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MSUD NEWSLETTER

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FROM THE PRESIDENT'S DESK

By Sandy Bulcher

2020 will be remembered as the year that Covid-19 changed our lives in some way or another. I am happy to have a job since so many have lost theirs. For the first time in my 38 year career as a nurse, though, I'm working from home a few days per week. Besides our livelihoods, Covid-19 has affected the health of some of those with MSUD and their families. I think about my MSUD family frequently and pray for your health and safety.

Covid-19 impacted our symposium which was to be held this summer in June. We made the decision in March to cancel the symposium when it became clear that it was unsafe to gather and risk the spread of Covid-19 among our vulnerable population. The symposium is our biggest event and a great opportunity to learn more about MSUD and connect with others. I hope that you are staying connected with each other and supporting each other as much as possible during this challenging time.

Good news, though. Planning for the next symposium has begun. It will be held in Lancaster, PA and hosted by the Clinic for Special Children in the summer of 2022. In the interim, we will continue to keep you abreast of new information through the newsletter, website and e blasts. Covid-19 can't stop us from working towards our goals. Please consider being more active in the areas of fundraising and advocacy. And as always, feel free to call or email me as needed. (740-972-5619, sandybulcher@gmail.com) ■

ADVANCING MSUD RESEARCH THROUGH A PATIENT REGISTRY

By Karen Dolins

Development of a Patient Registry was identified by our Scientific Advisory Board as our #1 priority. A robust registry will help inform the research community about the needs of the MSUD community. The more people who enroll in the Registry, the more powerful this tool will be.

As the NBS Connect registry has been discontinued, we have now partnered with Coordination of Rare Diseases at Sanford (CoRDS) to continue this essential work. We expect the registry to be "live" later this fall. Please look for an announcement which will be sent via mail, email and will be posted on our website.

The value of our registry increases with the number of participants enrolled. If you participated in the NBS Connect Registry, we thank you. We are grateful for the work of the Emory University Metabolic Genetics team in developing the NBS Connect registry, which was used as a template for our CoRDS registry. As there are differences in the information collected between the two registries, we hope you will continue your contribution by participating in this one as well. ■

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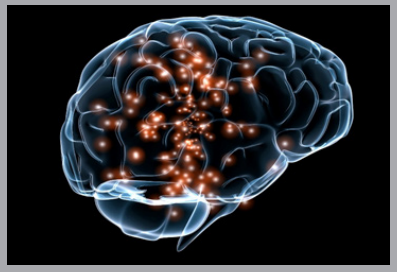

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From the Editor

By Karen Dolins

What a strange and stressful time this has been. Our family, like yours, has been consumed by the urgency of staying healthy now more than ever. We are grateful that we are all well, and hope that you are too. I am also grateful that Jonah Gross was willing to tell us about his experience with Covid-19. I'm sure you'll find his article gripping. While Jonah has recovered, we join the McCain family in mourning the loss of Christopher of unknown causes. His mom, Melinda, gives us a peek at who he was and shares some of what made him special.

This issue of the MSUD Family Support Group newsletter includes research updates, family stories, and food and nutrition information. You will also learn how you can help advocate for the needs of those with MSUD and help further our research efforts. I hope you will find this issue to be inspirational and informative.

We are thankful for the support of our advertisers, and for all of you who make us a community. ■

MEET THE NEW MSUD FAMILY SUPPORT GROUP SCIENTIFIC ADVISORY BOARD

***By Karen Dolins**, Board Secretary and MSUD FSG Research Lead*

A major goal of our board of directors was to create a scientific advisory board (SAB), a group of experts who would guide us as we develop our research portfolio. I am thrilled to report that a renowned group of scientists was invited to join, and all accepted!

We designed our SAB to include experts in a variety of areas including basic biology, neuropsychology, gene therapy, clinical care, and nutrition. Our SAB includes leaders in their fields who are helping us develop our research strategy, prioritize research projects, and evaluate proposals for funding that we receive.

Our first meeting was held remotely in June. The SAB was unanimous in identifying a MSUD Registry as an essential first step. Please read about our new Registry on the cover page of this newsletter.

Several SAB members are also helping evaluate research proposals submitted to the University of Pennsylvania's Orphan Disease Center. The worthiest candidates will receive grants funded by this year's Million Dollar Bike Ride.

MSUD Family Support Group Scientific Advisory Board*

David Fischler, PhD	Post-doctoral ORISE Fellow, Centers for Disease Control, Classical MSUD
Andrea Gropman, MD	Division Chief, Neurodevelopmental Disabilities and Neurogenetics at the Children's National Medical Center, Washington, DC
Irini Manoli, MD, PhD	Physician Scientist and Clinician Associate Investigator, Organic Acid Research Section of the National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH), Bethesda, MD
Gregory Rice, MD	Waisman Center at the University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI
Kevin Strauss, MD	Medical Director, Clinic for Special Children Lancaster, PA
Dan Wang, PhD	Assistant Professor, Horae Gene Therapy Center and RNA Therapeutics Institute University of Massachusetts Medical School, Worcester, MA
Tilla Worgall, MD, PhD	Associate Professor of Pathology & Cell Biology and Pediatrics, Columbia University Medical Center, New York, NY
Richard Wynn, PhD	Associate Professor, University of Texas Southwestern Medical Center Dallas, TX

**Bios will be posted on our website*

Complex MSD Formulas: Backed by Over 10 Years of Clinical Data

Complex MSD formulas from Nutricia North America reach an exciting milestone this year: these formulas have been available to provide advanced nutrition to individuals with maple syrup urine disease (MSUD) for 10 years. These formulas are backed by over 10 years of clinical data.

Complex formulas are specifically designed for MSUD and are supported by two scientific publications.*

There are three Complex MSD formulas for various ages and needs. Here is an overview of these specially designed formulas for MSUD:

Complex Junior MSD Drink Mix provides essential vitamins & minerals to **meet the needs of young children.** This formula can also be used during Sick Days when additional energy is needed.

Complex Essential MSD Drink Mix is Nutricia's higher protein option for children, teens, and adults (compared to Complex Junior MSD Drink Mix). This formula provides an **excellent source of calcium & vitamin D.** It is available in an easy-to-drink, smooth vanilla flavor.

Complex MSD Amino Acid Blend is a **concentrated source of MSUD protein.** Complex MSD Amino Acid Blend can be added to other MSUD formulas or low protein drinks and foods for more flexibility and variety.

Ask your clinic about Complex MSD formulas. All products shown are medical foods for the dietary management of MSUD and must be used under medical supervision.

*Strauss KA, et al. Mol Genet Metab. 2010;99:333-45 and Strauss KA, et al. Mol Genet Metab. 2020;129:193-206.

NUTRICIA

Advocacy Update - ACTION NEEDED! Medical Nutrition Equity Act

By Jordann Coleman

The Medical Nutrition Equity Act ensures public and private insurance coverage for medically necessary foods when prescribed by a physician. **The bill is of vital importance to the MSUD community**. It was originally introduced in 2018, during the 115th session of Congress, but never made it to the floor for a vote. The bill was reintroduced into the 116th Congressional session on May 2, 2019, and continues to gather more support. The House Bill (HR2501) currently has 74 co-sponsors (63 Democrats and 11 Republicans) and is led by Representatives Jim McGovern (D-MA) and Jamie Herrera Butler (R-WA). The Senate version of the bill (S3657) was introduced this past May and is led by Senator Joni Ernst (R-IA) and Senator Bob Casey (D-PA).

