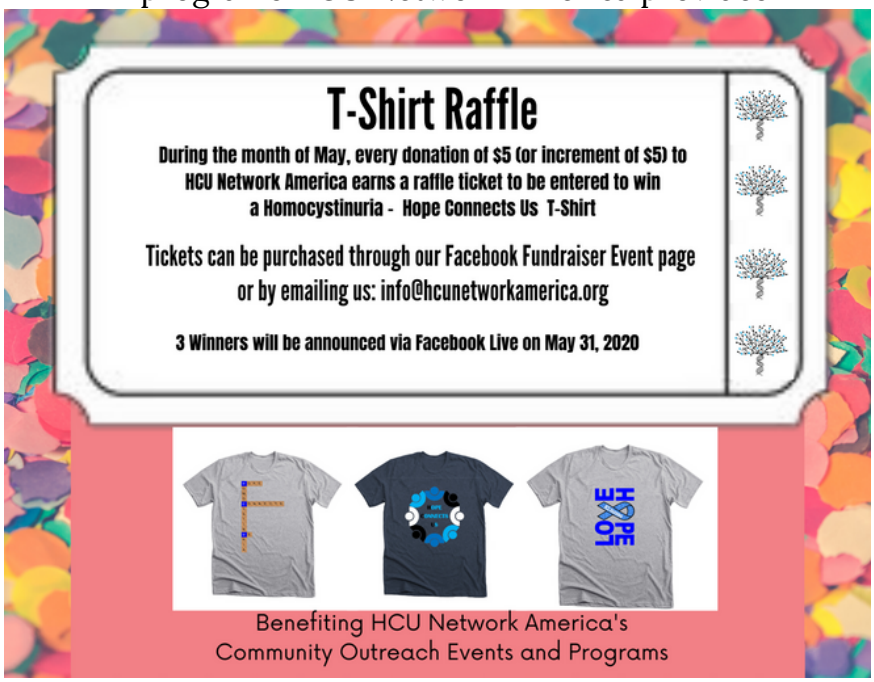
Because of the unexpected health crisis surrounding COVID-19, HCU Network America is taking the necessary precautions and postponing our virtualrace till later this year (likely early fall). While we know that in most cases our community members can safely partake, there are still other parts of the country where it's not safe because of the dense population and higher incidence rate.

We will be evaluating the situation and will update the community with new dates when it is appropriate. We will keep our race website live, but temporarily close registration till we have a new date in mind.
Thank you for your understanding -
The HCU Network America Fundraising Team

EVENTS

Now more than ever, our community needs hope!

Each raffle ticket sold helps support the numerous critical homocystinuria community outreach programs HCU Network America provides



COVID-19 Resources

- NORD Launches Financial Assistance Program for Rare Disease Community Members Impacted by COVID-19
  - April 15, 2020—At this time of crisis and with the health, safety and well-being of patients and caregivers as its top priorities, the National Organization for Rare Disorders (NORD®) today launched its COVID-19 Critical Relief Program to provide much-needed assistance to members of the rare community affected by the COVID-19 pandemic. The program provides financial relief that may be utilized to support critical, non-medical needs.
    - To learn more, visit: https://rarediseases.org/nord-launches-financial-assistance-program-for-rare-disease-community-members-impacted-by-covid-19/

- Healthwell Foundation Launches COVID-19 Ancillary Costs Fund
  - The coronavirus public health emergency has affected almost every aspect of our daily lives. If you or a loved one need assistance with costs associated with delivered food, medication, diagnostics, transportation and telehealth as a result of COVID-19 risk or incidence, we may be able to help.
    - To learn more, visit: https://www.healthwellfoundation.org/fund/covid-19-fund/?

- #IStayHomeForRare is proud to announce the opening of their new campaign and fund, providing immediate support to families and individuals in the rare disease community.
  - #IStayHomeForRare join us in solidarity with those staying home protecting the lives of children, family members, and friends living with rare diseases.
    - To learn more, visit: https://www.istayhomeforrare.org/apply

MEET THE RESEARCHER: INTERVIEW WITH KENNETH MACLEAN

BY LAURIEBONUCCI, MOTHER OF HCU PATIENT AND MEMBER OF PATIENT PARENT ADVISORY AND FUNDRAISING COMMITTEE

Ken Maclean PhD
Professor of Pediatrics
Ehst-Hummel-Kaufmann Family Endowed Chair
in Inherited Metabolic Disease
Department of Pediatrics
University of Colorado School of Medicine

Dr. Maclean was the 1st Recipient of HCU Global Grant Research Award, an effort that is jointly sponsored by HCU Network America and HCU Network Australia to support research on potential advances in the diagnosis and treatment of classical HCU. A grant of $40,000 was provided to support his project to investigate the potential usage of different metabolic strategies designed to increase the efficacy of betaine to treat CBS deficient homocystinuria (HCU), which was funded through contributions from the Hempling Foundation for HCU Research, donors to HCU Network Australia and the William R. Hummel Homocystinuria Research Fund.

Laurie Bonucci (LB): Tell us a little bit about yourself, Dr. Maclean?

Dr. Ken Maclean (KL): I came from England to the United States 22 years ago. I told my wife we were only coming for 2 years – now she doesn't believe anything I say. My children were born here. My Ph D was in Microbiology, Biochemistry and Genetics. I did a post doc on cancer research at the Royal London Hospital (which is famous for Jack the Ripper). I came to the US to work in the lab of Jan Kraus at the University of Colorado, which is when I started working on HCU. After working with Jan on the CBS Enzyme and its regulation, I became an assistant professor and got my own lab.

I decided to shift my focus to concentrate on what the consequences of the absence of the enzyme would be – how would that affect gene expression and biochemistry, and how would those changes affected pathogenesis and clinical sequelae, and how can we design treatments to affect that process and prevent those issues. We developed a mouse model that would be better than the current one as the mice would not get liver failure so we could do better experiments. More importantly, our mouse model of HCU is the only model that responded to betaine treatment in a manner consistent with that seen in human patients and when untreated, our mice showed a wide range of the pathogenic features common in the human disease. Consequently, our mouse model of HCU is extremely useful for understanding pathogenesis and for both improving existing treatments and the rational design and testing of new ones.

LB: How did you come up with the idea to study formate as a potential approach to improve betaine response?

KM: Patients with homocystinuria due to methionine synthase/cobalamin disorders were known to have a poor response to betaine. Formate or formic acid were studied by Professors Sean and MargaretBrosnan at Memorial University in Canada, who predicted formate levels would be higher in MTHFR and Methionine synthase deficient /Cobalamin patients than in classical HCU patients. I showed this was true with 2 different mouse models and wondered if this increased level of formate might be inhibiting the betaine response in remethylation disorders i.e. does formate "poison" the betaine effect in patients with these disorders. If this hypothesis were to be true, one might reasonably expect giving formate to HCU mice might impair their response to betaine as well. That was the theory but, adding further evidence to the idea that it's better to be lucky than smart, we saw the exact opposite. Instead when we gave formate to our HCU mice we saw HCY levels come down by 50% and when we gave it in combination with betaine, HCY came down to near normal, even in the presence of a full methionine/protein diet. This kind of lowering of homocysteine is quite simply phenomenal and we are now working to understand the full mechanism by which it works and how to apply it safely to human patients.

LB: So how did your study turn out to replicate these initial results?

KM: We have replicated the initial results multiple times and showed that relatively low doses of formate combined with betaine can bring HCY levels in mice to near normal even in the presence of a normal diet. We showed it did so at levels that would be considered safe but some safety concerns do still remain. We also showed that other metabolic disruptions caused by HCU were lessened or completely reversed. We confirmed that you do not see the same effect using other one-carbon donor compounds or serine, glycine or other amino acids that are capable of being converted to formate. And we also have promising evidence of some novel strategies to increase safety and further improve the efficacy of the betaine response that we are not yet ready to disclose due to Intellectual Property reasons.

LB: So do you think you would be able to administer the formate directly to patients?

KM: As formate can cause issues in the body at high levels, we are working on attaching the formate to another molecule like glycerol or glucose so it can be activated by an enzyme in the GI tract and gradually released into the body.

LB: Where will you go next with your research?

KM: We have finished the work funded by the HCUNAs grant, so we are looking for more funding for our basic research, and I am talking to potential commercial partners who are interested in coming up with a way to formulate formate for commercial use – for example, maybe even via a genetically engineered probiotic bacteria that could be taken with food. That bacteria would be unable to reproduce in the gut but would create a steady gradual supply of formate to amplify the betaine response.

LB: How do you see your research being able to change patient lives?

KM: We have short, medium and long term goals to help HCU patients
Short term – understand basic science as to how pathogenesis occurs using metabolomics, microarrays, RNA seq, proteomics. Using this approach, we now have candidate pathogenic mechanisms for everything that goes wrong in HCU patients and we will be investigating those further in our animal model of the HCU. We also hope short term to improve existing treatment – e.g. formate added to betaine

Medium term – We wish to design new treatments to allow better management and to enable HCU patients to follow a normal diet.

Long term – a cure – which will likely involve either gene therapy or gene editing

LB: Any Final Words for the HCU Community?

KM: Please know you're not alone – we are on your side and your support is invaluable. If anyone has any questions about HCU in general or wants to talk about where the research is going, I am available (during office hours) to talk to anyone. I know having a rare disease can be quite isolating – your neighbors don't understand what HCU is or what it feels like and your primary care doctors may not fully understand the disease. Know that you are not on your own and that we are working very hard every day to try and improve clinical outcome for HCU!

HCU IN THE NEWS

- **Tomas Majtan Receives Second Grant for the CBSDeficiency Global Grants Program**
  - On March 5, 2020 HCU Network America and HCU Network Australia announced the second recipient of their CBS deficiency global grants program – awarding a research grant to Tomas Majtan at the University of Colorado Anschutz Medical Campus in Aurora to explore a potential treatment for homocystinuria due to CBS deficiency. The research aims to investigate the potential benefits of thiol-based reductants in CBS-deficient homocystinuria (HCU). Dr. Majtan is an Assistant research professor of Pediatrics at the University of Colorado Anschutz Medical Campus, and has had a longstanding interest and involvement in homocystinuria research, including working with Dr. Jan Kraus to develop the Enzyme Replacement Therapy OT-58.
    - To read the full press release click here: https://hcunetworkamerica.org/second-recipient-of-the-cbs-deficiency-global-grants-program-announced/
- **OT Receives Rare Pediatric Disease Designation from FDA for OT-58 to Treat CBS Deficient HCU**
  - March 26, 2020 Orphan Technologies, a company dedicated to helping patients control their homocysteine levels, announced that OT-58 for the treatment of CBS deficient homocystinuria has been designated a rare pediatric disease (RPD) by the US Food and Drug Administration (FDA). Under the RPD program, if a new drug application for OT-58 is approved, Orphan Technologies is eligible to receive a priority review voucher that may be utilized for subsequent human drug applications. OT-58 has previously been granted both Fast Track Designation and Orphan Drug Designation by the FDA.
    - To read the full press release click here: https://www.businesswire.com/news/home/20200326005383/en/Orphan-Technologies-Receives-Rare-Pediatric-Disease-Designation
- Aeglea receives CTA for its Novel Engineered Human Enzyme Designed to Treat HCU (ACN00177)
  - April 08, 2020 Aeglea BioTherapeutics, a clinical-stage biotechnology company developing next-generation human enzyme therapeutics as solutions for diseases with high unmet medical need, announced the approval of its Clinical Trial Application (CTA) by the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) for ACN00177, a novel engineered human enzyme therapy designed to treat Homocystinuria, a serious metabolic disorder characterized by elevated plasma homocysteine levels, leading to a wide range of life-altering complications and reduced life expectancy. This enables Phase 1 studies in humans to begin.
    - To read the full press release click here: http://ir.aegleabio.com/news-releases/news-release-details/aeglea-biotherapeutics-announces-approval-clinical-trial

In this difficult time, it is important for you to stay informed. Get connected with Nutricia by signing up with Nutricia Connect. For each new sign-up, we will donate $5 to an organization shown here. (You can choose which when you sign up).

Learn more & sign up today.
https://bit.ly/2TwS5xn

Contact Register

What is the contact register?
The contact register is a secured private survey that allows you to share information on you or your family member with HCU with us. This includes where you are from, your relationship to homocystinuria, the patient's birthdate, gender, their exact diagnosis (e.g. CBS, cobalamin, or MTHFR), how they were diagnosed, and if the patient was diagnosed through newborn screening. This information is kept confidential and will not be shared unless you give us permission. By registering, you will be able to identify other patients in your state and request their contact information. You will also be able to access information posted over time that can only be shared with the patient community. (For example, we may have webinars that the expert presenter does not want to be publicly available, but is willing to share with the HCU community.)

What will this information be used for?
HCU Network America strives to inform patients and families with resources, create connections, and support advancement of diagnosis and treatment of HCU and related disorders. The information you provide helps us succeed in our mission - plan events, develop resources and educational tools, and ensure everything is being done to support timely and accurate diagnosis from birth. It also allows us to have informed conversations with doctors, pharmaceutical companies, and law makers. Your information helps us understand the landscape better so we can better advocate for you!

How do I participate?
The contact register form takes approximately 3-5 minutes to complete. You can find the form either by visiting our website and clicking on the "Contact Register" tab, or you can fill it out by going directly to: https://hcunetworkamerica.org/contact-register/