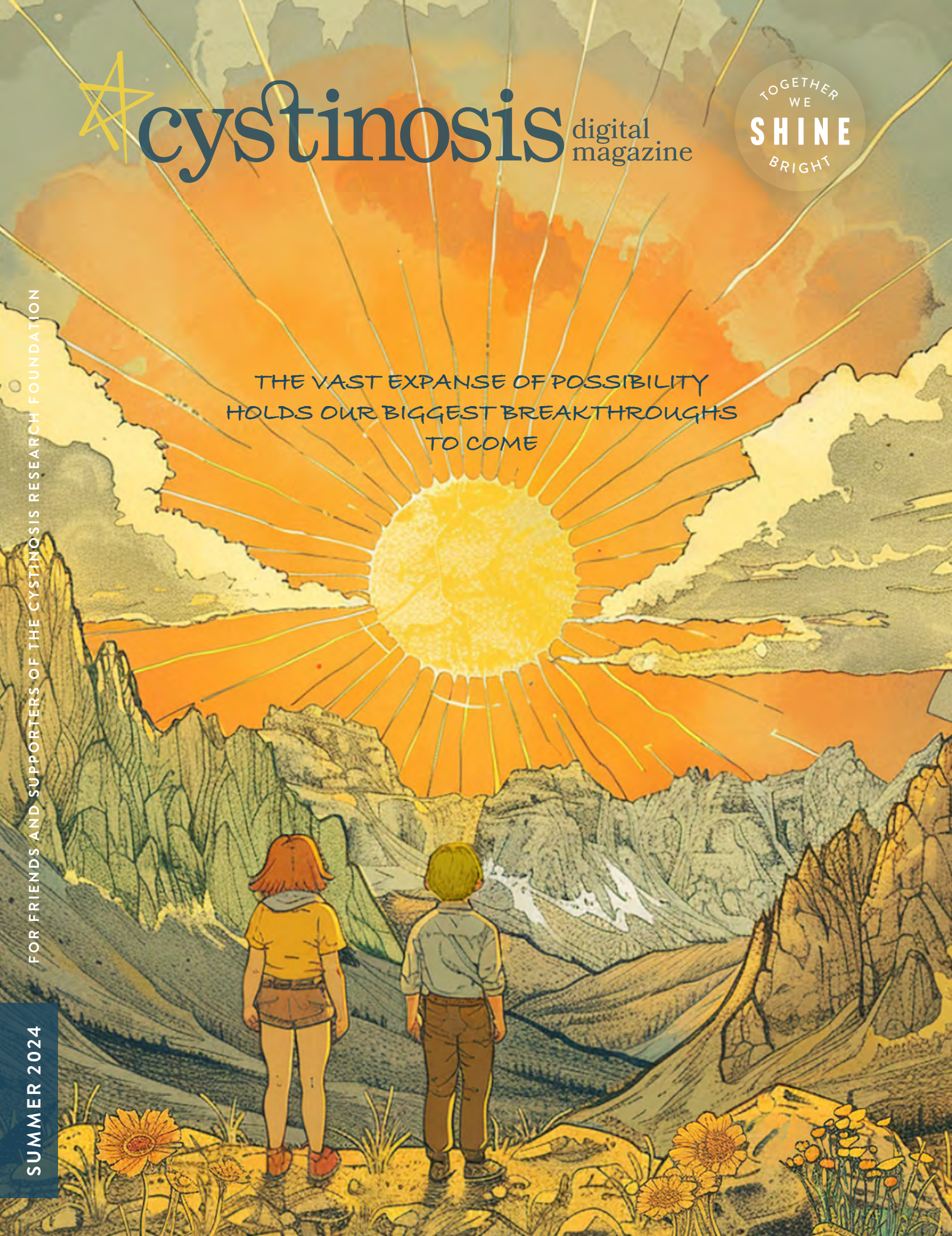
cystinosis digital magazine

TOGETHER WE SHINE BRIGHT



FOR FRIENDS AND SUPPORTERS OF THE CYSTINOSIS RESEARCH FOUNDATION

SUMMER 2024

CYSTINOSIS RESEARCH FOUNDATION

HISTORY IN THE MAKING

2003
- Natalie Stack Morgan 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.

2008
- First CRF International Research Symposium

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 now known as Procysbi®.
- First patient pilot study for an allogeneic stem cell study at UCLA.

2018
- FDA approval on December 19, 2018 for first autologous 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
- Second patient in stem cell and gene therapy clinical trial transplanted on June 29, 2020.
- Third patient in stem cell and gene therapy clinical trial transplanted on November 16, 2020.

2021
- Fourth patient in stem cell and gene therapy clinical trial transplanted on November 15, 2021.
- CRF partnered with Sanford CoRDS to create the new Cure Cystinosis International Registry (CCIR), the only international cystinosis patient registry in the world.

2022
- Fifth patient in stem cell and gene therapy clinical trial transplanted on March 29, 2022.
- Sixth patient in stem cell and gene therapy clinical trial transplanted on October 24, 2022.
- CRF Presents at IPNA pre-Congress Cystinosis Session in Calgary, Alberta, Canada, and hosts the first Family Conference.

2023
- CRF hosts the 8th Annual Cystinosis International Research Symposium in Irvine, CA, fostering continued innovation by connecting CRF researchers from around the world.
- Novartis purchases the cystinosis gene therapy program from Avrobio, guaranteeing the final phase of the stem cell transplant trial will soon become a reality.

2024
- *Cystinosis Magazine* goes digital!

SUMMER 2024

THE VAST EXPANSE OF POSSIBILITY HOLDS OUR BIGGEST BREAKTHROUGHS TO COME

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

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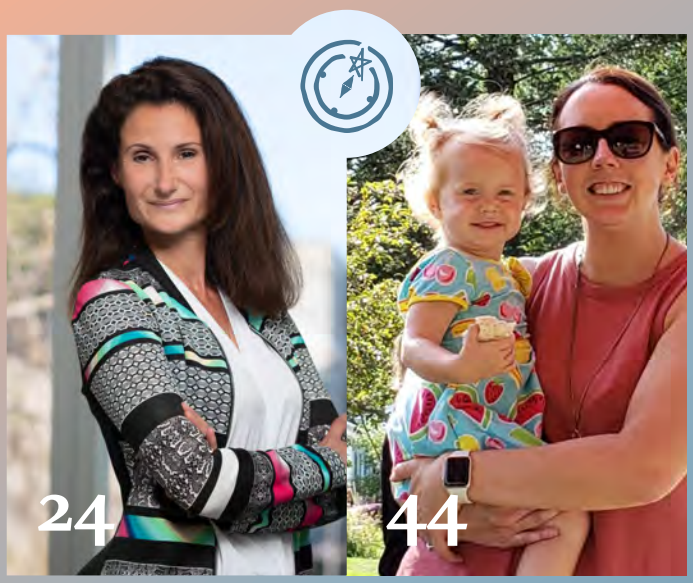
RESEARCH FOUNDATION

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 $70 million for cystinosis research in an effort to find a cure.



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WELCOME

ANNOUNCEMENTS

RESEARCH NEWS

FAMILY STORIES

JUNE
2024

Dear Family & Friends,

We are starting 2024 on a research high note. We just concluded the spring call for new research proposals and awarded eight new grants totaling $1,403,384 in research. We have made remarkable progress – these studies will help us reach new milestones bringing us closer to better treatments and a cure for cystinosis.

Since CRF was established in 2003, you have been by our side as we have traversed the cystinosis journey. We are incredibly grateful to you – our family and friends – for your steadfast commitment to the CRF research program. It is because of your commitment to our children and adults with cystinosis that we have reached milestones once unimaginable. You have been instrumental in helping us create one of the greatest success stories in the history of rare disease research.

The Cystinosis Research Foundation is the story of a community of people who came together to cure a rare disease. When most thought it was an impossible and far-fetched dream, our community thought otherwise! There is nothing more powerful or motivating than being told that your child has a disease that will ultimately take their life at a young age. Most of you have a loved one with cystinosis or have been touched by the story of a person with cystinosis and it is your compassion and commitment that has become part of our drive to find better treatments and a cure for cystinosis.

The Cystinosis Research Foundation was launched the day Natalie Stack wrote her birthday wish on a napkin – "to have my disease go away forever." Her simple but profound wish has reached thousands of people who have

A LETTER FROM
NANCY AND JEFF STACK

cystinosis
RESEARCH FOUNDATION

become part of the CRF community. Our lives have been immeasurably enriched by the growth of the CRF community and the constant support, and commitment to our research efforts.

Although it is difficult to comprehend because of the extensive portfolio of research today, but in 2003, there were only a handful of researchers in the world interested in studying this disease. In large part, it was because there was a lack of funding in both the private and public sectors. With our strategic approach to research, funding one study at a time in the early years, we changed the course of cystinosis.

Today, CRF has issued 238 grants in 13 countries and is on the brink of new discoveries about cystinosis, new treatments and a cure for cystinosis. CRF-funded researchers have published 109 articles in prestigious research and medical journals. The CRF community has single-handedly created a dynamic, collaborative global research community. CRF's commitment to research has led to two FDA approvals, multiple clinical trials, and numerous new discoveries about the pathogenesis of cystinosis. CRF has been the driving force for all cystinosis research and advances in treatment.

CYSTINOSIS MAGAZINE – CREATING A NEW LOOK

This digital issue of *Cystinosis Magazine* will share the good news about our research program and the hope it provides our community. You will be touched by the family stories and will learn more about what it means to live life with cystinosis. The magazine also features two in-depth interviews with Lauren Albrecht, PhD at UC Irvine in California and Paul Goodyer, MD at McGill University in Montreal, Canada.

Dr. Albrecht is a new researcher to CRF and her exciting work is focused on the lysosomes. Dr. Albrecht believes that understanding the lysosomes will allow us to better understand how breakdowns in cellular function contribute to cystinosis. Through her research, Dr. Albrecht hopes to uncover new disease processes and molecular targets that could create more effective therapies for cystinosis.

Dr. Goodyer's novel study involves collaborating with Moderna pharmaceuticals. By applying the technology behind Moderna's COVID-19 vaccine, specifically its mRNA technology, he hopes to adapt their novel mRNA technology to restore CTNS expression in cystinosis. If the concept works, it could "fix the disease." Please read more about these two exciting studies on pages 20 and 22.

STEM CELL AND GENE THERAPY CLINICAL TRIAL UPDATE

It was CRF's seed money and subsequent grants totaling over $6.5 million that launched Dr. Stéphanie Cherqui's life-changing stem cell and gene therapy study at UC San Diego. It is hard to believe that it has been four years since Jordan Janz, the first patient to volunteer for the stem cell and gene therapy trial, was treated. Since then, four other patients have been transplanted, and we are pleased to report that all five patients are doing well and thriving in their lives! We are grateful to the five patients who risked so much to give back to the entire cystinosis community to ensure that the stem cell and gene therapy treatment would one day be a reality for every person with cystinosis. The five patients will continue to contribute to our knowledge about cystinosis since they will be followed for many years by Dr. Stéphanie Cherqui and her team at UC San Diego.

The next phase of the clinical trial is being planned by Novartis, who bought the cystinosis gene therapy program from Avrobio in 2023. We will continue to advocate on behalf of the cystinosis community and hope to have news about the commencement of the next phase of the trial in the near future. Our goal is to ensure that the stem cell and gene therapy trial is available to every person with cystinosis throughout the world.

>>>>

CRF FUNDS $2,959,574 IN RESEARCH GRANTS IN 2023!

With the expertise and guidance of the CRF Scientific Review Board (Page 16), who carefully and thoroughly review every research application we receive, we are proud to share that 2023 was an extraordinary year for research. In 2023, CRF funded a total of 12 research grants in 13 countries totaling $2,959,574 in grant awards. The 12 research studies focus on understanding more about the pathogenesis of cystinosis, testing existing medications as possible treatments for cystinosis and understanding more about the complications of cystinosis. Learn more about the new studies on page 26.