We need your support to move this bill forward. Go to https://nutritionequity.org/contact-congress/ to send an auto-generated email to your members of Congress. You can also visit medicalnutritionequityfor.us to share why having coverage for medical nutrition is important to you and your family. Please share with your friends, family & social networks and ask them to contact their Congressional members. Together we can make coverage for medical nutrition a reality! ■

The 2020 Million Dollar Bike Ride

***By Butch Foster**, Team Scott Leader*

I would like to begin by saying what a great honor and privilege it was to be your team leader for this year's bike ride. Also, I would like to send a special thanks to the dedicated team of workers from the University of Pennsylvania's Orphan Disease Center who worked through the great challenges presented by the pandemic and made this year's event a reality. Although it was not held in Philadelphia, the show still went on and our Team Scott was able to raise enough to support one or two research projects for 2021.

This event is our one big fundraiser of the year and is critical to our goal of improving treatment, quality of life, and finding a cure for MSUD. We have been fortunate to be invited to participate in this event for the past three years and it is my hope that through hard work as an organization we can continue to participate for many years to come.

I would like to take this opportunity to ask those of you reading this newsletter to please think about helping make this event even bigger in the years to come. "Many hands make light work" is an old saying, and I hope you will all think about joining us in this great event in the future.

I would personally like to thank all of the participants in this year's MDBR for all of your hard work and dedication in making this a successful event. I would like to make a special shout out to Taryn Kessel for again leading us in the fundraising department. She is truly AMAZING! And finally to our great board of directors, I so appreciate all the hard work you do for the MSUD Family Support Group year in and year out. I enjoy working with such a dedicated group. ■

FAMILY NEWS

Matthew Christopher McCain

April 2003-May 2020

By Melinda McCain, mom

Our son, Matthew Christopher, was born April 2003 by emergency C-section to my husband Matthew and me. Newborn screening for MSUD was not yet available in Tennessee, although it would be added 6 months later. He was hospitalized at 1 week of age and diagnosed with classic MSUD at two weeks of age. Thank God that the geneticist was doing her rounds on the special care unit that day!

The first few years of life were stressful: lots of appointments, lots of therapy, and learning to feed a baby through a gtube. In addition to MSUD, Christopher (he went by his middle name) had difficulties with his legs and feet. His feet rolled inwards and his left leg was weaker than his right. He wore braces from the time he was a baby and had surgery to lengthen his tendons when he was 10 years old.

Through all these challenges, Christopher was a happy and smiling baby. As he grew, we thankfully didn't have as many hospitalizations, so he could be as "normal" as possible. Time flew, and before we knew it, he was in high school and had blossomed into an independent young man. Something we had wanted for him from day one.

He loved art, music, bright colors, Harry Potter, cats, and Jesus. He had just decided this year to become an art teacher at his elementary school. We were proud of him for overcoming so much and were excited to see what his future held. He did not let having a metabolic disorder, walking with a gait, and using a walker bring him down.

Unfortunately, on May 5, 2020, his heart stopped beating. The doctors were not able to determine why this happened. He had been to the doctor as he wasn't feeling well, and his leucine was normal. We are still dealing with the what ifs and the why of losing him after 17 short years and all he had been through.

We have hope because we know we will see him again in heaven one day! We continue on, knowing that he has given life to others. His heart beats on a few hours from here. He donated a kidney and liver to a local lady and his other kidney to a local man.

Hold on to your loved ones, we never know when their time may be called.
He was God's rainbow in our lives. ■

My Story is Not Like the Others

By Catarina Correia da Costa

Hello, my name is Catarina Correia da Costa, I am 26 years old and I live in Portugal. My parents are doctors. My father is a pediatrician and my mother is a child psychiatrist. I have a younger sister Maria who does not have MSUD.

It all started when I was born on April 29, 1994. A normal girl was born into the world, but it wasn't at all as my parents imagined it would be.

At 10 days of life I didn't gain weight, I didn't feed well at my mother's breast, I slept a lot, and I was always irritated. I also started having seizures. My parents took me to the ER, where the doctor said my mother knew nothing about babies because she was a psychiatrist. I was given a normal baby formula and soon after went into a coma.

The doctors had no idea what was wrong and how to get me out of the coma. Portugal did not include MSUD in newborn screening at that time, but my PKU test was negative. Luckily one doctor's wife worked in a lab for metabolic disorders so he sent my blood there. After 24 hours, at 13 days of age and still in a coma, the diagnosis was made and my parents received the news that their daughter had classic neonatal MSUD, the most severe form of the disease. My leucine levels were about 3860 mg/dL. Dr. Laura Vilarinho and her husband were the ones who saved my life. Several doctors at the hospital came to see me and to test me and smell my diaper that contained the smell of acrid syrup characteristic of the disease. Afterwards, a doctor contacted a medical expert in metabolic diseases in France, Dr. Jean Marie Saudubray, who faxed my parents 11 sheets with instructions for how to get me out of the coma. I had peritoneal dialysis and a month and a half later my parents took me home. During this time I had been fed through a gastrostomy tube, but my parents insisted they could feed me through my mouth. With hard work they were able to discontinue the tube feedings. When I was eight months old we went on vacation to Spain.

At that time in Portugal only Nutricia's MSUD 1 and 2 formula were available, and we had to pay for it. I ate fruit, vegetables, green beans and corn starch mixed with water and potato-free vegetable soup. My mother obtained valine and isoleucine from the hospital pharmacy. When I was two-and-a-half years old Dr. Saudubray came to the hospital to meet me because I was the first survivor with MSUD able to eat alone. I was able to talk and walk from eight months of age.

I followed my treatments at the Porto hospital with a varied medical team, until I turned four years old when we moved to Covilha where my mother got a job at the public hospital. With this employment the

state would help with the cost of the low protein foods that had arrived in Portugal that year. It was very expensive, but my parents paid for it so I could eat something else. In addition, in 2005 the Portuguese government began paying in full for the protein food that they sent us from the Jacinto Magalhaes Institute of Medical Genetics and the MSUD formula that we can order by prescription in the 6 metabolic disease treatment centers of the country.

I grew up and, contrary to what the French and Portuguese doctors said, I went to public school and had a normal education like any girl my age, had few decompensations, followed the diet and the levels remained normal. My parents had traveled a lot with me taking my special things. I completed my high school studies with good rankings and entered college in 2013.

I studied Portuguese and Spanish studies with very good classifications, and when I finished the degree in 2015 I went to live alone in Spain working as a Portuguese conversation assistant in Almendralejo. It was an unforgettable experience. In 2016 I returned to university in Covilha to study for a master's degree in Portuguese and Spanish teaching in high school. I finished with high grades.

I started working again in Spain (Badajoz), where my metabolic doctor was Mr. Dr. Luengo. I lived alone for a year and used Low protein food and Anamix Junior formula. This past year I went to work for the first time on the island of Flores, Azores, Portugal away from my parents as a Portuguese teacher. Now I am back living with my parents and sister in Covilha in Serra da Estrella, the highest mountain in Portugal, where I help as a volunteer providing educational programs to teachers.

I have traveled a lot with my parents and alone throughout my life. I have written a book of poetry in 2013 called "Poetry of One Life". I think MSUD research should continue so that we can build our lives independently. I continue with my protein food and take 430 mg leucine each day with about 100g of potatoes daily and with my amino acid formula MSUD 2, PFD1, MSUD Express from Vitaflo. I dream that one day I will have children and a family, also with the MSUD cure that even science will discover! ■

Derek Jones' 18th Birthday

Our son Derek, Classic MSUD, celebrated his 18th birthday on April 12 this year. As this was at the beginning of the quarantine, we celebrated by going to Chick-fil-A with all of his cousins and parked cars in a circle socially distanced as we had dinner. We made it a surprise for him as they had not seen each other for a month.

