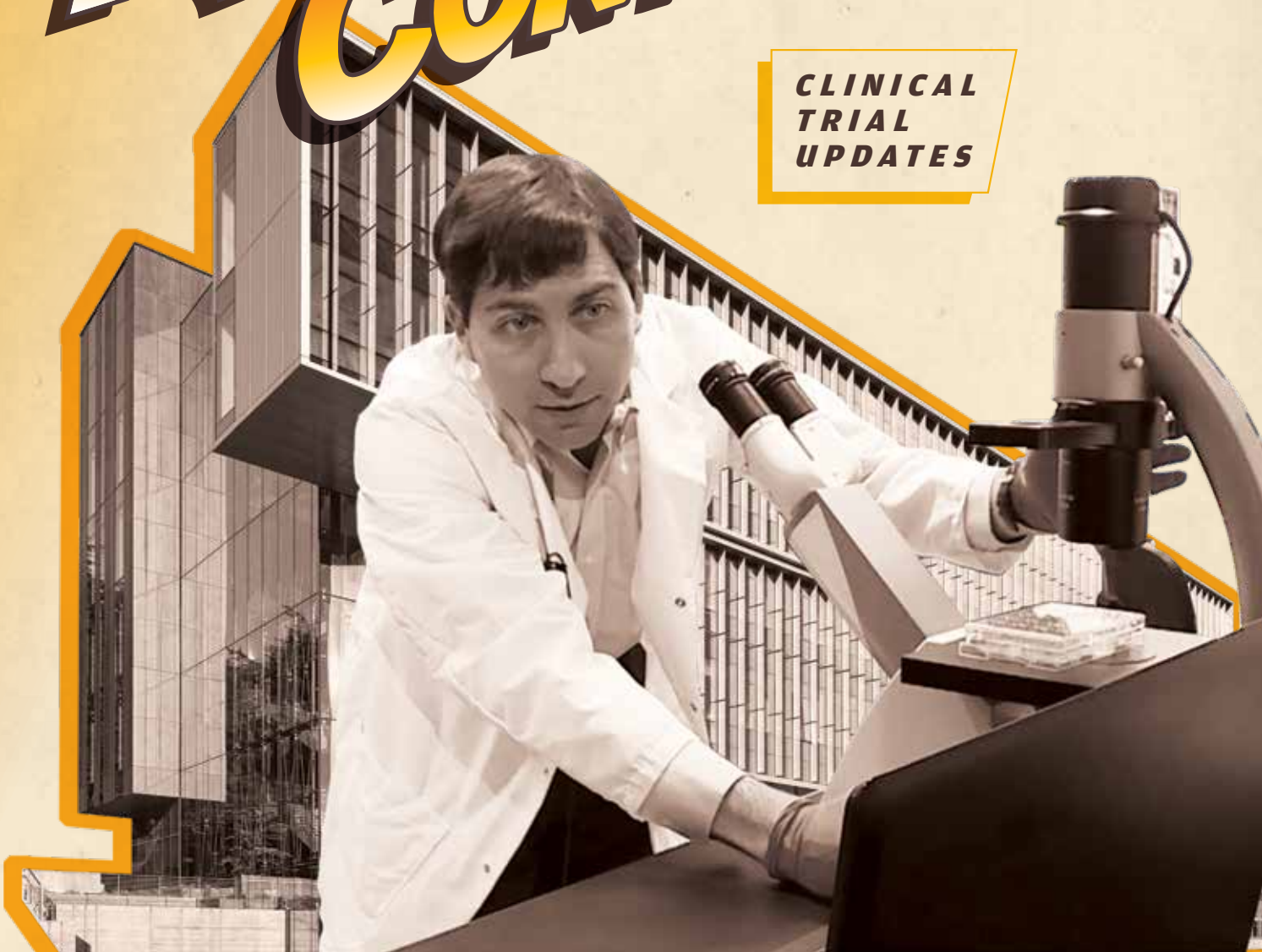
cystinosis magazine

TOGETHER WE SHINE BRIGHT

THE RESEARCH CONTINUES

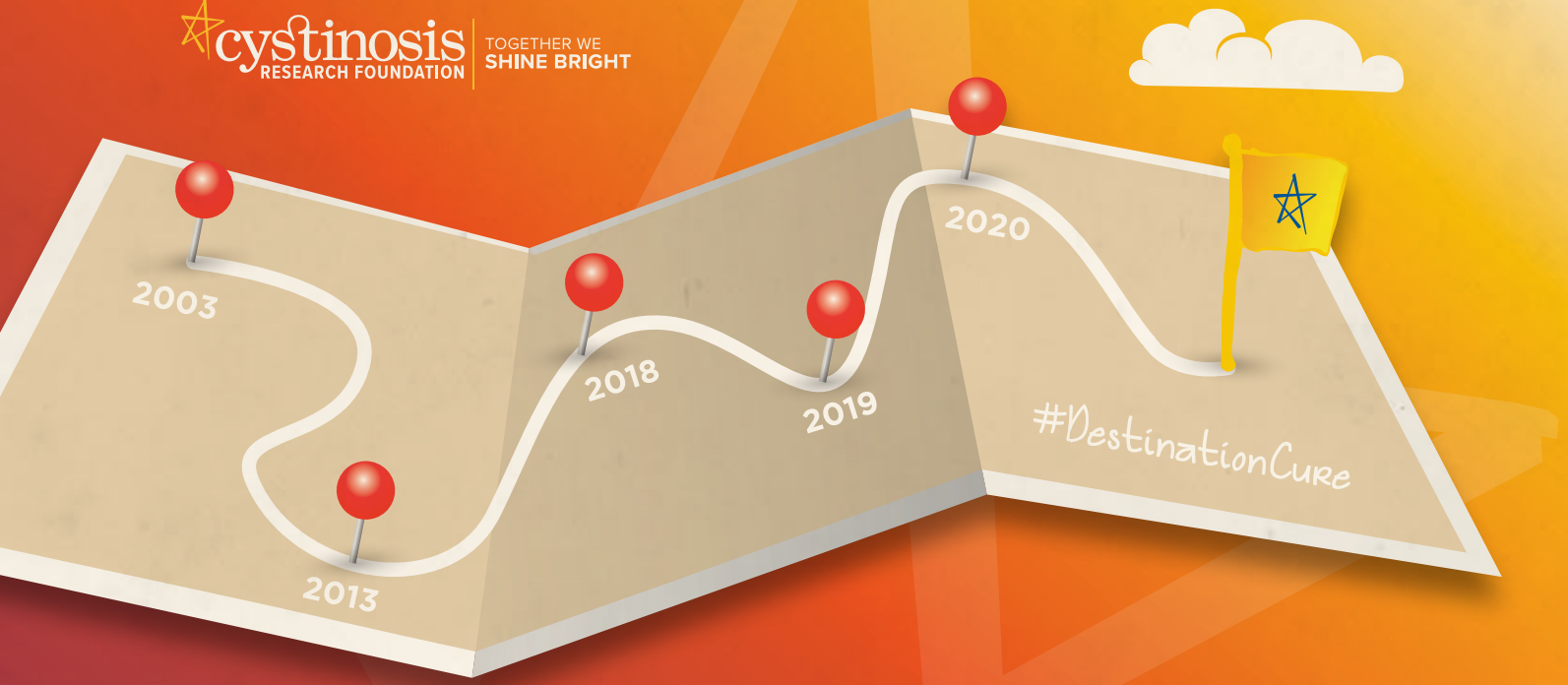
CLINICAL TRIAL UPDATES



FOR FRIENDS AND SUPPORTERS OF THE CYSTINOSIS RESEARCH FOUNDATION

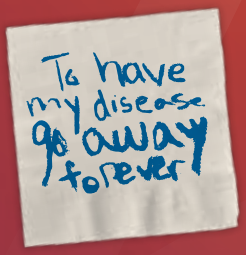
FALL 2020

cystinosis RESEARCH FOUNDATION | TOGETHER WE SHINE BRIGHT



2003

- Natalie Stack made a wish on the eve of her 12th birthday, "to have my disease go away forever."



- The Cystinosis Research Foundation was established with the sole purpose of raising funds to find better treatments and a cure for cystinosis.

2013

- FDA approval in 2013 for a delayed-release form of cysteamine. CRF funded every early clinical study that led to the discovery of the delayed-release form of the medication (EC cystagon, RP 103 and now Procysbi®).
- First patient pilot study for an allogeneic stem cell study at UCLA.

2018

- FDA approval on December 19, 2018 for first stem cell and gene therapy clinical trial to test a new treatment for cystinosis.

2019

- First patient in stem cell and gene therapy clinical trial transplanted on October 7, 2019.

2020

- Road to a cure! Today, CRF is the largest fund provider of grants for cystinosis research in the world, issuing 200 grants in 12 countries.
- Second patient in stem cell and gene therapy clinical trial transplanted on June 29, 2020.
- CRF has raised more than $58 million, with 100% of your donations going to support cystinosis research. CRF's efforts have changed the course of cystinosis and given new energy to its investigators and scientists.
- CRF's commitment to research has given hope and promise to the global community of cystinosis patients and their families.

THE RESEARCH CONTINUES...

The Cystinosis Research Foundation is grateful and motivated as new research unfolds. The stem cell and gene therapy clinical trial for cystinosis is making progress amid a global pandemic. Through generous funding, pioneering research and a compassionate community, together, we are navigating through these times, shining brighter than ever!

CONTACT US:
Please send suggestions and comments regarding *Cystinosis Magazine* to *nstack@cystinosisresearch.org.*

To receive our e-newsletter, *Star Facts*, send your email address to *zsolsby@cystinosisresearch.org.*

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FALL 2020

cystinosis RESEARCH FOUNDATION

CYSTINOSISRESEARCH.ORG
949 223 7610

NEW ADDRESS
19200 Von Karman Ave., Suite 920
Irvine, California 92612

The mission of the Cystinosis Research Foundation is to find better treatments and a cure for cystinosis by supporting bench, clinical and translational research. Since 2003, CRF has raised over $58 million for cystinosis research in an effort to find a cure.

cystinosis RESEARCH FOUNDATION

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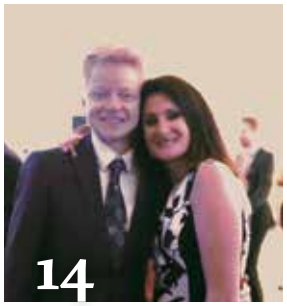

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CYSTINOSIS MAGAZINE IS A PUBLICATION OF THE CYSTINOSIS RESEARCH FOUNDATION

Dear FAMILY and FRIENDS

FALL 2020

Over eight months have passed since CRF made the heartbreaking decision to cancel its annual Natalie's Wish event. Since that time, so much has changed in the world and in our lives. I don't think any of us could have imagined what would be thrown our way – how our daily routines would be dramatically altered, that we would have to adjust to new ways of doing things, all while finding creative ways to cope with our new normal.

The world as we know it has certainly changed in just the course of a few months. The most difficult part for us has been the social isolation. We miss seeing all of you, but we know that better days are ahead, and we will be together when we can safely do so. As is the human spirit, we have found ways to connect and stay close through virtual meetups, socially-distanced visits and long phone calls. My genuine hope is that you and your families are safe and healthy and that you have found ways to enjoy life.

Although the world has changed in so many ways, life with cystinosis has not. Cystinosis is a relentless disease; our children and adults never have a day off. The medication protocol is demanding, requiring several medications to be taken around the clock. Pandemic or not, we remain resolute in our commitment to continue funding life-saving research. Our children's lives are at stake. We cannot lose momentum, but rather remain steadfast in our effort to find the cure for cystinosis.

ALTHOUGH THE PANDEMIC CAUSED SOME PAUSES AND DELAYS IN OUR RESEARCH PROJECTS AND CLINICAL STUDIES, WE ARE HAPPY TO REPORT THAT THE DELAYS WERE SHORT LIVED AND OUR RESEARCH TEAMS ARE BACK AND WORKING FULL TIME. EXPERIMENTS THAT WERE ON HOLD HAVE RESUMED AND OUR CLINICAL TRIALS HAVE BEEN CLEARED TO ACCEPT PATIENT VOLUNTEERS.

Natalie's birthday wish, "to have my disease go away forever" was written 17 years ago and remains our motivating force. Her wish became the wish heard around the world and has been a rallying cry for action in our community. CRF is the driving force of all cystinosis research and together we have transformed Natalie's wish into new treatments and clinical trials – giving new hope for a brighter future for our cystinosis community.

ONE YEAR LATER - UPDATE ON THE STEM CELL AND GENE THERAPY CLINICAL TRIAL

This is a big year for all of us! A little more than a year ago, on October 7, 2019, Jordan Janz became the first cystinosis patient to volunteer for the stem cell study. Since that time the second patient was transplanted on June 29, 2020 and the third patient will be transplanted in November 2020.

The road to new treatments is long and arduous, fraught with setbacks and disappointments. The reality is that not many research ideas make it from the bench to the bedside. However, when you have a determined, focused and persistent community committed to finding better treatments and a cure, wishes and ideas become reality. That is what we have done together.

CRF began working with Dr. Stéphanie Cherqui in 2007. She told us then that she was committed to finding a cure for our children and would never give up until she succeeded. CRF believed that a cure was within reach and we believed in Stéphanie. Finding a cure was our mission and we have been unrelenting in its pursuit.

We have proudly funded over $5.56 million for Stéphanie's research. Since that time, the seed money we provided years ago has been leveraged by $17.2 million from California Institute for Regenerative Medicine (CIRM) and over $5.4 million from the National Institutes of Health (NIH) and other funding agencies. It was not a straight path to FDA approval, but Stéphanie never gave up. In 2018, the FDA approved a clinical trial to test the safety of her treatment. Today, two patients have been transplanted and the third patient will be transplanted this month – the clinical trial is well underway.

The treatment involves taking hematopoietic stem cells from the patient and genetically modifying them with a lentivirus vector to insert a correct copy of the cystinosis gene. These stem cells (without cystinosis) are then transplanted back into the patient.

We celebrate and thank the first three patients for blazing the path toward the cure. One way to measure the success of the treatment is to measure cystine levels. A patient with cystinosis must take cysteamine throughout the day to control and lower cystine levels. So far, Jordan and the second patient have cystine levels low enough that they do not need to take cysteamine therapy. The genetically repaired cells are doing their job!

Thank you to our family and friends who believed that this day would come. We hope and pray that the positive trend continues and that this one-time stem cell treatment will stop the progression of cystinosis or be the cure.

We have a special interview with Jordan and his mom, Barbara Kulyk, on page 14. It is a story of hope, faith and giving back.

THE RESEARCH NEVER STOPS

With your help, CRF has become the largest fund provider of cystinosis research in the world. The reality is, without CRF and the millions of dollars we have funded in grants, we would not be where we are today. CRF has issued over 200 multi-year grants and many of those projects have been leveraged by other fund providers. Leveraging CRF grant money has helped accelerate the research process and led to more discoveries about the pathogenesis of cystinosis. As a result of our funding, CRF researchers have published over 87 articles in prestigious scientific journals. Our commitment to research has changed the course of this disease.

The progress we have made is extraordinary. CRF-funded researchers are responsible for leading the charge to an FDA-approved drug, an FDA-approved stem cell clinical trial, the creation of cystinosis animal models, and multiple clinical trials in the cystinosis field. These accomplishments have improved the quality of life for people with cystinosis, and more importantly, have allowed those with cystinosis to dream of a life free of this disease.

In 2003, there were only a handful of cystinosis researchers in the world. As a result of our efforts, there is now a thriving research community of hundreds of researchers around the world who work every day on behalf of our community. CRF-funded researchers have advanced our understanding of cystinosis and its complications which helps us identify potential new areas of treatments and research. We have accomplished all of this because you have partnered with us to fund research to find a cure.

MORE THAN $2.6 MILLION IN RESEARCH GRANTS AWARDED

To ensure your donations are always at work, and to keep the research cycle moving forward, CRF issues new grants twice a year. We are pleased to announce that this year, to date, CRF has awarded 10 new multi-year grants, four research grant extensions and one new grant for lab equipment. The new grants were awarded to researchers in Belgium, France, Italy, New Zealand, Switzerland and the United States, totalling $2,629,490. Please read about the new grants and learn more about the important research we are funding. The grant abstracts are listed on page 30. Before the end of this year, we will announce additional grant recipients.

We have highlighted two research projects in this issue. The first project is led by Dr. Reza Seyedsadjadi, a neurologist at Massachusetts General Hospital and an assistant professor of neurology at Harvard Medical School. Dr. Seyedsadjadi treats neuromuscular diseases and complications including muscle weakness and swallowing difficulties in patients he sees in his clinical practice. Dr. Seyedsadjadi's CRF-funded study is focused on distal myopathy and dysphagia in cystinosis patients, which are complications that are often seen in our adult population. The aim of his study is to learn more about progressive muscle weakness and swallowing difficulties so that we can improve quality of life and function for those with cystinosis. To date, CRF has funded and committed $590,381 to this important, groundbreaking research.

The other highlighted project, is a grant to AMMA Therapeutics, Inc. We interviewed Manish Singhal, MD, CEO of AMMA Therapeutics, Inc. about the newly funded project which will explore a novel technology to see if it can deliver the cystinosis medication, cysteamine, as a once-a-day subcutaneous injection. We were especially excited about this project because it is a collaboration between AMMA Therapeutics, inventor of the delivery technology, and Dr. Laura Rita Rega, an expert on cystinosis and a CRF-funded researcher at Ospedale Pediatrico Bambino Gesù (OPBG) Italy. The aim of the project is to develop another treatment option for patients – a treatment that is superior to the current oral cysteamine treatment. There are many side effects from oral cysteamine including gastrointestinal issues, odor, headaches, and nausea and round-the-clock administration of the medication. If this treatment works, it could mean an easier way to take cysteamine with fewer side effects which would improve the quality of life for those with cystinosis. See article on page 24.

Given the breadth of research currently funded, you can be assured that there will be more breakthroughs and life-changing treatments and discoveries in the near future. You have been with us every step of the way and we are forever grateful. We could not do this without you.

CRF RESEARCH HELPS OTHER DISEASES AND DISORDERS

Your support of cystinosis research extends far beyond our small community. Our discoveries are being applied to other more prevalent diseases and disorders. Discoveries made by our researchers have the potential to help millions of others with diseases and disorders similar to cystinosis. In fact, discoveries from our research teams are being applied to Friedreich's Ataxia, Danon disease, corneal diseases, kidney diseases and genetic and systemic diseases similar to cystinosis. We thank our CRF-funded researchers, scientists and clinicians whose tireless work has helped transform the understanding and treatment of cystinosis and other disease groups.

LOOKING AHEAD WITH RENEWED HOPE

As the world copes and adjusts to life in a pandemic, we remember that there will be better days ahead especially if we unite in an effort to help and protect each other. We know that life with cystinosis means daily struggles and challenges. We know there are no days off from cystinosis, but we have never given up. To the contrary, we have faced the challenges of cystinosis together and we have overcome obstacles and have found a path to better treatments and a cure. However, our job is not done; there is more work to do and with your help and support, we will undoubtedly succeed.

Thank you for embracing our community. For supporting our research efforts. For always believing that we could make Natalie's wish come true. You are part of our family and we feel privileged to have you by our side. If all goes well and it is safe to gather, we look forward to seeing you in person next year as we celebrate our cystinosis community!