DAY OF HOPE FAMILY CONFERENCE 2024

The CRF Day of Hope family conference was a huge success at the new venue in San Diego, California. The family conference was held at the Catamaran Resort Hotel just steps from beautiful Mission Bay. Families gathered from all over the world to learn about current CRF research studies, to meet others in the community and to celebrate our CRF community. The blend of research and community interactions created a hopeful and inspiring weekend. There is nothing more incentivizing than a community that is committed to research and to each other. Please enjoy the pictures from the Day of Hope conference and a conference synopsis on page 10.

APRIL – NATALIE'S WISH FUNDRAISING MONTH

We have dedicated the month of April to raising awareness about cystinosis and raising funds to support critical new research that will bring new hope to the cystinosis community. We are proud to announce that thanks to you, we raised $1,100,000 in April for research! Although we have accomplished amazing research discoveries and we have improved treatments for cystinosis, there is still much more to discover and understand about cystinosis. We are committed to continuing to support research that will add to the breadth of knowledge about the basics of cystinosis, research that improves current treatments and deliveries of treatments, and novel treatments that will ultimately cure cystinosis.

CRF has provided researchers the opportunity to successfully test their theories, which has in turn, allowed those same researchers to apply for grants from other funding sources, thereby leveraging CRF's initial grant awards. The ability to obtain other funding resources has accelerated and advanced research and expanded the field of cystinosis. Our success is a direct result of your support and partnership with us to fund research that will lead to a cure.

CRF RESEARCH LEADS TO NEW DISCOVERIES IN OTHER MORE PREVELANT DISEASES

Discoveries made by CRF-funded researchers are being applied to other diseases including Friedreich's ataxia, Danon disease, Alzheimer's disease, and other genetic and systemic diseases like cystinosis. CRF set out to find better treatments and a cure for cystinosis, but we have impressively, and with great hope, impacted other disease communities who can now apply discoveries made about cystinosis to their diseases, creating pathways to cures for their communities. We are changing lives and giving hope to people far beyond the cystinosis community.

WITH GRATITUDE

Our gratitude for your love, support, kindness, and commitment to all children and adults with cystinosis is endless. With your support we have funded studies that have led to two FDA approvals, numerous clinical trials, significant discoveries about cystinosis and all of that has put us one step closer to the cure. We are incredibly fortunate because we are surrounded by this community of families and friends who have joined us in the quest for the cure and who have helped create this global community of people including researchers and scientists who are dedicated to the children and adults with cystinosis.

Together we have touched so many lives, giving hope to families and those with cystinosis – we have found joy in living with cystinosis and have found a plethora of sliver linings bringing life and hope to our community.

Thank you for being part of the CRF family and our cystinosis community. We are forever grateful to you for supporting Natalie, and our beloved community.

With heartfelt thanks and gratitude,

Nancy and Jeff

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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 $70 million with 100% of your donations going to support cystinosis research.

EDUCATION

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

Zoe R. Solsby
Vice President

cystinosis RESEARCH FOUNDATION

CYSTINOSIS RESEARCH IMPACT — ENDLESS POSSIBILITIES

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. Buildup 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 600 people, mostly children, in North America, and about 2,500 people worldwide.

It is one of the 7,000 rare, or "orphan" diseases in the United States that collectively impacts 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 Morgan 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 of cystinosis research in the world and has funded 238 grants in 13 countries.

CRF has raised $70 million, with 100% of your donations going to support cystinosis research. CRF is the driving force of cystinosis research that has directly resulted in advances in treatment including the FDA-approval of Procysbi® and an FDA-approved stem cell and gene therapy clinical trial. We have accomplished milestones and given hope to the cystinosis community that a better quality of life and a cure for cystinosis is possible.

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TOGETHER, WE SHINE BRIGHT!

WE CELEBRATE
AND ARE GRATEFUL EVERY DAY FOR YOUR SUPPORT

FROM HERE
DONATE
WE CAN SEE A CURE

SINCE 2003, CRF HAS:

RECEIVED **1** **FDA-Approved Drug,** and **1** **FDA-Approved Clinical Trial**

FUNDED
238
Multi-Year Grants
in **13 Countries**

PUBLISHED
109 **Articles**
in Prestigious Scientific Journals by CRF-Funded Researchers

RAISED
$70 Million
for Cystinosis Research

IN 2023

CRF AWARDED **12** **New Research Grants in** **7** **Countries**
Totaling More Than $2,959,574 and

United States
Israel
France
Germany
Italy
Switzerland
Canada

CRF RESEARCHERS PUBLISHED **5** **Articles in Prestigious Scientific Journals**

100% OF YOUR DONATIONS DIRECTLY SUPPORT CYSTINOSIS RESEARCH

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.

YOU HAVE CHANGED THE COURSE OF CYSTINOSIS…
THANK YOU!

New Beginnings for the Day of Hope

BY STEPHEN JENKINS, MD

My family has been attending the Day of Hope family conference since 2011. My wife, Ashton, took our oldest son, Sam, that year. I was in medical school at the time and couldn't make it, but she came home so energized and hopeful. She told me all about this French scientist in San Diego who had cured cystinosis in mice. That's impossible, I remember thinking (and telling her). You can't just cure a genetic disease! It affects every single cell in the body! But I was intrigued and hopeful that I could attend the conference one day soon.

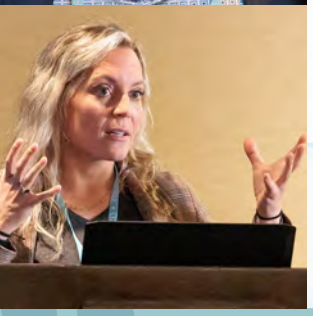
My first conference was in 2013. It was so validating to talk with other families who understood the daily struggles of cystinosis. We could talk about the extreme bedwetting and vomiting, feeding tube troubleshooting, and juggling the impossible medication schedule. We had met the Sturgis family earlier, and Sam was so excited to be reunited with his best bud, Hank. I heard Dr. Cherqui talk about her research for the first time, and I realized that gene therapy had come a long way. We attended the Natalie's Wish gala and were overwhelmed by the generosity of the Stack family and their friends. I came away with more light and hope than I'd ever felt since Sam's diagnosis.

Since that year we haven't missed a conference. Our boys look forward to Day of Hope more than any other event all year, including Christmas! They would rather go to Day of Hope than Disneyland. This last year, Sam had a countdown on his phone so he could tell me how many minutes were left until the Day of Hope.

Why do they love it so much? Cystinosis is a hard reality, and it doesn't get easier with age. When they go to the conference, they get to spend time with other children and adults who really understand what it's like to live with cystinosis. As a parent, I know what it's like to raise someone with cystinosis, but I don't know what it's like to take over 50 pills a day, to suffer from constant nausea and fatigue and other side effects, or to interact with bullies who make fun of the way I smell. But these other kids, like Henry Sturgis and Tina Flerchinger (who aren't really kids anymore!) know what it's like, and they help my kids feel normal and included. And you can't put a price on that.

When the COVID-19 pandemic led to worldwide shutdowns, we were pretty sad to miss the Day of Hope in 2020. We tried to re-create it at home in 2021 over zoom, but it wasn't the same. We were beyond excited to return to Newport Beach in 2022 to reunite with our extended cystinosis family.

After the 2023 Day of Hope conference, we started thinking about exploring a new destination. We have always loved Newport Beach, but we thought a change of scenery might be nice for the community. We took the leap and gathered on April 4-6 at the Catamaran Resort in San Diego. Although we met in a new place, it all felt very familiar as we saw old friends and met new families.



The Catamaran Resort was a hit. The hotel sits on Mission Bay and is across the street from Pacific Beach. Entering the resort felt like walking into the Tiki Room at Disneyland, with its lush tropical plants, waterfalls, koi ponds, and exotic birds. The kids loved the swimming pool area, which included an arcade with FREE VIDEO GAMES. My teenage boys were in heaven.

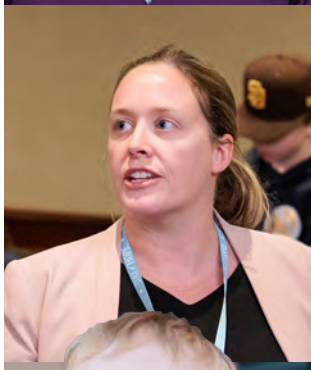
It was great to hear from our cystinosis physicians and researchers. Dr. Greenbaum from Emory University joined us for the first time and talked about the early years of cystinosis and managing Fanconi syndrome. Dr. Midgley from Alberta Children's Hospital talked about the challenges of cystinosis in adolescence and transitioning to adulthood. He currently cares for 13 adults and 7 children with cystinosis. Those patients in Calgary are very lucky!

Dr. Grimm talked about advances in kidney care, including the use of SGLT-2 inhibitors and GLP-1 agonists, and kidney transplantation, including the use of genetically modified pig kidneys. He talked about the National Kidney Registry for patients who have family members that aren't a donor match. Those family members can still donate a kidney to someone else and get a voucher so their child can still get a living donor kidney.

Dr. Freedman from University of Washington gave us an update on his kidney organoid project. His lab takes urinary cells from people with cystinosis and reprograms them into stem cells. He uses CRISPR gene editing to add a healthy copy of the cystinosis gene. These cells are then transformed into kidney cells, and injected into a cystinosis knockout mouse kidney, where they mature and engraft. Hopefully one day this could lead to gene-edited organoids in humans that could be grafted into native kidneys to improve kidney function.

Dr. Donny Suh from University of California, Irvine came to the conference for the first time to talk about the many ways cystinosis affects the eyes. Besides corneal crystals, cystine build-up also affects goblet cells in the conjunctiva which normally help produce the tear film. Damage to these cells leads to dry eyes and scarring. Crystals also deposit in the iris which can lead to glaucoma. Cystine deposition in the retina can lead to blindness. He is currently studying the effects of punctal occlusion plugs in the lacrimal ducts to keep tears on the cornea longer. He provided comprehensive eye exams all day Friday for many conference participants. It's wonderful to have someone from ophthalmology engaged in cystinosis research.

Dr. DiLeo from University of Pittsburgh gave an update on the cysteamine SoliDrop project for the eyes. Solidrops are a controlled-release formulation that use a gel-based eye drop that contains cysteamine-loaded microspheres. The hope is that it could be given once a day and would slowly release cysteamine to the cornea. It has been tested on rabbits and cystinosis knockout mice. The mice studies continue, and she is working on larger scale manufacturing for a potential clinical trial.



Dr. Catz from Scripps Research gave an update on his research in lysosome trafficking and autophagy. He has identified a drug, CA77, which improves renal function and Fanconi syndrome in cystinosis knockout mice.

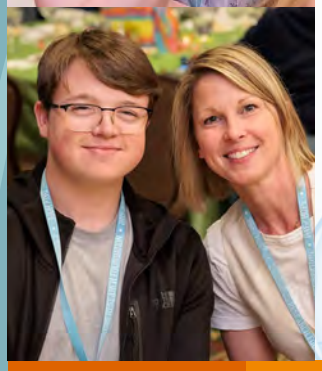
Dr. Jennifer Hollywood, who recently moved from University of Auckland, New Zealand to Ireland, came to the conference for the first time to talk about her research. She has created a cystinosis rat model, and she has tested a new cystine-depletion agent, called CF10, and found it works just as well as cysteamine, with much fewer side effects. This could be a very big deal, and toxicity studies in humans will begin in UK this year. She has also been testing everolimus, which inhibits mTOR and may improve autophagy, and found that when combined with cysteamine, it leads to superior reduction in cystine levels and improves Fanconi syndrome in rats.

Betty Cabrera returned to the conference to talk about the Gene Therapy Initiative at UC San Diego. The groundbreaking work done by Dr. Cherqui has led to gene therapy research for other rare diseases, including Dannon disease and Friedrich's ataxia. Thanks to a generous donation from Nancy and Jeff Stack, the Gene Therapy Initiative will continue to fund and develop these therapies.

Dr. Cherqui gave us an update on the stem cell trial that started in 2019. Six adults have been transplanted and are doing well. There have been no adverse effects related to the drug product. Patients with higher vector copy numbers (copies of the corrected gene) have had better decreases in cystine levels. Patients 4 and 5 have restarted a low dose of cysteamine.