Yukta Sewsunder - Classic MSUD Age 20

By Aradhana Sewsunker, Mom, South Africa

On the 11th August 2000, Yukta arrived into our world! A beautiful 3.2kg (7 lbs) baby girl, boasting an Apgar test of an almost perfect score of 9/10.

Sadly, within days, she developed a shrilling, high-pitched cry, an arched back, and a specific odor lingered around her. While being diagnosed with colic, Yukta's condition worsened. Apart from her constant cries, she had lost significant weight and her tiny body started to tremble frequently.

It became evident that unending trips to various specialists in different cities for a proper diagnosis was imperative. By August 20th a faint odor was detected on Yukta's skin that brought a sense of dread and foreboding. An indescribable fear crept into our minds and hearts as we began unpacking the reality of what was happening to her. In a way, the odor was the key to unlocking Yukta's medical condition. This haunting odor took us back in time to 1993, seven years earlier, when the birth of our first child ultimately led to his passing away, undiagnosed, at just 28 days old.

Determined and courageous enough to not allow a similar fate to befall Yukta, we stepped forward, presenting our findings to a group of medical practitioners as we remained baffled by this mysterious ailment threatening the life of this child.
A diagnosis of MSUD was finally confirmed on 28th August 2000. A medical support team was immediately put together to take charge of this medical crisis, a crisis because Yukta's condition was the first known case in the country. One of our immediate challenges was to locate specialised formula for Yukta. Before it arrived from Germany on September 19, 2000, Yukta had spent many weeks in the hospital, being tube-fed via the nose with a low-protein formula sourced from the Red Cross Children's Hospital in Cape Town, South Africa. This was a temporary measure until the correct formula became available, and kept Yukta somewhat stable.
Slowly, Yukta's health progressed. However, she presented with some irreversible damage. Through a critical focus on her recovery with a myriad of therapeutic programmes and interventions, Yukta managed to overcome many of her developmental and dietary challenges over the years.

Her developmental interventions included physical therapy, occupational and speech therapy, horse riding, karate, swimming, and dancing. In terms of her dietary interventions, she presently continues with Anamix formula accessed from England as Milupa in Germany stopped manufacturing the MSUD formula. All have contributed substantially to her growth, development, and overall well-being. To date, Yukta has had in total eight blood tests done together with occasional routine check-ups which generally include an ECG, MRI and EEG. As long as she adhered to her diet and was often in good health, her doctors didn't see the need for regular testing. In fact, she rarely visits a general practitioner because she does not often present with any health issues or risks.

Yukta has given us so much more than what fate has taken away. Her story is one of courage and tenacity. She fought for a place in our home and in our hearts and successfully continues to occupy these important spaces twenty years on!

Newborn screening for MSUD, which is routine in other countries, is not the norm in South Africa. Although there are many widely held views surrounding the screening of all newborns, and some doctors advocate for it, there are

Yutka continued on page 12

My Experience with COVID-19

By Jonah Gross

My name is Jonah Gross and I am a 26-year-old living with Classical MSUD. I always just thought of MSUD as a part of my life, but the year of 2020 has made me realize that complications can occur that can make a huge impact on my everyday life. I started to experience on and off fevers in the middle of March and I knew that this was not a good sign. With my sister and mom already having COVID-19, I knew it was only a matter of time. In late March I received a positive test for COVID-19. Here is my journey to recovery.

My early symptoms of these on and off fevers and my affected taste buds made it hard to cope with COVID-19 at home. I started to not be able to eat as much and began to vomit. After a couple of days at home my Genetics team and I came up with a plan and decided I would check into Lurie Children's hospital in Chicago.

A hospital stay is nothing new for me. Over the course of my life, I can't even count how many times I've paid a visit. This time was different. While I'm used to the hospital beds, nurses, IVs and everything in between, on this particular stay nobody really knew what to expect. To start, when I arrived at Lurie Children's Hospital I was immediately admitted into the ICU – alone as family members weren't allowed in. Over my many hospital stays, I have always been fortunate enough to have my family by my side; my mom or dad sleeping by my bedside, a revolving door of endless visits from family and friends – being alone was never something I was used to.

The first couple of days in the hospital were like any normal stay. My blood levels were nothing out of the ordinary compared to a normal hospital stay with MSUD for me. I was getting my fluid through my IV, and things were going as usual with my formula and diet. My initial symptoms were nothing more than the seasonal flu. In my mind, if I continued to rest, eat, and get the additional fluid needed I would be out of the hospital as good as new in a week. But as the days grew tougher I soon realized the challenges at hand and that this was going to be a much longer journey.

Around day 5 of my hospital stay there was a sudden change of events and things took a turn for the worse quickly. As soon as we thought my blood levels were leveling out the symptoms of COVID-19 began to increase. Getting out of bed grew tougher and around my 5-day mark, I realized that I was feeling shortness of breath when I had to get up to use the bathroom. As these were symptoms I had never experienced before, I grew fearful. I was put on oxygen immediately and had to deal with my loss of taste, nausea, and on and off fevers. Little did I know I was about to enter the most difficult days of my hospital stay.

As the symptoms of COVID-19 began to increase, so did my MSUD. My blood levels started to skyrocket. With all the unknowns of this new virus, nobody knew what would happen next. The days following were extremely tough; I was completely out of it. While the entire team at Lurie's were supportive and my family away from home, their main focus was keeping me on course with a restrictive diet, extra formula and fluids, while we waited to see how the virus played out. I continued to get IV fluids and lipids and increase my intake of formula during these tough times.

While dealing with the repercussions of the virus, the hardest part was having to face this alone. I became very scared, stressed, and anxious. All I wanted to do was be with my family. Facetime and Zoom were able to help me communicate with my family, but not having them physically present made everything more difficult. These uneasy feelings and the immense amount of stress

mixed with the COVID-19 symptoms and high MSUD levels led me to unusual side effects like hallucinations. It was scary to lose sight of where I was and not be fully aware of my surroundings. But, with staying in touch with my MSUD team and the amazing team at Lurie's we were able to get through these bumps in the road and find a light at the end of the tunnel. As the days went on, things began to slowly get better. My anxiety and stress subsided and my symptoms began to lessen. I finally was able to get some normalcy back into my life.

After 15 long days, I was able to finally be released from the hospital and reunited with my family. The moment I stepped foot out of the hospital, I felt the relief I needed to fight through this virus. Due to the amazing work of the hospital team, I was able to go home feeling like a new person and after only a week I was finally able to go back to work and live my normal life.

Living with MSUD has always been its own complication, but adding this unknown virus to the mix made us realize the reality of not knowing what to expect. While MSUD has always been a lifelong battle for me, I know it does not define the person I am. I am so lucky to have my metabolic team to get me through this difficult time. In a way I look at this experience as an opportunity to prove how strong I really am. I now know that no matter what comes my way, I can fight and win. ■

Yutka continued from page 10

no concrete plans, policies or guidelines in place for doctors or pediatricians. A crucial reason for this is the large budget constraints the healthcare system experiences. Almost all of the budget is allocated towards HIV and Tuberculosis. At a grassroots level, some parents-to-be see it as unnecessary or even as an added expense. It remains mainly up to the parents to decide if they want their newborn screened, at their own expense.

Looking ahead, Yukta's schooling career ended, quite sadly and abruptly due to Covid-19. However, this "busy-as-a-bee" human being has started up her own home industry, briskly embarking on a cupcake campaign for special and remedial teachers in various schools in our city.