With heartfelt thanks and gratitude,

Nancy & Jeff Stack

THE RESEARCH CONTINUES...

A note from NATALIE STACK

Me and Henry!

Dear Family and Friends,

2020 has been a year full of uncertainties. Who knew that a few months after the stem cell trial started, we would be in a worldwide pandemic. It took some time to adjust to the new normal, but it now feels routine. It has been eight months since the pandemic started; during that time, I have been able to really focus on myself, my career, and my family. I am so incredibly fortunate to not only be as healthy as I am today, at 29 years old, but also to have a stable job and a very supportive family.

My overall health is great—I have not had a kidney transplant yet and am hoping to be in the clinical trial someday in the near future. I still live in Irvine with my cat, Henry, and am close to my family. I have been a case supervisor at CASA OC (Court Appointed Special Advocates, Orange County) for two years and I have been able to challenge myself in my position. Though this year is not what any of us had in mind, it has been a year full of reflection and growth for me.

It has been a year since the first patient, Jordan, had the stem cell transplant. He is doing amazingly well and has not been on his medication for an entire year. This data is proof that the cure is here. The progress and success of the stem cell trial so far makes me believe that I have a future to look forward to.

Cystinosis is an exhausting disease. The around-the-clock medications, strong odor from medications, eye drops every hour, headaches, uncomfortable stomach pain, extreme fatigue, g-tubes, rickets, nausea, and sensitivity to light are just a few complications. The extreme fatigue affects me the most and on a daily basis. During the pandemic, I have had to work from home. I am able to work more efficiently and effectively because I am able to get the sleep I need each night in order to feel good the next day. I have not felt this productive and good for a long time.

Being surrounded by an incredible community has given me hope that cystinosis will not be forever. I believe that my future is promising and full of adventure – a future without the burden of an all-consuming disease.

As always, I am so very thankful to Stéphanie Cherqui, PhD and her team who are so dedicated to finding a cure for cystinosis. She is truly our hero. I am grateful for what Dr. Cherqui, my mom, and the rest of this community have done for not only me, but for all the other patients with cystinosis.

I am truly blessed to be alive and healthy. I am so thankful to this community for believing a cure will be found. Thank you for never giving up on my wish to have my disease go away forever.

Love,
Natalie

What is cystinosis?

Cystinosis is a rare, inherited, metabolic disease that is characterized by the abnormal accumulation of the amino acid cystine in every cell in the body. Build-up of cystine in the cells eventually destroys all major organs of the body, including the kidneys, liver, eyes, muscles, bone marrow, thyroid and brain. Medication is available to control some of the symptoms of this terrible disease, but cystinosis remains incurable. Cystinosis affects approximately 500 people, mostly children, in North America, and about 2,000 worldwide.

It is one of the 7,000 rare or "orphan" diseases in the United States that collectively impact approximately 30 million Americans.

Federal funding for research on cystinosis and other rare diseases is virtually non-existent and most pharmaceutical companies remain uninterested because financial rewards are too small. Yet, while there are only a small number of patients who suffer from any given "orphan" disease, knowledge gained by studying one disease often leads to advancements in other rare diseases and more prevalent and well-known disorders.

Our story

In 2003, Natalie Stack made a wish on the eve of her 12th birthday, "to have my disease go away forever." That same year, the Cystinosis Research Foundation (CRF) was established with the sole purpose of raising funds to find better treatments and a cure for cystinosis.

Today, CRF is the largest fund provider of grants for cystinosis research in the world, issuing 200 grants in 12 countries.

CRF has raised nearly $58 million, with 100% of your donations going to support cystinosis research. CRF's efforts have changed the course of cystinosis and given new energy to its investigators and scientists. CRF's commitment to research has given hope and promise to the global community of cystinosis patients and their families.

cystinosis RESEARCH FOUNDATION | TOGETHER WE SHINE BRIGHT

CHARITY NAVIGATOR ★★★★ Four Star Charity

PLATINUM

We celebrate our CRF community and are grateful everyday for your support.

CRF's highly strategic approach to funding has resulted in two FDA approvals and several human clinical trials. The research dollars we have invested have been leveraged by over $28 million in grants from other funding agencies. Not only does CRF research help our community, but our discoveries are applied to more prevalent diseases and disorders. CRF-funded research has the potential to help millions of others.

We want to thank our families, friends and donors who have remained steadfast in their commitment to finding better treatments and a cure. Thank you to the cystinosis researchers and scientists who are working around the clock on behalf of our children and adults with cystinosis.

Cure Cystinosis

International Registry

The Cystinosis Research Foundation is excited to announce that a new Cure Cystinosis International Registry (CCIR) will be launching soon. This improved patient-based international registry will be a central hub of information created by those living with cystinosis, their families and their caregivers. The deidentified information provided by patients and their families will be shared with cystinosis clinicians, researchers and scientists who are pursuing better treatments and a cure for cystinosis.

For patients, CCIR will provide an opportunity for involvement in research that will help develop and test new therapies and develop a cure for cystinosis. The registry will connect all of the stakeholders in the cystinosis community – the scientists, researchers, clinicians, pharmaceutical companies, patients and families – and provide them with resources that have never been available in one place before, all in an effort to accelerate better patient care.

Watch for upcoming announcements to register and be part of the cure!

Thank You!

With Your Support, We Surpassed the $200K Matching Gift Challenge!

Your generosity and commitment to research are extraordinary! Our goal was to raise $200,000, but you helped us surpass that. We are excited to report that we've raised a record-breaking $516,931! Thank you to the three generous families who launched the gift challenge and inspired all of us to match. We received donations from CRF families and friends from around the world, and as a result, we've raised an unprecedented amount in honor of our children and adults with cystinosis. These donations will allow CRF to accelerate research and help us fund new research grants this year. It is because of you that CRF is the leading fund provider of cystinosis research in the world. Together, we have created a vibrant and synergistic research community that works every day to find better treatments and a cure!

$516,931 Raised for Cystinosis Research

TOGETHER, WE HAVE CHANGED THE COURSE OF CYSTINOSIS

CRF and Canadian Families

UNITE TO FUND RESEARCH

THANK YOU CANADA

We are grateful to our Canadian cystinosis families who have partnered with CRF to fund research that will lead to better treatments and a cure. Working together, our two countries have united in an effort to raise awareness about cystinosis, advocate on behalf of all children and adults with cystinosis and ensure that we fund the most qualified researchers in the world. Although in-person events were canceled this year because of the global pandemic, families across Canada continue to organize and plan safe virtual events to raise money for research. Together, we have unlimited hope and boundless determination to find a cure for cystinosis.

Magic happens when countries work together!

Since 2016, Canadian families have directly funded CRF research with $763,012 in grant payments through the Aqueduct Foundation.

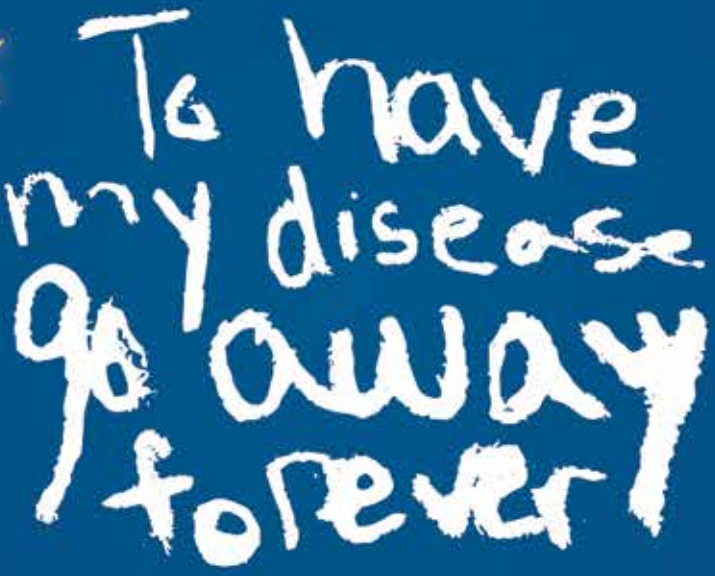
Sergio Catz, PhD
Raquel Gontijo, PhD
The Scripps Research Institute
"Novel Mechanistic and Translational Studies of Neutrophil-mediated Inflammation in Cystinosis"
$37,500

Sergio Catz, PhD
Farhana Rahman, PhD
The Scripps Research Institute
"Molecular Trafficking Regulators of Dynamic Organelles in Cystinosis"
$37,500

CRF is incredibly grateful for the support of our Canadian cystinosis families and friends.

Donations made by Canadians are channeled through Canada Helps, managed by the Aqueduct Foundation and administered by Cystinosis Awareness and Research Effort (CARE). Through Canada Helps, CARE has created an efficient and effective fundraising process, ensuring that Canadians receive a tax receipt. Canadians also have the option to donate directly to CRF if they so desire. If you would like to learn more about how to fundraise in Canada or donate, please contact: Zoe Solsby at *zsolsby@cystinosisresearch.org*.

Natalie Stack's *Original Wish*



Save The Date

Day of Hope Conference & Natalie's Wish Celebration

We are excited to learn, grow and celebrate with our entire CRF family!

Due to COVID-19, the event is subject to in-person gathering recommendations as provided by the California Department of Public Health.

when

August 2021
Specific Dates Coming Soon

where

Pelican Hill Resort
Newport Coast, CA

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CRF RESEARCH STUDIES AND CLINICAL TRIALS

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STEM CELL AND GENE THERAPY CLINICAL TRIAL UPDATE:
JORDAN JANZ — FIRST PATIENT, FIRST YEAR

'Our Greatest Year'

IN THE TWELVE MONTHS SINCE HE BECAME THE FIRST CYSTINOSIS PATIENT TO RECEIVE A STEM CELL TRANSPLANT, JORDAN JANZ HAS SEEN HIS LIFE CHANGE IN WAYS BIG AND SMALL. THE NEW NORMAL IS GROWING ON HIM.

By Dennis Arp

Think of how different our world was just a year ago. In early October 2019, we had no idea that a pandemic was on the horizon, bringing disease and disruption to countless lives around the globe. What a challenging year it has turned out to be.

Like so many who live with cystinosis, Jordan Janz has known health challenges throughout every year of his existence. Janz and his family have a special perspective on the 12 months just completed.

Jordan with his mom, Barbara Kulyk.

"I know for the rest of the world, it's been terrible," said Barb Kulyk, Janz's mom. "But for us, it's our greatest year."

On October 7, 2019, Janz became the first cystinosis patient to undergo a transplant of genetically modified autologous stem cells. The procedure made Janz a pioneer as it also culminated 13 years of groundbreaking research by Dr. Stéphanie Cherqui – research made possible by more than $5.56 million of support from the Cystinosis Research Foundation.

After receiving the transplant of his own modified cells, Janz spent three weeks in a San Diego hospital recovering from the procedure. Ever since – throughout his return to his home in Alberta, Canada, and his transition to a new and exciting phase of his journey – Janz has carried with him the hopes of the cystinosis community.

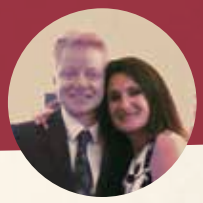
COULD THIS BE THE CURE EVERYONE HAS SOUGHT FOR SO LONG?

Janz's lab numbers are good, and he has been off cysteamine since the stem-cell transplant. He's taking less than half the number of pills he did before the procedure, and he's free of so many of the symptoms and side effects that used to dominate his life.

Those are all really big things, but they are not the only things. The hair Janz lost has come back in darker, and his skin tone is much rosier than it used to be. Then there's Kulyk's favorite change – one that will resonate with many cystinosis parents.

"I am deeply thankful to the volunteers who participated in the stem cell transplant. They have been the pioneers of this new therapy, taking the risks without knowing the benefits. I am humbled to see the work of many years and countless hours become a reality. Going from bench to bedside has been a tremendous challenge that has been possible because of the support and funding of Cystinosis Research Foundation, CIRM and NIH. We have lived this journey all together and I hope this new treatment will become a reality for the entire community."

— Stéphanie Cherqui, PhD



Jordan with Dr. Stéphanie Cherqui, 6 months before transplant.

"I love how Jordan smells," Kulyk said, referring to the sulfur-like scent that comes with taking cysteamine. "When Jordan started taking some form of cysteamine, he was only 9 months old, so he never really had that baby smell. Now he smells like a baby to me. He probably doesn't want to hear that at 21, but it makes my heart ache that he now smells like my other four children. It's one of those little things – I know that I sound like a nut saying it. But it's the little things that make such a difference and make it all worth it."

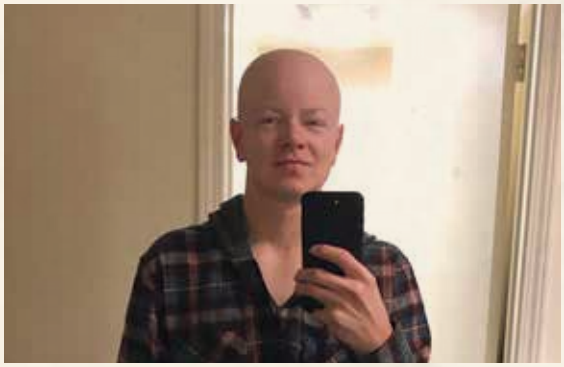
For Janz, the year since his procedure hasn't been without its own set of tribulations. Even before the transplant, he had to undergo a round of chemotherapy, and during his convalescence after the procedure, he had an appendectomy that was unrelated to the stem-cell transplant. Then, in an effort to return to normalcy as quickly as possible, he went back to working a full-time schedule at his job in his hometown of Consort, Alberta.

Janz loves that his regimen has gone from a high of 50-plus pills a day to 24 now – many of them to protect the health of his kidneys and buttress his immune system.

"I can go to my girlfriend's house, and I don't have to pack all these pills, like I used to," Janz said. "I can go out with friends and not have to be back at exactly a certain time to make sure I take the next dose."

To be sure, Janz is still adjusting to his new normal. He gets fatigued more often than he would like, and he has his down days. In early October, as he prepared to return to San Diego for two weeks of additional follow-up testing, he was asked for this article: "Are you feeling better?"

"Yes and no," he said. "I think it will continue to get better as time goes on, but right now, I'm feeling a little iffy."



Jordan Janz and Hailey Wilson.

Janz and his family celebrate that he is not experiencing symptoms of cystinosis, and his average granulocyte cystine level has been consistently in the range hoped for by his doctors.

"But he went through a lot," Kulyk noted. "In another year, I think he'll feel even better. We're at a good place, but as far as that instant gratification feeling? You just want to feel better; you want to have a cure. The energy will come back – this is short term, not long term."

Janz is still a bit reluctant to think in terms of a cure.

"Sometimes I'll catch myself saying it, and then I'll correct myself – well, we're not sure yet. I don't want to say it and put bad luck on things," Janz said.

Jordan in August, 2020 – 10 months post transplant.

"We do a lot of knocking on wood around our house," Kulyk added with a smile. "The other day I told someone, 'I have a chronically ill son,' and then I thought – is it 'had a chronically ill son?' I don't really know where we fit right now. Maybe we are our own fit."

As so many people have worked tirelessly for so long pursuing a cure for cystinosis, the disease and its affects have remained a given for Janz and other patients. Cystinosis has not just been part of their lives, but part of their identity.

Now, as Kulyk says: "OUR STORY HAS CHANGED A BIT."

Now it's "a cool story" that Janz can tell, if he chooses to. "I used to have this disease, then I did this, and now I don't have to take these pills, and I don't have to fly to Chicago every three months to get the pills."

Many cystinosis patients and their families want to hear Janz's story and to thank him for stepping up to be the first to undergo the stem-cell transplant.

"I'm still getting text messages and Facebook messages asking how I'm doing," Janz said. "From all over the world, too – from Afghanistan and Turkey, Brazil, Australia. It's so cool that people want me to know that I'm in their thoughts."

They are in his as well. It's clear that the bond he and his family share with the cystinosis community means a lot to Janz, and it remains at the center of his thinking.

"It's definitely on my mind all the time," he said.

The wonderful friends Janz has made – the countless people who have supported him and his family, as they have supported other cystinosis families – those friendships undoubtedly will endure. But that's different from allowing yourself to consider the possibility of a world in which cystinosis no longer hangs like a cloud over so many lives.

What about that transformation in thinking?

"We lived an awful long time with cystinosis for us to just change – to have that mind shift," Kulyk said. "But we're working on it."

Date: August 1, 2020

Principal Investigator: Benjamin S. Freedman, PhD

PROJECT:

Developing A Therapeutic Strategy For Cystinotic Nephropathy With iPS Cells

Major goals of the project: The goal of this proposal is to use human induced pluripotent stem (iPS) cells and derived kidney organoids to screen and develop therapeutics for cystinotic nephropathy. Specifically, we will use kidney organoids as a surrogate for human tissue to explore the potential of renal regeneration, gene therapy and compound screening for the development of cystinosis therapies. The work will be performed in three Specific Aims. In our first aim, we will reprogram a cohort of cystinosis patient cells into iPS cells that could be further developed into *bona fide* regenerative therapeutics, and transplant these into animals. In our second aim, we will develop techniques to restore *CTNS* function in kidney cell types, by applying cutting edge gene therapy techniques in differentiating organoids. In our third aim, we will recreate the cellular pathophysiology of cystinosis in a petri dish to gain specific insight into why tubular cells die and how this can be prevented chemically. These aims have not changed.

Progress towards key milestones: In our third reporting period, we presented at the Cystinosis Research Symposium, which was very beneficial, and have continued to grow our collaborations with other groups in the cystinosis community including Dr. Bruce Barshop and Dr. Elena Levtchenko. Dr. Freedman published a commentary paper with fellow cystinosis researcher Dr. Alessandro Luciani (Luciani and Freedman, *Kidney International* 98, 54-57), which discusses the use of induced pluripotent stem cells for modeling endocytic disorders and Fanconi syndrome. For our milestones, we have made progress in establishing and characterizing our new cohort of cystinotic iPS cell lines and derived organoids, which are not yet published. We are conducting a careful phenotyping of these cells, using several different cell lines and controls. Our work implanting the cells into animals has provided the first glimpse of in vivo grafts from cystinosis patients. We have also improved our ability to conduct genome editing in organoids as a model of gene therapy for cystinosis. Each of these is described in further detail below.

1 **Determining the disease phenotype of a cohort of cystinotic organoids derived from iPS cells.** An important goal is to re-create the phenotype of nephropathic cystinosis *in vitro.* We have found that our mutant iPS cell lines accumulate cystine, based on cystine assays performed by Dr. Barshop in San Diego. To confirm this result, we have repeated the experiment and sent Dr. Barshop a second batch of samples, including both iPS cells and derived organoids, with defined total protein levels. This will help us verify that cystinosin is not functional in these cells. To complete characterization of our stem cell lines, we have implanted these into an animal model, to form teratoma tumors. We have also initiated a collaboration to sequence the genetic mutation in our patient cell lines, which will increase their value for the community.