After Dr. Cherqui's talk we had a panel with four of the trial participants: Jordan Janz, Jacob Seachord, Tyler Joynt, and Kurt Gillenberg. They spoke openly about their experiences with the stem cell trial, including the side effects of chemotherapy, fertility preservation, and life after transplant. All of them are glad they did the trial. It was inspiring to hear from them.

On Saturday we heard from a new researcher, Dr. Lauren Albrecht, from UC Irvine. She is investigating novel pathways in the lysosome that are affected by cystinosis, including a process called methylation, which is not rescued by cysteamine therapy. This could provide a novel therapeutic target. It's always wonderful to hear from new, enthusiastic scientists.



Next, we heard from Dr. Barshop, who talked about the difficulties of measuring cystine levels. His lab in UC San Diego is the gold standard for cystine measurement, and he is always working on new ways to improve accuracy.

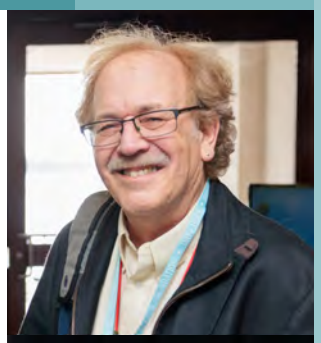
After Dr. Barshop we heard from Dr. Paul Goodyer from McGill University in Montreal. He is working with Moderna to develop an mRNA treatment for cystinosis. An infusion of cystinosin mRNA could lead to higher levels of the normal cystinosin protein in the body. Moderna has multiple similar therapies in the pipeline, including a Phase 2 trial for a disease called propionic acidemia. Preliminary studies in cell culture and mice are ongoing.

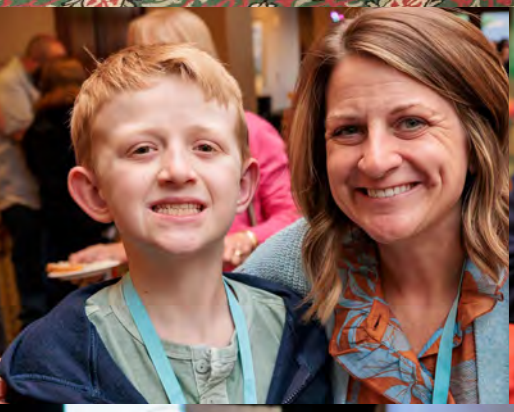
In addition to hearing from researchers, we had multiple families share their experiences with cystinosis. Leah and Devin Fehr, from Saskatchewan, Canada, talked about their son James and his journey with cystinosis. They have put on some creative fundraisers over the years!

Kristen Murray talked about her son Seth, and their annual Circle of Hope fundraiser. She also highlighted the many fundraising efforts of families in the cystinosis community, from golf tournaments and galas to lemonade stands and online auctions. She shared a quote from Margaret Mead that I think captures the passion of our community: “Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it’s the only thing that ever has.”

We also heard from teenager Henry “Hank” Sturgis from Sandpoint, Idaho. He talked about not letting cystinosis stop you from pursuing your goals and dreams and showed an action reel of all the awesome things he’s done on ski slopes and lakes and in airplanes. All the adolescents came to cheer him on. He has a supportive and big fan club, and my boys were right there with them. It was moving to hear about his love for other kids and families in the community. He did a fantastic job.

After the morning sessions we had breakout groups based on ages. I attended the newborn to 4-year-old group, and it was cool to see families talk about their challenges





and support each other. In some ways I'd forgotten what it's like to be at that stage, but I was impressed by the determination and ingenuity of those parents.

After the breakout sessions we had a panel of adults living with cystinosis. This is always a highlight of the conference, and it is cool to see some new faces up there. They shared great advice on things like medication adherence, school, work, transplants, and friends. I appreciated their willingness to be candid and vulnerable with the packed audience.

And just like that, the conference was over! It always feels like a whirlwind. I'm so grateful to the conference co-chairs: Brian Sturgis, Jill and Clay Emerson, and Kristen Murray, for the hard work of planning and putting on the conference. And we couldn't have done it without the expertise and attention to detail of Zoe Solsby and Stacy Johnson, and the generosity of Jeff and Nancy Stack. It's so amazing to be part of such an organization, and we are already looking forward to planning next year's conference. I hope to see you there!

2024 Day of Hope Family Conference co-chairs: **Kristen Murray, Dr. Stephen Jenkins, Clay Emerson, Jill Emerson, and Brian Sturgis.**

LEARN MORE ABOUT THE DAY OF HOPE FAMILY CONFERENCE

APRIL'S MONTH-LONG FUNDRAISER WAS A HUGE SUCCESS

THANK YOU!

We are grateful to everyone who donated to the Natalie's Wish Fundraiser. Your donations totaling over $1.1 million will help us accelerate research projects and fund new research studies this year! Together we will continue to build our research community, support clinical trials, and initiate new, innovative research studies.

CRF is the driving force of cystinosis research in the world. CRF has funded 235 studies in 13 countries since 2003 which has directly resulted in advances in treatments, including the FDA-approval of Procysbi® and an FDA-approved stem cell and gene therapy clinical trial. We have accomplished milestones and given hope to the cystinosis community that a better quality of life and a cure for cystinosis is possible.

Your support has the power to shape our future, with 100% of your donations going directly to research. 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. It's not too late donate and celebrate two decades of research impact and changing lives!

Thank you for never giving up, always supporting our research efforts and your commitment to Natalie's Wish!

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CYSTINOSIS RESEARCH FOUNDATION

SCIENTIFIC REVIEW BOARD

The CRF Scientific Review Board (SRB) is composed of leading cystinosis scientists, researchers, and clinicians from around the world. We are indebted to our Scientific Review Board members for their leadership, guidance and commitment to improving the lives of adults and children with cystinosis. THANK YOU!

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THANK YOU FOR THE YEARS OF DEDICATION TO THE CYSTINOSIS COMMUNITY

SUMMER 2024

RESEARCH UPDATES

WHERE COMMUNITY MEETS DISCOVERY

BONDING WITH NEW CRF RESEARCH COLLEAGUES AND CYSTINOSIS FAMILIES ENERGIZES **DR. LAUREN ALBRECHT** AS SHE PURSUES CLUES TO BETTER TREATMENTS AT THE CUTTING EDGE OF CELLULAR INQUIRY.

by Dennis Arp

Dr. Lauren Albrecht's high-beam smile flashes at full volume as she reflects on her research journey and the embrace that has welcomed her into the cystinosis community.

"Everyone is so passionate about understanding this disease and improving the lives of patients," she says of the research colleagues and families she met at the recent Cystinosis Research Foundation (CRF) Day of Hope Conference. "This is clearly a unique and special community."

But even in the glow of her enthusiasm, the UC Irvine research scientist remains motivated by a previous passage through darker days. It wasn't so long ago that she languished in the depths of her own first-hand experience with kidney disease.

"In my 20s I was diagnosed with lupus, and I was so disappointed with the treatment options that were available," says Dr. Albrecht, assistant professor in UC Irvine's School of Pharmaceutical Sciences. "Kidney transplant was presented as basically the only option out there. I was thinking, if I'm going to get out of this, I want to devote myself to research on kidney diseases because this is where my time will be best invested."

Years later, her experience as a patient continues to shape the trajectory of Dr. Albrecht's career as a research scientist. After her diagnosis, she sought out Dr. Isidro Salusky, the head of nephrology at UCLA, where she was a postdoctoral fellow. She professed her new research obsession.

"I said that I was dedicating myself to curing kidney disease, and do you want to work together," she recalls. "He was excited to work with a basic researcher."

Now Dr. Albrecht has her own lab at UC Irvine, and she's the one carrying the excitement forward. Thanks to CRF grant support, she has launched a new project with great promise for insights into the parts of cystinosis that persist even when patients adhere to prescribed regimens of cysteamine – the longstanding and highly effective treatment for the disease.

"We want to better understand how breakdowns in cellular function contribute to cystinosis," Dr. Albrecht says. "To do this, we need to focus on understanding the lysosome – the specialized compartment inside cells that's essential for regulating proteins."

UNDERSTANDING THE LYSOSOME

From previous research, scientists know that cystinosis wreaks havoc on lysosomes. But the resulting molecular consequences and the disruption of downstream cellular signaling are not well understood. Of particular interest to Dr. Albrecht is "kidney-bone crosstalk" – a recently discovered signaling pathway that may offer clues to cellular health aiding patients with cystinosis as well as those with other diseases.

"We want to better understand this new signaling phenomenon," she says. "The key science word here is methylation, which can regulate this signaling by putting proteins in the lysosome. It's a big new thing with lots of promise. Everyone in my lab is studying methylation in the context of the lysosome."

Specifically, the researchers in her lab are finding that an emerging protein tag for lysosomes called MrDegron is

CYSTINOSIS RESEARCH STAR

LAUREN V. ALBRECHT, BS, PhD

ASSISTANT PROFESSOR
Pharmaceutical Sciences Dept, School of Pharmacy & Pharmaceutical Sciences, Developmental and Cell Biology Dept
School of Biological Sciences, University of California, Irvine

misregulated in the bones and kidneys of cystinosis patients. By plugging holes in the current knowledge gap, Dr. Albrecht's research has a good chance to uncover new disease processes and molecular targets that would allow physicians to intervene with more effective therapies for cystinosis.

The project puts the biologist and her labmates where many cystinosis patients need them – studying bone and kidney disease that isn't responding to cysteamine treatment.

"Our preliminary data reveals that aberrant lysosomes result in signaling processes that are independent of cystine, which could contribute to therapy-resistant disease processes," she adds.

FOUNDATIONAL RESEARCH AS A PATH TO A CURE

Given the breadth of cystinosis research these days, Dr. Albrecht knows that there are numerous pathways to insights that improve the lives of patients.

"I would love to achieve a cure," she says. "For us, being aligned with curing means understanding the fundamental basis of the lysosomes in this disease. I really believe that restoring the gene therapy has been revolutionary, and that understanding the fundamental biology puts us on the path toward curing the disease."

At the heart of this foundational research project made possible by CRF donors is "visualizing what is going on inside of a cell and inside of this tissue using a super high-resolution microscope," Dr. Albrecht adds.

"We're constantly on the microscope – we have someone on it right now, doing an experiment just today, analyzing lysosomes because we think we have uncovered some new fundamental biology already by studying cystinosis."

The benefits of CRF support are as sharply focused in Dr. Albrecht's mind as the cells under her microscope.

"Without CRF, we definitely would not be on the path for a cure, because improving treatments and eventually finding a cure depends on us designing experiments that are extremely specific to this disease," she says. "There's just not another opportunity to be so devoted to understanding cystinosis."

COLLABORATIVE SPIRIT IN FOCUS

Beyond CRF financial support, Dr. Albrecht says her work is lifted by the collaborative connections the foundation provides. As an example, she notes that bone tissue provided by fellow CRF-funded researcher Dr. Justine Bacchetta is now yielding insights via Dr. Albrecht's microscopy.

"I'm confident that this collaborative spirit will continue to grow as we get more data and reach out to more researchers," the biologist says.

CRF is also distinguished by the opportunities that connect CRF-supported researchers with cystinosis families, Dr. Albrecht adds.

She had never attended an event like the Day of Hope Conference.

"Every time I sat down at a table, I became so close with a new family," she says. "They were so open in sharing everything about their experience, and the kids are so curious about the science. I told them, 'You should come to my lab because we do some really fun things there.'"

Two of the students in Dr. Albrecht's eight-member lab joined her at the conference.

"We were all completely moved by the experience," she says. "We came away understanding so many more things and with so much motivation to figure everything out."

Going as far back as her childhood, Dr. Albrecht has found motivation in the joys of discovery. These days, she also weaves into her sense of purpose the multifaceted power of her own experience enduring the challenges of kidney disease as well as the wellspring of goodwill that comes from the community that surrounds her.

No wonder then that the wattage of her optimism lights up her lab.

"I love science – there's something special about the day-to-day work of discovery," she says. "All of us in the lab are extremely excited about seeing what we can do. We feel the energy and urgency, which is really powerful."