When we reflect on Yukta's life from early childhood into adulthood we see a journey of sleepless nights: the meltdowns, endless medical consultations, the judgemental stares, the tears… yet, somewhere there is a smile of pleasure and we think…it was all well worth the time and sacrifice. ■

THE MSUD FAMILY SUPPORT GROUP NEEDS YOUR SUPPORT!

The MSUD Family Support Group eliminated its membership dues two years ago. We now rely solely on donations to fund our day to day activities and research. Unlike many other support groups, the MSUD Family Support Group is a 100% volunteer organization. None of its officers or directors receive monetary compensation for their efforts.

General donations are used to fund expenses associated with:

- Connecting MSUD families. This includes the biannual newsletter, maintaining our web site, and all expenses associated with the biennial symposium.
- Supporting advocacy efforts to ensure that the needs of our community are met. An example is informing legislators about the importance of the Medical Nutritional Equity Act, which would require insurance companies to pay for medical formula.
- Administrative expenses, such as accounting and legal costs, and board meetings.

Research donations are used to fund expenses associated with:

- Supporting research projects which could improve the day to day lives of MSUD families and improve treatments for MSUD patients. We supported the development of the MSUD mouse model which is routinely used in MSUD research, and recently funded the first stage of a project to develop a home leucine monitor.
- Supporting research to find a cure for MSUD, such as gene therapy.

We greatly appreciate any donation you may choose to make.

To donate by check:
Checks should be made out to MSUD Family Support Group and mailed to David Bulcher Treasurer, 4656 Winding Oak Drive, Delaware, OH 43015

To donate electronically:
Visit our website at: http://msud-support.org/donate
Please note in the comments section of your check or Paypal donation whether funds should be deposited into the general or research fund. ■

Low Protein Baking for Fall

Autumn is in the air! The smell of warm spices in your kitchen as you prepare these Low Protein Sugar Cookies will get you in the spirit of Fall. This recipe uses Loprofin Baking Mix from Nutricia. This baking mix makes it easier to whip up delicious and MSUD diet-friendly baked goods for your family.

To get more tasty low protein recipes like this one delivered to your inbox, sign up for Nutricia Connect! Join us to stay in the loop on resources, recipes, and more for the low protein diet. Plus, when you sign up, you're eligible to receive a FREE shaker bottle!*

Low Protein Sugar Cookies

Ingredients:

- 1 stick (1/2 cup) butter or margarine (room temp.)
- 50 grams (1/4 cup) granulated sugar
- 175 grams (about 1 1/2 cups) Loprofin Baking Mix, plus 1-2 Tbsp for rolling out dough Loprofin Baking Mix is available for purchase on MedicalFood.com
- 2-3 Tbsp cold water
- Powdered sugar, for decorating

Optional Flavorings (Add one or more in Step #2):

- 1/2 tsp vanilla or almond extract
- Zest of 1/2 of a lemon or orange
- 1 tsp cinnamon or ground ginger

Method:

1. Preheat oven to 300°F.
2. Place the butter or margarine and sugar in a mixing bowl and beat until smooth.
3. Stir in the Loprofin Baking Mix and any of the optional flavorings.
4. Using one hand, squeeze the mixture until it comes together, adding sufficient water to make a manageable ball of well-mixed dough.
5. Lightly dust your surface with Loprofin Baking Mix. Roll out the dough to about 1/4-inch thickness.
6. Cut the dough into shapes using a cookie cutter and place onto a lightly greased baking tray.
7. Bake at 300°F for 20-25 minutes until pale golden brown.
8. Remove cookies from baking tray while still warm and cool on a wire rack.
9. Once cooled, dust with powdered sugar or mix together a quick glaze of powdered sugar and water to drizzle over the top.

Makes 12 cookies.

Loprofin Baking Mix is a main ingredient in these sweet Low Protein Sugar Cookies. Loprofin Baking Mix is available on MedicalFood.com.

Nutritional Information**	Per Recipe	Per Cookie
Calories***	1630	136
Protein	1.6 g	0.13 g
Phenylalanine	63 mg	5 mg
Leucine	106 mg	9 mg
Tyrosine	50 mg	4 mg

** Nutritional information may vary based on ingredients used (For example, the various optional flavorings for the cookies).

*** Calories listed are for undecorated cookies; topping cookies with powdered sugar or glaze will increase calories.

For more low protein recipes and other support delivered to your inbox, sign up for Nutricia Connect! And when you join, you're eligible to receive a FREE shaker bottle.

**Offer valid through 12/31/20. While supplies last.*

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An Introduction to MSUD Easy Tablets

By Ashley Park, MS, RD, LD, Galen US, Inc.

This article is sponsored by Galen US.

To see an example of how their formula alternative, MSUD Easy Tablets can be incorporated into your formula routine, continue reading the overview below

What are MSUD Easy Tablets?
MSUD Easy Tablets are a leucine, isoleucine, and valine free amino acid based medical food for the dietary management of Maple Syrup Urine Disease (MSUD) in patients aged 3 years and above under strict medical supervision1. MSUD Easy Tablets are an alternative to traditional powdered or ready to drink MSUD formulas and provide 10 grams of protein equivalent and 55 calories per 11 tablets1.

Do MSUD Easy Tablets provide the same nutrition as powdered or ready to drinks formulas? MSUD Easy Tablets do not contain vitamins and minerals1, so a daily multivitamin may be needed. The MSUD Easy Tablets are also lower in calories per serving compared to some MSUD formulas. While fewer calories can be a good thing if you are working with your dietitian on weight loss or looking to free up more calories for foods, it's important to ensure you are meeting your calorie needs if switching from a higher calorie formula. In the next section, you will see an example of how the calories provided by medical food changes when substituting a portion of a nutritionally complete formula with MSUD Easy Tablets. Also included are some low protein ideas to make up any needed calories without sacrificing your daily protein or leucine goals!

Example showing how calories can change when substituting a portion of a nutritionally complete formula with MSUD Easy Tablets.

Please note, this demonstration is serving only as an example and the actual amounts will vary depending on the nutrient composition of the starting formula prescription and amount of starting formula prescription being replaced with MSUD Easy Tablets. MSUD Easy Tablets are only to be used under strict medical supervision and as directed by your physician or dietitian.

Chart For MSUD Easy Tablets

Current Formula (EXAMPLE)	Protein Equivalents (g)	Calories
Powdered nutritionally complete formula mixed with water to make 32 fl oz split into 4 servings per day	60	820

Substituting 1 Serving of Current Formula with MSUD Easy Tablets (EXAMPLE)	Protein Equivalents (g)	Calories
MSUD Easy Tablets (16 tablets)	15	80
Powdered nutritionally complete formula mixed with water to make 24 fl oz split into 3 servings per day	45	615
Total	**60**	**695**

125 Calories to make up

Ideas to make up the extra calories. Please note: nutrition information listed below has been obtained from USDA nutrient database or manufacturer data.