Ultimately, we seek to identify tissue-scale phenotypes that would provide insight into the mechanisms of nephropathic cystinosis. The importance of identifying such phenotypes was also emphasized during conversations with experts in the field during the recent CRF Research Symposium. We initially observed that differentiation of cystinosis lines into kidney organoids and particularly podocytes appeared to be impaired, particularly in our patient-derived cell lines. In more recent follow up experiments, however, we have found that cell lines with cystinosis mutations can differentiate efficiently into mature kidney organoids with well-defined tubules and podocytes. We are currently modifying culture conditions to identify tissue-scale phenotypes. We are also investigating whether cysteamine can rescue the cystine accumulation and its effects on the organoids.

CRF has supported Dr. Freedman since 2018, awarding $392,316 for his important study at the University of Washington Medicine/ Nephrology, using human induced pluripotent stem (iPS) cells and derived kidney organoids to develop therapeutics for cystinotic nephropathy. His August 2020 report outlines the progress he has made towards the aims of the study. We are excited about his progress and the potential his work has for our cystinosis community.

2 **Isolating and implantation of nephron progenitor cells (NPC).** An important aspect of our plan is to implant human kidney progenitor cells into mouse kidneys to determine their ability to engraft and form structures that could be safe and functional. When we previously implanted mature organoids beneath the kidney capsule of mice, these engrafted and became vascularized from the host. However, maturation remained incomplete, and non-kidney cells became enriched in the graft over time (*Experimental and Molecular Medicine,* 2019). Having established this as a baseline, we are currently implanting earlier-stage NPC, with the hypothesis that these may show improved engraftment. We are conducting these experiments with iPS cells from patients with cystinosis, to determine whether mutations affect the grafts. Our experiments to date indicate that NPC derived from patients with cystinosis can successfully grow in the animal model. One week post-implantation, human NPC structures (renal vesicles) were visible in the graft. At later time points, podocytes, proximal tubules, and distal tubules appeared in nephron-like structures (Figure 1).

This is interesting proof of principle that supports the possibility of growing new kidney tissue *in vivo* from patients with cystinosis. We are currently quantifying and analyzing these findings, to determine whether the grafts show signs of being functional or express cystinosis-specific phenotypes. We are also expanding these experiments to include NPC from additional patients.

FIGURE 1. Nephron-like structures from cystinosis patients. Small portion of an NPC graft three weeks post-implantation. Red, human cells; green, podocytes; magenta, proximal tubules.

3 **Progress towards gene therapy.** We are developing an off-the-shelf methodology to perform gene therapy for cystinosis in the kidneys, using organoids as a surrogate for patient tissue. Our greatest interest lies in developing the use of CRISPR-Cas9 ribonucleoprotein (RNP) complexes to integrate a wild-type copy of *CTNS* into the genome. We had previously succeeded in obtaining a 3% editing rate using GFP as a readout. By refining the timing of treatment with the RNP, we have now improved this to 20% editing. We have also completed the design of our *CTNS* rescue vector, which will be inserted into genomic safe harbor loci using CRISPR-Cas9 and will be inducible with doxycycline so we can control the levels of cystinosin.

In addition to CRISPR RNP, we are exploring the utility of more established platforms for gene transfer including adeno-associated virus (AAV) and lentivirus in organoids. Here too, timing of virus addition proved to be important. We obtained substantial infection of organoids with three different lentiviral promoters, in collaboration with Dr. Elena Levtchenko (Leuven University, Belgium). One of Dr. Levtchenko's students obtained a travel award to visit our laboratory in September and further assist with these experiments. We have also obtained successful infection of organoids with two different AAV serotypes, which may represent a safer option *in vivo* compared to lentivirus.

RESEARCH

HOPE

CURE

Logistical, personnel and manuscripts in preparation. Cystinosis has grown into a major focus of our lab. The COVID-19 pandemic has raised some challenges. Only critical staff have been allowed to come into the lab, and the month of April we had limited staff and operations. During this time it was unclear what the guidance was or how severe the outbreak would be. Since that time, the first wave of cases has resolved, and it became clear that we were permitted to continue work in the laboratory, in accordance with safety guidelines. This is because research related to human disease and therapeutics development is considered essential work in the state of Washington. We have therefore been able to continue to make progress on this important project. Unfortunately, during this vulnerable time, Ivan Gomez, who was helping to engineer cell lines and transplant these into animals, was recruited by a pharmaceutical company, and resigned his position in our lab. Ivan's effort on the project has, however, been replaced by Thomas Vincent, a second year Bioengineering PhD student who is highly motivated about kidney regeneration. Thomas has completed all of his animal training, is helping maintain our mouse colony, and has learned to perform implantation surgeries and analyze them. Other personnel remain unchanged. We are completing work on our manuscript about iPS cell derivation from urinary cells, and strategizing for funding applications to continue the cystinosis project.

THE RESEARCH CONTINUES...

Future work:
In the coming funding period, we will complete

(1) establishment of our cohort of cystinosis patient lines, including recently recruited patients (the study is ongoing);

(2) phenotyping of cystinotic organoids and attempt to rescue these with treatments such as cysteamine;

(3) characterization of grafts resulting from NPC injection into mouse kidneys from multiple patients with or without cystinosis; and

(4) development of our gene therapy methodology to re-introduce *CTNS* into kidney organoid cultures. We also hope to submit a manuscript describing derivation of our cell lines and demonstrating their use, as well as apply for additional funding to support these projects. This will be a busy season for cystinosis work and we are looking forward to it.

We are very grateful for the support and opportunities the Cystinosis Research Foundation provides and hope that you and the community are doing well during these turbulent times.

Bene

CRF FUNDING PUTS FOCUS ON DIFFICULTY SWALLOWING

A HARVARD-BASED STUDY PROVIDES PROGRESS ON UNDERSTANDING MUSCLE WEAKNESS

By Dennis Arp

It's something we all might take for granted – an action done without thought. Then one day, a cystinosis patient tries to swallow, and the muscles constrict. The harder the patient tries, the more the throat tightens, stopping the intake of needed sustenance. But beyond that, food can lodge in the airway, and muscular weakness can make it hard to push out aspirated material, so the patient is unable to breathe freely.

For many cystinosis patients, these scenarios become all too real. In some studies, as many as half the patients assessed had swallowing abnormalities.

Dr. Reza Seyedsadjadi, a neurologist at Massachusetts General Hospital and an assistant professor of neurology at Harvard Medical School, treats neuromuscular diseases and complications, including muscle weakness and swallowing difficulties that greatly affect patients he sees in his clinical practice.

Now, thanks to a grant from the Cystinosis Research Foundation (CRF), he's working to close a major gap in clinical trials by performing experiments to better understand the evolution of muscle weakness and difficulty swallowing.

"Neuromuscular complications, including muscle weakness and dysphagia (swallowing difficulties), are not very well studied nor well understood," said Dr. Seyedsadjadi, co-principal investigator on the research project with Lee Rubin, PhD, co-chair of the Harvard Stem Cell Institute Nervous System Disease Program.

"With the loads of medications many cystinosis patients have to take each day, myopathy (muscle weakness) and dysphagia (difficulty or discomfort in swallowing) can have major effects on patients' well-being and quality of life," Dr. Seyedsadjadi added.

Because cystinosis affects all the muscles and organs of the body, often it's just a matter of time before the muscles involved with swallowing are affected. As cystinosis patients live longer, the problem becomes more prevalent. Add in the need for some patients to take as many as 40 pills a day, and the impact of swallowing difficulties becomes even more pronounced.

It's no surprise, then, that compliance with demanding medication regimens becomes an overwhelming challenge.

"It is possible that by being compliant with medications, there will be less involvement of muscle tissues overall," Dr. Seyedsadjadi said. "But we know that despite optimal treatment, some patients will continue to have worsening in their swallowing and experience more muscle weakness."

Still, there is progress to report. There were three major outcomes from the recent CRF-funded study

CLINICAL, NEUROPHYSIOLOGICAL AND PATHOLOGICAL CHARACTERIZATION OF MYOPATHY AND DYSPHAGIA IN ADULTS WITH NEPHROPATHIC CYSTINOSIS; EVALUATION FOR INHERENT MUSCLE RESILIENCE AND REGENERATIVE CAPACITY

REZA SEYEDSADJADI, MD | MASSACHUSETTS GENERAL HOSPITAL

REZA SEYEDSADJADI, MD

conducted in Boston by Dr. Seyedsadjadi and his colleagues. First, the research team succeeded in defining an outcome measure for myopathy that's specific to cystinosis. In addition, it also gathered metrics establishing a baseline for clinical outcomes that show potential for comparison in future trials. And finally, researchers looked more deeply at the mechanisms of swallowing, as patients received a specific kind of respiratory treatment that shows promise for improving function.

"With those who were slightly more affected, we could show possible improvement in their swallowing mechanics using this specific respiratory training module," Dr. Seyedsadjadi said.

The treatment tested involves video fluoroscopy using a contrast, or fluid.

With the training module, "some patients were able to pass the fluid (through swallowing) in a more organized fashion," Dr. Seyedsadjadi said.

So, with this and perhaps other forms of specialized training, patients with impairments might be able to improve the efficiency of their swallowing. But is there a chance that they might also restore lost function?

It is not easy to predict, and it partially depends on the stage of the disease, according to Dr. Seyedsadjadi.

"We know from our experience with other muscle diseases that if you can reverse the process that leads to muscle damage early on, it is possible to return a portion of the function," he said. "However, if the muscle is damaged beyond a certain point, that could make it difficult to recover function."

Another element of the research project funded by CRF will look at muscle resilience in cystinosis patients. This is where the project's partnership with Harvard's Stem Cell Institute comes into play.

"We are planning to obtain muscle biopsies from some of the patients, and we will try to look at possible regenerative capacity in the muscle tissue for a possible interventional study in the future," Dr. Seyedsadjadi said. "This will help us better understand resilience of swallowing and limb muscles for future studies, and whether certain regenerative techniques could potentially be used in the treatment of muscle weakness and swallowing difficulties in these patients."

Another next phase for the research project would be to design an interventional study using speech therapy techniques to see if that might improve muscle function, the doctor said.

Dr. Seyedsadjadi noted that there was one more lesson he and his colleagues took from the completed study. They are impressed with the wholehearted commitment made by patients, families and the entire community to see research projects like his succeed.

Patients traveled from far to take part in the study.

"Even compared with other rare diseases, the commitment of the cystinosis patient population and their families is exemplary," Dr. Seyedsadjadi said. "That's an important reason why this has been and will be fruitful."

Of course, the project wouldn't be possible without the support of CRF, the doctor added.

"Funding is very important, but it's also the environment CRF has which made things possible," Dr. Seyedsadjadi said. "The foundation is adept at bringing together investigators and patients. That's instrumental in making things happen."

NOVEL TECHNOLOGY OFFERS A NEW DOSE OF HOPE

DRUG-DELIVERY INNOVATION MAY LEAD TO ONCE-A-DAY INJECTION OF CYSTEAMINE

By Dennis Arp

For Dr. Manish Singhal, it all started with a "crazy idea." Now, his notion is turning into a new research study with life-changing potential for those who live with cystinosis.

Dr. Singhal's company is at the center of the study, which is funded by the Cystinosis Research Foundation (CRF). The project will explore a novel technology to see if it can deliver the cystinosis medication cysteamine as a once-a-day subcutaneous injection. If the possibility is realized, daily life will get much better for cystinosis patients.

When it was first suggested to Dr. Singhal that his firm's technology might work with cysteamine, he sought advice from a fellow Bay Area colleague, Dr. Paul Grimm, Professor of Pediatrics and Medical Director of the Pediatric Kidney Transplant Program at Stanford University School of Medicine. Grimm is the one who told him his "crazy idea" actually had a lot of merit.

Dr. Grimm invited Dr. Singhal to visit his clinic, where Dr. Singhal met cystinosis patients and their families for the first time.

"Before this opportunity came on my radar, I knew very little about cystinosis," said Dr. Singhal, chief executive officer of Hayward, California-based AMMA Therapeutics, Inc., which is developing the technology to be investigated in the study. "Once I learned more, it started to look like this would be a good fit. And on a personal level, I became convinced that something has to be done to improve the lives of these patients. We're excited to have the chance to begin looking deeper into the possibilities."

Oral cysteamine is the only treatment option available to most cystinosis patients, but unfortunately the treatment comes with unpleasant complications and side effects. Cysteamine is a sulfur-based drug with a disagreeable taste and odor. Almost all of those with cystinosis have to endure the unpleasantness multiple times every day as they ingest oral cysteamine.

Beyond the taste and odor, cysteamine is not always absorbed uniformly when taken orally. The new drug-delivery technology may allow the medication to be given as a once-a-day subcutaneous injection, similar to an insulin shot, alleviating many of the drawbacks associated with oral cysteamine.

Independent work has demonstrated in small animals that a cysteamine injection is feasible using the new drug-delivery technology. The CRF-funded study will seek to provide a broader understanding of how well cysteamine works when it's injected into subcutaneous tissue. Investigators will also seek to learn how much of the medication needs to be delivered to achieve efficacy, and whether there are any safety issues with the system.

The technology being tested is "a fundamentally different approach to drug delivery," Dr. Singhal said.

"With traditional drug-delivery technologies, you basically have a matrix and a drug; you put the drug into the matrix, and then you put that into the body," he explained. "Our matrix only happens when our technology and the drug molecule interact. So, there isn't a preformed matrix."

DEVELOPMENT OF A ONCE DAILY SUBCUTANEOUS INJECTION OF CYSTEAMINE BITARTRATE

MANISH SINGHAL, MD, *CEO*
MICHAEL SEKAR, PhD, *PRINCIPAL INVESTIGATOR*
AMMA THERAPEUTICS, INC., HAYWARD, CALIFORNIA
LAURA RITA REGA, PhD, *CO-PRINCIPAL INVESTIGATOR*
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

MANISH SINGHAL, MD
CEO, AMMA THERAPEUTICS, INC.

This technology consists of peptides – small, simple proteins. AMMA Therapeutics has designed these peptides to interact with drug molecules, creating an active system, unlike traditional drug-delivery technologies, which are passive.

When the peptides interact with a drug molecule, they form nanoparticles that can be injected.

"The advantage is that we're able to target drug molecules that are difficult, like cysteamine," Dr. Singhal said. "How is cysteamine difficult? One way is that it's water-soluble, so with a traditional delivery technology, cysteamine will just leech out of the matrix, and you can't control the release of the drug."

The AMMA Therapeutics technology is called BAIT NPT, reflecting how the peptides hold onto the drug molecule, "kind of like when you go fishing and bait a fish," Dr. Singhal said.

In addition to holding the drug molecule in place, the technology enhances stability, further allowing for consistent release of the medication.

"The technology really seems to be well-suited for this application," Dr. Singhal said.

AMMA Therapeutics and Dr. Singhal are partnering on the project with Dr. Laura Rita Rega, an expert on cystinosis who practices in the Division of Nephrology and Dialysis at Bambino Gesù Children's Hospital and Research Institute in Italy. The collaboration came about through connections with researchers whose names are familiar to cystinosis patients and families: Dr. Francesca Emma and Dr. Stéphanie Cherqui. Both perform research supported by CRF and are generous with their time as they consult with other cystinosis researchers.

Dr. Rega works with Dr. Emma and is well versed in the rodent model targeted for use by the new project. She also understands the pre-clinical aspects of cystinosis. "She knows how we should evaluate the efficacy of our treatment system versus what's already available today," Dr. Singhal said.

The research team so far has collected some limited data on subcutaneous injection using the new technology, but there are significant hurdles ahead on the way to a consideration of human clinical trials, Dr. Singhal said.

"I try to be cautious about possible timelines," he said. "There are still a lot of unknowns we will have to grapple with. While the molecule itself is well characterized, our technology is very new and still has to be characterized."

If the project doesn't hit any major technical hurdles, Dr. Singhal said he is targeting an investigational new drug application with the federal Food and Drug Administration in the latter half of 2022. If the phases of clinical trials also proceed without setbacks, "it's conceivable that we could be in position to file for the New Drug Application (NDA) by 2025," he added.

"This research represents a great unmet need, and I'm confident that recruitment of patients will go relatively quickly, especially with the support of CRF," Dr. Singhal said.

CRF's financial support is vital to the project and is the most obvious benefit of the collaboration, Dr. Singhal said. But it's also invaluable to have the external validation and the connections to a supportive community that the foundation provides.

"It is really hard to build the kind of network CRF has put together," Dr. Singhal said. "One thing that has struck me consistently in my interactions with all of the scientists is their dedication to improving the lives of the patients. I've been in the drug industry for almost 20 years now, and I've seen a lot of projects. I can say that I've never seen a community as dedicated as this one. It makes this project a pleasure to work on."