FROM THE PANDEMIC, A DOSE OF HOPE

APPLYING THE TECHNOLOGY BEHIND MODERNA'S COVID VACCINE, **DR. PAUL GOODYER** CHARTS A NEW PATH TO A CYSTINOSIS BREAKTHROUGH.

by Dennis Arp

Thorny problems seldom get solved by staying where you are. But in this case, not only did a promising opportunity for research come to Dr. Paul Goodyer's doorstep, but it also invited him to dinner.

Now Dr. Goodyer is seizing the chance to create new possibilities for cystinosis patients.

It all began in the early days of the COVID-19 pandemic, when the pharmaceutical company Moderna was leveraging its breakthrough mRNA technology to fast-track development of a vaccine. A Moderna research scientist traveled to Montreal to give lectures on the company's process at McGill University, where Dr. Goodyer is a professor of pediatrics and human genetics as well as a clinical physician.

A research bond was born.

"I had dinner with the Moderna scientist, and I said, 'Well, if you can use this fantastic strategy to produce a protein just by typing in the code, and you can use that technology for the vaccine, why can't we do the same thing for cystinosis?'" Dr. Goodyer recalls. "He thought about it and we decided it should be possible."

Over the next several years, the researchers kept in touch, even as Moderna scientists remained laser focused on the myriad details of producing the COVID vaccine. Eventually, Dr. Goodyer circled back with his Moderna colleagues to see if the time was right to activate the cystinosis project.

"Let's go for it," came the reply.

Thanks to grant support from the Cystinosis Research Foundation (CRF), the Moderna mRNA technology used for the COVID vaccine may offer the unforeseen chance to treat cystinosis.

BUILDING ON DECADES OF PERSPECTIVE

Nearly five decades of treating cystinosis patients and tracking numerous pathways of research have prepared him for this moment. His readiness and resolve are evident in his description of the project.

"By delaying organ deterioration, cysteamine has given hope to the cystinosis community. But cysteamine addresses only one of the multiple cellular functions disrupted by CTNS mutations. We aim to capitalize on a 'silver lining' to the COVID-19 pandemic by collaborating with Moderna scientists to adapt their novel mRNA technology to restore CTNS expression in cystinosis."

He's confident that by plugging in the normal sequence of the cystinosis gene code, he and his colleagues "can use that blueprint to instruct our cells to make normal cystinosin protein. Provided that we can express enough CTNS protein in the right place within our cells, it should fix the disease."

As he says that last sentence, Dr. Goodyer adds a joyful lilt to his voice. It all seems so simple – "It should fix the disease." And yet woven into the statement's simplicity is the power to transform lives.

Dr. Goodyer has witnessed both the heartbreak and hope inherent in the cystinosis experience. He first started working on the disease in the late 1970s with McGill biochemical geneticist Dr. Charles Scriver.

"He was part of a gang of researchers in North America working fervently to develop a treatment for cystinosis," Dr. Goodyer says. "They all did experiments on different molecules and eventually decided that cysteamine was the way to go."

A COMMITMENT TO ADVANCING RESEARCH

Recalling his days as a young researcher in the McGill lab, Dr. Goodyer can still conjure memories of the exhilaration cysteamine generated. Finally, there was a promising treatment.

That excitement extends like a generational throughline connecting previous breakthroughs to the ongoing quest for more.

CYSTINOSIS RESEARCH STAR

PAUL GOODYER, MD

ASSOCIATE MEMBER
Department of Medicine, Division of Experimental Medicine
McGill University Health Centre, Montréal, QC, Canada

As Dr. Goodyer begins this new two-year research journey adapting the Moderna mRNA technology, there are countless steps to take and hurdles to clear on the way to clinical application. Still, there's considerable optimism.

"We don't have to work out the stabilization of the RNA (a building block of protein synthesis). A huge team of Moderna scientists has solved many of those technical problems," Dr. Goodyer says. "We now have to learn how to adapt mRNA technology to cystinosis."

A key challenge is getting enough expression of the CTNS protein in the tissues of cystinosis patients "to get the job done." the researcher notes. "If we can restore CTNS mRNA to about 10% of normal, this would likely be sufficient to ameliorate the disease."

The long-term vision is to treat patients with intermittent injections of LNP (lipid nanoparticle) containing normal CTNS mRNA, in a manner that quells the many events that drive organ deterioration.

"Moderna scientists are able to stabilize the mRNA," Dr. Goodyer says. "This is important, because we want the mRNA to make cystinosin protein for as long as possible before another injection is needed. Limiting the number of injections is an important goal for patients and their families".

"Moderna scientists had also worked for years before the pandemic to refine their mRNA delivery system", says Dr. Goodyer. "The mRNA is wrapped in a little lipid oily micro drop that's injected into the patient. Each of those micro drops is taken up by our tissues, releasing the mRNA inside. To adapt this to cystinosis, we will work with Moderna colleagues to target LNPs to the key tissues affected by cystinosis."

RAMPING UP A PROJECT FULL OF PROMISE

So now the laborious but immensely rewarding work of discovery begins. In this earliest phase of the project, it's important to choose the right reagents.

"We want it to have an mRNA for cystinosin (the protein defective in cystinosis), but there actually are two forms of cystinosin protein in every cell, and we realize that we need to check out both," he says. "We also have to be sure the mRNA gets to the right place, so we've asked Moderna to add a little fluorescent tag that will allow us to visualize the proteins made by each mRNA".

The scientists hope to prove that they can not only normalize the accumulation of cystine in the cells, but they can also determine which of the two cystinosis mRNA produces a protein that will fix autophagy – an important process of cellular recycling. During this proof-of-principle phase, testing will be done in the lab, using cultured cells from our patients.

"We'll save the hardest part for last, and I imagine that might come this winter or perhaps next year," Dr. Goodyer says. "We'll arrive at that point when we are ready to test Moderna formulations in novel cystinotic mice that we generated prior to the pandemic."

Throughout the two-year process, the doctor will work closely with Moderna scientists.

"I'm an optimist," he adds. "By collaborating with colleagues at Moderna and with funding from the CRF, we will find out whether we can achieve enough delivery of normal CTNS mRNA to repair the damage done by mutations of the CTNS gene."

Having a partner like the CRF fuels Dr. Goodyer's optimism.

"They and their donors are crucial to the process," he says. "This research just wouldn't be possible without them."

Over his many years of working to improve lives, Dr. Goodyer has celebrated numerous successes and persevered through various setbacks. Perhaps more than most researchers, he is equipped to find an element of hope in a global pandemic.

"COVID shut down research on so many subjects, including mine on cystinosis. So many suffered in so many ways," he says. "But the crisis has also created an unexpected opportunity for something good. If every cloud has a silver lining," he says, "we want this one to include a ray of hope for cystinosis patients."

UPDATE ON THE

Stem Cell and Gene Therapy Clinical Trial

BY STÉPHANIE CHERQUI, PhD
UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Cystinosis Research Foundation is pleased to share a brief update on the stem cell and gene therapy clinical trial led by Stéphanie Cherqui, PhD. In 2007, CRF provided the first grant to Dr. Cherqui that launched her stem cell study. Since that time, CRF has awarded $6,473,807 million in research grants to Dr. Cherqui. As a result of her work, the FDA approved the first stem cell and gene therapy clinical trial for cystinosis in 2018. Dr. Cherqui and her team at University of California San Diego (UCSD) successfully led Phase 1/2 of the clinical trial which was completed when the final patient was transplanted in 2022. Last year, Novartis purchased the stem cell clinical program and will sponsor the next phase of the clinical trial and seek final FDA approval.

What is the status of the stem cell and gene therapy clinical trial?

The phase 1/2 clinical trial at UC San Diego has successfully completed patient enrollment with six treated patients, who received autologous gene-modified hematopoietic stem cells. Five patients have enrolled to the long-term follow up study and will be followed for 15 years post-stem cell transplantation. The upcoming phase of the trial will be overseen by Novartis. I advise Novartis or provide information as required.

How are the first five stem cell transplant patients doing overall? Have any of the patients resumed oral cysteamine and if they have, do you consider that a setback or is the stem cell transplant working, just not as effectively?

Overall, the patients are doing well. Patients 4 and 5, whose vector copy number (VCN; the number of vectors per cell) is below 1, have resumed low-dose cysteamine treatment. A VCN below 1 indicates that fewer stem cells possess the healthy CTNS gene compared to patients 1, 3, and 6, whose VCN is above 1. Nonetheless, for patients 4 and 5, there is still expression of the CTNS gene in a portion of the stem cells, resulting in a reduction of cystine and cystine crystal levels compared to baseline. Therefore, although a VCN below 1 may be less effective, it could still be crucial for the long-term preservation of tissues.

How long will you follow the first five stem cell patients and what happens to the data you collect?

Patients will be followed for a total of 15 years after the stem cell transplant. The data will be shared with Novartis who is preparing for the next phase of the clinical trial, and the FDA.

Is there anything you would like to say to the first five patients who volunteered for the study?

Continuing to monitor the progress of the five patients participating in the long-term follow-up after their stem cell transplants is incredibly meaningful. We keep collecting data and learning about the impact of the gene-modified stem cells for cystinosis over time.

It is also heartwarming to learn about the developments in the patients' lives such as career changes, marriage, and the arrival of new children. Last month, during the Day of Hope conference, it was particularly touching to have four out of the five patients join me on stage to share their insights about their experiences with the clinical trial.

CRF RESEARCHER,
STÉPHANIE CHERQUI, PhD

CYSTINOSIS RESEARCH FOUNDATION

2023 RESEARCH & FELLOWSHIP GRANT AWARDS

TOTAL AWARDS:
$2,959,574

12 GRANTS

7 COUNTRIES

CRF IS THE LARGEST FUND PROVIDER OF GRANTS FOR CYSTINOSIS RESEARCH IN THE WORLD, ISSUING 238 GRANTS IN 13 COUNTRIES SINCE 2003.

SPRING 2023

Sergio Catz, PhD (Mentor) and Juan Yu, PhD (Fellow)
Scripps Research
"Studies of global inflammation in patients with cystinosis"
$150,000 TWO-YEAR FELLOWSHIP

Ester De Leo, PhD and Francesco Emma, MD
Bambino Gesù Children's Hospital
"Efficacy and safety of genistein in Ctns-/- rats"
$209,550 TWO-YEAR STUDY

Olivier Devuyst, MD, PhD and Alessandro Luciani, PhD
University of Zürich
"SGLT2 inhibitors reveal new therapeutic opportunities for cystinosis"
$320,000 TWO-YEAR STUDY

Olivier Devuyst, MD, PhD and Francesco Emma, MD
Bambino Gesù Children's Hospital
Maintenance of CTNS Rat Model
$40,000 TWO-YEAR STUDY

Paul Goodyer, MD and Elena Torban, PhD
Research Institute of the McGill University Health Centre
"mRNA therapy for cystinosis"
$240,000 TWO-YEAR STUDY

FALL 2023

Lauren Albrecht, BS, PhD and Renata Pereira, PhD
University of California, Irvine, and University of California, Los Angeles
"Investigating novel regulators of lysosomes and osteocyte signaling in cystinosis"
$357,047 TWO-YEAR STUDY

Yael Borovitz, MD, Ittai Fattal, MD, Shelly Levi, MD and Daniel Landau, MD
Schneider Children's Medical Center, Israel
"Efficacy of dipyridamole for hypercalciuria in hypophosphatemic tubulopathies: a prospective interventional study"
$27,500 TWO-YEAR STUDY

Stéphanie Cherqui, PhD
University of California, San Diego
"Advancing the understanding of the renal Fanconi syndrome in cystinosis"
$330,577 TWO-YEAR STUDY

Benjamin Freedman, PhD
University of Washington
"Developing a therapeutic strategy for nephropathic cystinosis with iPS cells"
$437,778 TWO-YEAR STUDY

Bruno Gasnier, PhD
CNRS/University of Paris, France
"A critical role for cystinosin during mammalian embryonic development"
$404,000 TWO-YEAR STUDY

Maren Leifheit-Nestler, PhD, Malgorzata Szaroszyk, PhD and Dieter Haffner, MD
Hannover Medical School, Germany
"Cystinosis-associated myopathy: Impact of musclin gene therapy and exercise"
$277,2887 TWO-YEAR STUDY

Ming Li, PhD and Jacob Kitzman, PhD
University of Michigan
"Investigating the degradation mechanism of cystinosis mutant"
$165,834 ONE-YEAR STUDY

SEE LAY ABSTRACTS STARTING ON NEXT PAGE

Investigating novel regulators of lysosomes and osteocytes in cystinosis

Lauren V. Albrecht, BS, PhD, *Principal Investigator*
Renata C. Pereira, PhD, *Co-Principal Investigator*
UNIVERSITY OF CALIFORNIA, IRVINE, AND
UNIVERSITY OF CALIFORNIA, LOS ANGELES

OBJECTIVE/RATIONALE:

This research aims to understand how cellular dysregulation contributes to cystinosis. We focus on understanding the lysosome, a specialized compartment that is essential for regulating the breakdown of proteins. While it is well-established that lysosomes are altered in cystinosis, the molecular consequences and signaling events downstream are not well understood. By addressing this gap in knowledge, our studies aim to uncover new disease processes and molecular targets for therapeutic intervention.