Food	Serving	Protein (g)	Calories	Tips
Applesauce	1 cup	0	106	Mid morning or afternoon snack
Apple Juice	1 cup	0	113	Use to take serving of MSUD Easy Tablets
Olive Oil	1 tbsp	0	116	Drizzle on roasted veggies or low protein pastas or mix with herbs and spices and used as a dip for low protein bread
Heavy Whipping Cream	2 tbsp	0.6	104	Beat to make whipped cream and add as a topping for strawberries or other fresh fruit
Honey	1.5 tbsp	0.1	96	Add to a low protein breakfast smoothie made with frozen fruit and almond or coconut milk or drizzle on your whipped cream and fresh fruit above
Flavored Non-dairy Creamer (such as Coffee Mate Italian Sweet Cream)	1.5 fl oz	0	105	Add to morning coffee, low protein hot or cold cereals, or low protein smoothie
Coconut milk ice cream	1/3 cup	0.4	100	Evening snack or dessert

References: 1. MSUD Easy Tablets Data Sheet, Jun 2020.
MAT-GAL-US-000049 Date of Preparation: August 2020 ■

SATURDAY NIGHT ZOOM CHATS

By Susan Needleman

The current pandemic has left many of us feeling isolated and alone. With MSUD you are never alone, though! Join MSUD Families of all abilities and ages as we meet online through Zoom Saturday nights at 8:30PM EST. We share our perspectives on a wide range of MSUD and non MSUD topics and offer each other's perspectives on challenges we have faced, while connecting with others with MSUD. For more information or to join, please email Susan Needleman (an MSUD adult herself), at slneedleman@yahoo.com.

Please note that these virtual meetups are not run by medical professionals, and are not intended to give medical advice, but to share and listen to personal experiences of other MSUD patients. You should always contact your clinic before making any changes to your MSUD treatment. ■

Acer Therapeutics Update
ACER-001 (taste-masked, immediate release sodium phenylbutyrate)

By Chris Schelling, CEO

"I hope everyone is doing well and is healthy."

This is a saying most have adopted into their daily greetings. For the MSUD community, it's a not-so-small miracle if you can actually say, "Yes we are. Thank you very much!" I've always been amazed at how resilient families are that have loved ones with metabolic disorders – living with incredible pressures on a daily/weekly/eternity basis, yet always fighting, pushing forward, never giving up. I have to believe this resiliency serves you all well during this pandemic…certainly much better than the general population. But every once in a while, I imagine it would be nice to get some help, have something go right, to make things a little easier – perhaps now more than ever.

To this end, I'd like to provide you all with an update on ACER-001, a new formulation of sodium phenylbutyrate which was shown in studies by Dr. Brendan Lee at Baylor College of Medicine to lower leucine levels in some individuals with MSUD. Now, I'm the first to admit that this program has taken significantly longer than we all hoped it would to get to this point. When I started Acer, my plan was to have the drug approved in less than 5 years, and we're rounding the corner on 7 years. Drug development timelines can be very frustrating, but we've stuck with it and I'm pleased to report that we have made significant progress over the past year.

To start, the drug itself (what we call the formulation) was finalized. This is the part of our development that has taken the longest to get right. We needed to mask the horrible taste of phenylbutyrate while not affecting how the drug gets absorbed in the body. It's a fine balance – the more taste-masked coating (coat weight) we applied, the less absorbable the drug became (and vice versa). We had developed three different formulations with three different coat weights and needed to test which formulation was optimal in a clinical trial with healthy volunteers. We successfully did this in mid-2019, and the results allowed us to select our lead drug.

Taking the lead drug, we then conducted a second clinical trial in late 2019 with healthy volunteers. We compared ACER-001 to Buphenyl (non-taste-masked sodium phenylbutyrate), to show that both drugs are absorbed nearly identically. This is called a bridging study, and it's what the FDA needs to see in order to approve ACER-001. In reviewing the results of this bridging study, we learned something very interesting – that when phenylbutyrate is given with a meal the absorption of the drug is reduced in half. Conversely, if ACER-001 can safely be given prior to eating a meal then nearly twice as much drug can enter into the body than if it's given with food! This was a major finding, and it potentially has a significant positive impact on treating MSUD.

Over the past year, we've had multiple interactions with the FDA to learn more about what is required to get ACER-001 approved in the US. They've requested we conduct some additional safety studies in animals, and they would also like to make sure the drug is stable in a variety of storage conditions (think shelf life). If things go well, we will apply to the FDA in the first half of next year to be approved to treat Urea Cycle Disorders (UCD, the same disease Buphenyl and Ravicti are approved to treat).

You may ask yourself, "How does getting ACER-001 approved to treat UCDs help MSUD patients?" Well, it moves things along quite a bit for the development timelines. Most, if not all, of the supportive information around the drug will be complete, and we can focus on conducting the clinical trials to determine whether ACER-001 is able to effectively lower leucine levels by a meaningful amount.

The clinical trial for MSUD patients should get started next year. I will point out that this is going to be an expensive trial, and we'll need to raise additional money to support the effort. We have a plan to raise this money over the next six months, and if successful, we should be able to begin enrolling patients around mid-year. We expect that nearly all patients may respond to therapy, and therefore can be enrolled in the trial. Research published in 2010 by Dr Brendan Lee et al. at Baylor College of Medicine supports that even patients with less than 1% enzyme activity can see meaningfully lower levels of leucine following administration of phenylbutyrate.1 Unfortunately, patients with double null mutations are not expected to benefit from phenylbutyrate as their enzyme has no residual activity to increase with therapy. We will keep the MSUD Family Support Group updated on our progress and will need your help to participate in the clinical trial.

I hope this has provided a helpful update on the ACER-001 program. We look forward to keeping the momentum rolling into next year. And I hope you all remain well and healthy (and resilient!) 1 Hum Mol Genet. 2011 Feb 15; 20(4): 631–640.

Cows for the Cure: Using Cows to Develop a Potential Cure for MSUD

By Mariah Everett
Research Associate, Clinic for Special Children

The two treatments currently available for MSUD, dietary therapy and liver transplantation, have significant drawbacks, so the Clinic for Special Children (CSC) wanted to find a better solution. We are working with the Li Weibo Institute for Rare Diseases Research at the University of Massachusetts (UMass) Medical School and the Cummings School of Veterinary Medicine at Tufts University to develop a new gene replacement therapy for MSUD with the help of some very special cows. The CSC and UMass, with the help of the MSUD Family Support Group, have raised money to develop this new treatment.

What is gene therapy?
Gene therapy is an innovative way to treat, and potentially cure, genetic disorders. Gene therapy uses a modified virus to insert a working copy of a gene into target cells, allowing the functional protein that was lacking to be produced and correcting the genetic error at the root of the condition. The virus' genetic information is replaced with the working gene of interest, so the virus acts like a delivery truck of the working gene. The type of virus most commonly used for gene replacement therapy is the adeno-associated virus (AAV), a virus found in nature but that does not cause people to become sick when infected by it. There are different types of AAVs that are good at inserting genes into specific types of cells. The AAV9 subtype works well with muscle cells, and it the virus we plan to use for gene therapy in MSUD.

For MSUD, gene therapy would introduce a working copy of the BCKDHA and BCKDHB genes, those that are non-functional in classic MSUD. The working gene would direct the cells to produce the functional protein necessary to break down leucine, isoleucine, and valine—the branched-chain amino acids that the body cannot break down in MSUD. The goal of the gene replacement therapy would be to normalize the amounts of these amino acids, enabling patients with MSUD to follow a normal diet and prevent decompensation when ill. Gene therapy is a quickly growing field and gene replacement therapies have been approved for other genetic disorders, such as spinal muscular atrophy and a form of genetic blindness. It is important to know that the new gene inserted by the virus does not integrate into the person's genetic makeup so it is not heritable, which means it cannot be passed down to future generations.