THE IMPACT OF CRF RESEARCH

AREAS OF RESEARCH FOCUS & GRANTS AWARDED SINCE 2002

New Drug Discovery Cysteamine, New Medications and Devices

30 GRANTS

Ghanashyam Acharya, PhD
BAYLOR COLLEGE OF MEDICINE, HOUSTON, TEXAS

Francesco Bellomo, PhD
Francesco Emma, MD
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

NEW

Pierre Courtoy, MD, PhD
Christophe Pierreux, PhD
DE DUVE INSTITUTE, LOUVAIN UNIVERSITY MEDICAL SCHOOL, BRUSSELS, BELGIUM

Laura Rita Rega, PhD
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

Antonella De Matteis, MD
TELETHON INSTITUTE OF GENETICS AND MEDICINE, NAPLES, ITALY

Ranjan Dohil, MD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Francesco Emma, MD
Laura Rita Rega, PhD
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

Paul Goodyer, MD
MONTRÉAL CHILDREN'S HOSPITAL, MONTRÉAL, QUÉBEC, CANADA

NEW

Jennifer Hollywood, PhD,
Alan Davidson, PhD
UNIVERSITY OF AUCKLAND, AUCKLAND, NEW ZEALAND

NEW

Michael Sekar, PhD
AMMA THERAPEUTICS, INC., HAYWARD, CALIFORNIA
Laura Rita Rega, PhD
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

Vincent Stanton, Jr., MD
Patrice Rioux, MD, PhD
THIOGENESIS THERAPEUTICS, INC., SAN DIEGO, CALIFORNIA

Eye-Corneal Cystinosis Research

10 GRANTS

Ghanashyam Acharya, PhD
BAYLOR COLLEGE OF MEDICINE, HOUSTON, TEXAS

Stéphanie Cherqui, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

NEW

Morgan Fedorchak, PhD
Kanwal Nischal, MD, FRCO
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE, PITTSBURGH, PENNSYLVANIA

Jennifer Simpson, MD
UNIVERSITY OF CALIFORNIA, IRVINE, IRVINE, CALIFORNIA

Kang Zhang, MD, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Cystine Measurement and Cysteamine Toxicity Study

10 GRANTS

Bruce Barshop, MD, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

NEW

Shawn Davidson, PhD
PRINCETON UNIVERSITY, PRINCETON, NEW JERSEY

Thomas Jeitner, PhD
NEW YORK MEDICAL COLLEGE, VALHALLA, NEW YORK

Elena Levtchenko, MD, PhD
UNIVERSITY HOSPITAL, LEUVEN, BELGIUM

Kidney Research

22 GRANTS

Robert Chevalier, MD
UNIVERSITY OF VIRGINIA,
CHARLOTTESVILLE, VIRGINIA

Pierre Courtoy, MD, PhD
Christophe Pierreux, PhD
DE DUVE INSTITUTE, LOUVAIN
UNIVERSITY MEDICAL SCHOOL,
BRUSSELS, BELGIUM

Olivier Devuyst, MD, PhD
UNIVERSITY OF ZÜRICH,
INSTITUTE OF PHYSIOLOGY,
ZÜRICH, SWITZERLAND

Allison Eddy, MD
BC CHILDREN'S HOSPITAL,
VANCOUVER, CANADA

Benjamin Freedman, PhD
UNIVERSITY OF WASHINGTON,
SEATTLE, WASHINGTON

Elena Levtchenko, MD, PhD
UNIVERSITY HOSPITAL,
LEUVEN, BELGIUM

Robert Mak, MD, PhD
UNIVERSITY OF CALIFORNIA,
SAN DIEGO,
LA JOLLA, CALIFORNIA

Tara McMorrow, MD
UNIVERSITY COLLEGE DUBLIN,
BELFIELD, DUBLIN, IRELAND

Philip Newsholme, PhD
CURTIN UNIVERSITY,
PERTH, WESTERN AUSTRALIA

Daryl Okamura, MD
SEATTLE CHILDREN'S
RESEARCH INSTITUTE,
SEATTLE, WASHINGTON

Laura Rita Rega, PhD
BAMBINO GESÙ CHILDREN'S HOSPITAL,
ROME, ITALY

Mary Taub, PhD
UNIVERSITY AT BUFFALO,
THE STATE UNIVERSITY OF NEW YORK,
BUFFALO, NEW YORK

Skin, Muscle and Bone

13 GRANTS

Justine Bacchetta, MD, PhD
Irma Machuca-Gayet, PhD
HOSPICES CIVILS DE LYON
UNIVERSITÉ DE LYON,
LYON, FRANCE

Robert Ballotti, PhD
Christine Chiaverini, MD, PhD
FACULTÉ DE MÉDECINE,
NICE, FRANCE

Andrea Del Fattore, PhD
Giulia Battafarano, PhD
BAMBINO GESÙ
CHILDREN'S HOSPITAL,
ROME, ITALY

Paul Grimm, MD
STANFORD UNIVERSITY
SCHOOL OF MEDICINE,
PALO ALTO, CALIFORNIA

Mary Leonard, MD, MSCE
STANFORD UNIVERSITY
SCHOOL OF MEDICINE,
PALO ALTO, CALIFORNIA

Robert Mak, MD, PhD
UNIVERSITY OF CALIFORNIA,
SAN DIEGO,
LA JOLLA, CALIFORNIA

Richard Reimer, MD
Jacinda Sampson, MD, PhD
Mary Leonard, MD, MSCE
Paul Grimm, MD
Trinh Tina Duong, MPT
Feliks Kogan, PhD
STANFORD UNIVERSITY,
PALO ALTO, CALIFORNIA

Reza Seyedsadjadi, MD
Lee Rubin, PhD
MASSACHUSETTS GENERAL HOSPITAL,
BOSTON, MASSACHUSETTS

Thyroid

1 GRANT

Pierre Courtoy, MD, PhD
DE DUVE INSTITUTE, LOUVAIN
UNIVERSITY MEDICAL SCHOOL,
BRUSSELS, BELGIUM

CONTINUED ON NEXT PAGE

CONTINUED FROM PAGE 27

AREAS OF RESEARCH FOCUS & GRANTS AWARDED SINCE 2002

Molecular Study of Cystinosis in the Yeast Model

3 GRANTS

Bruno André, PhD
UNIVERSITÉ LIBRE DE BRUXELLES, GOSSELIES, BELGIUM

Anand Bachhawat, PhD
IISER MOHALI, MANAULI, PUNJAB, INDIA

David Pearce, PhD
UNIVERSITY OF ROCHESTER MEDICAL CENTER, ROCHESTER, NEW YORK

Genetic Analysis of Cystinosis

5 GRANTS

Katy Freed, PhD
TEXAS BIOMEDICAL RESEARCH INSTITUTE, SAN ANTONIO, TEXAS

Sihoun Hahn, MD, PhD
SEATTLE CHILDREN'S HOSPITAL, SEATTLE, WASHINGTON

Elena Levtchenko, MD, PhD
UNIVERSITY HOSPITAL, LEUVEN, BELGIUM

Eric Moses, PhD
TEXAS BIOMEDICAL RESEARCH INSTITUTE, SAN ANTONIO, TEXAS

Minnie Sarwal, MD, PhD
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SAN FRANCISCO, CALIFORNIA

Neurological

16 GRANTS

Angela Ballantyne, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Miriam Britt Sach, MD, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Rita Ceponiene, MD, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Florian Eichler, MD
MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS

NEW

Sophie Molholm, PhD
John Foxe, PhD
ALBERT EINSTEIN COLLEGE OF MEDICINE, BRONX, NEW YORK

Aude Servais, MD, PhD
NECKER HOSPITAL, PARIS, FRANCE

Amy Spilkin, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Doris Trauner, MD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Cure Cystinosis International Registry (CCIR)

1 GRANT

Ranjan Dohil, MD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Rat Model for Cystinosis

3 GRANTS

EXTENDED

Francesco Emma, MD
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

EXTENDED

Olivier Devuyst, MD, PhD
UNIVERSITY OF ZÜRICH, ZÜRICH, SWITZERLAND

THE IMPACT OF CRF RESEARCH

Stem Cells and Gene Therapy: Bone Marrow Stem Cells, Induced Pluripotent Stem Cells, Gene Therapy and Gene Editing

33 GRANTS

EXTENDED

Stéphanie Cherqui, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Alan Davidson, PhD
THE UNIVERSITY OF AUCKLAND, GRAFTON, AUCKLAND, NEW ZEALAND

Bruno Gasnier, PhD
PARIS DESCARTES UNIVERSITY, PARIS, FRANCE

Paul Goodyer, MD
MONTRÉAL CHILDREN'S HOSPITAL, MONTRÉAL, QUEBEC, CANADA

Patrick Harrison, PhD
UNIVERSITY COLLEGE CORK, CORK, IRELAND

Vasiliki Kalatzis, PhD
INSTITUTE OF MOLECULAR GENETICS OF MONTPELLIER, MONTPELLIER, FRANCE

Winston Kao, PhD
Hassane Amlal, PhD
UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO

Daniel Salomon, MD
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

Holger Willenbring, MD
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SAN FRANCISCO, CALIFORNIA

Cellular and/or Molecular Studies of the Pathogenesis of Cystinosis

56 GRANTS

EXTENDED

Corinne Antignac, MD, PhD
IMAGINE INSTITUTE (INSERM U1163), PARIS, FRANCE

Francesco Bellomo, PhD
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

NEW
Sergio Catz, PhD
Raquel Carvalho Gontijo, PhD
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

NEW
Sergio Catz, PhD
Farhana Rahman, PhD
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

Sergio Catz, PhD
Nadia Zgajnar, PhD
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

Antonella De Matteis, MD
TELETHON INSTITUTE OF GENETICS AND MEDICINE, NAPLES, ITALY

Olivier Devuyst, MD, PhD
Zhiyong Chen, PhD
UNIVERSITY OF ZÜRICH, ZÜRICH, SWITZERLAND

NEW
Olivier Devuyst, MD, PhD
Alessandro Luciani, PhD
UNIVERSITY OF ZÜRICH, ZÜRICH, SWITZERLAND

NEW
Liang Feng, PhD
Xue Guo, PhD
STANFORD UNIVERSITY, PALO ALTO, CALIFORNIA

Bruno Gasnier, PhD
Yann Terras, MSc
PARIS DESCARTES UNIVERSITY, PARIS, FRANCE

Taosheng Huang, MD, PhD
UNIVERSITY OF CALIFORNIA, IRVINE, IRVINE, CALIFORNIA

Elena Levtchenko, MD, PhD
UNIVERSITY HOSPITAL, LEUVEN, BELGIUM

Ming Li, PhD
Jacob Kitzman, PhD
UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN

Alessandro Luciani, PhD
UNIVERSITY OF ZÜRICH, ZÜRICH, SWITZERLAND

Gennaro Napolitano, PhD
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

Norbert Perrimon, PhD
HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

Giusi Prencipe, PhD
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

Matias Simons, MD
Marelja Zvonimir, PhD
IMAGINE INSTITUTE, PARIS, FRANCE

Jess Thoene, MD
TULANE UNIVERSITY SCHOOL OF MEDICINE, NEW ORLEANS, LOUISIANA

Lab Equipment for Cystinosis

4 GRANTS

Ghanashyam Acharya, PhD
BAYLOR COLLEGE OF MEDICINE, HOUSTON, TEXAS

NEW
Stéphanie Cherqui, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIFORNIA

Sergio Catz, PhD
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

CRF RESEARCH GRANT AWARDS

Sergio Catz, PhD, *Research Mentor*
Raquel Carvalho Gontijo, PhD, *Research Fellow*

The Scripps Research Institute, La Jolla, California

"Novel Mechanistic and Translational Studies of Neutrophil-Mediated Inflammation in Cystinosis"

$150,000 TWO-YEAR STUDY

Sergio Catz, PhD, *Research Mentor*
Farhana Rahman, PhD, *Research Fellow*

The Scripps Research Institute, La Jolla, California

"Molecular Trafficking Regulators of Dynamic Organelles in Cystinosis"

$150,000 TWO-YEAR STUDY

Pierre Courtoy, MD, PhD, *Principal Investigator*
Christophe Pierreux, PhD, *Co-Principal Investigator*

de Duve Institute, Louvain University Medical School, Brussels, Belgium ($5,500)

Laura Rita Rega, PhD, *Principal Investigator*

Bambino Gesù Children's Hospital, Rome, Italy ($37,301)

"Secondary Treatment of Ctns -/- Rats by Oral Dibasic Amino-Acids, with Focus on Fanconi Syndrome"

$42,801 SIX-MONTH STUDY

Shawn Davidson, PhD, *Principal Investigator*

Princeton University, Princeton, New Jersey

"Metabolomics of Hematopoietic Stem Cell Therapy in Ctns -/- Mice"

$160,244 ONE-YEAR STUDY

Olivier Devuyst, MD, PhD, *Principal Investigator*
Alessandro Luciani, PhD, *Co-Principal Investigator*

University of Zürich, Zürich, Switzerland

"New Model Systems for Integrated Drug Discovery in Cystinosis"

$290,000 TWO-YEAR STUDY

Morgan Fedorchak, PhD, *Principal Investigator*
Kanwal Nischal, MD, FRCO, *Co-Principal Investigator*

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

"Development of a Topical Controlled Release Cysteamine Eye Drop"

$410,810 TWO-YEAR STUDY

Liang Feng, PhD, *Research Mentor*
Xue Guo, PhD, *Research Fellow*

Stanford University, Stanford, California

"Molecular Mechanisms of Cystinosis"

$150,000 TWO-YEAR STUDY

2020 SPRING GRANT AWARDS

$2,629,490

Jennifer Hollywood, PhD,
Principal Investigator
Alan Davidson, PhD,
Co-Principal Investigator

University of Auckland, Auckland, New Zealand

"A Pre-Clinical Drug Study Using Cysteamine/Everolimus Combination Therapy to Treat Cystinosis Knock-Out Rats"

$200,530 TWO-YEAR STUDY

Sophie Molholm, PhD,
Principal Investigator
John Foxe, PhD,
Co-Principal Investigator

Albert Einstein College of Medicine, Bronx, New York

"The Development of Neuromarkers of Cognitive Disfunction in Cystinosis"

$333,164 TWO-YEAR STUDY

Michael Sekar, PhD, *Principal Investigator*
AMMA Therapeutics, Inc., Hayward, California

Laura Rita Rega, PhD, *Co-Principal Investigator*
Bambino Gesù Children's Hospital, Rome, Italy

"Development of a Once Daily Subcutaneous Injection of Cysteamine Bitartrate"

$304,064 ONE-YEAR STUDY

EQUIPMENT GRANT

Stéphanie Cherqui, PhD

University of California, San Diego, La Jolla, California

HRT3-RCM

$82,320 PURCHASE TOTAL

GRANT EXTENSIONS

Corinne Antignac, MD, PhD, *Principal Investigator*

Imagine Institute, Paris, France

"Intra-Dermal Imaging of Subjects with Cystinosis Using Confocal Microscopy"

$31,306 ONE-YEAR EXTENSION

Stéphanie Cherqui, PhD, *Principal Investigator*

University of California, San Diego, La Jolla, California

"Intra-Dermal Imaging of Subjects with Cystinosis Using Confocal Microscopy"

$102,755 ONE-YEAR EXTENSION

Olivier Devuyst, MD, PhD, *Principal Investigator*

University of Zürich, Zürich, Switzerland

"Development and Characterization of a Rat Model of Cystinosis"

$115,500 ONE-YEAR EXTENSION

Francesco Emma, MD, *Principal Investigator*

Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

"Development and Characterization of a Rat Model of Cystinosis"

$105,996 ONE-YEAR EXTENSION

SEE 2020 SPRING
LAY ABSTRACTS
STARTING ON THE NEXT PAGE
>>>>>

Novel mechanistic and translational studies of neutrophil-mediated inflammation in cystinosis

Sergio Catz, PhD, *Research Mentor*
Raquel Carvalho Gontijo, PhD, *Research Fellow*
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

OBJECTIVE/RATIONALE:

Neutrophils are the most abundant white cells in human blood, representing an essential part of our immunity to fight against infections through the production and release of toxic substances. Uncontrolled release of these toxic products can also cause damage to the human body. Previous data from our laboratory showed a dysregulated mechanism of neutrophil activation, known as secretion, in cystinosis.

PROJECT DESCRIPTION:

We found that cystinotic neutrophils have exacerbated secretion of the most toxic type of granules (azurophilic granules) and, consequently, high levels of these pro-inflammatory factors were found in circulation in cystinotic mice. Our hypothesis is that the uncontrolled inflammatory process mediated by neutrophils contributes to renal failure through the damage of kidney cells (proximal tubule cells). Our research plan proposes to study the mechanisms that lead to neutrophil dysregulation and inflammation and to test compounds (drugs) with the potential to attenuate neutrophil basal activation in cystinosis.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The importance of this project is two-fold: First, our studies will help elucidate cellular and molecular mechanisms of inflammation in cystinosis. Second, it is expected that our translational studies will help develop novel treatments to decrease inflammation and improve cellular and renal function in cystinosis.

ANTICIPATED OUTCOME:

We expect that these studies will lead to a better understanding of inflammatory processes in cystinosis. We also expect that the completion of our research plan will lead to the design of new therapeutics for inflammation in cystinosis.

Molecular trafficking regulators of dynamic organelles in cystinosis

Sergio Catz, PhD, *Research Mentor*
Farhana Rahman, PhD, *Research Fellow*
THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, CALIFORNIA

OBJECTIVE/RATIONALE:

Lysosomal storage diseases are caused by genetic defects leading to anomalous accumulation of metabolites in lysosomes, the degradative and recycling compartment of the cell. These toxic products, when accumulated in large amounts, can be harmful to humans. The cells utilize recycling mechanisms (autophagy) to preserve energy and nutrients. Defects in autophagy cause cell malfunction. We discovered that the specialized recycling mechanism named chaperone-mediated autophagy is defective in cystinosis.

PROJECT DESCRIPTION:

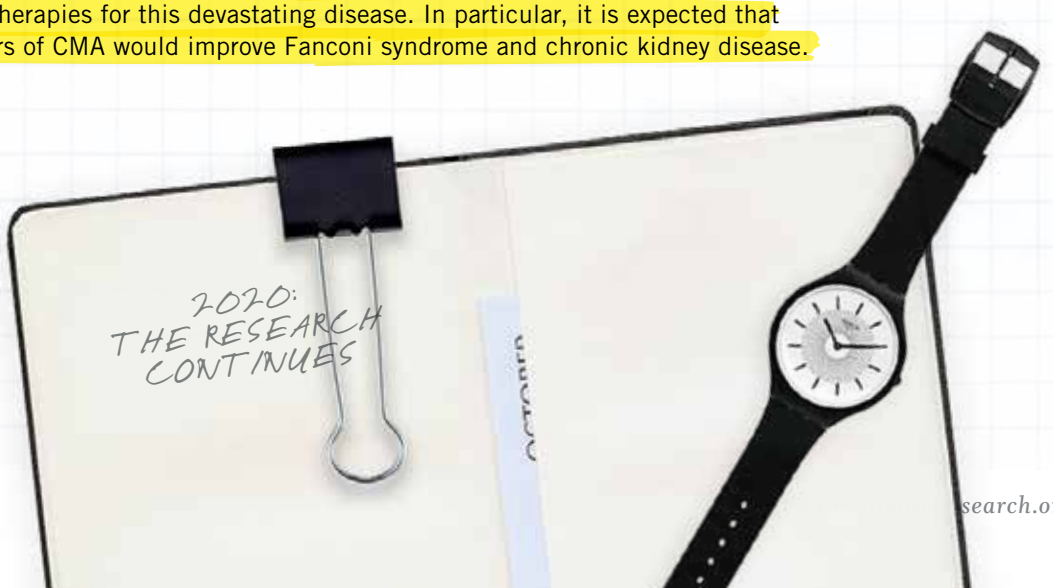
We propose to use state-of-the-art microscopy approaches and functional assays to develop a comprehensive understanding of the mechanisms of autophagy in cystinosis. We also propose to utilize novel activators of autophagy to improve cell and kidney function in cystinosis using animal models of the disease.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The importance of this project is two-fold: First, our studies will help elucidate important autophagy pathways downregulated in cystinosis. Second, it is expected that our translational studies will help develop novel treatments to improve renal function in cystinosis.

ANTICIPATED OUTCOME:

We expect that these studies will help develop new therapies to complement current therapies for this devastating disease. In particular, it is expected that enhancers of CMA would improve Fanconi syndrome and chronic kidney disease.



Secondary treatment of *Ctns-/-* mice with dibasic amino acids: safety, efficacy and mechanism(s)

Pierre Courtoy, MD, PhD, *Principal Investigator*
Christophe E. Pierreux, PhD, *Co-Principal Investigator*
DE DUVE INSTITUTE, BRUSSELS, BELGIUM
Laura Rita Rega, PhD, *Co-Principal Investigator*
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

OBJECTIVE/RATIONALE:

Our CRF-supported research demonstrated that endocytic recapture of ultrafiltrated plasma proteins driven by megalin in kidney proximal tubular cells (PTCs; in brief the "megalin pathway") is the main cause of cystine accumulation and tissue alterations in cystinotic mice (*Ctns-/-*) kidneys. Ongoing investigations suggest that the megalin pathway can be significantly inhibited, resulting in primary disease prevention, by long-term dietary supplementation with natural dibasic amino-acids already used to treat other genetic diseases, or consumed by body-builders. This new project will assess the benefit of a secondary protection, when lesions are already present.