PROJECT DESCRIPTION:

We build on previous findings that osteocytes, a type of bone cell, may contribute to bone defects in cystinosis. Additionally, a novel lysosomal pathway, not restored by current treatments, was identified. Specifically, we find that a newly discovered protein tag for lysosomes, MrDegron, is misregulated in bone and kidney of cystinosis patients and disease models. We hypothesize that lysosomal signaling dysregulation plays tissue-specific roles in promoting cystinosis. The research has two aims: 1) Understanding the role of lysosomes in osteocytes, and 2) Investigating a novel methylation-dependent lysosomal pathway essential across tissues. Innovative approaches, including advanced microscopy and proteomics, will be used to gain insights from cultured cells, patient tissues, and murine models. The findings could reveal the fundamental basis of the disease and potential new targets for correcting pathways resistant to current treatments.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

TThis project will impact current cystinosis treatments by studying bone and kidney disease where cysteamine treatments are not fully effective. At the completion of these studies, we aim to delineate novel mechanisms of disease to benefit bone disease children and young adults that is not well-understood. Our preliminary data reveals that aberrant lysosomes result in signaling processes that are independent of cystine, which could contribute to the disease processes that are resistant to cysteamine treatments.

ANTICIPATED OUTCOME:

We expect to discover how misregulated lysosomes results in altered signaling in cells and tissues. By studying the new molecular signal, MrDegron, that delivers proteins into lysosomes, we expect to elucidate novel biological processes and pathways for designing therapeutics. By studying osteocytes, a bone cell type that was previously ignored in cystinosis and known to regulate kidney-bone crosstalk, these studies could yield new insights in the role of altered organ communication during disease progression or diagnosis.

Efficacy of Dipyridamole for hypercalciuria in hypophosphatemic tubulopathies: a prospective interventional study

Yael Borovitz, MD, *Principal Investigator*
Ittai Fattal, MD, *Co-Principal Investigator*
SCHNEIDER CHILDREN'S MEDICAL CENTER, ISRAEL

OBJECTIVE/RATIONALE:

The aim of our proposed study is to interfere in the pathophysiological pathway that lead to nephrolithiasis, nephrocalcinosis, and eventually chronic kidney disease in patients with cystinosis, Dent disease and similar hypercalciuric-hyerphosphaturic tubular disorders. We will examine the effects of Dipyridamole on urine Pi and calcium excretion, serum levels of 1,25OH2D, PTH and urine supersaturation.

PROJECT DESCRIPTION:

All patients will receive a uniform nutritional consultation. Two weeks after implementing the nutritional plan, baseline 1,25OH2D, 24 hour urine collection of calcium, creatinine, Pi, magnesium, potassium, citrate, uric acid, chloride, protein, microalbumin, urea, sodium and oxalate will be evaluated. Patients unable to collect urine will be evaluated by spot urinary samples. Dipyridamole will be given for 3 months, dose will be adjusted by weight. Parameters will be evaluated longitudinally at 0, 2, 4 and 12 weeks from study drug initiation:

– Blood pressure, blood chemistry, complete blood count. Threshold for maximal Pi reabsorption, corrected for GFR (Tmp\GFR) Blood 1,25OH2D and PTH and 24 hour urine collection for citrate, calcium, creatinine,oxalate, sodium, uric acid, potassium, urea and Pi will be evaluated again at the end of the study.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Since there is no targeted treatment available for hyperphosphaturic diseases associated with hypercalciuria, such as cystinosis, the renal prognosis is dismaying. As many authorities consider hyperphosphaturia as the major cause for renal deterioration, reduction in urine Pi excretion can potentially reduce the rate of kidney disease progression. All patients will be actively treated and if Dipyridamole treatment will show a positive effect, we will advise the attending nephrologist and the patient to continue treatment beyond the study period.

ANTICIPATED OUTCOME:

Primary outcome will be a change in Tmp/GFR from baseline. Reducing phosphaturia for a long period may slow the progression towards end stage kidney disease.

The results of this study may serve as a basis for the performance of a prospective double blind placebo controlled trial, to find additional therapeutic strategies for this aspect of cystinosis as well as other tubulopathies.

Advancing the understanding of renal Fanconi syndrome in cystinosis

Stéphanie Cherqui, PhD, *Principal Investigator*
UNIVERSITY OF CALIFORNIA, SAN DIEGO

OBJECTIVE/RATIONALE:

Despite the fact that cystinosin, the protein involved in cystinosis, is expressed in all the organs, the renal Fanconi syndrome is the first manifestation of cystinosis that presents early in life of the patients while other complications appear years later. Numerous studies investigated the cause of the specific sensitivity of the kidney cells to the absence of cystinosin. While the matter is still unresolved, it is apparent that specific function(s) of cystinosin in the kidney beyond cystine transport explain the early Fanconi syndrome in cystinosis.

PROJECT DESCRIPTION:

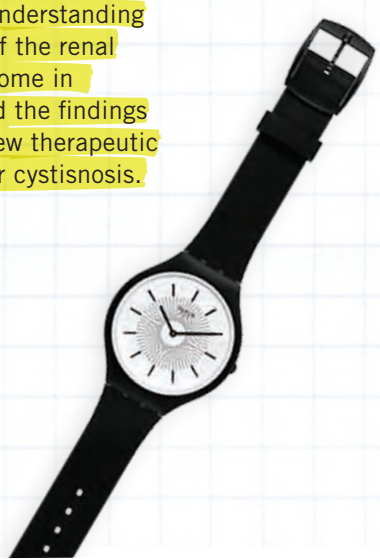
We identified a novel interaction of cystinosin with a transport exchanger protein in the kidney cells that may advance the understanding the cause of the renal Fanconi syndrome in cystinosis. The transporter is the Na/H exchanger, NHE3, a major absorptive sodium transporter expressed the apical membrane of the proximal tubules of the kidney and in the gastrointestinal epithelial cells. We confirmed this interaction in both the yeast model and in kidney cells. We also showed co-localization of cystinosin and NHE3 in cells. Furthermore, we showed that NHE3 was mislocalized in CTNS-deficient kidney cells, and that the trafficking of NHE3 was defective within the kidney cells missing cystinosin. Therefore, cystinosin has a role in the cellular localization and/or function of NHE3 in the kidney proximal tubules, and in its absence, NHE3 is dysregulated participating to the renal Fanconi syndrome in cystinosis. This project aims to determine how cystinosin and NHE3 interact and the impact of the absence cystinosin on NHE3 and other transporters in kidney proximal tubules. The studies will be conducted in vitro in the yeast and human kidney cell models, and in vivo in the Ctns-/- mice.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The elucidation of the mechanism of NHE3 transport regulation, expression and function in presence or absence of cystinosin may advance the understanding of the renal Fanconi syndrome and could open new therapeutic avenues in cystinosis treatment.

ANTICIPATED OUTCOME:

The proposed project should advance our understanding of the cause of the renal Fanconi syndrome in cystinosis, and the findings may lead to new therapeutic approaches for cystisnosis.



Developing a therapeutic strategy for nephropathic cystinosis with iPS cells

Benjamin Freedman, PhD, *Principal Investigator*
UNIVERSITY OF WASHINGTON

OBJECTIVE/RATIONALE:

The goal of this proposal is to utilize human stem cells and mice to understand nephropathic cystinosis and develop therapeutics. The kidney is a particularly sensitive organ in cystinosis, leading to kidney failure at an early age. We will derive kidney-like structures (organoids) from cystinosis stem cells, to reproduce this disease in lab dishes and understand why kidneys are so vulnerable. We will furthermore test whether stem cells treated with a gene therapy can form healthy kidney tissue in a new mouse strain with cystinosis.

PROJECT DESCRIPTION:

We will take powerful stem cells from patients with cystinosis, and use these to reproduce classic symptoms of cystinosis in kidney a petri dish. Through detailed analyses, we will test whether a new form of programmed cell death is causing the disease. We will also test whether treating these cells with gene therapy can alleviate these symptoms. To understand the potential of these cells for kidney regeneration, we will use a new type of cystinotic mouse, which is capable of accepting human tissue grafts. We will implant our cystinosis cells into the kidneys of this mouse, before or after treating these cells with gene therapy. The grafts will be examined for signs of new functional kidney tissue inside the mouse host, and also for any residual symptoms of cystinosis.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

This project will (a) provide new insight into the mechanisms and determinants of cystinosis in kidneys, in particular the pathway of programmed cell death that occurs in kidney cells; (b) pave new roads to discover therapeutics, including regenerative therapies and gene therapies, which require further development; and (c) establish a new mouse strain for the sustained study of cystinosis in a variety of cell types and conditions, including new gene therapies and a living animal model capable of accepting human cells.

ANTICIPATED OUTCOME:

We expect to discover that cystinosis kidney structures in a petri dish will suffer from a new type of programmed cell death, due to increased cystine. We know these cells can die, but we seek to understand how it happens at the molecular level, so that we can develop therapies. Gene therapy to restore proper levels of functional cystinosin protein is expected to have dramatically beneficial effects on kidney cells. Stem cell grafts in our new cystinosis mouse are expected to exhibit more sophisticated signs of cystinosis, such as crystal formation, which we hope will also be remedied by gene therapy.

A critical role for cystinosin during mammalian embryonic development

Bruno Gasnier, PhD, *Principal Investigator*
CNRS/UNIVERSITY OF PARIS, FRANCE

OBJECTIVE/RATIONALE:

Cystinosis occurs when a specific gene, responsible for a protein called cystinosin, is not working properly. This protein is essential for moving an amino acid called cystine out of a cell structure called the lysosome. In our earlier studies with mice, we found a surprising connection between cystinosin and another lysosomal protein. When both genes are inactivated, the development of embryos is severely impaired, showing a new role for cystinosin. We have figured out that this role involves providing nutrients to the developing embryo, but we still do not understand how cystinosin is involved. This research aims to answer that question.

PROJECT DESCRIPTION:

In our previous work, we found that both cystinosin and its genetic partner are crucial for the nutrition of mammalian embryos in the early stages before the placenta starts working. This nutrition process relies on a special tissue called the yolk sac. The yolk sac breaks down proteins from the mother to produce amino acids and other nutrients needed for the growing embryo. When both cystinosin and its partner are missing, this early nutrition process is seriously affected and a wide range of amino acids is affected. However, we are still trying to understand how these two proteins work together. Why do they compensate for each other when just one is missing? How do they cooperate in this process?

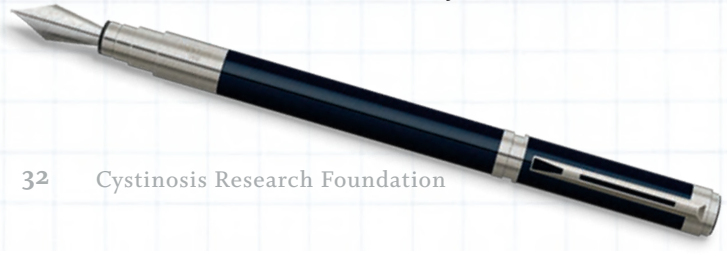
To figure this out, we will test how cystinosin and its partner affect specific biochemical pathways suggested by a technique called metabolomics. We will use various scientific approaches to examine the candidate pathways. Additionally, we will try to fix the faulty pathways by treating the mice with drugs.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Our study may uncover new insights into cystinosis. On one hand, similarities between the yolk sac and the kidney (the first main target of cystinosis) could help us understand common disease mechanisms in these tissues. On the other hand, the interplay between cystinosin and its partner might suggest unexpected ideas about how metabolism is affected in cystinosis and how other genes influence the severity of the disease.

ANTICIPATED OUTCOME:

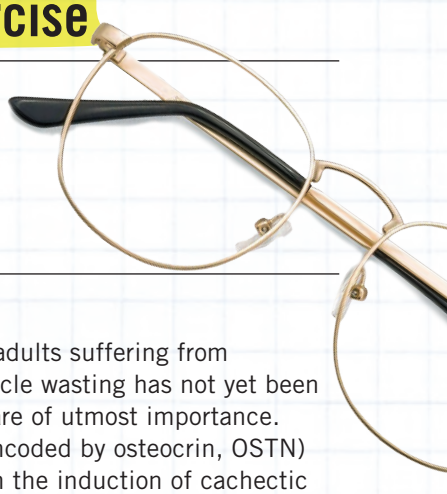
This research will reveal new roles of cystinosin in the body. Understanding how it works with another lysosomal protein and identifying the biochemical pathway in which they cooperate will give us a broader understanding of the physiological function of cystinosin. This fundamental knowledge could lead to fresh ideas about the disease mechanisms.



Cystinosis-associated myopathy: Impact of musclin gene therapy and exercise



Maren Leifheit-Nestler, PhD, *Principal Investigator*
Malgorzata Szaroszyk, PhD, *Co-Principal Investigator*
Dieter Haffner, MD, *Co-Principal Investigator*
HANNOVER MEDICAL SCHOOL, GERMANY



OBJECTIVE/RATIONALE:

Cystinosis-associated myopathy is a frequent complication in children and adults suffering from nephropathic cystinosis. The direct association between cystinosis and muscle wasting has not yet been adequately investigated and innovative, effective and preventive therapies are of utmost importance. We recently identified that the skeletal muscle-derived myokine musclin (encoded by osteocrin, OSTN) is reduced in wasting muscles from Ctns-/- mice, which was associated with the induction of cachectic genes suggesting a causative role of musclin deficiency in the pathogenesis of cystinosis-associated myopathy. Interestingly, preclinical studies have shown that musclin can be stimulated by exercise, thereby improving muscle strength in mice. Therefore, we propose that re-induction of musclin in cystinosis restores muscle strength thereby improving cystinosis-associated myopathy.

PROJECT DESCRIPTION:

In this study, we propose to investigate whether a therapeutic re-induction of musclin synthesis in Ctns-/- mice via AAV (adeno-associated virus) based gene therapy can mitigate pathological muscle loss in progressive cystinosis-associated myopathy and improve muscle strength, structure and function. By targeting gene therapy with AAV-Ostn, we expect to improve muscle health and thereby an important cystinosis-associated comorbidity. In addition, we will evaluate if exercise in Ctns-/- mice stimulates musclin synthesis in skeletal muscles thereby reducing myopathy and enhancing physical endurance. As an extension to transcriptional, biochemical and histological analyses of skeletal muscles und kidney function, we also want to assess muscle strength and function by measuring grip strength, tetanic muscle strength, fatigue and endurance capacity in vivo. Finally, we will investigate underlying molecular pathways of musclin-mediated improvement of muscle strength, structure and function in Ctns-/- mice, with the focus on mitochondrial biogenesis, to generate preliminary data and thus a working hypothesis for future specific studies.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The proposed studies address directly the goal of the CRF to find treatments to improve life for cystinosis patients. Data obtained in this project will investigate for the first time the role of musclin in cystinosis-associated myopathy and draw attention to a promising new biomarker that will assess muscle health. At best, musclin could be used as a therapy to counteract muscle wasting and improve muscle strength and overall quality of life with cystinosis.

ANTICIPATED OUTCOME:

Cystinosis patients present with progressive muscle weakness, impaired grip strength and muscle atrophy despite adequate nutrition, which markedly impairs the quality of life. Our central hypothesis is that re-induction of musclin restores muscle strength and overall muscle health and thereby improves myopathy in cystinosis. We propose to investigate if a re-expression of musclin by AAV-based gene therapy or exercise regenerate muscle strength and ameliorates cystinosis associated myopathy. Of note, should our hypothesis be confirmed, musclin therapy would be a promising intervention to improve muscle health and thereby overall quality of life and psychosocial rehabilitation in cystinosis patients.

Investigating the degradation mechanism of cystinosis mutant

Ming Li, PhD, *Principal Investigator*
Jacob Kitzman, PhD, *Co-Principal Investigator*
UNIVERSITY OF MICHIGAN

OBJECTIVE/RATIONALE:

While some view it as an "overkill" for grocery stores to discard expired food that is still consumable, a parallel scenario occurs within our cell, where a stringent protein quality control (QC) system occasionally exhibits a tendency to "overkill" newly synthesized proteins. In certain cystinosis patients with genetic mutations, their cystinosin undergoes premature destruction despite its functional status. Investigating this QC system holds the potential to prevent untimely cystinosin degradation in patients, paving the way for innovative treatment strategies.

PROJECT DESCRIPTION:

Aim 1: Our initial goal is to further characterize fast-degrading CTNS mutants. Employing a low-level expression system, we will screen documented mutants from the ClinVar database and unstable mutants identified by Dr. Liang Feng's laboratory.

Aim 2: The second objective is to identify the specific E3 ubiquitin ligases responsible for ubiquitinating the fast-degrading cystinosis mutants. Once these ligases are identified, our overarching goal is to develop small-molecule inhibitors targeting them. These inhibitors may hold the potential to serve as the basis for a novel treatment strategy by stabilizing cystinosis mutants.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Our research aims to unveil a novel mechanism contributing to the pathogenesis of cystinosis. We posit that the premature degradation of specific cystinosin mutants may result from an "overkill" triggered by the protein quality control system. Identifying methods to inhibit this quality control system could emerge as an innovative strategy for treating cystinosis.

ANTICIPATED OUTCOME:

Our study aims to illustrate the involvement of protein quality control in the pathogenesis of cystinosis. Additionally, we will pinpoint the machinery responsible for the premature degradation of cystinosis mutants and unravel their underlying mechanisms.

RECENTLY PUBLISHED STUDIES

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.

scientific reports 2023

Pierre Courtoy, MD, PhD, and Christophe Pierreux, PhD

de Duve Institute & Université Catholique de Louvain, Brussels, Belgium

"Dietary supplementation of cystinotic mice by lysine inhibits the megalin pathway and decreases kidney cystine content."

In this recently published article in the journal Scientific Reports, CRF-funded researchers further explore the role of the protein megalin. Megalin is an important protein which plays a critical role in endocytosis and molecular transport. Previous research has shown that removal of megalin in the mouse model of cystinosis eliminates cystine accumulation in the kidney. Therefore, researchers focused on the potential inhibition of megalin through a very specific diet modification which included elevated levels of two dibasic amino-acids (dAAs). When compared to a control diet, cystinotic mice with the experimental dAAs diet showed significantly decreased kidney cystine levels. The research suggests that prolonged dietary-based manipulation of the megalin pathway in kidneys is feasible, well-tolerated, and can be effective in reducing renal cystine accumulation. However, while similar preliminary experiments in a rat model of cystinosis provided similar benefits as it relates to kidney cystine accumulation, the diet manipulation in the rat model resulted in further deterioration of the proximal tubular cells leading to more severe Faconi syndrome.

frontiers 2024

Giusi Prencipe, PhD

Laboratory of Rheumatology, Ospedale Pediatrico Bambino Gesù, Rome, Italy

"Nlrp2 deletion ameliorates kidney damage in a mouse model of cystinosis."

There remains some mystery behind the exact mechanisms of the proximal tubule damage that begins essentially at birth in children with cystinosis. This damage results in the development of Fanconi syndrome characterized by nutrient loss, poor growth and extreme thirst/excessive urination among other issues. In this CRF-funded study published in the journal Frontiers in Immunology, Italian researchers further investigated the role of inflammation as it relates to disease progression in the mouse model of the disease. The Nlrp2 gene plays a critical role in the body's cellular-level inflammatory response and previous work has documented this in cystinotic human proximal tubular cells. The results of this study showed that cystinotic mice, which also had the Nlrp2 gene suppressed, had markedly improved outcomes as it related to kidney function and disease progression. The results suggest that potential new drugs or other treatments which target inflammation via Nlrp2 could provide future promise.

To read and/or download the articles published, go to:

WWW.CYSTINOSISRESEARCH.ORG/PUBLISHED-STUDIES

THE IMPACT *of* CRF RESEARCH

AREAS OF RESEARCH FOCUS & GRANTS AWARDED SINCE 2003

SINCE 2003, THE CYSTINOSIS RESEARCH FOUNDATION HAS RAISED AND COMMITTED MORE THAN $70 MILLION FOR CYSTINOSIS RESEARCH, MAKING THE CRF THE LARGEST PROVIDER OF GRANTS FOR CYSTINOSIS RESEARCH IN THE WORLD. OUR DEDICATED RESEARCHERS AND SCIENTISTS ARE WORKING IN 13 COUNTRIES AROUND THE WORLD TO FIND BETTER TREATMENTS AND A CURE FOR CYSTINOSIS.

CLICK BELOW TO SEE EACH AREA OF RESEARCH FOCUS & GRANTS AWARDED IN DETAIL:

WWW.CYSTINOSISRESEARCH.ORG/IMPACT

Cystine Measurement and Cysteamine Toxicity	10 GRANTS
Cellular and/or Molecular Studies of the Pathogenesis of Cystinosis	65 GRANTS
Stem Cells and Gene Therapy: Bone Marrow Stem Cells, Induced Pluripotent Stem Cells, Gene Therapy and Gene Editing	34 GRANTS
New Drug Discovery Cysteamine, New Medications and Devices	32 GRANTS
Neurological	17 GRANTS
Eye-Corneal Cystinosis Research	11 GRANTS
Kidney Research	26 GRANTS
Thyroid	1 GRANT

CONTINUED ON NEXT PAGE >>

THE IMPACT *of* CRF RESEARCH

AREAS OF RESEARCH FOCUS & GRANTS AWARDED SINCE 2003

<< CONTINUED

Skin, Muscle and Bone	*20 GRANTS*
Molecular Study of Cystinosis in the Yeast Model	*3 GRANTS*
Genetic Analysis of Cystinosis	*5 GRANTS*
Cure Cystinosis International Registry (CCIR)	*1 GRANT*
Rat Model for Cystinosis	*4 GRANTS*
Lab Equipment for Cystinosis	*9 GRANTS*

CLICK TO SEE EACH AREA OF RESEARCH FOCUS & GRANTS AWARDED IN DETAIL: *WWW.CYSTINOSISRESEARCH.ORG/IMPACT*

SUMMER 2024

FAMILY STORIES

COMMUNITY FUNDRAISING

FROM HERE

DONATE

WE CAN SEE A CURE


baby einstein
ASE RETURN

By Nick and Karalee Zimmerman, Stella Sol's parents
RIVER FALLS, WISCONSIN

Our Light TO THE WORLD

February 26, 2023: A beautiful baby is peacefully born at home as the sun rose and unsurprisingly, she is later named Stella Sol—a true light to the world. Instantly in that moment, as a mother and father, you start imagining the future for your child – a future of love, health, and happiness – and you hope for a life of ease for them. And as a mom or dad you will do anything in your power to make that happen.

Fast forward nine months and see us three sitting in a hospital room, staring at our beautiful light hooked up to wires and machines, and after several weeks still having no answers. Nine months of bliss was quickly flushed away by heartbreak and sadness for the life we were hearing our daughter had in store. Any future we once dreamt of for our daughter and family crushed and truly life went blank, and all light went dark.

This is Stella's journey, and our journey as her mother and father.

Stella's first nine months of life were incredible, and dare I say... incredibly normal. She was a happy, chubby baby who loved her mama and dada and lots of nursing, which makes a lot of sense now. She hit all her weight benchmarks and milestones on time if not early. Frankly, she was the complete opposite of failure to thrive – this girl was thriving!

As Thanksgiving approached, so too did her sickness. But her sickness would come and go, leaving us as mom and dad completely perplexed but nowhere near panicking.

Panic set in the weekend after Thanksgiving as she was no longer thriving, nor was she our vibrant Stella Sol we knew. She spent the whole weekend crying in agony, so we knew it was time to get her checked. Through the first few visits we got no answers other than constipation, dehydration, and some normal sickness. After multiple stops and multiple hospitals over the course of a week, we were admitted into the ER at Children's. This is where darkness truly crept in. Stella needed IV's, heart monitors, spinal taps, catheters and more. We fought through a seizure-like episode that left us truly thinking we were about to see Stella for the last time on earth. Darkness clouded every day, hour, minute and second as fear and confusion swarmed us.

HOW COULD OUR PERFECTLY HEALTHY SUNSHINE GIRL BE SO SICK?

Throughout our first two-week stay in the hospital, a few conditions were ruled out, but nothing was learned of what it actually was. Constant fussiness continued while she received infusion after infusion of electrolytes, yet her levels were not normalizing.

Due to Stella's ability to thrive for nine months with cystinosis, it had nephrologists puzzled. We were told it likely was merely an Acute Kidney Injury—oh, →

↳ wouldn't that have been nice. A few days later another

nephrologist came in debunking the AKI theory and suggesting we test for a thing called cystinosis.

Cystinosis? We had never heard of this besides preliminary google searches of Stella's symptoms. So, mom and dad quickly became Google doctors, and there we sat in our hospital room reading words and phrases like "complete kidney failure by 10", "transplants", "blindness" and "terminal".

After feeling every imaginable emotion and praying the results would be negative for cystinosis, we were discharged with a very regimented routine of oral supplements that of course she hated and barely tolerated. Three days later we went back to the ER for another sickness and what we didn't know would be another two weeks stay in the hospital.

Fast forward to December 21st. the first day of winter, the day of diagnosis and G-tube surgery, and the darkest day of the year – quite literally and figuratively. This was the darkest day of the year and our lives. There we sat in our hospital room realizing our entire life, plan, future, is nothing without Stella. We felt as though we were the ones fighting for our life. Parents are supposed to be able to protect their children and keep them safe. But we were powerless to cystinosis.

Twenty-four hours later post G-tube and diagnosis, we were finally headed home, just in time for Stella's first Christmas. So, we packed up our hospital room and mini-Christmas tree and got out of there! Once we arrived home the emotion was uncontrollable... finally, we were home. We embraced as one in the kitchen and emotion overwhelmed us to tears.

The next few months were a blur between puking, sickness, supplements, and doctor appointments –coupled with the realization of what new life was. But, as the months went on, we began to settle into a new routine of citrates and Cystagon, but most importantly...we began seeing the light. Not only for our life but we were beginning to see our Light again—that is the Stella girl we knew.

We accepted. We adapted. We found joy in the tiniest of moments because at that time that is literally all we had. Although a life-changing diagnosis for Stella and our family, there is still so much joy to be had. Yes, Stella has cystinosis, but she is not defined by it.

A big part of this newfound positivity came from the CRF Day of Hope conference. I'm sure all the readers can close their eyes and be transported back to remembering their first Day of Hope. Being around those who truly "get it" was an incredibly refreshing feeling.

Although life is different, we cling to hope. Hope for a cure, hope for Stella's future to be full of love, health, and happiness, even hope for our future as her mother and father because we have our journey too. But really this is her story, and we are part of it.

So, while we wait for the cure that is hopefully coming soon, you will find us trusting God's plan, living life to the fullest, clinging to the joy, and showing Stella she can do anything... even change the world with all the light she brings to it.

And she will change the world.

OUR LIGHT TO THE WORLD

trusting God's plan
living life to the fullest
clinging to the joy
showing Stella she can change the world
with all the light she brings to it

It Takes A Village

our whole family is thriving

Because of LaLa

By Katie Kanupke, Josie's mom
CROWN POINT, INDIANA

My sister, Laura Christopherson, "LaLa" to my children, has been by my side since I was nineteen months old. She is my best friend who, very often, gets mistaken for my twin. Since the birth of my son, Brendan (without cystinosis) Laura has been a source of unwavering support. After her beautiful daughter Ella, was born in 2015, Brendan had a new best buddy too. We were always on the go, driving an hour plus to meet up every weekend or have a sleepover.

In February of 2017, Josie was born, and I remember that summer as my happiest. After an increasingly worrisome fall, it became apparent that something was not right with Josie. She was not gaining weight, she was gulping bathwater, she was constipated, and had a myriad of symptoms until she was diagnosed with cystinosis in December 2017.

LaLa was there every step of the way-taking my daily phone calls with the newest possible diagnosis, she helped keep Brendan's daily routine as normal as could be, all while raising her own daughter and keeping a full-time job. She was and continues to be - six years later - the only other caregiver for Josie besides Tom and me. She swiftly jumped in with no hesitation to learn everything about this disease and administer meds. Because of LaLa, our first fundraiser for CRF was held in her own home, with an outpouring of support from some people we didn't even know. LaLa has been the backbone of every fundraising event since.

In 2021, Laura, her husband Eric, and Ella moved from Illinois to be within minutes of us in our new home in northwest Indiana. In 2022, Laura was able to secure a kindergarten position at Josie's school and was her math teacher. Josie was having a hard time adjusting to the full-time curriculum and was struggling with her behavior. Once she was able to see LaLa every day, there was a significant change. Laura advocated for her with other teachers, explaining the disease, reminding them about her need for extra water refills and potty breaks, and was there to help the school nurse with any questions. Because of LaLa, Josie finished her first year strong.

She often encourages Tom and me to go away for a night or two to reconnect and relax. We never have to worry about Josie overheating, missing doses of Procysbi®, or getting her G-tube clogged and having to come home early (a clog has happened, and she handled it liked a champ).

Last summer we were able to take a weekend vacation to Colorado and had a wonderful time. I struggle with the guilt of Laura providing the around the clock medications, food doses, and the lack of sleep she will encounter, so I try not to ask her too often, but I know she doesn't mind.

Her reassurance, compassion and love for our daughter is unmatched. Because of LaLa, our whole family is thriving.


RANDY'S
DONUTS

Cystinosis doesn't define us.

By Holt Grier, 18 years old
HUNTERSVILLE, NORTH CAROLINA

During the first years I had cystinosis, I never thought too much of it. It was just another thing I had to do, you know? Just like making my bed or cleaning my room, cystinosis just felt like another random part of my life that I had to deal with. "Make sure to take your pills. Eat so you don't get sick!" These phrases have been bolted in my mind just like the other stereotypical suburban kid quotes such as, "Did you remember to make your bed?" and "Can you do the dishes for me, honey?"

But now that I've gotten older, and since I'm about to graduate high school, I've noticed a lot of differences I have from my peers. For example, I remember seeing how strong everyone else was, not realizing muscle atrophy was taking such a toll on me. I also remember feeling very self-conscious about being so pale. I'm not gonna lie, thinking this way sucks. I don't want to feel bad about my body. And it sure doesn't help when people who have no idea what you're going through tease or belittle you. Though when I went to this year's CRF Day of Hope cystinosis conference, something felt different.

I met some awesome people at the conference. And what made this year's visit more special than previous years was the fact that, for the first time, I noticed that the people there looked similar to me. Their muscles were atrophying, they were pale, etc. Even though these people have these qualities, they don't let them set them back. This made me feel welcomed, less isolated and inspired. I've met people with cystinosis who are police officers, gym bros, and so many other people that don't let too many crystals in their body prevent them from doing what they love, or effect how they interact with others. Cystinosis doesn't define us.

I'm still struggling with cystinosis, and myself for that matter. But knowing that I have other people by my side, and a group Snapchat that goes off every five seconds full of kids with cystinosis, makes me feel a lot better. I know I will get through this, and I know that we will all get through this.

To the community of Jenna & Patrick's Foundation of Hope supporters:

By Teresa & Kevin Partington

SACRAMENTO, CALIFORNIA

Jenna and Patrick had a successful first year away at college, and Kevin and I enjoyed a year of visits to San Francisco and Moscow, Idaho, to see how they were faring. We prepared their medications monthly and put them in the mail (with cookies!) or delivered them on our visits. They both plan to return to their respective universities as soon as possible, but it is time for each of them to receive a kidney transplant.

Last month, I dropped Jenna off to visit her brother at San Francisco State University for the weekend. I said to her as she got out of the car (only partly in jest): "Jenna, a 'light' discussion with your brother would be about which of you will have a transplant first and which of you will be getting your Dad's kidney if he's approved to donate." It's such an absurd and heavy discussion to ask 19-year-old siblings to have, it felt best to handle it with humor! Three days later, I learned that Jenna would like to go first, and because of that, she'd receive Kevin's kidney if he is approved to donate.

The kidney is one of the first organs affected by the genetic disease cystinosis. Cystinosis causes cells to die, crystalize, and stick to the inside of all body tissues: muscle, spleen, corneas, brain… and kidneys. We knew that, at some point, a kidney transplant would be inevitable for Patrick and Jenna. For both of them, it's time.

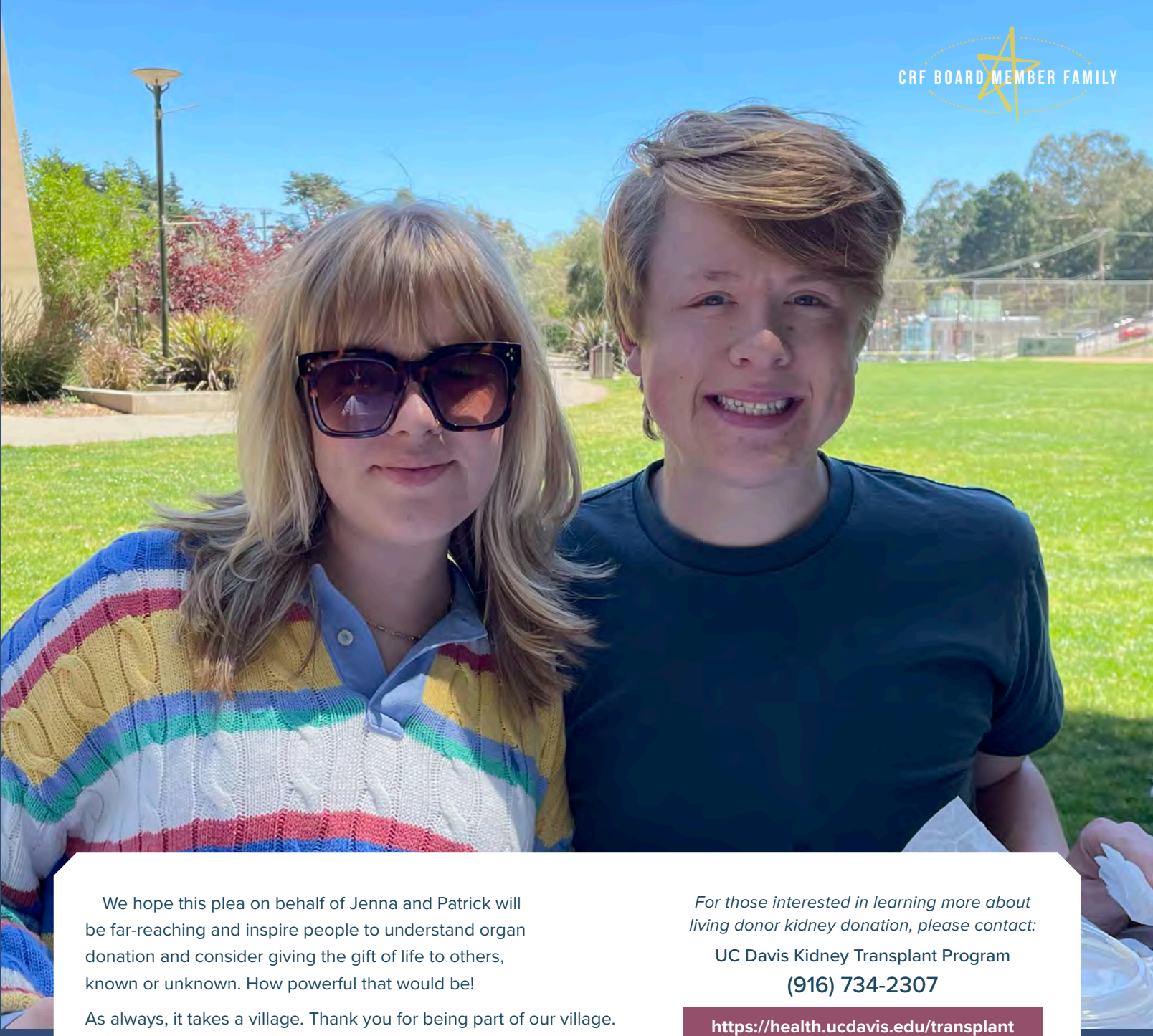
For nearly 19 years, we have shared Jenna and Patrick's health story with you, our incredible community of friends and family. We will never be able to repay our debt of gratitude for your support of Jenna & Patrick's Foundation of Hope and our family. Even so, we find ourselves vulnerable to asking for a whole new kind of help.

Kidney transplants have become a reliable treatment for people like our children who have reached end-stage renal failure. Before dialysis becomes necessary, their doctor has recommended beginning the process of kidney transplants for Patrick and Jenna. Decades of research show that a kidney transplant from a living donor is the superior option. Living donor kidneys last longer, and transplants are planned and scheduled, eliminating the long wait and emergent process often involved in receiving a deceased donor organ. My cancer history eliminates me as a potential living donor. Kevin is currently undergoing evaluation.

With this letter, we are prayerfully sharing Jenna and Patrick's need for a living donor and asking for your positive thoughts as they embark on this part of their cystinosis journey.

It is awkward to need the organs of others. Whether it's a deceased donor or a living donor, and whether it's my husband or my friend, it's a frightening, vulnerable, and desperate position to find oneself in. To think that in our family of four, three may undergo major abdominal surgery in the next year…it's a lot to process!

Below is contact information for the UC Davis Organ Donor/Kidney Transplant program and a web address for their informative website. Ilf you or someone you know would like to learn more about donating, please contact UC Davis directly, as HIPPA laws protect potential donors. Our family will have no access to the names or health information of those who inquire about living kidney donation. →



We hope this plea on behalf of Jenna and Patrick will be far-reaching and inspire people to understand organ donation and consider giving the gift of life to others, known or unknown. How powerful that would be!

As always, it takes a village. Thank you for being part of our village.

For those interested in learning more about living donor kidney donation, please contact:

UC Davis Kidney Transplant Program

(916) 734-2307

https://health.ucdavis.edu/transplant

When a person has cystinosis, the kidneys are the first organs to be severely affected. Most people with cystinosis need a kidney transplant in their teen years. We know several people in our community who are currently in need of a living donor. If you are interested in donating your kidney to someone in our community, we would be forever grateful for your gift of life.

Donating a kidney to a stranger can help someone live a longer, healthier life. Over 100,000 people are in need of a kidney transplant. Roughly 6,000 people donate their kidney every year. Less than 5% of those 6,000 living kidney donors donate to someone that they do not know; this type of donor is known as a Good Samaritan donor and there are multiple paths for Good Samaritans to go down if they wish to donate. If you want to learn more about kidney donation, the family voucher program or how to start a kidney chain click on the National Kidney Registry link for more information.

https://www.kidneyregistry.org/for-donors/i-want-to-help-a-stranger-in-need-of-a-kidney/

FROM HERE, WE CAN SEE A CURE.

DONATE

TOGETHER, WE ARE one

COMM UNITY FUND RAISING

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

1 PURPOSE. 1 JOURNEY. 1 CURE.

Rare Disease Day – February 29, 2024

RARE DISEASE DAY®

RARE DISEASE DAY – THANK YOU

With your generous support, we were able to continue giving a voice to the voiceless this Rare Disease Day 2024! We thank you for continuing to show your commitment to our small but mighty community through your generous donations raising more than $7,310. Every dollar goes directly to fund research for better treatments and a cure for cystinosis.

Without you, we would not be where we are today, but there is much more to be done. While we wait for the stem cell trial to be a treatment reality for all people with cystinosis, we continue to seek better treatments for our children and adults with cystinosis. We thank you for remaining dedicated to this journey; together we are changing lives!

RAISED over $7,310

The McAllister Family – Ashley, Duncan, Graham, and Isla – Oklahoma City, Oklahoma

1ST ANNUAL

THE FIRST ANNUAL CRF PICKLEBALL TOURNAMENT

The McAllister family recently organized a fundraising tournament for CRF to raise money in honor of their daughter Isla and in support of cystinosis research. The unique Pickleball tournament was held at the Chicken N Pickle in Oklahoma City. Their community of family and friends turned out to support Isla and learn more about the challenges of living with cystinosis. The venue facility space was limited, but the enthusiasm was contagious as the participants enjoyed the challenge of Pickleball and the festive atmosphere of fundraising activities. At the end of the event, more than $6,350 was raised for cystinosis research! Thank you to the McAllister family for hosting the first Pickleball tournament for CRF. We are grateful for your commitment and support of our mission to fund research for better treatments and a cure for cystinosis.

RAISED over $6,350

The Hartz Family – Lauren, Jimmy, Landon, and Jordan – Pittsburgh, Pennsylvania

LOTS OF LOVE FOR LANDON GOLF OUTING

The 12th Annual Lots of Love for Landon Charity Golf Outing was held on May 31 at the Black Hawk Golf Course in honor of Landon Hartz. The sold-out field of 229 golfers took over two courses and enjoyed a perfect day of golf competition and camaraderie. Following the tournament, the enthusiastic crowd shared dinner and the opportunity to bid on a wide array of auction items to raise over $40,000 this year, which is an all-time high. Since 2012, the golf outing has contributed $260,000 to support cystinosis research! Thank you to the dedicated volunteers, amazing golfers, generous donors, and the organizing committee of Jason Hartz, Brad Hamilton, Jason Whitfield, Derek Even, Josh Larrow, and Jimmy Hartz, who worked diligently to ensure the tournament's success. We are grateful to Lauren, Jimmy, their family, and friends for their dedication and commitment to CRF, thank you. Together we are helping to improve the lives of those with cystinosis through research!

RAISED over $40,000

12TH ANNUAL

The Emerson Family – Jill, Clay, and Brooke – Hammonton, New Jersey

FISHING FOR BROOKE'S CURE

The Ninth Annual Fishing for Brooke's Cure was wrapped up as the anglers, who fished all day, caught a total of 518 fish making this their best tournament yet! Generous friends and family made donations which amounted to more than $40,000, and a generous donor matched those donations for a fundraising total of $87,200!

RAISED $87,200

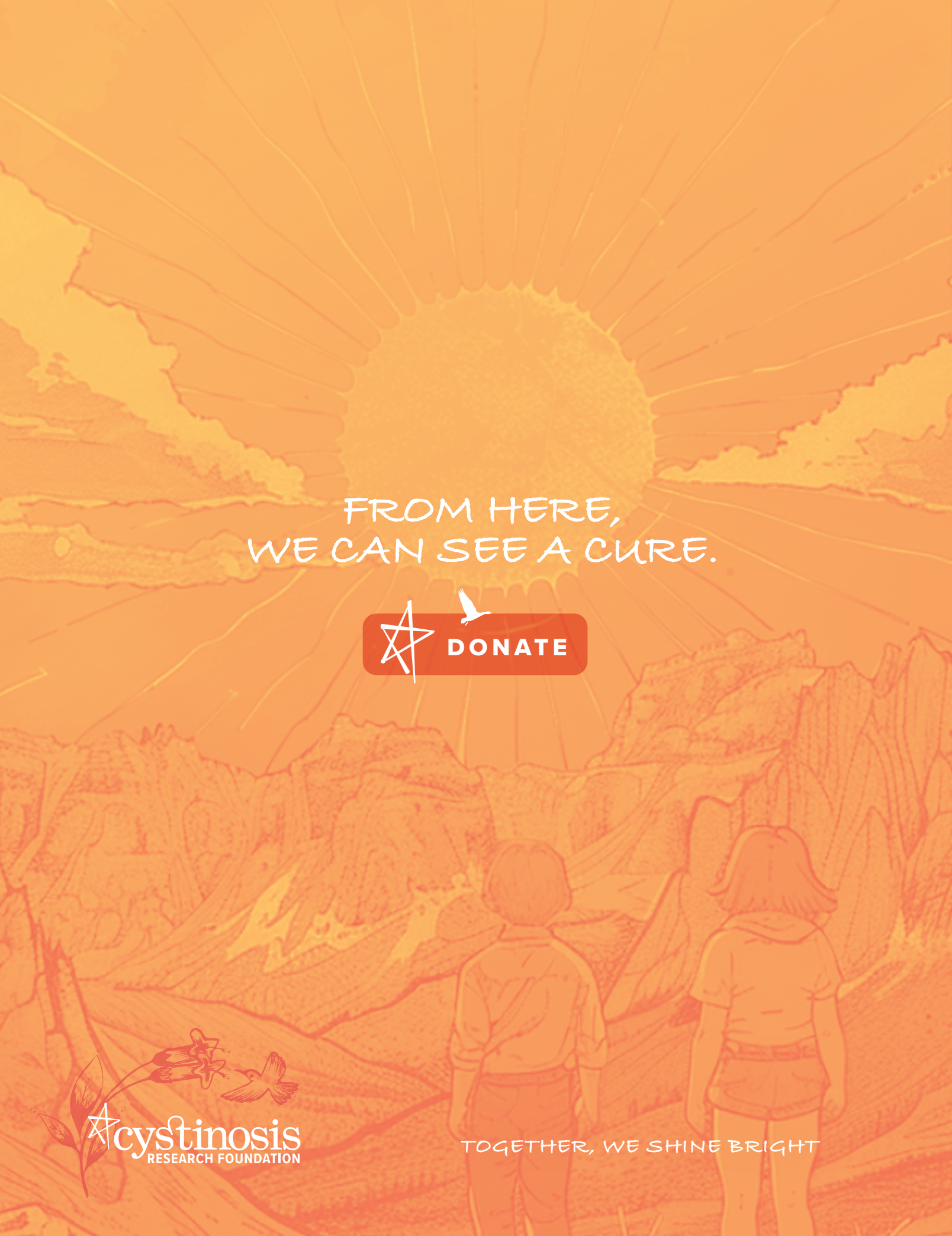
The annual fishing fundraiser began in 2016, and since then has raised $297,000 for cystinosis research in honor of Brooke. Thank you to the Emerson family, and the amazing anglers for their unwavering support and commitment to raise money to support life-changing research for all children and adults with cystinosis!

9TH ANNUAL

The Lanken Bonneau Family – Vanessa, Sylvan, and Fera – Montreal, Québec, Canada

A NOT SO SILENT NIGHT CHRISTMAS 2023 FUNDRAISER

This past December, A Not So Silent Night – A family Christmas with the Wainwrights / McGarrigles raised money for cystinosis research. The extended family gathered at the Olympia Theatre in Montreal and shared seasonal songs to a sold-out crowd. Sylvan and Vanessa, wish to thank Martha, Rufus, and the rest of the family, as well as the many guest singers and volunteers who gave their time and talent, resulting in $15,000 being raised in honor of Fera for the Canadian Cystinosis Research Foundation through the Aqueduct Foundation. Thank you to the Lanken Bonneau Family and their friends for their dedication and commitment to CRF as our Canadian partners to support cystinosis research. Together, we are helping fund research worldwide for improved treatments and a cure for cystinosis!


FROM HERE,
WE CAN SEE A CURE.
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RESEARCH FOUNDATION
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