Why cows?
Currently, most research investigating MSUD is done using genetically-engineered mice with the condition, but mice with MSUD are not like people with the condition: mice mostly break down branched-chain amino acids primarily in the liver and not in the muscles, while people break down these amino acids primarily in the muscles. Nonetheless, liver transplant works in people because the liver cells with the working gene produce enough of the missing protein to break down the branched chain amino acids to nearly normal levels.
Since the mouse model does not work well for MSUD, other animal models are needed. About 30 years ago, MSUD was discovered in herds of Hereford and Shorthorn cattle. However, with selective breeding of the cows, MSUD had all but disappeared from the cattle. Then, a few years ago, cases of Hereford calves with MSUD appeared in Indiana and Iowa. It turns out that MSUD in cows closely mimics MSUD in people, which makes it a better animal to use for gene therapy research than mice.

There are three main reasons why cows are better for gene therapy research:

1. Cows and humans break down branched-chain amino acids in the same tissues. If we test our gene therapy in cows instead of mice, we will have a better idea of how it will work for humans because the tissues that do this work are similar between cows and people.

2. The most common mouse model used for MSUD research only appears to have milder disease. When mice are produced with classic MSUD, they die shortly after birth. Therefore, researchers use a mouse that can break down these amino acids at about 5-6% the normal rate. This difference means that MSUD in the mice is not as severe as classic MSUD in humans. On the other hand, Hereford cattle with MSUD cannot break down branched-chain amino acids at all, just like humans with classic MSUD. So MSUD in the cows is just as severe as classic MSUD in people.

3. Calves are a similar size to humans, which will make it easier to figure out the right dose of gene therapy to use in people. When mice are used, the dose for humans is based on a mathematical calculation only. With cows, finding the right dose for a person will be easier and more precise.

What is next?
We have created Hereford calf embryos that have classic MSUD. These embryos will be implanted into mother cows. When they are born, the calves will be given the gene replacement therapy under development using the modified AAV9 virus. We will then follow the calves to make sure that the gene therapy is safe and effective. We will also determine what dose of the gene therapy needs to be given for it to work. If all goes as planned, we hope to start a clinical trial using our gene therapy to treat MSUD in humans in the next few years. ■

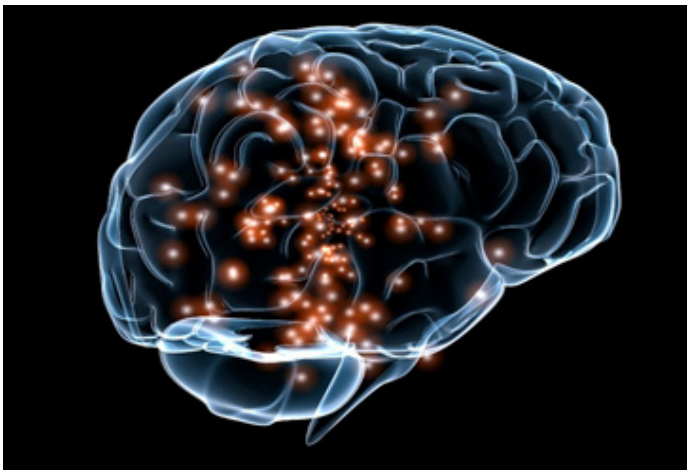
Impact of Maple Syrup Urine Disease on the Brain

By Diana Shellmer, PhD
Children's Hospital of Pittsburgh

Maple Syrup Urine Disease (MSUD) has been associated with various developmental, cognitive, academic, quality of life, and psychological concerns that are related to the impact of MSUD on the brain. The level to which each individual with MSUD is impacted depends on a variety of factors including how quickly an individual is diagnosed (e.g., prenatal screening or after symptom presentation), the severity/variant of MSUD, the number and intensity of metabolic crises experienced by the individual, experience of seizures and/or coma type episodes, level of brain swelling, and the day to day control of metabolic levels.

Classical MSUD is the most common variant of MSUD and unfortunately also the most severe. Even with strict dietary control (i.e., low protein diets and use of specialized formula) metabolic instability is common and illness (e.g., a cold), injury (e.g., a broken bone), and physiologic stress (e.g., becoming overheated/dehydrated, cold exposure, emotional strain) can make it more difficult to maintain balanced leucine, isoleucine, and valine levels. Leucine, isoleucine, and valine are branched chain amino acids (BCAAs) that individuals with MSUD cannot breakdown easily and which can then build up in plasma (the part of a person's blood that carries protein) and body tissues. This build up in turn can affect the central nervous system including the brain in multiple ways.

Increased levels of BCAAs in the brain can cause cell death, block the transport of other amino acids that affect neurochemistry (i.e., how chemical substances affect the physiology of the brain), and affect how quickly and effectively substances move about and work in the brain. For example, when BCAAs are not in balance they can block the transport of amino acids involved in dopaminergic, serotonergic, and noradrenergic systems. These systems affect mood, cognition, behavioral regulation (e.g., being able to start/stop behaviors), sleep, memory, learning, and emotions. In addition, poor adherence to diet restrictions can reduce communication between brain structures by limiting how quickly messages travel and how many connections there are within the brain.



As a result of the impact on the brain individuals with MSUD may experience a variety of challenges, including:

• Developmental Delay:
Developmental delays can include growth retardation, slow and/or lack of attainment of developmental milestones (e.g., walking, talking), feeding delay and/or oral motor delay, oral aversion, and/or cognitive delay. Delays can manifest themselves early in the developmental trajectory or evolve after metabolic crises. Fine and gross motor functioning as well as social and cognitive functioning can be impacted.

• Academic and Executive Functioning Concerns:
Learning disabilities and/or delays are not uncommon in individuals with MSUD. Many patients describe a fog-like state that does not allow them to think clearly and quickly. Clinical presentations vary and can include math learning disabilities, reading disabilities, attention and memory concerns, and organizational difficulties. Patients who have experienced significant metabolic crises may evidence a wide range of academic concerns that require special education support.

• Dietary:
Due to the common dietary restrictions in patients with MSUD, a number of individuals develop feeding intolerance, oral/motor delays, and/or oral aversions. These presentations vary, for example, some patients have difficulty with the mechanics of chewing and/or swallowing, while others have difficulties adjusting to the various textures of food.

• Quality of Life:
Individuals with MSUD have lifestyle restrictions such as dietary and activity restrictions, and physical limitations that may be associated with their condition. In addition, given that a metabolic crisis may develop unexpectedly patients can also experience increased stress and difficulties adjusting to their diagnosis and associated medical needs.

• Psychological Concerns:
Mood disorders, attention disorders, and behavioral disorders are generally common among individuals with MSUD. Anxiety, depression, and Attention Deficit Hyperactivity Disorder (ADHD) and/or subclinical types of ADHD are generally well

documented. There is suspicion that extended metabolic imbalance over the lifetime can lead to a mood disorder (e.g., depression/anxiety) even in patients who have not had severe metabolic crises. Further, adjustment to a lifelong chronic illness and the associated treatment can cause emotional strain and worsen psychological conditions.

Potential Treatments and Outcomes:

Given the range of concerns that may be present for individuals with MSUD, it is important to remember that treatments and support services can make significant positive impacts on function. Early detection, newer and more specialized formulas, and close metabolic monitoring can limit the negative impact of MSUD on the brain. By increasing metabolic stability, neurophysiology, neurochemistry, and brain structure can be improved leading to better outcomes. In addition, use of supportive therapies such as physical and occupational therapy, mental health treatment, and academic supports can help individuals with MSUD develop effective strategies for navigating the challenges that may be present.

Liver transplantation is another available option for individuals with MSUD. By replacing the liver an individual with MSUD now can produce enough enzymes to break down the BCAAs that used to build up in the body. As such, liver transplantation is considered a metabolic cure for MSUD and can lead to more metabolic stability even with a liberalized diet including protein rich foods which in the past were restricted and/or prohibited. Increasing protein in the diet of a child with a developing brain can help supplement brain growth and overall physical and cognitive development. Although individuals with MSUD typically receive a recommended amount of protein in their diet, balancing the needs of a growing child with appropriate protein intake can be a challenge particularly during rapid periods of growth. A liberalized diet can eliminate the chances that too much protein is consumed leading to a crisis episode. In addition, this added security helps families live without the daily fear of a metabolic crisis episode. The liberalized diet can decrease the stress of closely following a protein restricted diet, create greater freedom for the individual with MSUD, and improve brain physiology simply by decreasing the release of stress hormones.

Our research in patients with MSUD who have undergone liver transplantation has found stabilization or improvement of neurocognitive functioning as defined by IQ (intelligence quotient). For IQ to remain stable or increase throughout childhood, adolescence, and young adulthood, individuals have to "know more and be able to answer more questions correctly" each time they take an IQ test. For example, a 15-year-old adolescent with MSUD would need to answer more questions correctly than his/her 10-year-old self in order to obtain the same IQ score. In addition, anecdotal reports by individuals with MSUD during clinical follow-up suggest improved clarity of thought, concentration, and memory. Prior to transplant individuals with MSUD describe experiencing a fogginess to their thinking and difficulty learning new information when their BCAA levels were elevated. Post-transplant individuals describe feeling they can think more clearly. Although this clarity in thinking has not been evaluated in direct relation to IQ it may reflect an improved ability to process and learn new information.

There are many challenges related to MSUD and its day to day management. However, there are also many advances that have developed over the last couple of decades that appear to be positively influencing brain function.

Editor's Note: If you would like to ask Dr. Shellmer a question, she invites you to email her at Diana.Shellmer@chp.edu. Please specify "Questions About MSUD Newsletter Article" in subject line. ■

AAV gene therapy for MSUD*

Jenny A. Greig, Ph.D., Matthew Jennis, Ph.D., and James M. Wilson, M.D., Ph.D.

Editor's Note:
This study was supported by a grant from the MSUD Family Support Group with funds raised during the 2018 Million Dollar Bike Ride.

Maple syrup urine disease (MSUD) is a rare genetic disease characterized by the dysfunction of the branched-chain alpha-keto acid dehydrogenase (BCKDH) complex. BCKDH metabolizes branched-chain amino acids; without functional BCKDH, there is a build-up of branched chain amino acids in the blood and urine. There is currently no cure for MSUD and treatments are limited to carefully monitoring a restricted diet with the potential for a liver transplant. These limited approaches highlight the unmet medical need to develop a novel treatment for this disease.

For gene therapy approaches for MSUD, a normal healthy copy of the gene containing the mutation is produced and inserted into a viral vector. We utilized an adeno-associated viral (AAV) vector for this study. The AAV vector was administered through the circulatory system in a one-time injection. Cells in the body take up the vector and begin to express functional copies of the affected gene. The functional protein produced can break down the branched-chain amino acids and

AAV Gene Therapy continued on page 23

Kinase Inhibitors: Implications for Treating MSUD

By Richard M. Wynn, PhD
University of Texas Southwestern Medical Center

Protein kinases are enzymes involved in various cellular functions. Across the human genome about 2% of all human genes encode for protein kinases (~550 total genes). Improper regulation of protein kinases is implicated in various human diseases, including cancer formation and dysfunctional metabolism. The advent of protein kinase inhibitors has led to a paradigm shift in therapy. Several protein kinase inhibitors have been approved by the FDA in the last few decades, with the promise of many more therapies to come for targeting kinases.
Branched-chain dehydrogenase kinase (BDK) helps regulate the breakdown of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine. BDK offers a therapeutic target for variant forms (intermediate, intermittent, and thiamine-responsive) of MSUD with residual (5%-40%) enzymatic activity, which accounts for an estimated 40% of all known MSUD mutations. Blocking BDK activity, however, would not solve "classical" MSUD patients, due to the absence of enzyme complex activity.

Successful therapeutic use of a branched-chain dehydrogenase kinase (BDK) inhibitor could potentially accomplish several key goals for regulating elevated BCAAs/BCKAs, as seen in treatable MSUD (intermediate, intermittent and thiamine-responsive patients):

• Reduce toxic metabolites (breakdown products) of BCAAs/BCKAs—Kinase inhibitors could enhance the breakdown of BCAAs and BCKAs, thereby reducing toxic levels and promoting normal metabolism and neurodevelopment.

• Minimize catabolism (breakdown) of the body's proteins—which would help to maintain control of BCAAs/BCKAs.

• Promote adequate protein synthesis—restoring normal levels of BCAAs and BCKAs in the tissue and plasma will lead to a more normal pattern of protein synthesis.

Modulation of branched-chain dehydrogenase kinase (BDK) activity constitutes a major mechanism for regulating systemic BCAA concentrations. BDK is inhibited by the keto-acids derived from leucine, resulting in the activation of the enzyme complex in perfused rat hearts. Leucine serves as a "feed-forward" nutritional signal that promotes BCAA disposal through the inhibition of BDK activity. Several small molecules have shown promise in the inhibition of the BDK including sodium phenylbutyrate (NaPBA). Some patients on a NaPBA regimen demonstrated more than 25% lower plasma BCAA amino acid concentrations (see Figure 1). Researchers at Baylor College of Medicine in Houston examined patients with urea cycle disorders (UCDs) and found a reduction in BCAA/BDKAs, leading to follow-up studies to determine whether the drug could be a therapeutic option for MSUD. Acer Therapeutics has developed a new formulation for NaPBA (ACER-001) which will mask the taste and increase palatability (see article in this issue of the newsletter).

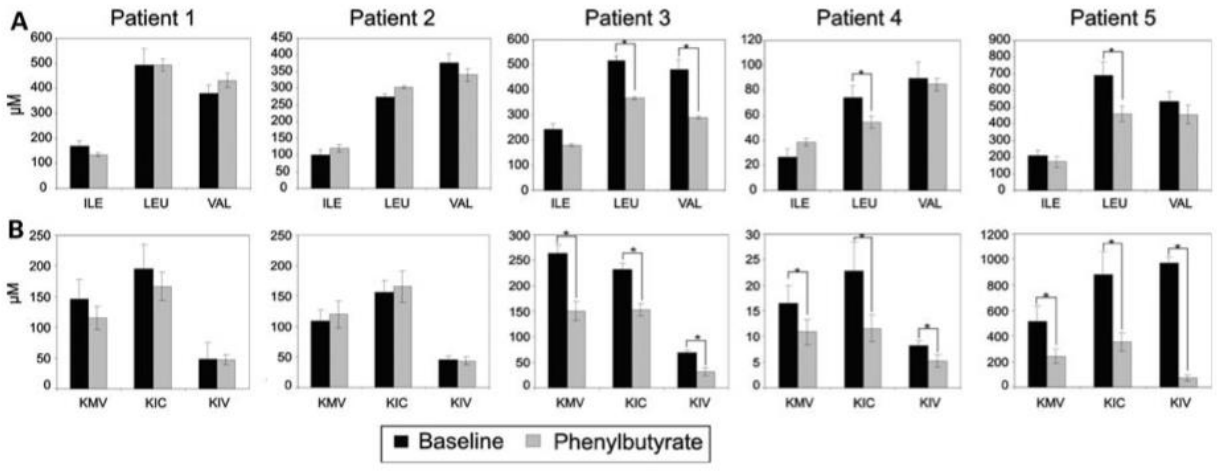


Figure 1. BCAA metabolites in MSUD subjects. (A) BCAA in MSUD patients before and after phenylbutyrate (NaPBA) treatment. ILE, isoleucine; LEU, leucine; VAL, valine. * $P \leq 0.05$. (B) BCKA in MSUD patients before and after NaPBA treatment. KMV, α-keto-β-methylvalerate; KIC, α-ketoisocaproate; KIV, α-ketoisovalerate. * $P \leq 0.05$ (from Brunetti-Pierri et al., 2010).