PROJECT DESCRIPTION:

This project is a collaborative effort between teams based in Brussels and Rome. Cystinotic female mice will be fed from 6 months of age, without or with supplementation by L-lysine or L-arginine in solid diet. Every 3 months, blood and urine analyses will monitor inhibition of kidney protein recapture and global function. Mice will be euthanized at 12 months to assess kidney structure and PTC subcellular/molecular anatomy, with a focus on endocytic function. We will also address whether protection only relies on the inhibition of endocytic uptake, or further involves an anabolic effect via mTOR signaling. To this aim, we will substitute natural (L-amino acids) with their D-stereoisomers, which should equally inhibit megalin but not trigger mTOR signaling. This information will be important for patient monitoring.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

This translational project extends our investigations aiming at harnessing the megalin pathway, as a key source of cystine accumulation in PTCs of cystinotic mice. Our current hypothesis is that high concentrations of dibasic amino-acids in the primary ultrafiltrate can inhibit megalin, thus strongly decrease the recapture of plasma proteins which release cystine upon lysosomal digestion. This upstream approach should be complementary to lysosomal purging by cysteamine. We will also explore whether supplementation impacts mTOR signaling so as to promote PTC anabolism and prevent autophagy.

ANTICIPATED OUTCOME:

Using a validated mouse model of nephropathic cystinosis, we expect to find that simple dietary supplementation with either L-lysine or L-arginine, natural amino-acid building blocks of human proteins, is safe and can significantly delay progression of kidney lesions and dysfunction, as suggested by preliminary data. If confirmed, this study will pave the way for multicentric pilot testing in cystinotic children.

Metabolomics of hematopoietic stem cell therapy in Ctns-/- mice

Shawn Davidson, PhD, *Principal Investigator*

PRINCETON UNIVERSITY, PRINCETON, NEW JERSEY

OBJECTIVE/RATIONALE:

Transplantation of blood-derived stem cells from a healthy mouse can restore normal metabolism in mice with cystinosis. The degree of metabolic correction seems to be determined by the number of transplanted stem cells that migrate to each tissue, and the ability of those cells to form connections to nearby cells. The goal of this project is to develop new methods to measure the degree of metabolic correction provided by stem cell transplantation, and to test the effects of various drugs and natural substances on the performance of transplanted stem cells to see if transplantation outcomes can be improved.

PROJECT DESCRIPTION:

This project has three phases. First, methods will be developed to measure levels of cysteamine, cystine and related compounds in mouse tissues using a new technology called tissue imaging mass spectrometry (TIMS). The goal is to visualize metabolism at the level of individual cells. Second, TIMS will be used to characterize the metabolic profile of tissues in three groups of mice: normal, cystinosis and cytinosis corrected by stem cell transplantation. These studies may provide additional insight into the mechanisms by which stem cells influence the metabolism of surrounding cells. Third, a tiny implantable drug delivery device (microdevice) will be used to individually administer compounds (including drugs and natural substances) to different tissues of cystinosis mice transplanted with healthy stem cells. The effect of the compounds on stem cell migration and metabolic correction (e.g. lowering cystine levels) will be measured using TIMS.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Previous research supported by CRF has shown how transplanted stem cells correct the metabolic defect in cystinosis: they send out long thin filaments that connect to surrounding cells. Metabolites and lysosomes are exchanged between cells via those filaments. This project will quantify the magnitude of metabolic correction mediated by stem cells at the tissue and cell level by imaging metabolite levels across tissues. In the third phase of the project, potential modulators of stem cell function will be investigated using a microdevice.

ANTICIPATED OUTCOME:

An improved understanding of how stem cells modulate cysteamine and cystine metabolism in cystinosis, and possibly the identification of molecules that improve stem cell engraftment (i.e. encourage more stem cells to migrate to a given tissue) or increase the production of filaments connecting stem cells to surrounding cells.

New model systems for integrated drug discovery in cystinosis

Olivier Devuyst, MD, PhD, *Principal Investigator*
Alessandro Luciani, PhD, *Co-Principal Investigator*
UNIVERSITY OF ZÜRICH, ZÜRICH, SWITZERLAND

OBJECTIVE/RATIONALE:

Cystinosis is a lysosomal storage disease caused by inactivating mutations in the *CTNS* gene encoding the proton-driven transporter cystinosin that exports cystine out of the lysosome. The loss of cystinosin leads to accumulation of cystine within the lysosome, skewing its degradative function and causing a major dysfunction of epithelial cells that line the proximal tubule of the kidney. The current therapy for cystinosis, cysteamine, facilitates lysosomal cystine clearance and greatly delays progression to kidney failure but is unable to reverse proximal tubule dysfunction. Thus, there is an urgent need to identify novel, affordable and safe therapeutics for cystinosis.

PROJECT DESCRIPTION:

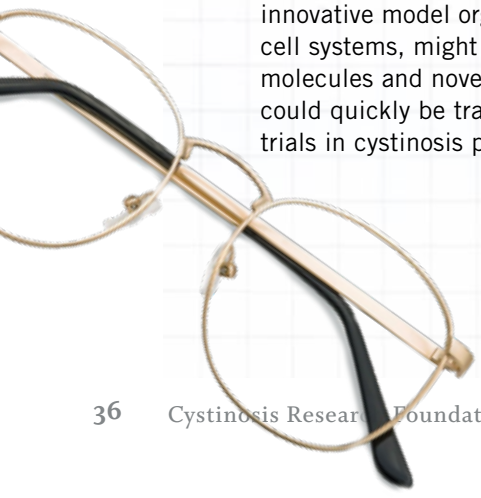
In this proposal, we plan to combine computational methods, innovative model systems and phenotype screens to accelerate drug discovery and development in cystinosis. We will (i) apply a systems biology-based drug repurposing approach to devise unbiased libraries of small-molecule compounds that might potentially reverse cellular and molecular pathways deregulated in cystinosis. We will then (ii) combine these repurposed libraries with cystinosin-deficient and reporter zebrafish lines of autophagy-lysosome pathways and proximal tubule function to generate and prioritize a list of lead compounds that might normalize autophagy-lysosome degradation systems and proximal tubule function. We will finally (iii) validate the lead compounds identified by zebrafish-derived phenotypic screens in physiologically relevant PT cellular systems and advance "first-in-class" drugs to in vivo testing in the recently available *CTNS* knockout rat model of cystinosis.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

These studies, based on drug repurposing using phenotypic screens in innovative model organisms and relevant cell systems, might yield viable small molecules and novel drug targets that could quickly be translated into clinical trials in cystinosis patients.

ANTICIPATED OUTCOME:

These investigations will allow us to gain critical insights in the cellular and molecular pathways that could be targeted (or monitored) before there is any structural, irreversible damage of the kidney. The molecular mechanisms identified in cystinosis might also be relevant for other forms of epithelial disorders and for a better understanding of the progression towards chronic kidney disease.



Development of a topical, controlled release cysteamine eye drop

Morgan Fedorchak, PhD, *Principal Investigator*
Kanwal Nischal, MD, FRCO, *Co-Principal Investigator*
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE, PITTSBURGH, PENNSYLVANIA

OBJECTIVE/RATIONALE:

The primary objective of this research is the development and rigorous in vitro and in vivo testing of a novel drug delivery system for patients with infantile cystinosis who have corneal crystals. This objective is a key step towards the overall goal of translating a convenient and comfortable alternative to frequent administration of cysteamine drops. The studies proposed herein support the achievement of this goal by testing the hypothesis that the issues of frequent dosing, low bioavailability, and shelf stability of cysteamine can be lessened through the use of controlled release technology and our innovative and unique topical delivery system.

PROJECT DESCRIPTION:

We will use the following experimental strategies to continue development of our ocular cysteamine drug delivery system. First, we will demonstrate effectiveness of the gel drops in the mouse cystinosis model. The dosing of cysteamine/gel eye drops will be confirmed in these studies and crystal density reduction compared to that of Cystaran eye drops. Next, we will determine the in vivo biodistribution in healthy rabbits. This is a method for determining where the drug is distributed throughout the body and in what amounts, which will provide valuable safety data. We will complete these studies with the appropriate controls for additional time points to complement mouse data in part 1. Lastly, we will hold a pre-IND meeting with the FDA to finalize plans for required testing in an external facility. We will also determine the appropriate manufacturing site and protocol for the materials.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

If successful, the gel drop will provide a level of comfort and convenience not currently available to cystinosis patients without compromising the ability to reduce crystal density. The data collected in our studies will also provide powerful information about dosing and distribution of drugs that can be applied to future products and studies. Our goal is to help develop the safest and most effective cystinosis eye drop to-date, whether through our own technology or by assisting other researchers with our findings.

ANTICIPATED OUTCOME:

We anticipate that upon optimizing the dose in our rodent studies, the drop will be proven effective at once daily administration. We further anticipate that the drop will be safe and show acceptable drug levels in the cornea in our rabbit studies. Lastly, we expect that the need for additional studies with the FDA will be minimized following completion of these studies and that manufacturing will be straightforward once we have thoroughly researched available contract facilities.

Molecular mechanism of cystinosis

Liang Feng, PhD, *Research Mentor*
Xue Guo, PhD, *Research Fellow*
STANFORD UNIVERSITY, STANFORD, CALIFORNIA

OBJECTIVE/RATIONALE:

Defective transport of cystine across the membranes of lysosomes causes its abnormal accumulation, which eventually leads to cystinosis. Hence, elucidating how small molecules are translocated across lysosomal membranes is crucial to understanding the causes of cystinosis and devising potential therapies to treat it. This project's aim is to investigate multiple key aspects of lysosomal membrane transport, which will help reveal how the transport function supports normal physiology and what might cause the dysfunction that triggers pathogenesis.

PROJECT DESCRIPTION:

To gain insights into how small molecules are shuffled across lysosomal membranes, we will probe the transport process through several approaches. We will study purified membrane transport proteins and assess the determinants of their function in a well-defined system. This will enable us to tease out key factors for their function. Moreover, given that protein dynamics are critical for carrying out the transport function, we will perform biophysical characterizations to probe the sample's dynamic properties. We will also investigate the transport process in a membrane environment through functional characterizations. These studies together will provide important insights at the molecular level into how small molecules are translocated across the lysosomal membrane.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Small molecule transport across the membrane is essential to maintaining lysosomal homeostasis, and cystinosis is a lysosomal storage disorder in which cystine accumulates due to faulty transport. Many fundamental aspects of this process remain unknown. The proposed research will provide critical insights into the molecular basis of cross-membrane transport processes of lysosomes. This will advance our understanding of the cause of cystinosis and may provide new avenues for developing novel therapeutic strategies.

ANTICIPATED OUTCOME:

The proposed research will help to define the protein dynamics relevant to cystinosis, yield important insights into how transport across the lysosomal membrane happens and shed light on potential means for modulating it. This new knowledge will help us better appreciate the molecular properties of membrane transport proteins on the lysosome, as well as the etiology and potential treatment of cystinosis.

A pre-clinical drug study using a cysteamine/everolimus combination therapy to treat cystinosis knock-out rats

Jennifer Hollywood, PhD, *Principal Investigator*
Alan Davidson, PhD, *Co-Principal Investigator*
UNIVERSITY OF AUCKLAND, AUCKLAND, NEW ZEALAND

OBJECTIVE/RATIONALE:

We have discovered that Everolimus, a drug used to treat organ rejection and cancer, has therapeutic potential to treat cystinotic cells and kidney organoids grown in our laboratory, particularly when combined with cysteamine. To progress to clinical trials, it is necessary to first test this treatment in a relevant animal model. We have developed and characterized a new rat model of cystinosis that closely resembles the progression of the human disease including cystine loading, cystine crystals in the eyes and tissues, Fanconi syndrome and kidney damage. The focus of this project is to test the new combination treatment in our rat model of cystinosis.

PROJECT DESCRIPTION:

The overall goal of the project is to test whether the drug combination of Everolimus and cysteamine can prevent the onset of Fanconi syndrome and kidney damage in our rat model of cystinosis. To do this we will work toward three specific aims:

Aim 1: We will first determine the correct dosing regimen of cysteamine that will result in a 50% reduction of cystine levels in the rat. This is important as it will allow us to observe any benefit that Everolimus may have.

Aim 2: We will then determine the dosing regimen for Everolimus. To test whether the drug has a beneficial effect, we will investigate if the onset of Fanconi syndrome and kidney damage is delayed or lessened in Everolimus-treated cystinotic rats. As cysteamine is unable to reverse Fanconi syndrome in humans, this will be the biggest benefit of this new treatment.

Aim 3: Finally, we will test both drugs together and measure several outcomes such as Fanconi syndrome onset, cystine loading, kidney damage and function.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

New treatments are needed urgently for cystinosis. While cysteamine does a very good job at removing cystine build-up in cells, Fanconi syndrome is not reversed and kidney damage is not completely prevented. This suggests that there are other factors that need to be targeted. We think that the combination of cysteamine with Everolimus has the potential to solve this shortcoming of cysteamine monotherapy. If successful, this study will provide the first pre-clinical evidence in a new animal model that cystinosis can be more effectively treated with a combination drug therapy. The data collected will justify advancing a clinical trial in patients with cystinosis.

ANTICIPATED OUTCOME:

To facilitate the testing of new cystinosis treatments, we have generated a rat model of cystinosis. These animals develop a cystinotic disease that closely resembles that seen in humans. Such a rat model is highly valuable for gaining new insights into the pathogenesis of cystinosis and will be a major advance for the cystinosis field. In addition, the cystinosis rat model is ideal for pre-clinical drug testing studies, such as the Everolimus/cysteamine combination therapy we are developing. We anticipate that the combination treatment will prevent the onset of Fanconi syndrome in our cystinotic rats. In the long-term, an Everolimus/cysteamine combination therapy offers the promise of improving health outcomes in individuals with cystinosis and reducing their kidney damage and other symptoms.

The development of neuromarkers of cognitive dysfunction in cystinosis

Sophie Molholm, PhD, *Principal Investigator*
John Foxe, PhD, *Co-Principal Investigator*
ALBERT EINSTEIN COLLEGE OF MEDICINE, BRONX, NEW YORK

OBJECTIVE/RATIONALE:

Advances in medical care are leading to increased lifespan in patients with cystinosis. Consequently, understanding how brain function is impacted by the disease becomes ever more relevant and meaningful to individuals living with cystinosis. This project aims to gain a better understanding of how brain function is affected in this population, focusing on auditory and visual processing and memory. Characterizing these processes will also potentially result in the identification of markers of brain function, which can be important in, for example, testing the outcomes of a treatment.

PROJECT DESCRIPTION:

Families visit us for two days and participate in a series of computer and paper-and-pencil tasks. On the first day, we assess verbal and non-verbal abilities, attention, etc. using standardized tests. We offer a brief report of this evaluation. On the second day, we use electrophysiology (EEG), a painless, non-invasive method of detecting the electrical activity that naturally occurs in the brain, to assess how the brain reacts to tones and images, how well it integrates different information and to test memory functions. During the EEG, the participant engages in simple computerized tasks.

We will enroll 25 individuals with cystinosis, 25 unaffected controls and 25 controls with chronic kidney disease, which will allow us to understand whether what we see in cystinosis results from the mutation or, rather, is a consequence of kidney dysfunction.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

This project will advance the understanding of the impact of cystinosis on the brain. Brain and cognition are the basis for academic success and overall daily functioning. Consequently, understanding how the brain of people with cystinosis operates will allow us to identify areas where interventions should focus and to derive advice on how to best leverage strengths and address weaknesses. This new understanding may also be used, for example, to measure progress in clinical trials.

ANTICIPATED OUTCOME:

This work will reveal novel information on how brain function is affected by cystinosis. It will add to what we currently know by testing if what we consider to be part of the profile of cystinosis is mainly associated with the mutation, or if it is more generally seen in people with kidney dysfunction. We will do thorough characterizations of cognitive and neural function, identify strengths and weaknesses and determine brain markers that can be used to assess treatment effectiveness.

Development of a once daily subcutaneous injection of cysteamine bitartrate

Michael Sekar, PhD, *Principal Investigator*
AMMA THERAPEUTICS, INC., HAYWARD, CALIFORNIA
Laura Rita Rega, PhD, *Co-Principal Investigator*
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

OBJECTIVE/RATIONALE:

Oral cysteamine is the only treatment option for cystinosis today. Unfortunately, patients must endure ingesting large amounts of cysteamine multiple times a day which can be challenging and can cause significant side effects. Additionally, absorption of cysteamine taken orally can be highly variable. A new drug delivery technology may allow cysteamine to be given as a single subcutaneous injection (similar to an insulin injection) once a day that could overcome many of the drawbacks associated with oral cysteamine. Independent work has demonstrated that a sustained cysteamine injection in small animals is feasible using the new drug delivery technology.

PROJECT DESCRIPTION:

The project will be a collaboration between AMMA Therapeutics, inventor of the delivery technology, and Dr. Laura Rita Rega, an expert on cystinosis research at OPBG Italy. The project has three major components – improving the existing cysteamine injection formulation in the lab, demonstrating improved sustained release in normal animals and determining efficacy in a cystinosis rodent model. While the existing cysteamine injection formulation may be sufficient, AMMA will conduct a more comprehensive screening and testing of potential cysteamine formulations in the lab and then test them on normal animals. Thereafter, Dr. Rega will test the formulations on the rodent cystinosis model over a period of time to make sure that the cysteamine injections actually result in the improvement of cystinosis.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The aim of the project is to develop another treatment option for patients. Despite the many drawbacks of taking cysteamine orally, its unstable nature and rapid removal from the body has hindered its use as an injection. Being able to stabilize cysteamine and slowly release it over a period of time using a new drug delivery technology may finally enable a patient-friendly subcutaneous injection, making drug delivery easier for patients with fewer side effects, resulting in improved treatment adherence, clinical outcomes and quality of life.

ANTICIPATED OUTCOME:

Cysteamine administered via injection has not been well studied. Though the project is more focused on product development, we will gain a better understanding of cysteamine when it is delivered into the subcutaneous tissue, how much cysteamine needs to be delivered to achieve efficacy and potential safety issues. Knowledge gained through this project will further the advancement of cysteamine injection towards IND and eventually clinical trials.

CALL FOR RESEARCH PROPOSALS

When Nancy and Jeff Stack established the Cystinosis Research Foundation in 2003, they were committed to aggressively funding cystinosis research to ensure the development of new and improved therapies and a cure for cystinosis. But never in their wildest dreams could they have imagined what has been accomplished in 17 short years. Since its inception, CRF has funded 200 multi-year research studies in 12 countries. Our researchers have published 87 articles in prestigious journals as a result of CRF funding. Every dollar donated goes directly to support cystinosis research.

The goal of CRF is to accelerate promising cystinosis research toward clinical trials. To that end, CRF prioritizes research that will lead to better treatments and a cure for cystinosis. CRF issues grants for bench, clinical and translational research, with a strong emphasis on translational and clinical research. CRF is interested in supporting new investigators and encourages them to apply either as research fellows or investigators.

In September, CRF announced $2.5 million was available for the Fall 2020 call for research proposals and fellowship grants. The grant awards will be announced at the end of December 2020.

In June 2020, CRF issued 10 new research grants, 4 grant extensions and 1 equipment grant totaling over $2.6 million which brings us closer to better treatments and a cure. All research applications received by CRF are evaluated by CRF's Scientific Review Board (SRB), composed of the leading international experts in the field of cystinosis. The SRB provides independent, objective reviews and recommendations for each research proposal submitted based on the NIH scale of standards. Additionally, the SRB follows grant review guidelines established by CRF and advises the foundation on the scientific merits of each proposal.

In 2010, CRF established the Cure Cystinosis International Registry (CCIR) to serve as a hub of information about cystinosis and its complications. Currently, the CCIR is being updated and enhanced to include answers to new questions about recently approved treatments and additional information about the effects of cystinosis. The site will include a Professional Research Portal so that researchers and scientists who register can access and view de-identified, aggregate cystinosis patient information. The registry will provide essential information that will help us accelerate research and better understand the challenges of cystinosis.

Cure Cystinosis
International Registry

WWW.CYSTINOSISRESEARCH.ORG/APPLY-FOR-RESEARCH-GRANT

CRF is excited about the future of cystinosis research and is grateful to researchers for their interest in the cystinosis community. We look forward to working together to find better treatments and a cure for cystinosis.

PUBLISHED STUDIES

2020

CRF-FUNDED RESEARCHERS have been instrumental in advancing the field of cystinosis through the publication of articles in prestigious journals. Published articles enable other scientists, pharmaceutical companies and the cystinosis community to learn more about the pathogenesis of cystinosis, to explore ideas for novel treatments and to prepare for clinical trials. We congratulate all of the published, CRF-funded researchers who have dedicated their careers to the children and adults with cystinosis.

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

PROTECTION OF CYSTINOTIC MICE BY KIDNEY-SPECIFIC MEGALIN ABLATION SUPPORTS AN ENDOCYTOSIS-BASED MECHANISM FOR NEPHROPATHIC CYSTINOSIS PROGRESSION *published June 2020 in the* ***Journal of the American Society of Nephrology*** *by* ***Pierre Courtoy MD, PhD,*** *and* ***Christophe Pierreux, PhD***
de Duve Institute, Brussels, Belgium

CELL-BASED PHENOTYPIC DRUG SCREENING IDENTIFIES LUTEOLIN AS CANDIDATE THERAPEUTIC FOR NEPHROPATHIC CYSTINOSIS *published July 2020 in the* ***Journal of the American Society of Nephrology*** *by* ***Laura Rita Rega, PhD,*** *and* ***Francesco Emma, MD***
Bambino Gesù Children's Hospital, Rome, Italy

International Journal of Molecular Sciences

BONE DISEASE IN NEPHROPATHIC CYSTINOSIS: BEYOND RENAL OSTEODYSTROPHY *published March 2020 in the* ***International Journal of Molecular Sciences*** *by* ***Justine Bacchetta, MD, PhD,*** *and* ***Irma Machuca-Gayet, PhD***
Hospices Civils de Lyon, Lyon, France

MITOCHONDRIAL DYNAMICS OF PROXIMAL TUBULAR EPITHELIAL CELLS IN NEPHROPATHIC CYSTINOSIS *published January 2020 in the* ***International Journal of Molecular Sciences*** *by* ***Francesco Bellomo, PhD,*** *and* ***Francesco Emma, MD***
Bambino Gesù Children's Hospital, Rome, Italy

MUSCLE&NERVE

CLINICAL TRIAL READINESS STUDY OF DISTAL MYOPATHY AND DYSPHAGIA IN NEPHROPATHIC CYSTINOSIS *published July 2020 in the* ***Muscle & Nerve Journal*** *by* ***Reza Seyedsadjadi, MD,*** *and* ***Florian Eichler, MD***
Massachusetts General Hospital, Boston, Massachusetts

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THANK YOU FOR YOUR DEDICATION TO THE GLOBAL CYSTINOSIS COMMUNITY

WELCOME

NEW SCIENTIFIC REVIEW BOARD MEMBERS

The CRF Scientific Review Board (SRB) is composed of leading cystinosis scientists, researchers and clinicians from around the world. CRF is proud to welcome two new members to the Board, Larry Greenbaum, MD, PhD, FAAP, division director of pediatric nephrology, the Bernard Marcus professor of pediatric nephrology, Emory School of Medicine, and executive clinical director, Children's Healthcare of Atlanta and Aude Servais, MD, PhD, Nephrology Department, senior physician, Necker Hospital, Paris, France. We are indebted to our Scientific Review Board members for their leadership, guidance and commitment to improving the lives of our adults and children with cystinosis. Thank you!

LARRY GREENBAUM, MD, PhD, FAAP is division director of pediatric nephrology and the Bernard Marcus professor of pediatric nephrology at the Emory School of Medicine in Atlanta. He is also the executive clinical director of pediatric nephrology at Children's Healthcare of Atlanta, Georgia. He received his MD and PhD degrees from the Yale School of Medicine and completed a residency in pediatrics and a fellowship in Pediatric Nephrology at the UCLA School of Medicine.

Dr. Greenbaum conducts clinical research in a variety of areas in pediatric nephrology, including renal osteodystrophy, cystinosis, urinary tract infections, chronic kidney disease and nephrotic syndrome. He co-edited the textbooks *Practical Strategies in Pediatric Diagnosis and Therapy* and *Clinical Pediatric Nephrology*. He is a major contributor to the *Nelson Textbook of Pediatrics*. He has received multiple awards for teaching residents and medical students. Dr. Greenbaum is serving as the immediate past president of the American Society of Pediatric Nephrology and is on the Steering Committee of the Pediatric Nephrology Research Consortium. He was previously the Chair of the Executive Committee of the American Academy of Pediatrics Section on Nephrology.

AUDE SERVAIS, MD, PhD is a senior nephrologist at the Department of Adult Nephrology at Necker Hospital, Paris Descartes University in France. She received her medical degree from Paris Descartes University where she specialized in Nephrology in 2004. She performed her PhD studies and defended her PhD thesis in Physiology and Physiopathology at Paris VI University in 2010.

Dr. Servais is a referent in adult nephrology in the Reference Centre for Child and Adult Hereditary Renal Diseases (MARHEA) and in the Reference Centre for Inherited Metabolic Disorders at Necker Hospital. She is Vice Chair of the board of the ERA-EDTA Working Group on Inherited Kidney Diseases. Her research interests include the management of cystinosis in adolescents and adults, genetics of focal segmental glomerulonephritis and Alport syndrome and C3 glomerulonephritis. Dr. Servais is also the Principal Investigator of the European Cystinosis Cohort, founded by RaDiCo, French Rare Disease Cohorts (RaDiCo-ECYSCO), which aims to generate data that will contribute towards clinical studies, epidemiology of cystinosis and improvement of care. She has authored more than 100 research articles in peer-reviewed journals.

LEADERSHIP. GUIDANCE. COMMITMENT.

cystinosis RESEARCH FOUNDATION | TOGETHER WE SHINE BRIGHT

CRF FAMILY STORIES

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She asked for Patrick most while in the hospital, craving the company of the person who understands her plight best.

HEALING, LEARNING AND FINDING JOY

Goodness, 2020 has been a BENDER! For everyone, everywhere, this year has been unpredictable and unprecedented. Last March, we added COVID-19 to the health concerns that we work to manage in this household, along with cystinosis. Disease is a frightening reality of the human condition, and we are grateful to those in the world of medicine who educate, research and provide treatments for the health and comfort of all citizens. Every household is fighting *through* or *for* something, no doubt.

> ... WE ARE GRATEFUL TO THOSE IN THE WORLD OF MEDICINE ...

This household remains focused on a 15-year fight against cystinosis. While the pandemic slowed the phase one trial for gene therapy for cystinosis for a few months, things are back on track and patient #3 will soon be transplanted. Incredible! We will keep working to raise funds for cystinosis research as we keep Jenna and Patrick healthy, looking toward the day when they might be a part of the phase two or phase three FDA trials for gene therapy and stem cell transplant for cystinosis.

By Teresa Partington, Jenna and Patrick's mom
SACRAMENTO, CALIFORNIA

HEALING, LEARNING AND FINDING JOY

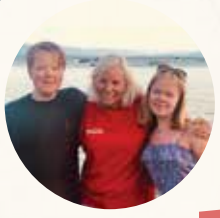
Jenna is currently two weeks post-surgery and determinedly recovering from an osteotomy (bone cutting/straightening) of her right leg. Previous surgeries for guided growth implants to correct her knocked knees were not successful. The discomfort and appearance of her legs led Jenna to make the difficult but mature decision to get her legs, one at a time, surgically modified. The fact that she is able to recover at home during this unique time of online/distance learning is a silver lining in the pandemic. Jenna has handled the fear, pain and responsibility that have come with this surgery gallantly. She has been visited by friends, showered with special get-well gifts and eaten plenty of Chipotle and Chick-fil-A, while binge-watching the series "Teen Wolf" with her dad.

Patrick is growing much taller, which is causing his once-repaired knees to become knocked again. Because he has plenty of growth left, he will be having guided growth implant surgery again in the coming months. It goes without saying that we've gotten to know the staff at Shriners quite well. We would never have predicted that orthopedic complications of cystinosis would be the kids' greatest challenge, but it really has been the focus of the last few years.

The subtle effects of cystinosis are so quiet and slow. Kidneys fail, bones become deformed, spleens enlarged and eyes are clouded with crystals, all so slowly, but with devastating outcomes. Cystinosis affects EVERY CELL of the body, making it unique in the world of gene therapy. Dr. Stéphanie Cherqui is proving to be a pioneer in the treatment of disease that reaches beyond a singular system or organ of the body, as the corrected CTNS gene that is being given to trial patients is predicted to reach ALL the cells of an individual with cystinosis, rescuing tissues throughout the body.

Our race against the slow progress of research has not been fast enough to rescue the bones or even the kidneys of Jenna and Patrick, so those will continue to be treated in the ways of modern medicine. Both kids will recover from their orthopedic surgeries just in time for kidney transplants, which, based on their kidney function, are predicted to take place in about a year. Jenna and Patrick are both on the deceased donor transplant list and will have their procedures at Lucille Packard Children's Hospital at Stanford University. Living donor kidneys are ideal, and we hope that Kevin will be a match for one of the kids (I am not a candidate due to my cancer history). A person interested in learning about becoming a living kidney donor candidate for Jenna or Patrick can email the transplant coordinator, *gjames@stanfordchildrens.org*, to inquire. I can't believe we've reached the day that I'm floating this idea out there to a community that has already been beyond supportive. But alas, time marches on.

Jenna & Patrick's FOUNDATION OF HOPE

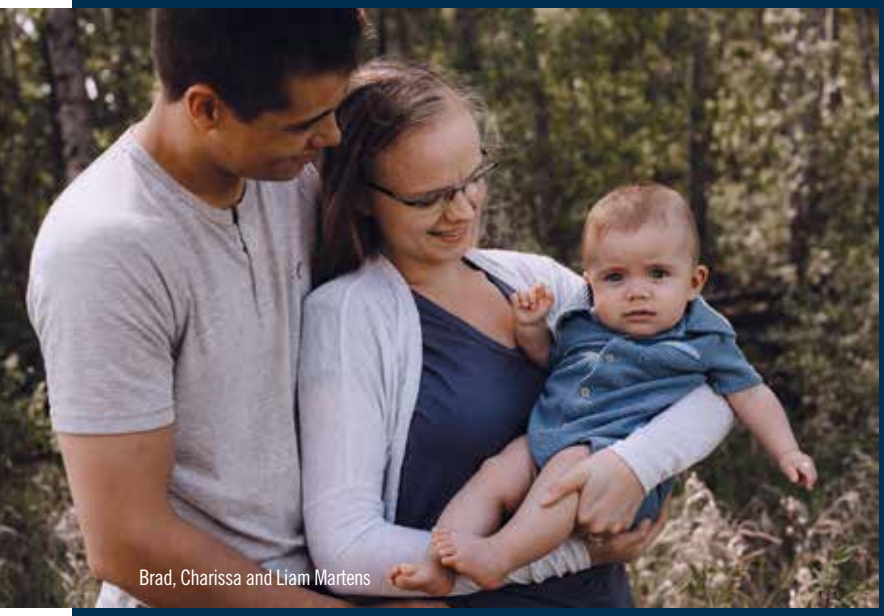


All this information makes one eager for continued progress, which comes by the way of funding research! Shannon Bell, a family friend and CEO of NorCal Beverage Company, played in a golf tournament recently, raising funds for Jenna & Patrick's Foundation of Hope and ultimately, CRF. Following the tournament Shannon had raised over $65,000, doubling her goal. This will be our main charity event of 2020, a year that has made gathering for fundraising nearly impossible. We are grateful to Shannon and all those who have supported her in Sacramento's Villara Capital Cup golf tournament.

Each time I write these updates I'm reminded of what Jenna and Patrick are up against. Day to day, they are pretty normal teenagers. Patrick prefers the quiet privacy of his bedroom, where he goes to school, sleeps and plays video games. His room is a safe cocoon in which to be 15 years old and grow, learn and think about years ahead. Jenna loves Harry Styles, the aforementioned "Teen Wolf," fashion and her happily decorated bedroom, where she too, sleeps and learns. Jenna, a comfort-seeker, prefers to have family or friends around most of the time. Even better: if they will tickle her arm or join her to "watch a show." She asked for Patrick most while in the hospital, craving the company of the person who understands her plight best.

Today's world is heavy with conflict and concern. Our family strives to have succinct, truth-driven discussions regarding the newsy, social media-driven, polarized world in which we live. There is little time or energy for angst and anger when one is healing, learning and finding joy in the day-to-day. Jenna and Patrick are tackling monumental challenges with grace and strength. Just as cystinosis is slow and subtle in its progression, we are seeing Jenna and Patrick's inspiring stories offering perspective as they progress through their lives. Kevin and I will continue to do our best to guide them, working to impart change in the world through our two remarkable kids. We have the easy work.

Read more about Villara Capital Cup Golf Tournament on page 71!



Brad, Charissa and Liam Martens

By Charissa Martens
BLACKFALDS, ALBERTA, CANADA

I was diagnosed with cystinosis at birth.

My older sister also has the disease. The medications and appointments were just a normal part of my life. My parents did a good job of making our childhood as normal as possible. For as long as I can remember

husband Brad and I starting our family. After a consultation with an obstetrician where we talked about the risks associated with getting pregnant, we were told it was safe for us to start trying. There were a lot of unknowns about how my pregnancy would go, and we hadn't heard of anyone else getting pregnant with cystinosis who has not yet had a transplant.

BLESSED WITH

I have wanted to be a mom. My biggest dream as a little girl was to start a family one day. I remember my doctor bringing up the fact that Cystagon® was not known to be safe to take while pregnant, and that made me realize how much cystinosis could actually affect my life as I got older. With me being so healthy, I had never really thought about how cystinosis could impact my future.

Thankfully, I have been blessed with amazing doctors. They have always been very positive and encouraging when I brought up the idea of my

The doctor's biggest concern was me going off a couple of my medications, including Procysbi®, which would probably have an effect on my kidney function. For me, the risk was worth it. I wanted cystinosis to have as little control over my life as possible.

It did not take long for us to get pregnant; we were thrilled. My pregnancy went very well from the start. My baby and I were both watched very closely. I had many ultrasounds and every time they told me everything looked good! My biggest struggle with being pregnant was the bladder infections, which

AMAZING DOCTORS

eventually led me to getting an infection in my blood. The antibiotics got rid of the infection and I was feeling good again. We were thankful that I ended up having such a good pregnancy. I felt better than a lot of healthy pregnant women would have felt.

It was very unexpected when our son Liam was born seven weeks early. They did not know the cause and as far as we know it was unrelated to cystinosis. He was so tiny but such a huge blessing! We spent 23 days in the NICU and Liam did amazing! He has been a fighter from day one. Although he had a bit of a rough start, I feel so blessed to have such a healthy son. I have so much respect and sympathy for parents of sick kids. Those 23 days in the NICU were hard. I can't imagine what my parents went through when my sister and I were diagnosed and especially with my sister being sick for so long before being diagnosed. Now that I have someone else to take care of, I have to make more of an effort to remember to take care of myself and take all my medications. My kidney function has dropped slightly since pregnancy, but I am still very healthy. All the risks and hard days have been so worth it. Our son has brought so much joy into our lives, I can't imagine my life without him. I love being a mom.

I know that nothing is impossible.

By Jessica Jondle
BOISE, IDAHO

If you had asked me to introduce myself two years ago to a room full of cystinosis families and CRF supporters, that introduction might have gone something like this: I'm Jessica. I'm a former middle school teacher and administrator and current content manager in the digital media space. I'm an avid hiker — a passion that even took me to the roof of Africa, Kilimanjaro. I was diagnosed with cystinosis at 22 months old and had a kidney transplant from a deceased donor at age 18 after two years of dialysis. That borrowed organ has lasted me 21 years and counting. I've been married to my high school sweetheart for 13 of those years.

Today, all those things are still true. But my introduction would be simple: **Hi. I'm Evangeline's mom.**

And here's why, even without all the explicit talk of my medical history, that's still hugely relevant to this community. We (she and I) wouldn't be here without the cystinosis research that has led to better treatments, longer lifespans and increased quality of life.

In fact, I recently asked my mom what she would have said had someone told her more than three decades ago that she would live to see her youngest daughter have a daughter of her own — at the "advanced maternal age" of 37, no less. (Gotta love those medical labels, although I suppose this one beats the now somewhat obsolete "geriatric pregnancy" designation).

"I probably wouldn't have believed it," was her reply. Here's the hard truth: In 1983, when I was diagnosed, we didn't know anyone in their 30s with cystinosis, despite being well connected with families around the country via chain letters and occasional gatherings. And we certainly didn't know anyone who had given birth.

So why the "probably" qualifier, despite my entry into this world at such a dark time in cystinosis history? Why didn't my mom just say, "Never in a million years would I have believed that"? It was, after all, an era when parents of newly diagnosed children were told to go home, enjoy their time with their little one, wait for death — often considered inevitable before reaching double digits.

In a word: **Faith.** Faith that God can do the impossible. Faith that God can work through incredible researchers, generous donors, the sharing of knowledge and a little girl with a wish scribbled on a napkin. The faith of my parents, for certain, but also the faith of very good doctors who told them that times could change and that I should proverbially and literally roller skate with rickets in the meantime. (Hence the title of my book).

And now, the faith passed on by my parents lives in me as I look at my toddler. Go ahead, tell me that I'll live to see my daughter have a daughter. It seems far-fetched. And yet, as I look at the amount of research funded by CRF – and consider the juxtaposition of my own toddlerhood and Eva's – I know that nothing is impossible.

From the bottom of my heart, thank you – from Eva's mom.

Reflections *on my* Golden Girl!

By Beth Anne Haarer, Natalie's Nana
CORONA DEL MAR, CALIFORNIA

We are called so many endearing names by our grandchildren... "Nana" is mine and it never ceases to bring a smile to my face, a picture to show or a story to share.

Today brings many thoughts about Natalie. Her story began 29 years ago on February 13, 1991 as she was ushered into this world. What excitement and joy! Blond, blue-eyed and so healthy looking – what could possibly change that?

But it happened. Natalie was not eating well, and her diapers had a strange odor. Nancy, her mother, took her to the pediatrician and after much research, the diagnosis was made. Natalie had cystinosis, an orphan disease with only 2,000 cases worldwide. Natalie's prognosis was not good – a liver tumor, eating problems, kidney disease and eye issues. And yet, Natalie continued to charm us with her smile and infectious laugh.