Recently, researchers at UT Southwestern Medical Center in Dallas have been attempting to improve BDK inhibitors. To this end researchers have isolated a benzothiophene derivative compound, designated as BT2, which has been shown to be a novel BDK inhibitor with better kinase inhibition. BT2 binds to the same location as NaPBA, but with higher potency and longer lasting effects. The availability of BT2 as a stable BDK inhibitor may have clinical ramifications for treating variant forms of MSUD by lowering BCAA/BCKA levels.

One problem with high levels of BCAAs is that they can compete for the absorption of other important amino acids. High plasma levels of BCAAs can reduce production of the neurotransmitter serotonin, by limiting uptake of its precursor, tryptophan, into the brain. Mice treated with BT2 have been shown to have lower BCAA levels and a higher concentration of tryptophan transported into the brain, thereby restoring normal neurotransmitter function. Treatment with BT2 shows that BCAAs can be lowered with a kinase inhibitor, leading to more normal physiological function, especially in the brain.

Finally, metformin, a widely used antidiabetic drug was reported to reduce levels of BCKAs in cells called fibroblasts derived from MSUD patients by as much as 20%-50%. The drug treatment also significantly reduced BCKA levels in muscle (by 69%) and serum (by 56%) isolated from the mouse model of intermediate MSUD (iMSUD). The same study showed that metformin reduces free radicals which can damage tissues. However, the direct metabolic target and underlying mechanism leading to the lowering of BCKA levels in vivo remain to be determined.

A number of companies are interested in the therapeutic arena for BCAAs. A list of some newer biotech companies are presented here.

Pfizer
Intelligence gathering for Heart Failure Therapeutic Area "Branched Chain Ketoacid Dehydrogenase Kinase Inhibition Alters Substrate Utilization and Gene Expression in Myocytes" (Abstracts from the American Heart Association's Basic Cardiovascular Sciences 2019 Scientific Sessions: Integrative Approaches to Complex Cardiovascular Diseases)

Janssen/Amgen
Intelligence gathering for Metabolic Disease treatment including orphan diseases such as MSUD

Ramino-Bio
Recently initiated preclinical activities to identify small molecule BDK kinase inhibitors for the treatment for metabolic diseases. Founded in March 2019 at the FuturRx biotech incubator financed by the Israel Innovation Authority (IIA), Takeda Ventures Inc., OrbiMed Israel Partners, Johnson & Johnson Innovation (JJDC), and RMGP Bio-Pharma Investment Fund

Acer Therapeutics
ACER-001 Phase 2 trial for Maple Syrup Urine Disease
Re-formulated, immediate release, taste-masked sodium phenylbutyrate (NaPBA)
ACER-001 (NaPBA) is non-selective against BDK kinase ■

Lipid nanoparticle mRNA treatment for MSUD

Jenny A. Greig, Ph.D., Matthew Jennis, Ph.D., and James M. Wilson, M.D., Ph.D.

Maple syrup urine disease (MSUD) is a rare genetic disease that leads to a build-up of the branched-chain amino acids in the blood and urine. MSUD is caused by mutations in one of three genes that produce proteins forming the branched-chain alpha-keto acid dehydrogenase (BCKDH) complex. Current treatments for MSUD are limited to carefully monitoring a restricted diet with the potential for a liver transplant, thus highlighting the unmet medical need to develop a novel therapeutic approach for this disease.

For lipid nanoparticle (LNP) mRNA therapy, a normal healthy copy of the gene containing the mutation is produced and inserted into a LNP. The LNPs are routinely administered via intravenous injection every few weeks. Liver cells known as hepatocytes, take up the LNP and begin to express functional copies of the affected gene. The functional protein produced can break down the branched-chain amino acids and prevent toxic buildup of these amino acids and their byproducts in the blood.

We had previously evaluated LNP mRNA therapy in a mouse model of a less severe, intermediate form of MSUD. These intermediate MSUD mice are deficient in the mouse form of the DBT subunit of BCKDH, but have low-level expression of the human form of DBT, which is required to prevent the neonatal lethality seen when the mouse DBT gene is mutated. Intermediate MSUD mice exhibit decreased survival beginning at weaning and display elevated BCAA levels reminiscent of MSUD patients. Weekly administration of LNPs significantly increased survival and decreased blood leucine levels compared to control groups of untreated intermediate MSUD mice. Based on this success, we went on to evaluate the same treatment approach in a mouse model of classic MSUD.

The classic MSUD mouse model is deficient in the mouse form of DBT and these mice do not survive past the second day of life. We evaluated the use of LNPs to deliver mRNA in these mice by administering LNPs to them on days 0 and 3 of life. Starting on day 7, mice received weekly or biweekly administration of LNPs. This treatment extended survival of the classic MSUD mouse model to a mean survival of 5 days in a group of 22 treated classic MSUD mice. Some mice in this study survived to 11, 13, 15, and 40 days. Therefore, we can conclude that LNP mRNA therapy may be a treatment option for both classic and intermediate forms of MSUD. ■

AAV Gene Therapy continued from page 20

prevent toxic buildup of these amino acids and their byproducts in the blood.

We believe that targeting the liver with a gene therapy approach will work as liver transplants are effective for MSUD – both strategies replace the mutated gene with the normal version by different methods. However, the liver is not the only site of BCKDH activity in humans. Muscle is responsible for approximately 60% of the total BCKDH activity of the body, compared to approximately 10% activity from the liver. An alternative gene therapy approach involves correcting the mutated gene in both liver and muscle. We evaluated both gene therapy approaches in a mouse model of intermediate MSUD.

Intermediate MSUD mice are deficient in the mouse form of the DBT subunit of BCKDH, but have low-level expression of the human form of DBT, which is required to prevent the neonatal lethality seen when the mouse DBT gene is mutated. Intermediate MSUD mice exhibit decreased survival beginning at weaning and display elevated BCAA levels reminiscent of MSUD patients. A single intravenous injection of AAV vector designed to target the liver did not sufficiently ameliorate all aspects of the disease in this mouse model. A similar effect occurred when a combined approach (a vector designed to express the normal version of the DBT gene in both liver and muscle) was injected intravenously. This underscored the need for an alternative approach.

When intermediate MSUD mice were administered with the combined approach (a vector designed to express the normal version of the DBT gene in both liver and muscle) intramuscularly, survival of this mouse model was drastically increased across all doses studies. In addition, serum leucine levels remained near normal levels in the mid- and high-dose vector groups throughout the length of the study. To further assess the effectiveness of this treatment, intermediate MSUD mice that received the combined vector approach by intramuscular injection were challenged with a high-protein diet. This gene therapy approach protected intermediate MSUD mice from the lethal high-protein challenge, with intermediate MSUD mice that did not receive the vector prior to the high protein diet challenge being euthanized when they invariably displayed signs of metabolic crisis. Therefore, administering a gene therapy vector that expresses in both the muscle and liver may be a viable alternative treatment option for patients with MSUD. ■

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