Nancy and Jeff never had a day or night free from Natalie's needs. Alexandra, her sister, only a year older was curious about Natalie's schedule of medications, water and special attention. It was a challenge to have a baby with cystinosis and a toddler trying to understand her sister's constant medical and emotional needs.

One evening, my husband Don and I volunteered to watch Natalie so Nancy and Jeff could have a night out. It took them a half-hour to show us how to measure and mix all her medications and how to make her crib and little pajamas as waterproof as possible before putting her to bed. It was quite an awakening to see how their once normal life was turned upside down. The prayers, hope and suggestions from family, friends and neighbors were many and welcomed.

Cystinosis has always been part of Natalie's life even when she could not fully comprehend its meaning. To support her, Don and I held the first cystinosis

fundraiser at Forest Highlands in Flagstaff, Arizona, raising a total of $13,000! Natalie was the star, smiling with delight and signing autographs. In her address to the crowd, she said, "I have cystinosis. It's important because my mommy and daddy think it's important!"

Natalie was a sensitive and shy child growing up, often unable to say what was bothering her. She was obsessed with becoming a teacher and carried her "briefcase" around with pages and pages of "homework" for her Madame Alexander dolls who were her "students." As she grew up, she continued her desire to learn and study, eventually graduating from Georgetown University and then on to University of Southern California where she earned a master's degree in social work. Now she is working at Court Appointed Special Advocates, continuing her focus on children who have many needs.

At bible camp, Natalie was one of the children called on to answer the question, "What would you do if it was your last day on earth?" Natalie said she didn't want to say "have a party" like the other kids, so she didn't say anything at all. This took place near Natalie's 12th birthday, which happened to be the same year she wrote her wish on a napkin: "to have my disease go away forever."

More recently, Saturday luncheons have been my treasured time with her. She picks up lunch for us at Gary's Deli or Ruby's and we sit on the patio, masks and all, and share, listen, laugh, cry and even gossip. We always talk about Natalie's favorite topic, her handsome cat named Henry. She has dozens of pictures of him on her phone in his handsome cat poses.

> Golden hair, golden spirit, golden laugh. All there in one amazing young woman.

On a recent Saturday, we talked about the "almost cure" for cystinosis and about Jordan and how brave he is to undergo the first treatment. She's hopeful that she will be one of the patients in the near future. She shared her worries and anxieties about the transplant and wonders how her body will react to the chemo, but she knows that the transplant will likely mean doing away with all of the meds, eye pain and doctor visits, which would be a miracle! Natalie hopes her participation will benefit and contribute to a cure for the entire cystinosis family. We also talk about how over the years she has had extraordinary doctors constantly doing research to find the cure. With Dr. Cherqui pioneering the stem cell and gene therapy, miracles are truly happening!

Over the years, Natalie has never ceased to warm our hearts with her gentle smile, unselfish ways, humbling attitude and quiet strength. I often call Natalie my "Golden Girl" or "GG"! I think of her as pure love and a valuable, precious gift. Golden hair, golden spirit, golden laugh. All there in one amazing young woman. Her calm and loving spirit have truly enriched my "Nana" life!

Perhaps at the next cystinosis gathering they can set aside a table for grandmothers only, so that we can share our stories about our remarkable, courageous, brave and loving grandchildren!

A Little about the Happenings in the Life of Holt Grier

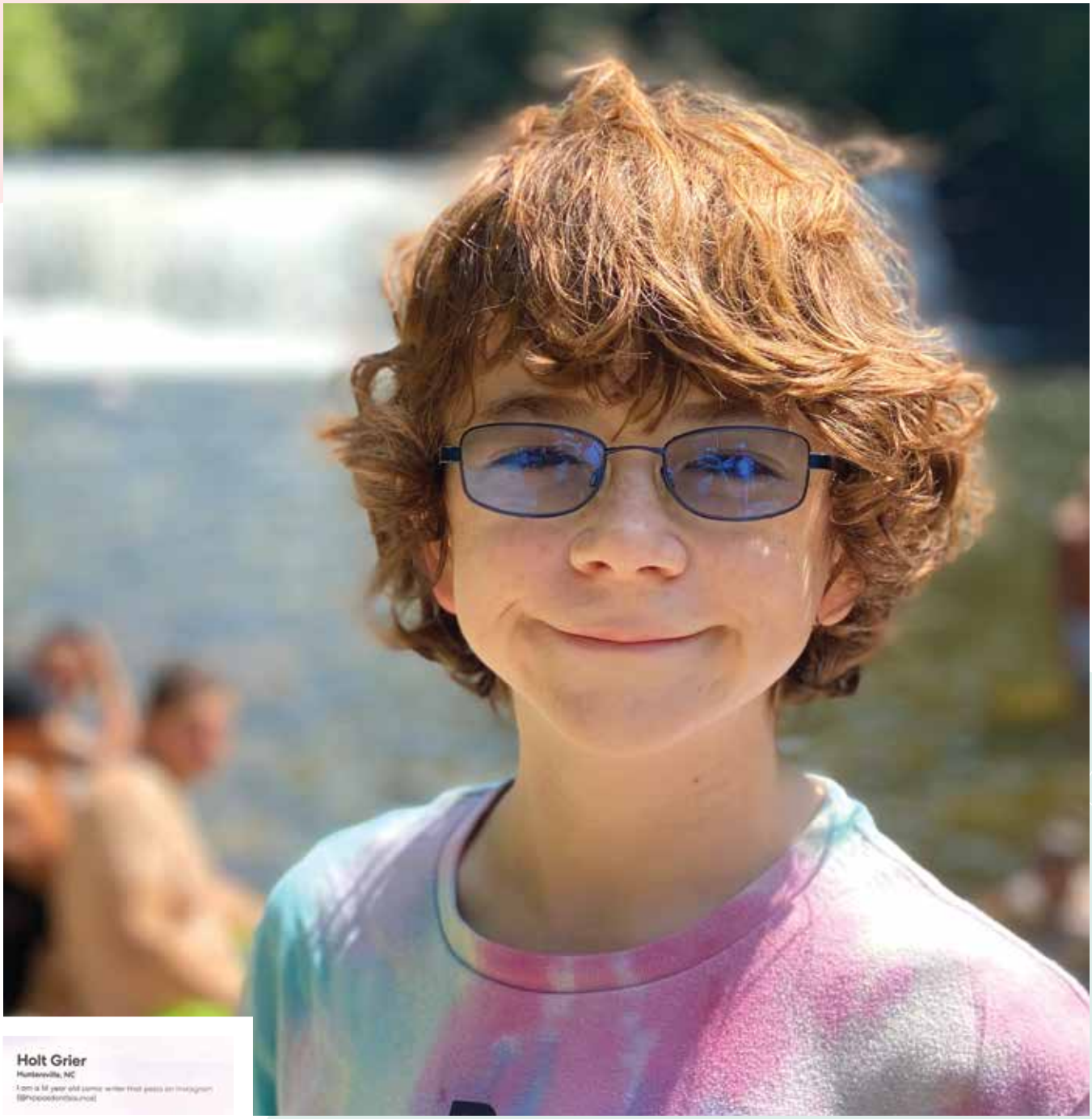
By Holt Grier
HUNTERSVILLE, NORTH CAROLINA

With the cystinosis cure on its way, and the total garbage fire that is 2020, I thought I would share my progress of cystinosis, and how I am getting by this year. Today at the doctor's office, Dr. Vanderwel said I am 5.1 feet tall! This is all thanks to a shot I take each night called growth hormone. I am very grateful that I am on it because I am able to mature with my friends. On another note, I am also very grateful (and very excited) for the cystinosis cure. I really hope I can volunteer for the trials and help to stop this condition. I don't know why, but it's like I have a passion to do this, almost like it's my duty. I hope I can volunteer soon.

I also would like to talk about this thing called The Flag Project. This was a contest where you had to draw a flag that had the chance to be hung and flown at Rockefeller Plaza in New York City. I was very happy to hear that I was one of the people who won the contest. I drew a flag that had a comic about New York City. My aunt and uncle were the ones who told me about this contest, and my uncle actually won, too! It's nice to see your art flown in New York. I am forever grateful for this.

In school related news, I am now in 8th grade. It's crazy to think I will be in high school next year (I really hope that COVID is over by then). I am in one of the few schools that is in-person with its education. Honestly, it's not much different from regular school. It's basically the exact same, but with masks and social distancing. I am a little nervous though. Being in school during a pandemic is nerve wracking because you never know if you or someone around you might get COVID-19. I might even say I like online school better because I get to wake up later and it's not as demanding. But I do miss my friends when I'm doing it. There are pros and cons for both.

Recently, I went hiking with friends in the mountains. It was really fun and all, however my feet and ankles started to act up. One of the side effects of cystinosis is that it will give you rolled in ankles and flat feet. This is one issue I have yet to solve. My feet don't hurt as much nowadays, except for when I walk long distances. It's like my feet become even more flat and my ankles become more rolled in. A similar situation is happening to my neck and shoulders. We do not have lockers in our school this year, so my backpack is twice as heavy, which is not helping with the problem at all. It's also hard because a lot of the chiropractors are closed due to COVID-19. If anyone reading this has some solutions, do you think you could help a brother out?



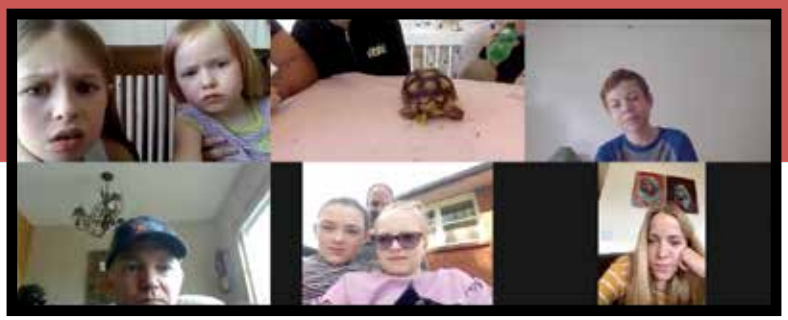
Holt Grier
Huntersville, NC

In quarantine, I have picked up many hobbies, most of which are video game habits. For example, a game called Animal Crossing. Animal Crossing is a life simulator game, which makes it perfect for quarantine. I don't know what I would have done those early days of quarantine without it. Speaking of video games, I am also looking forward to this game called Star Wars: Squadrons. It's a game where you are a pilot of either the Galactic Empire or the New Republic from Star Wars. I've always had an interest in flying so I am very happy about this game. Speaking of Star Wars, I have become a total geek about it in this pandemic. Besides Star Wars, I have tried to pick up other hobbies I'm interested in, however I became too lazy to commit to them. I also might have overworked myself because I was trying to learn nearly 10 hobbies at once. At least I learned not to put too much pressure on myself.

Those are all my thoughts on 2020 and cystinosis for now. Hopefully COVID-19 will pass soon, and we can all meet up with each other at our next cystinosis conference.

Day of Hope AT HOME

By Stephen Jenkins, MD, Sam and Lars' dad
SALT LAKE CITY, UTAH



Like everyone else in the cystinosis community, our family was very sad that the Day of Hope family conference had to be canceled earlier this year due to the COVID-19 pandemic. The kids were especially sad that they wouldn't get to see their cystinosis friends. In order to cheer ourselves up, we decided to have our own Day of Hope family conference at home.

Normally on Thursday night at the conference, we all get together for introductions, and we share our wishes and hopes. We decided to share our wishes on social media. This year Lars wished for a cure that does not require an IV (he really hates needles), and Sam wished for a new video game. My wish this year was that the gene-corrected autologous stem cell transplant would provide a lasting cure for cystinosis and that my boys will be able to get it in the near future. We made fajitas, and Ashton even made homemade churros to dip in chocolate, just like at the Day of Hope.

While we couldn't replicate all the magic and great scientific talks of the Day of Hope, we felt like we could at least try to replicate the wonderful food. The kids love the breakfast buffets with all you can eat bacon at the Day of Hope, so the next morning we cooked up A LOT of bacon. Sam's favorite activity last year was making personal pizzas with the hotel chef, so we helped the kids make their own pizzas, and we were able to do a video chat with their favorite person in the world, Henry Sturgis. That night we had a barbecue in the backyard, which wasn't nearly as good as the barbecues we usually have on the beach at the Day of Hope. However, we did eat delicious ice cream sundaes and battled with light-up wands.

One of the best parts of the Day of Hope is dropping your kids off at the babysitter's. They get all you can eat snacks and really fun activities. One of those activities is usually an exotic animal petting zoo. We invited the cystinosis community on Facebook to join us for a virtual petting zoo where we showed our tortoise, hedgehog, rabbit, bearded dragon and new puppy. It was fun to see everyone else's pets, too! That night, in lieu of the Natalie's Wish gala, we had chicken and fries and watched the newest CRF video.

While the Day of Hope at home was fun and involved a lot of delicious food, it was a poor substitute for the real thing. We can't wait for 2021 and hope that the pandemic will be under control by then. We hope to see you there!

JJ AND BROOKE

A Friendship THAT WILL LAST A Lifetime

By Jill Emerson, Brooke's mom
HAMMONTON, NEW JERSEY

Our journey to a cystinosis diagnosis for our daughter, Brooke, wasn't a direct route. Luckily for us, once we received the diagnosis, we found ourselves in the office of Dr. Joshua (JJ) Zaritsky. With his signature bowtie, outgoing personality and unwavering positivity, JJ instantly made us feel at ease, and Brooke immediately took to him. He nicknamed her "Brookie" during our first appointment, and their amazing relationship blossomed from there.

JJ is a fantastic doctor; we call, email and text him about every bug and medical issue Brooke has, even unrelated to cystinosis. He always responds and never makes us feel like we are a bother. Even when we are – yes, we know it can be overkill with all of the texts and emails! We always email him with research updates and any news on clinical trials or potential new treatments, and he always responds with "Amazing News!!!" or "Awesome!!!" He is Brooke's, and our, personal cheerleader along this journey, and that is what makes him not only a great but a one-of-a-kind doctor. We often refer to him as the "quarterback" of Brooke's cystinosis team. Every rare disease family deserves and needs a JJ.

As she has grown older, Brooke has begun experiencing anxiety around health-related issues and hospitals. However, she is unphased by the blood draws and hospital visit she knows accompany her appointments with JJ, simply because she gets to see him. When Brooke misses a day of school because of quarterly doctors' visits, she proudly returns to school and tells anyone who will listen: her teachers, the school nurse, and her friends, that she was with JJ, her friend and doctor.

Not only have JJ and Brooke forged an amazing relationship built on trust and friendship, but we have come to rely on JJ's support and friendship, as well. From the very first visit, he assured us that Brooke's "future is bright" and that "we should worry about how to pay for Brooke's college tuition and wedding," and not the typical things one worries about when faced with a cystinosis diagnosis. While he is realistic about those things, he also helps us remain focused on the big picture and encourages us to remember that Brooke is young, and there are many advancements on the horizon thanks to the research funded by CRF. He continually reminds us

Read how the music compilation, 'Twenty Years Away' will benefit CRF!
PAGE 70

that this journey is a marathon, not a sprint; we've found that his advice has really helped us approach cystinosis in a healthy manner for our sake, as well as Brooke's. He always makes sure that we as parents are doing well, and always encourages and cheers us on. Without fail, we walk away from every appointment feeling good about the job that we are doing as Brooke's parents and caregivers.

If you ask Brooke what her favorite thing about JJ is, she says "It's that he loves me, and I love him." His role as someone who Brooke loves and trusts will continue to be important as she gets older and her understanding of cystinosis evolves. We always joke that we have a dozen years to convince JJ to become an adult nephrologist so Brooke never needs to transition to a different doctor, because realistically we cannot imagine finding a better doctor or traveling this journey without JJ. Luckily, he has told us that "even when Brookie is 40," he will still be here for her. And we know that is true, and that JJ and Brooke will forever be teammates and friends. Long after cystinosis is cured, Brooke's and our friendship with JJ will still remain.

NEVER TAKE
A MOMENT
FOR GRANTED

A NEW NEW NORMAL

By Erin Little, Olivia's mom
PORT ELGIN, ONTARIO, CANADA

As a mother to a child with cystinosis, we are familiar with the phrase "a new normal." I think it has been the phrase used by every family with cystinosis we have ever met; it usually comes with laughter and tears as we embrace the extreme changes and challenges that we are met with. Our "new normal" felt like what a surfer must go through, always trying to ride the waves with no guarantee of waves or the certainty of riding them. A new normal has been embracing uncertainty. A new normal has meant dealing with paralyzing anxiety as we await a test result. A new normal has been dealing with things when I did not have a choice. A new normal has been praying for a miracle and working for it behind the prayers. A new normal has meant a lot of change, having no control over many things, and learning to control the things I can, like how we live.

When COVID-19 made its grand entrance, we had to pivot to a new normal once again and there have been many lessons. Our biggest lesson always continues to be how we live in moments of uncertainty. There are so many things we all miss; personal connection seems to be at the top of the list. We were sad to have to cancel many events due to COVID-19 but it hasn't stopped us from living. We have had to be creative in how we do things and find the positive in all the negatives. We have had to learn to celebrate differently from birthdays to fundraising. We had to cancel our annual Swing, Shoot, and Liv Golf Classic and instead of it being a write off year we decided to move forward with "A Day to Liv." We had 80 golfers show up to golf, people running marathons, watching Packers games, reading books on the beach, walking puppies, dinner gatherings, James day at the farm, a hike in the woods and spending time with people they love.

Cystinosis and COVID-19 have a similar lesson, to never take a moment for granted and to live life to the fullest no matter how scared we can be. We walk forward every day in love instead of the fear around all the uncertainty and things we cannot control. And we take one day at a time, and never forget to live.

CYSTINOSIS, COVID, AND SURF CAMP

Summer 2020 was filled with new accomplishments, uncertainty and changing times. Summer seemed to start earlier this year with both school and work going remote and online. It is times like this you realize how big or small your house really is. We made the best of it, though. I was proud of Henry as he focused on his daily schedule and took not only school, but also COVID seriously.

By Brian Sturgis, Henry's Dad
SANDPOINT, IDAHO

Surf Camp started in July. It was really just an idea to get family and friends together a few times each week to water ski and wake surf, but it turned into much more. One dad quickly took the role of coach and set a goal to make sure everyone over the age of 10 learned to wake surf. Henry embraced the challenge and every morning he would ask, "What time are we going out in the boat?" The determination he showed to learn a new sport was something I hadn't seen from him before. It paid off huge! By the end of the summer, he had learned how to surf and received the "Ride of the Year" award at our Labor Day awards banquet. The comradery that Surf Camp created was amazing and we look forward to it again next summer!

Henry is 14 now and complains more often about his feet and legs hurting. He has trouble running and has pain in his feet, knees and legs. We are seeing a specialist to look at options to release the pressure that his flat feet are putting on his legs and will see another specialist this fall to see if surgery is necessary. We follow the stem cell trial closely and Henry often asks if I have any news. We are praying that the cure will be a reality soon.

After months of uncertainty and debate, the decision was made for Henry's small private school to return to in-person. School started (8th grade) just after Labor Day weekend and we hope that everyone remains healthy so they can continue to go.

With school in session and cold mornings, we can feel fall coming. We are looking forward to winter!

Optimism

Landon's super power!

By Lauren Hartz, Landon's mom
PITTSBURGH, PENNSYLVANIA

"Mommy, do I know everything that I need to know about cystinosis?"

My stomach dropped a bit. We hadn't yet shared with Landon that those with cystinosis will need a kidney transplant at some point in their lives, many before their high school graduation. We hadn't shared that people with cystinosis have died at such a young age – a decade or more before his parents, who could live another 40 or 50 years.

"Well, you know a lot of it. What we haven't talked about is how cystinosis can cause the kidneys to stop working so that people with cystinosis need to get a kidney transplant. This means that someone who is a good match can donate his or her kidney, or someone who has died who has given permission for the kidney to be donated, to someone who needs it."

I could tell that he was thinking about this.

"So, some day I might need a new kidney? Like, when I'm older, like in high school or college?"

"Maybe. But what I will tell you is that your kidneys are very healthy right now, so we are pretty sure that you have a while. Some people have been just a little older than you and some are grownups when they need it."

"And maybe cystinosis will be cured before I need that, right?"

"We hope so, buddy."

Our conversation stopped at that point because we had to finish cyber schooling. We had lunch and decided to go to the track so that Landon and his brother, Jordan, could ride their bikes. The coronavirus has allowed us, and forced us, to be creative with learning. This was "gym class." Landon decided to walk with me instead.

LANDON INFORMED ME THAT HE SHOULD BE ABLE TO WALK TO THE PARK ON HIS OWN AND SHOULD GET A CELL PHONE. THE PARK, MAYBE. THE PHONE, NOPE.

"Mommy, I really wish I didn't have cystinosis."

"Oh yeah, how come?"

"It makes me the smallest in my grade."

"Well, that may be true although Daddy was as small as you were at your age so you may be small anyway."

"Yeah, and I can't go down the slip and slide on my belly."

"Yeah, that's true. I like that you figure out how to do things even when you have to do it differently than other kids."

"I can't wait until it's cured because then I can get rid of my Mic-Key button."

"You can do that if you work on swallowing pills."

"I know. But I will just wait."

"Yep, I get it. Look buddy, things are going very well with the cure study. I feel really excited for what's happening. But here is something I want you to consider… let's say that a cure doesn't happen or if it's a long time before you are able to get the treatment, don't hold off on anything while you wait. That's why Daddy and I encourage you to try things and work hard for what you want. The cure will be wonderful, and even if it's a long time or doesn't happen for some reason, you are still wonderful just the way you are and will live a great life."

Landon is 10 years old now, and informed me that he is now a pre-teen which means he should be able to walk to the park on his own and should get a cell phone. The park, maybe. The phone, nope. The physical burdens that cystinosis places on us, as caregivers, feels less than it did when Landon was a baby. Cystinosis doesn't impact our day-to-day lives in the same way that it did when he was little. I'm grateful for that.

With that being said, the emotional impact is becoming more apparent. Landon is a thinker, a lot like his dad, and is emotional like his mom. Lucky guy, right? Actually, he is. He feels deeply which you will notice when he squeezes his fists and cries when his brother makes him mad and with his deep belly laugh when he is reading "Big Nate" books. It's one of his super powers. This last conversation went well, because he has optimism and hope for the cure. My prayer for my boy, and for our cystinosis family, is that the cure will be an option for everyone soon, and until then, keep living your life while honoring your needs, and be your wonderful self.

Out of the Comfort Zone Out into Nature

By Marcu Alexander, Hadley's mom
BOISE, IDAHO

Hadley was diagnosed with cystinosis in 2012 when she was 18 months old. The news was devastating, and it felt like our lives would never be normal again. The first couple years after diagnosis were extremely difficult. When we thought we had things figured out something new would pop up and we felt like we were back to square one. After starting the myriad of medications, Hadley's health drastically improved. However, the side effects from the drugs caused other issues to develop. There was a g-tube for medications, refusal to eat food, daily vomiting, and the constant changing of diapers and bedding. Normal tasks became challenging and we no longer could pick-up and go do fun things without thoughtful planning. Our lives were directed by a strict schedule of medications, blood draws and doctor's appointments.

As years passed, the challenges we initially faced were no longer all-consuming. We had a routine that worked well for our family and we no longer felt overwhelmed by her disease. Both of our children were able to participate in extracurricular activities and were thriving both intellectually and socially. We still couldn't go places on a whim and vacations took a lot of planning due to Hadley's needs, but it was always worth the extra effort to make life feel as normal as possible.

Hadley started school and began making new friends. Soon after she wanted to start having sleepovers like her big sister, Stella. Any cystinosis family will explain how challenging sleepovers can be for a child with this disease who frequently pees and requires a diaper at bedtime. At age six Hadley was determined to ditch the diapers and was successful with the help from Indomethacin and a bed-wetting alarm. This provided her with a new level of independence and confidence she hadn't experienced before.

Last year, Hadley began swallowing pills which has given her even more freedom and autonomy. Hadley didn't tolerate the oral liquid medications after diagnosis, so a g-tube was placed so her meds could be administered directly into her stomach. It was a lifesaver for us for many years and I'm grateful we had a way to deliver her meds without any issue. Thankfully, it didn't take long for her to transition all her meds to pills and we were able to remove her g-tube in March of this year. It was a surprisingly emotional moment for our family, especially for Hadley who doesn't remember life without her trusty "tubie." We were excited to celebrate Hadley's big milestone with a trip to Disneyland before sharing her cool scar

with all her friends at the CRF's Day of Hope family conference in April. Unfortunately, the world was hit with the global pandemic and all the fun things we had planned were canceled. We were heartbroken to miss out on Disneyland but more so, we were incredibly sad the family conference was canceled and that we'd miss seeing our cystinosis friends.

As spring turned into summer and the threat of COVID-19 grew, we realized our lives weren't going to resume normalcy for quite some time. We tried to make the best of the situation, but as parents we felt pain for our daughters who suddenly couldn't play with their friends and who rarely left our home. So, when we found out there were some openings for a week-long whitewater rafting trip on the Middle Fork of the Salmon River with a group of our family and friends, we jumped at the opportunity. My husband and I experienced the magic of rafting on the Middle Fork a couple of years ago and it was one of the highlights of our lives. We decided that once the girls were older, we'd go back on the trip as a family. We also knew Hadley wasn't well enough to spend a week out in the wilderness and it would be difficult with a g-tube and all the supplies. However, since she swallows pills now, wakes up to use the restroom and has been in overall good health, we decided now was as good a time as any. We couldn't wait to introduce Stella and Hadley to this little slice of heaven so close to our home in the Frank Church Wilderness of Idaho.

Our trip was organized by a well-known outfitter in our area, Middle Fork Rapid Transit (MFRT). The owners of MFRT are old friends and long-time supporters of our cystinosis non-profit, Hearts for Hadley. Each year they donate river trips at our annual Hearts for Hadley benefit and have supported us throughout our journey since Hadley's diagnosis. Since we'd been on a trip with MFRT before, we already knew several of the guides and that they would take extra special care of Hadley. This included an endless supply of fresh spring water and six gallons of milk to last her throughout the week.

The trip was magical and I'm so happy we made the decision to go. Everyone in the group committed to spending two weeks in quarantine before the trip to reduce the risk of spreading illness which allowed everyone to relax and forget about the craziness in the world for a few days. I watched my girls along with their cousins and friends explore nature as they stepped outside their comfort zones and fell in love with the beauty of the Idaho wilderness. Hadley couldn't tackle all the hikes due to knee issues and being tired out easily, but she did an exceptional job and I'm so proud of what she did accomplish. She kept a positive attitude and had the time of her life! By the last day she slowed down, and I could tell she needed some rest. We went to bed early that night and by the next morning she was ready to finish the last leg of the trip and was back to her perky self. The trip was meaningful in so many ways that it's hard for me to adequately put into words. But one thing is for certain, it reminded me how far Hadley has come since the early days of her diagnosis and how she has developed into a strong and capable individual who won't let cystinosis determine how she lives her life!

TOGETHER, WE ARE one

1 PURPOSE. 1 JOURNEY. 1 CURE.

The following pages celebrate the events dedicated to awareness and a cure by our cystinosis community. Together, we are stronger. Together, we are one!

Internet

CYSTINOSIS FAMILIES AND FRIENDS SUPPORT RESEARCH THROUGH FACEBOOK FUNDRAISING

We are forever grateful to all those who have set up fundraisers to support the important research being done to improve treatments and ultimately find a cure for cystinosis. And now, with Facebook Fundraiser, it has never been easier! **As of October 21, 2020, our Facebook friends have raised over $58,894 to support CRF.** Additionally, because Facebook does not charge fees on fundraisers for nonprofits, all that money will go directly to cystinosis research in support of the 2020 Fall grant awards!

To get started, go to this web address: *www.facebook.com/fund/CystinosisResearchFoundation*

1 PURPOSE. 1 JOURNEY. 1 CURE.

Emma Suetta — Etna, California

LILLYANNA'S LEMONADE STAND FOR A CURE BAKE SALE

The Suetta Family hosted their 6th Lillyanna's Lemonade Stand and Bake Sale for a Cure in the fall, their second this year. The family feels blessed by the small community that turns out in a big way to support them in their quest for a cure. After the summer bake sale sold out in three hours, they decided to have another bake sale in the fall. They baked for three days straight, making over 1,200 cupcakes, sweet breads and cookies. **The sale opened at 9 am, where the baked goods sold out in only four hours, with the proceeds totaling $5,000.** Shelly immediately contributed the funds to the CRF Matching Gift Challenge, doubling their donation! Can you imagine that a small-town lemonade stand could generate that kind of revenue? Well, the Siskiyou County community has proven they know how to support a wonderful cause! We are grateful to Shelly, Derek, Lillyanna and Emma for their baking skills and tireless efforts in supporting cystinosis research for a cure. Thank you, Suetta family!

Everly Turner – Central Point, Oregon

CALLI PARKER'S FUNDRAISER FOR EVERLY TURNER

Angie Parker and Haven Combs have been friends since their daughters, Calli and Paisley, attended preschool together, and Calli just turned ten years old this summer. For her birthday, Calli decided to do a fundraiser through Facebook for CRF, in honor of Paisley's little sister, Everly Turner, that has cystinosis.

Calli also created a donation box to take around to local businesses during the weeks leading up to her birthday. Her goal was to raise $300 for cystinosis research to help Everly and other kids beat this disease. When Calli and her family delivered the box to Everly, **they proudly announced they had exceeded their goal and presented $459 to Everly for cystinosis research.** Thank you to Calli and the Parker family, for supporting cystinosis research!

TOGETHER, WE ARE one

Lily Beauregard, Swansea, Massachusetts

THE BEAUREGARD FAMILY, 2ND ANNUAL CHILI COOK-OFF

The 2nd Annual Chili Cook-off was organized by Shelli Pereira in honor of Lily Beauregard to support cystinosis research. The event was enthusiastically supported by the communities of Fall River and Swansea, Massachusetts. A wide variety of chili was prepared and enjoyed by guests as they listened to the music of Billy Leetch, Lacey Cheryl and Mike Mahoney. **At the end of the afternoon, more than $6,547 was raised for CRF and cystinosis research.** Courtney, Kevin and Lily are grateful for the generosity of their friends and neighbors and for joining the quest for a cure!

Brooke Emerson – Hammonton, New Jersey

TWENTY YEARS AWAY – n5MD MUSIC COMPILATION BENEFITING CYSTINOSIS RESEARCH FOUNDATION

n5MD is an Oakland, California-based niche music label founded in November 2000 by Mike Cadoo. The label has a large catalog of music including a wide variety of experimental and electronic music.

Clay Emerson, whose six-year-old daughter Brooke has cystinosis, records music as a member of the electronic music duo, Loess, along with his good friend Ian Pullman. Loess has been fortunate enough over the last 17 years to release music under the n5MD label.

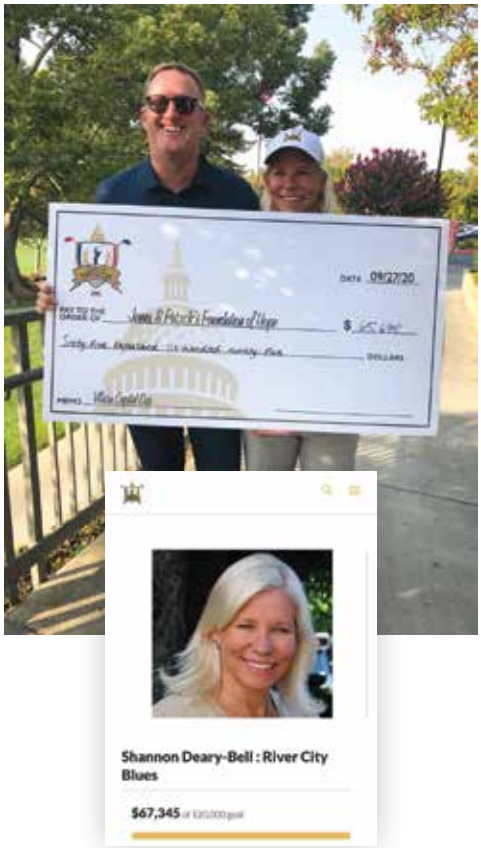
Since learning of Brooke's diagnosis, Mike and n5MD have generously and consistently supported the Emerson's annual CRF fundraising efforts. Recently, Mike approached Loess and Nancy Stack about his plans to release a compilation to commemorate the label's 20th anniversary and donate all proceeds to CRF.

In Mike's words: "The basic concept for Twenty Years Away was to celebrate such a milestone in the label's history; however, I wanted to do something more by contributing all proceeds to a cause that is close to us at n5MD."

On behalf of the entire cystinosis community, we want to thank Mike for his thoughtfulness and generosity which will provide much-needed fundraising in a time when it is so hard to come by. We also want to thank all of the artists from around the world who donated their time and music for the compilation.

Twenty Years Away features 31 original tracks showcasing artists who have worked with n5MD over the past 20 years. **The compilation will be available to buy and stream on November 6, 2020, on their website *http://n5.md/twenty*.**

1 PURPOSE. 1 JOURNEY. 1 CURE.



Jenna and Patrick Partington – Sacramento, California

SHANNON BELL RAISED $67,345 PLAYING GOLF IN HONOR OF JENNA & PATRICK PARTINGTON

On the weekend of September 25-27, Shannon Bell participated in Sacramento's esteemed fundraising event, the Villara Capital Cup Golf Tournament. Shannon, CEO of NorCal Beverage, has played in the tournament since 2015 and is a close friend of Teresa and Kevin Partington. Each year she selects Jenna & Patrick's Foundation of Hope (JPFH) as her charity of choice, playing in honor of twins Jenna and Patrick Partington. **Shannon competed on local golf courses for three days, and her efforts were rewarded by her raising over $65,000 for JPFH and cystinosis research.**

Shannon and her friend, Tom Walcott of Colliers International, have partnered in the past to raise more than $225,000 in honor of Jenna and Patrick. Thank you to the Partington Family and their dear friends in the Sacramento community who have so generously supported their cause to fund cystinosis research for better treatments and a cure!

In Memory of Samantha Grover – Exeter, New Hampshire

FIRE AND SPICE BISTRO HOST FUNDRAISER IN MEMORY OF SAMANTHA GROVER

Melani and Kevin Taillon, owners of Fire and Spice Bistro in Newfields, New Hampshire, hosted a special evening in memory of Samantha Grover who passed away last year. Zackery Guidice, Samantha's cousin is a bartender at the restaurant and helped organize the evening. Samantha was a kind and loving person who is missed every day by the cystinosis community. **Thank you, Melani and Kevin, and the entire staff at Fire and Spice Bistro, for supporting CRF.** Every dollar helps us fund critical research that will give hope to our children and adults living with cystinosis.

It Takes A Village

CYSTINOSIS COMMUNITY

CALENDAR OF EVENTS

GIVING TUESDAY

SAVE THE DATE DECEMBER 1, 2020

Mark your calendars for Giving Tuesday! This yearly event will be even more important this year since most in-person cystinosis events were canceled. Cystinosis is a relentless disease that effects every part of the body. CRF is committed to funding research to find better treatments and a cure. On December 1st, let's come together to keep the research going. Every dollar you donate will help ensure that every cystinosis patient has access to better treatments and, potentially, a life without cystinosis!

We would like to acknowledge all families for their support of cystinosis research, unfortunately some events may have passed by the time this issue is mailed.

March 2021

6TH ANNUAL FISHING FOR BROOKE'S CURE
HOPE FOR BROOKE, BROOKE EMERSON
Location to be determined - depends on the tides

Saturday, March 27, 2021

2400 FT OF SCHWEITZER
24 HOURS FOR HANK, HENRY STURGIS
Schweitzer Mountain, Sandpoint, Idaho
Contact Brian Sturgis, bsturgis@simulstat.com

August 2021 Dates Coming Soon

CRF DAY OF HOPE FAMILY CONFERENCE
Pelican Hill Resort, Newport Coast, California

August 2021 Date Coming Soon

CRF NATALIE'S WISH CELEBRATION
Pelican Hill Resort, Newport Coast, California

Monday, September 27, 2021

NATALIE'S WISH FORE A CURE GOLF TOURNAMENT
Pelican Hill Golf Club, Newport Coast, California

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cystinosis RESEARCH FOUNDATION

MISSION

The mission of the Cystinosis Research Foundation is to find better treatments and a cure for cystinosis by supporting bench, clinical and translational research. Since 2003, CRF has raised over $58 million with 100% of all your donations going to support cystinosis research.

EDUCATION

The CRF is dedicated to educating the medical and public communities about cystinosis to ensure early diagnosis and proper treatment.

CHARITY NAVIGATOR ★★★★ Four Star Charity

PLATINUM

RESEARCH

HOPE

CURE

cystinosis RESEARCH FOUNDATION | TOGETHER WE SHINE BRIGHT

CRF RESEARCH STUDIES AND CLINICAL TRIALS

STATUS **UPDATES**

FALL 2020

DISCOVERIES LOG

MECHANISM OF BONE MARROW STEM CELL-MEDIATED THERAPY IN THE MOUSE MODEL OF CYSTINOSIS

STÉPHANIE CHERQUI, PhD | UNIVERSITY OF CALIFORNIA, SAN DIEGO

DEVELOPING A THERAPEUTIC STRATEGY FOR CYSTINOTIC NEPHROPATHY WITH iPS CELLS

BENJAMIN "BENO" FREEDMAN, PhD | UNIVERSITY OF WASHINGTON

CLINICAL, NEUROPHYSIOLOGICAL AND PATHOLOGICAL CHARACTERIZATION OF MYOPATHY AND DYSPHAGIA IN ADULTS WITH NEPHROPATHIC CYSTINOSIS; EVALUATION FOR INHERENT MUSCLE RESILIENCE AND REGENERATIVE CAPACITY

REZA SEYEDSADJADI, MD | MASSACHUSETTS GENERAL HOSPITAL

DEVELOPMENT OF A ONCE DAILY SUBCUTANEOUS INJECTION OF CYSTEAMINE BITARTRATE

MANISH SINGHAL, MD, *CEO*
MICHAEL SEKAR, PhD, *PRINCIPAL INVESTIGATOR*
AMMA THERAPEUTICS, INC., HAYWARD, CALIFORNIA
LAURA RITA REGA, PhD, *CO-PRINCIPAL INVESTIGATOR*
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY