cystinosis magazine

TOGETHER WE SHINE BRIGHT

The Wish is alive

FOR FRIENDS AND SUPPORTERS OF THE CYSTINOSIS RESEARCH FOUNDATION

SPRING 2022

cystinosis RESEARCH FOUNDATION | TOGETHER WE SHINE BRIGHT

To have my disease go away forever

2003

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

2013

- FDA approval in 2013 for a delayed-release form of cysteamine. CRF funded every early clinical study that led to the discovery of the delayed-release form of the medication 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 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.
- **Road to a cure!** Today, CRF is the largest fund provider of grants for cystinosis research in the world, issuing 213 grants in 12 countries.
- CRF has raised over $63 million, with 100% of your donations going to support cystinosis research. CRF's efforts have changed the course of cystinosis and given new energy to its investigators and scientists.
- CRF's commitment to research has given hope and promise to the global community of cystinosis patients and their families.

CYSTINOSIS CURESEARCH FOUNDATION

As we look back on almost 20 years of relentlessly and tirelessly fundraising for a cure, we are overwhelmed with gratitude for our community. To our donors, thank you for your endless support and generosity. To our researchers, thank you for your dedication to improving the lives of those with cystinosis. To the first five patients in the clinical trial, thank you for your courage and selflessness. Together, We Shine Bright!

SPRING 2022

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

The entire cost of *Cystinosis Magazine* is underwritten by friends of the Cystinosis Research Foundation.

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The mission of the Cystinosis Research Foundation is to find better treatments and a cure for cystinosis by supporting bench, clinical and translational research. Since 2003, CRF has raised over $63 million for cystinosis research in an effort to find a cure.

cystinosis RESEARCH FOUNDATION

WELCOME

RESEARCH UPDATES

ANNOUNCEMENTS

FAMILY STORIES

CYSTINOSIS MAGAZINE IS A PUBLICATION OF THE CYSTINOSIS RESEARCH FOUNDATION

What is cystinosis?

Cystinosis is a rare, inherited, metabolic disease that is characterized by the abnormal accumulation of the amino acid cystine in every cell in the body. Build-up of cystine in the cells eventually destroys all major organs of the body, including the kidneys, liver, eyes, muscles, bone marrow, thyroid and brain. Medication is available to control some of the symptoms of this terrible disease, but cystinosis remains incurable. Cystinosis affects approximately 600 people, mostly children, in North America, and about 2,000 worldwide.

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

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

Our story

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

Today, CRF is the largest fund provider of grants for cystinosis research in the world, issuing 213 grants in 12 countries.

CRF has raised more than $63 million, with 100% of your donations going to support cystinosis research. CRF's efforts have changed the course of cystinosis and given new energy to its investigators and scientists. CRF's commitment to research has given hope and promise to the global community of cystinosis patients and their families.

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cystinosis RESEARCH FOUNDATION
TOGETHER WE SHINE BRIGHT

The Wish is alive

SPRING 2022

NATALIE'S WISH COMES TRUE

It is with a grateful heart that we share the most glorious news about Natalie! On Tuesday, March 29, 2022, Natalie was the fifth and first female cystinosis patient to receive the stem cell and gene therapy treatment developed by Stéphanie Cherqui, PhD, at University of California, San Diego.

The months preceding the transplant were intense and fraught with uncertainty and medical challenges. Although at times we were overwhelmed by the sheer volume of tests conducted prior to being approved for transplant, tests that included biopsies, copious blood draws, eye exams, neurological evaluations and more, the tests were another step towards realizing Natalie's wish made 19 years ago "to have my disease go away forever."

It was a relief and a blessing when Natalie was given the go-ahead to be the fifth patient in the stem cell and gene therapy trial. Although we had read all of the details about the trial and signed consents confirming we were aware of the procedures and commitment, we were still astounded by the preparation required prior to transplant.

On March 21, the day before Natalie entered the hospital, she had a Peripherally Inserted Central Catheter (PICC) line placed in her arm. The PICC line has a thin tube that runs through a vein into a larger vein in the body which is used for blood draws, infusions and for the delivery of the amazing, repaired stem cells.

On the third day in the hospital, Natalie received four days of eight rounds of chemotherapy to destroy the old, cystinosis cells in her body and to make room for the transplanted cells. Natalie's immune system was wiped out and she suffered the side effects of chemo for over a week, however, once the transplanted cells started to multiply and engraft, she started to feel better.

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On March 29, the transplant day finally arrived. We witnessed the repaired cells, no longer carrying the CTNS gene, delivered to the hospital room in two small bags containing millions of cells. The cells were gently pushed through the PICC line, one bag at a time, until all of the new cells were transplanted.

Watching the cells return to Natalie looked so simple, but we were acutely aware of what it took to create those repaired cells. The complicated and long road to make those repaired cells include a dedicated and brilliant researcher, Dr. Stéphanie Cherqui, the miracle of gene repair, science and medicine, the support of our family and friends, and millions of dollars in research money from generous donors. As she was being transplanted, I relived the day Natalie made her wish in 2003 and I was overwhelmed with emotion. The impact of her wish, made so long ago, was now a reality. It was her wish but it was the wish heard around the world. Soon the treatment will be a reality for all of those with cystinosis.

Natalie was in the hospital for 25 days and was ready and eager to go home. It was a beautiful sunny afternoon which reminded us how fortunate we were and how much we have to be thankful for. Natalie is recovering well. She takes long walks every day and also sleeps long hours! Healing is her job for the next few months. She is immunosuppressed so she is very cautious and cannot go out in crowded public spaces for a couple more months. Masks are a requirement for all of us when we are around her – fortunately, we are used to them!

Natalie is an independent, young woman with her own life and career but when you are a parent of a child with a rare disease, and you have worried, fought, researched and prayed for your child's care and health for the entirety of their life, you cannot easily let go. I often say "we" when I talk about Natalie's experiences but it is really all "her" – she is the fierce one, the fighter, the woman with grit, the person who kept hope alive even when I know life was hard and challenging

for her. When Natalie received the stem cell treatment, she was relaxed and peaceful. For me, I could finally exhale; I felt a sense of relief and surrender, we had reached the finish line. Now, it is up to Natalie's own repaired cells to heal her body and repair the damage caused by cystinosis.

How can we ever thank Dr. Cherqui and all of you for the love, support, financial commitment, and prayers throughout the years? You have given Natalie the gift of a new life, a life free of cystinosis. In the hospital on the day of the transplant, the nurse gave Natalie a shirt that read, "Happy birthday to me." Yes, March 29, 2022, is Natalie's second birthday, the day she was given a chance to live a long and healthy life – a rebirth, a miracle!

NATALIE'S WISH EVENT – THE MONTH OF APRIL

We are incredibly grateful to all of you who donated to the Natalie's Wish fundraiser held throughout the month of April. We created a heartwarming video, "A Wish Granted" featuring the Partington family and their journey with cystinosis. The video can be viewed on our website at www.cystinosisresearch.org/natalies-wish-2022. Once again, because of the pandemic, we were forced to cancel the in-person event so we pivoted to a virtual fundraiser and raised an astounding $1,354,521 for cystinosis research. Every dollar you donate goes directly to research to fund the best and the brightest researchers in the world. Thank you for your generosity and steadfast commitment to research.

GATHERING AGAIN - THE DAY OF HOPE FAMILY CONFERENCE

The highlight of 2022 will most certainly be the recent Cystinosis Research Foundation (CRF) family conference held March 31-April 2 because we were together again, in-person to celebrate the cystinosis community and to learn more about the research projects CRF funds. We had 36 families attend the conference from four countries. We had 11 researchers present fascinating talks at the conference which included presentations about muscle wasting, kidney health, a novel treatment for ocular cystinosis, artificial intelligence and drug libraries, stem cells, iPS cells to grow mini kidneys and more! The best part of the weekend was seeing everyone, reconnecting with people, meeting new families and renewing our collective commitment to continue to fund cystinosis research until we have better treatments and a cure. We look forward to 2023 when we will gather again. We recorded many of the presentations which can be found on our website at www.cystinosisresearch.org/day-of-hope-2022.

RESEARCH REMAINS OUR FOCUS - NINE RESEARCH GRANTS AWARDED IN 2021 - $2,152,223

We have built a collaborative, thriving international research community made up of the most talented and committed researchers who have dedicated their careers to our children and adults with cystinosis. Our hope for a brighter future for our children and adults with cystinosis hinges on their discoveries.

CRF is the largest fund provider of cystinosis research in the world. Our research projects have led to new discoveries about cystinosis, new clinical trials and two FDA approvals. CRF has issued 213 multi-year grants, eight extension grants and nine equipment grants. Numerous CRF researchers have received grants from other funding sources, thereby leveraging CRF's initial grant awards. Our strategic approach to research and our emphasis on collaboration has accelerated research and has expanded the field of cystinosis. CRF funded researchers have published 100 articles in prestigious research and medical journals. Our success is a direct result of your support and partnership with us to fund research that will lead to a cure.

CRF has created a continuous cycle of research studies by seeking new research applications twice a year and awarding new grants twice a year. We are pleased to announce that in 2021, we awarded nine new grants totaling $2,152,223. The grants were awarded to researchers in France, Italy, Switzerland and the United States.

CRF RESEARCHERS GIVE US HOPE

We hope you will be as excited as we are to learn more about the exciting research we fund. We have profiled three research teams in this issue of the magazine. The first researcher is Shawn Davidson, PhD, who is an expert on metabolomics. He is developing methods to measure the degree of metabolic correction provided by stem cell transplantation. He will test the effects of multiple drugs and natural substances on the performance of transplanted stem cells. **PAGE 56**

The team of Andrea Del Fattore, PhD, and Giulia Battafarano, PhD, are studying bone defects caused by cystinosis, specifically how cystinosis disrupts the development of healthy bones. The goal is to find and illuminate pathways to treatment that will restore normal bone function. **PAGE 54**

The next two researchers, Pascal Laforêt, MD, PhD, and Hélène Prigent, MD, PhD, are studying how to improve neuromuscular involvement in adults with cystinosis. It is well known that there is potential for muscle complications as patients age and the effects of the disease advances. Drs. Laforêt and Prigent, will study the rate of muscle failure and the long-term consequences of symptoms. **PAGE 58**

THE UCSD STEM CELL AND GENE THERAPY CLINICAL TRIAL

CRF has proudly supported and funded Stéphanie Cherqui, PhD, at UC San Diego for her groundbreaking stem cell and gene therapy work since 2007. CRF has awarded over $6.1 million in grants for her research. The effect of our investment resulted in over $22.7 million in additional grants to Dr. Cherqui from other funding agencies including California Institute for Regenerative Medicine (CIRM) and the National Institutes of Health (NIH). More importantly, the FDA approved a clinical trial for six patients to test Dr. Cherqui's stem cell and gene therapy treatment.

Natalie was the fifth patient to be transplanted and thanks to the courage and bravery of the first four patients, especially Jordan Janz, Jacob Seachord and Tyler Joynt who preceded Natalie and whose transparency and openness about the trial helped make Natalie's experience less stressful and more positive. We thank all five patients for blazing the path to a new treatment that we hope will be the cure for cystinosis or stop the progression of cystinosis. We are pleased to report that all five of the transplanted patients are doing extremely well and remain off oral cysteamine therapy. The genetically repaired cells have engrafted and are doing their job!

Statistically, it is not often that bench research results in an approved FDA trial, however, this small but united cystinosis community is unstoppable and made it their mission to find a cure for cystinosis. We have accomplished so much together and will continue to fund life-saving research.

CYSTINOSIS CURE RESEARCH FOUNDATION

THE EXPANSIVE IMPACT OF CRF RESEARCH

Cystinosis research has an impact on other more prevalent diseases and disorders. Discoveries made by CRF funded researchers are being applied to Friedreich's Ataxia, Danon disease, corneal diseases, kidney diseases and genetic and systemic diseases similar to cystinosis. The success of our research program is a direct result of the leadership and commitment of our CRF Scientific Review Board who work diligently throughout the year reviewing the merits of every research application we receive and recommending only the best and most promising studies for funding. We thank the Scientific Review Board (SRB) for their guidance and dedication to the CRF research program and the cystinosis community. To learn more, visit www.cystinosisresearch.org/leadership.

OUR GRATITUDE RUNS DEEP

We know you will thoroughly enjoy meeting all of the patients and families who shared their amazing and inspiring stories with us in this magazine. You will be introduced to Tyler Joynt, the fourth patient to be transplanted and learn about how the transplant has given him new life and hope. We thank our families and patients for sharing their cystinosis journeys with us. Each story unites us and reminds us how connected we are and how fortunate we are to have each other.

We know that cystinosis impacts us every day so in turn, CRF will relentlessly pursue better treatments every day. The research we fund will result in more breakthroughs, life changing treatments, clinical trials and discoveries in the years to come. Although we have made progress, our job is not done; there is more work to do and with your help and support, we will succeed. We have faced the challenges of cystinosis together, we have overcome obstacles and together we have found a path to better treatments and a cure. We remain resolute in our obligation to help every child and adult with cystinosis.

Our deepest gratitude for your steadfast support of our research program and for your commitment to making Natalie's wish come true. Together we celebrate all our accomplishments because together, we have turned a little girl's wish into a treatment that might be a cure for cystinosis! A remarkable feat by you, our caring, kind, generous and loving cystinosis community.

With heartfelt thanks and gratitude,

Nancy & Jeff

Cystinosis Cure Foundation

A Note from Natalie Stack

Wow, what a year 2022 has been so far! I have a wonderful boyfriend in my life, I just got a new puppy, the beloved show, *This is Us* is ending, and I was the 5th patient to receive a stem cell transplant! For those of you who don't know the show, *This is Us*, the show's message is that everyone is connected in some profound way; a stranger to you may be the person who changes your life forever or may be someone who becomes the most important person in your life. I feel connected to so many of you - you have changed my life for the better.

People who come into your life, come into it for a reason; and that is how I feel about my life. My parents were meant to adopt me, and they have become the most important people in my life. The cystinosis community was meant to be connected, to support each other and love one another through the good, the bad and the ugly. Dr. Stéphanie Cherqui, who was once a stranger in all of our lives, is now the one person who has changed our lives forever. This is our story.

Since the start of 2022, it has been a year of all things medical for me. I began the year with three weeks of daily tests to qualify for the stem cell clinical trial. The daily testing and long drives down to UC San Diego consumed most of my life for the first month of this year but now, five months later, I am recovering from what is certainly the most significant milestone in my entire life.

The testing for the clinical trial included a multitude of tests such as strenuous eye exams, a skin biopsy, mole mapping, an awkward rectal biopsy, grip strength tests, neurological functioning tests and of course multiple blood draws. It was a lot to manage and stressful on my body, but I knew it was what was needed to qualify for the clinical trial. At the end of the three weeks, I had one final procedure - apheresis. My stem cells were collected over the course of two days and taken to UCLA for repair. This was the final stretch before the team would call me to say I was approved (or not) for the clinical trial.

During this time, while I was anxiously waiting, I tried to make the most of the time left before I was admitted to the hospital for an extended period of time. As soon as I heard that I was able to participate in the clinical trial, a flood of emotions came over me. I was happy, relieved, stressed, nervous and fearful all at the same time. There was a period of time when I started to worry about what might happen but realized that I was overthinking things and that the process was completely out of my hands. I choose to embrace each moment and take things one day at a time. This was my time to shine. I had to let go of all the pain and struggles I have had over the years caused by this horrible, rare disease. It was time to let go and leave it up to a higher power.

March 22, 2022 was the day I entered Jacob's Medical Center, 6th floor, Room 634. I had no idea what to expect. The floor was exclusively for Blood and Bone Marrow transplant patients and the floor had purified air and a designated nutrition service just for 6th-floor patients. There was a gym and a beautiful view from the huge windows in each room, a private bathroom and a nice size television. It didn't seem too bad.

The first night I was there I was informed that I had a blood clot in my chest due to the insertion of the PICC line in my arm. I thought to myself, "How could this happen now? What if something bad happens to me? What if I can't do the trial anymore? It has been too long of a journey; this can't be happening". The blood clot issue paused the trial briefly. Needless to say, I was incredibly worried but once I talked to the doctors and they gave the okay to start the chemotherapy one day later, I realized I was overreacting. There were four days of chemotherapy, two sessions a day, for two hours from 4:00 a.m. - 6:00 a.m. and 4:00 p.m. – 6:00 p.m. The actual chemotherapy was easy, but the aftermath was torture.

My new puppy, Wesley

Approximately twelve days after the chemotherapy, the side effects hit me. I was nauseous, weak and had headaches, dry skin, a dry mouth, and severe mucositis. I shaved my head. I had horrible, painful sores in my throat, so I could not eat anything for five days. I could barely drink water and could not swallow my medications. I was on a powerful pain medication every four hours, but the pain did not go away. Not being able to drink enough water and having an excessively dry mouth was torture for me considering my chronic kidney disease and the need for copious amounts of water. I was craving water like never before.

As my blood counts improved, I started to feel better and the mucositis gradually went away. After 25 long days in the hospital, the doctors allowed me to go home! I was thrilled to be home to make my own food and sleep in my own bed! I am currently recovering well at home and taking it one day at a time.

I am so glad that I decided to do this clinical trial for cystinosis. Even though it was scary to do, the possibility that the treatment could save my life makes it all worthwhile. My hope is that I will no longer need to take Procsybi® and that this will be the cure for cystinosis. I hope that one day soon, all of us with cystinosis can receive this treatment and be free of cystinosis. I know we still have a long way to go, but this is the very beginning of what could be something truly miraculous.

I want to thank the cystinosis community and families for being so determined to raise money to find better treatments for this disease. We are at a monumental time for cystinosis and that is because of your true commitment to our community. The generosity, love and passion this community has and their relentless drive to find a cure for cystinosis has shown through every step of the way - I am forever grateful.

Lastly, I want to thank my parents, Dr. Cherqui and her team for making this happen. Dr. Cherqui, thank you for being our shining star. You gave this entire community hope for a cure when we didn't think it was possible.

My parents, especially my mother, have given me a second chance at life. Their fierce commitment and advocacy for me and others with cystinosis are remarkable. I am beyond grateful to my parents for taking their little girl's wish seriously. I will never have the right words to say how much I love them.

Above all, thank each and every one of you for never giving up on my wish - to have my disease go away forever.

Love, Natalie

Cure Cystinosis International Registry

The New CCIR, One Year Later

By Clay Emerson, PhD

CCIR Committee Member and Brooke Emerson's dad

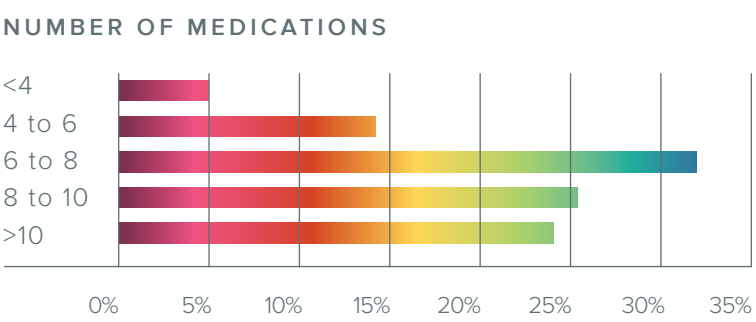
Hammonton, New Jersey, USA

Introduction

The new Cure Cystinosis International Registry (CCIR) was launched in the Spring of 2021. In just the first year, patients from 17 different countries have participated in the registry. With 141 patients and counting, the registry provides a critical link between patients and researchers. Due to the ultra-rare nature of the disease as well as the myriad of complications the disease presents, progress towards improved treatment and an ultimate cure for cystinosis can only be possible with the valuable input from our limited patient community.

Medications

Cystinosis literally affects every cell in the body which leads to a wide variety of disease complications. As a result, the medication regimen for people battling cystinosis is monumental. Most of these medications require adherence to strict round-the-clock dosage timing and often must be taken in a manner so that they do not interfere with other medications. This results in a complex medication schedule. Current data from the CCIR indicates that most patients take more than eight different types of medication throughout the day, with some participants taking as many as 13 different types of medication requiring up to 25 individual doses per day.

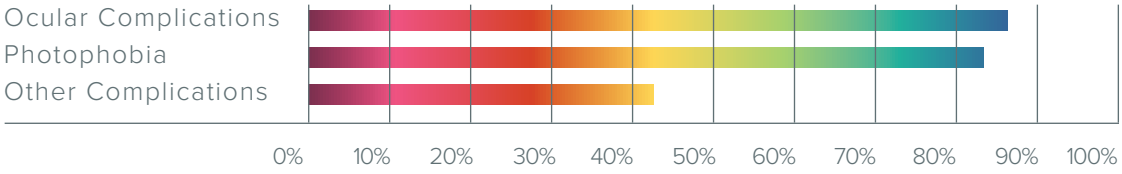


Cure Cystinosis
International Registry

Ocular Complications

Cystinosis impacts the eyes in many ways, however, one of the primary impacts is the formation of cystine crystals in the cornea. The cornea of the eye is somewhat unique as it does not contain blood vessels. Cysteamine is currently the only drug which slows the progression of cystinosis. However, due to the nonvascular nature of the cornea, oral dosing of this drug does not prevent cystine accumulation in the cornea. These cystine crystals are often present and visible by an ophthalmologist by 12-18 months of age. The crystals refract light and lead to extreme sensitivity to light; a condition called photophobia. They also often lead to general eye discomfort and the sensation of a foreign object in the eyes, described by some patients as sandy or gritty feeling. Current treatment requires a rigorous dosing routine of up to hourly administration of eye drops containing an ophthalmic solution of cysteamine. Advancements in the management and treatment of the ocular manifestations of cystinosis are clearly needed. Data from the CCIR illustrates how important medical advancements in this area would be for patients living with cystinosis. Despite current available treatments, almost 90% of patients report many of the classic ocular complications of the disease with almost 90% of responding participants reporting photophobia and another 42% reporting additional issues. These additional issues include dry eyes, blurry vision or trouble focusing, sandy or gritty or foreign body sensation, and eye pain or burning sensation among others.

OCULAR COMPLICATIONS



Conclusion

In just its first year, the new patient registry is already helping to inform researchers and ultimately accelerate the development of better treatments and a cure for cystinosis. The value of the registry will only truly be realized with patient participation. We strongly encourage patients or caregivers to participate in the registry and help identify the needs of patients with cystinosis and accelerate research. The questionnaire takes about 40 minutes to complete and registration is simple. Please visit the CRF website to sign up today!

THE VALUE OF THE REGISTRY WILL ONLY TRULY BE REALIZED WITH PATIENT PARTICIPATION

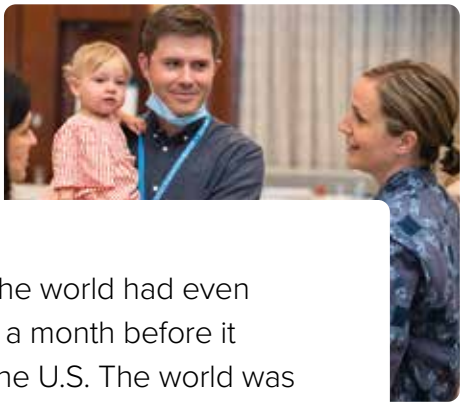
www.cystinosisresearch.org/cure-cystinosis-international-registry

2022

day of hope

CRF FAMILY CONFERENCE

By **Stephen Jenkins, MD** *(Thursday, Friday)*
and **Clay Emerson, PhD** *(Saturday)*



The last time we met at the Day of Hope was in 2019, before the world had even heard of SARS-CoV-2. The 2020 conference was tragically cancelled a month before it was set to occur, when the first COVID-19 cases started to appear in the U.S. The world was locking down, and we could not risk letting the novel virus run rampant in our rare disease community. As the pandemic raged on, plans for a 2021 conference evaporated, and we set our hearts on 2022. When cases of the omicron variant surged in late 2021, we thought we might have to cancel again. Fortunately, new cases plummeted in February, and with the widely available vaccine, we finally felt safe to get together again.

Since the Island Hotel never reopened once the pandemic began, we returned to our previous venue, the Balboa Bay Resort. Going back was like a trip down memory lane. The conference began on Thursday night with our traditional Mexican feast. It was a great night to catch up with old friends and meet new ones. My boys immediately found Henry Sturgis and did not let him out of their sight.

We finally felt safe to get together again.

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Friday morning, we gathered for introductions and a message from CRF Founder and President, Nancy Stack. She shared with us the incredible news about her daughter Natalie, who became the fifth person to receive the gene-corrected stem cell transplant on March 29. Everyone had an opportunity to stand up and share a little bit about themselves, as well as their hopes and dreams for themselves and their families. It was especially moving after a three-year break.

After our introduction session, we launched into the science talks. I gave a short presentation on the basics of cystinosis, including the now famous Lego analogy (courtesy of my wife), for explaining how mutations in genes lead to multi-system diseases. This was the first year my 12-year-old son, Samuel, attended some of the talks, and it was fun to see him sitting in the front row next to Henry Sturgis, of course.

Next, Dr. Paul Grimm from Stanford University spoke to us about managing Fanconi syndrome and polyuria. He talked about the importance of dosing electrolytes multiple times during the day to maintain levels in the therapeutic range. This is especially true for bicarbonate (or citrate), which is necessary to maintain the normal pH of the blood. If there is too much acid in the blood, it causes damage to the bones. Dr. Grimm also shared a new paper, published by Dr. Francesco Emma, a member of the CRF Scientific Review Board and others, about an international cohort of 453 cystinosis patients. One of the findings of this study was that patients who took indomethacin had no worse kidney function than those who did not take it. Indomethacin is an NSAID that can help reduce fluid and electrolyte losses from the kidneys.

After Dr. Grimm we heard from Dr. Julian Midgley from Alberta Children's Hospital, in Calgary, Alberta, Canada. He talked about the challenges of cystinosis in adolescence and young adulthood, and the importance of a planned transition from pediatric to adult nephrology care. One interesting point he shared is that it is safe to take cysteamine therapy while breastfeeding. He actually measured cysteamine levels in the breastmilk of his patient and they were negligible.

Next, we heard a recorded presentation from Dr. Benjamin Freedman from University of Washington. Dr. Freedman collected urine from people with cystinosis, from which he isolated adult cells. He turned these cells into pluripotent stem cells, which he

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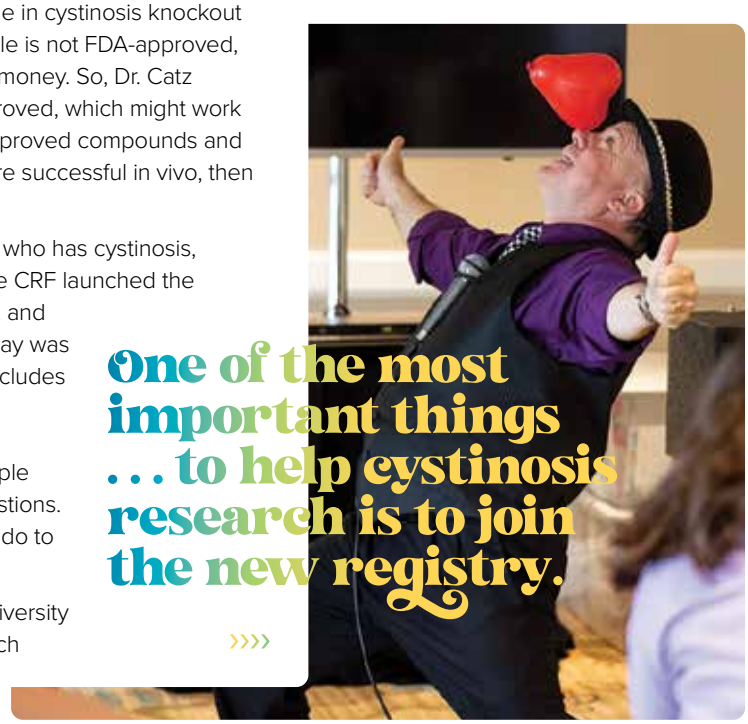
reprogrammed into kidney cells. He can then grow the kidney cells to form mini kidneys in dishes. They have also transplanted some of these human cells into the kidneys of living mice, and the cells integrate into the organ. The goal one day is that cells taken from the urine of someone with cystinosis could be fixed with gene editing, grown into new kidneys, and these could be transplanted back into the person with cystinosis. It sounds like science fiction, but that's the exciting direction stem cell research is going!

After lunch we returned to hear from Dr. Sergio Catz, from The Scripps Research Institute. Dr. Catz has been researching cystinosis for over a decade now, and he has multiple interesting projects running in parallel. In the past, he has identified a molecule, QX77/CA77, which restores an important protein, LAMP2A, to the lysosomal membrane, which is important for a cellular process called autophagy, which is impaired in cystinosis and not corrected by cysteamine. He has assessed this molecule in cystinosis knockout mice, and it helps improve their Fanconi syndrome. This molecule is not FDA-approved, so getting it to human patients will take many years and a lot of money. So, Dr. Catz decided to look for other compounds that are already FDA-approved, which might work in a similar way. He is screening a drug library of 12,000 FDA-approved compounds and has already identified 331 potential candidates. If any of these are successful in vivo, then we could move toward a human trial much faster.

Next, Dr. Clay Emerson, who is the father of Brooke Emerson, who has cystinosis, spoke to us about the Cure Cystinosis International Registry. The CRF launched the original CCIR many years ago, but a lot has changed since then, and most of the questions and information has become outdated. Clay was instrumental in creating the new registry questionnaire, which includes 135 questions about diagnosis, treatment and all areas affected by cystinosis, including the eyes, kidneys, muscles, bones and neurological system. Numerous cystinosis researchers and people with cystinosis reviewed the questionnaire and contributed questions. One of the most important things individuals with cystinosis can do to help cystinosis research is to join the new registry.

Following Clay, we heard from Dr. Morgan DiLeo, from the University of Pittsburgh School of Medicine. She has continued her research



One of the most important things . . . to help cystinosis research is to join the new registry.

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on controlled-release eye drops, which turn from liquid to solid when they go in the eye. The drops are filled with microspheres loaded with cysteamine. She has finished testing the drops in rabbits, which tolerated the solid drop well, and she detected adequate drug levels in the eyes. She has also been testing the drops in cystinosis knockout mice, which is a lot harder, because mice have very small eyes. She hopes to show the drops are efficacious in the mice before going to the FDA later this year to discuss a human trial.

After Dr. DiLeo, we heard from Dr. Veenita Khare, who works in Dr. Cherqui's lab. She is trying to solve the mystery of why cystinosis causes Fanconi syndrome, which does not seem to be entirely explained by cystine accumulation in lysosomes. She thinks it has something to do with a transporter protein in the kidney called NHE3, which normally absorbs sodium in the proximal tubule. This protein appears to interact with the cystinosin protein, and in people with cystinosis, this interaction is likely impaired. This might explain why they lose so much sodium and water in the proximal tubules.

Overall, the results were inspiring and hopeful.

After Dr. Khare, we heard an update on the stem cell gene therapy trial from Dr. Stéphanie Cherqui. Five patients have now received the transplant, and she has good follow-up data on two of them. White blood cell cystine levels in these patients have gone down to normal despite not being on cysteamine. This makes sense since the white blood cells come from the transplanted bone marrow, but is the same effect seen in the other tissues? That is the million-dollar question! Dr. Cherqui showed us that skin and rectal biopsies do show a reduction in cystine crystals, and so do images of the corneas. This suggests that the stem cells are assisting other cells in the body too, as she previously showed in mice. Another curious change they noted was that patient one and patient three have darker hair color now, which is not unusual after chemotherapy, but may also suggest correction in previously impaired melanin synthesis. Overall, the results were inspiring and hopeful.

Next, we had a panel with two of the trial patients, Jacob Seachord and Tyler Joynt, along with Jacob's mother, Rocky, and Tyler's wife, Jody, and Dr. Cherqui. It

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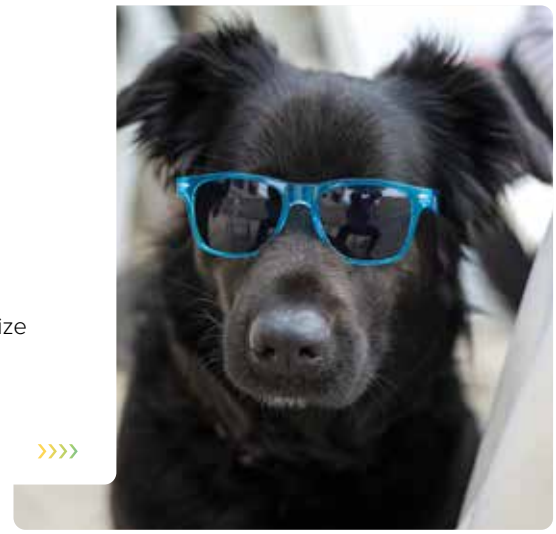
was very cool to hear about their experiences getting the transplant and what their lives are like after. They both said that the transplant was not as bad as they thought it would be. Fortunately, neither of them had significant side effects from the chemo. They talked about the hardest thing was being stuck in the hospital, which could be boring. Jacob talked about how he feels much stronger now and can work harder at his job. Tyler was just transplanted six months ago, but says he's already gained his strength back to where he was pre-transplant. Neither of them misses being on cysteamine!

That concluded the Friday sessions. We got together for a wonderful dinner on the bayfront lawn. The food was excellent, and the company was even better. There was a live band and my son Sam had too much fun filming Henry Sturgis dancing with Tina Flerchinger. There were also balloon animals, light up wands and a wacky photo booth. The kids had a blast.

Everyone was up early on Saturday morning to hear crowd favorite Dr. Paul Grimm with another talk, this one aptly titled "Kidney Transplant Smorgasbord." With kidney transplant still being a reality for people with cystinosis, Dr. Grimm covered the full variety of relevant topics including planning for a transplant, post-transplant medication compliance and the future of kidney transplant. His look into the future included recent developments in genetically modified pig organ transplant (yes, it is becoming a real thing), and the use of allogenic stem cell transplant as a potential replacement for post-transplant anti-rejection medications.

Next, Stacey Sullivan MS CCC-SLP and Natalie Grant provided updates on the ongoing study entitled Myopathy and Dysphagia in adults with cystinosis. Dr. Reza Seyedsadjadi is leading the study at Massachusetts General Hospital and is still actively enrolling patients. This presentation focused on some of the late onset complications of cystinosis related to muscle weakness and difficulties with swallowing. As expected, early results show that muscle weakness and difficulty in swallowing are commonplace in adults with cystinosis. The study aims to characterize the pathophysiology of these complications to develop treatments and improved management of these late-onset difficulties.

Crowd favorite, Dr. Grimm!

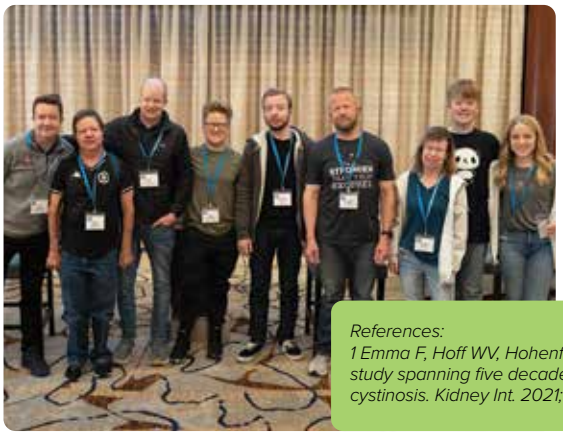


Finally, Robert Mak, MD, PhD, of Rady Children's Hospital at the University of California, San Diego, provided a comprehensive presentation on muscle wasting in children with cystinosis. His presentation included discussion on the relationship between muscle mass reduction, metabolic rate, and poor appetite as they relate to a syndrome known as cachexia. His studies have shown that vitamin D deficiency plays a significant role in the process. He discussed vitamin D supplementation for children with cystinosis, while stressing the importance of proper testing to ensure proper dosing – enough but not too much. Most interesting were the results of his genetic studies in mice which illustrated the surprising role that the inflammation process plays in preventing and correcting muscle wasting and metabolic dysfunction in cystinosis.

Following the scientific research presentations, smaller break-out sessions were held among attendees. Patients and families were able to compare notes on growing up with cystinosis or raising a child with the condition. Patients and families shared experiences ranging from mental health to medication tips. Finally, the adult panel discussion featured nine adults with cystinosis from across the country and beyond. The panelists were extremely generous, open and honest and shared their life experiences with cystinosis. Topics of discussion were broad and included the ongoing stem cell trial, exercise, medication compliance, and independence. The insight provided by these brave adults was the most valuable part of the conference.

The 2022 Cystinosis Research Foundation Day of Hope Family Conference was a tremendous success. Our numbers were fewer this year, but that did not stop us from making new connections and giving each other enormous support. It was rejuvenating to hear about ongoing research, and we are so hopeful about the future. The kids are already counting down the days until next year.

We are so hopeful about the future.



References:
1 Emma F, Hoff WV, Hohenfellner K, et al. An international cohort study spanning five decades assessed outcomes of nephropathic cystinosis. Kidney Int. 2021;100(5):1112-1123. doi:10.1016/j.kint.2021.06.019

From the bottom of our hearts, THANK YOU to everyone who donated to Natalie's Wish fundraiser! **Thanks to your generosity, we raised an incredible $1,354,521!** 100% of your donations will go toward learning more about cystinosis and discovering new, improved treatments!

Thank you to everyone who joined us for our month-long Natalie's Wish Fundraiser, a celebration of our CRF community and the brilliant researchers fighting to create better treatments and a cure for cystinosis! While we were all raising funds to support our cystinosis researchers, Natalie – 19 years after wishing for a cure – had the stem cell and gene therapy treatment on March 29th with the hopes of being cured of cystinosis!

Over the past 19 years, you have shared in the highs and lows that we have experienced along our journey toward a cure and now it is time to celebrate all that we have accomplished together. We shared with you the strides we have made in cystinosis research, and we rekindled connections within our community by sharing heartfelt stories from some of our CRF families.

Please visit our website where we host a series of short videos that are complete with information about the research you have funded, the projects you have supported and the milestones you have helped us achieve this year.

Since CRF was first founded, Natalie's wish for a cure has united us in our fight against cystinosis, and though we could not be together in person this year, we will always be united in our hope for a cure.

CYSTINOSISRESEARCH.ORG/NATALIES-WISH-2022

Family Fundraising
FROM AROUND THE WORLD

IN MEMORY

TANNER EDWARDS - $40,170

SHANNON PAJU - $2,000

SUSAN ELLYN THOMAS - $1,100

WESTON TSCHANNEN - $10,000

In 2021, our global community helped raise over $1,453,734 for cystinosis research!

YOUR GENEROSITY CONTINUES TO GIVE US HOPE — A HOPE THAT UNITES US. TOGETHER, WE SHINE BRIGHT!

Hearts for Hadley

Tina's Hope for a Cure

Lola's Curl for a Cure

Aidan's Army

Hopes & Wishes Foundation

Joshua's Journey of Hope

Jenna & Patrick's Foundation of Hope

Help Lily Blossom

Kenzie's Driving Fore a Cure

Caleb's Cause

Chance For Chase

Liv-A-Little Foundation

Hope for Holt

Emma's Wish

Molligans Fore Morgan

24 hours for Hank

Pins for a Purpose

Bailey Believes — His Hopes, His Dreams and a Cure

Lots of Love for Landon

Race For Nicole

Pars Fore Preston

Getting Jolly for Josie

#CYSTINOSISSTRONG

Hope for Brooke

KMI — A Cure for Keegan

Amanda's Hope for a Cure

Fore Fathers

Aarav's Time To Shine

Hope for Hayden

Sam & Lucy's Hope for a Cure

Gabbie's Wish — cure cystinosis

Abbi's Road to a Cure

Seth's Circle of Hope

UNITED STATES

KATIE AHNEN - $310

HADLEY ALEXANDER - $34,548

ISAAC ANDREWS - $6,000

LILY BEAUREGARD - $11,731

JACKSON BLUM-LANG - $351,300

OLIVER BRITTEN - $5,000

NOAH BROWN - $1,050

CHASE CHODAKOWSKY - $430

JOSHUA CLARKE - $10,000

MIA COPELAND - $800

ADDISON COX - $1,550

BAILEY DEDIO - $800

EMMA DERYCKE - $1,245

ELEANOR DICKS - $275

JONAH DOCKERY - $390

BROOKE EMERSON - $39,428

JAMES 'DREW' ENDSLEY - $575

TINA FLERCHINGER - $56,315

COLLINS GALLOWAY - $41,197

CALEB GOWAN - $747

HOLT GRIER - $2,813

CARTER HALL - $2,065

NICOLE HALL - $7,815

LANDON HARTZ - $27,197

THE JACKSON CHILDREN - $2,482

SAM & LARS JENKINS - $6,757

JESSICA JONDLE - $3,236

TYLER JOYNT - $765

JOSIE KANUPKE - $4,919

SHANNON KEIZER - $1,500

DEVLIN KEON - $275

AARAV KHALASI - $7,961

HAYDEN KIRCHHOF - $36,550

JAKE KRAHE - $6,240

KENZIE LAWATSCH - $2,645

KALEB LAWSHE - $2,600

JACKSON LIMA - $600

LOLA LONG - $8,450

LACEY LOWERY - $835

PRESTON LUKE - $620

AYLA & OTTO MAHER - $65,552

KEEGAN MANZ - $1,985

STELLA GRACE MILLER - $3,960

BRADY MURDOCH - $3,006

AIDAN O'LEARY - $60,910

EMMA & GRACIE PATTERSON - $1,295

EMILY PATTERSON - $100

JENNA AND PATRICK PARTINGTON $108,015

HENLEY PARCEL - $1,345

MORGAN PEACHMAN - $850

ABEL & PAUL PRUITT - $57,833

KATIE ROY - $2,000

GRACE SEVEL - $1,070

CHARLIE SIMPSON - $341,469

CIENNA SMITH - $2,500

BRIAN SMITH - $1,000

MITCHELL SMITH - $2,100

HENRY STURGIS - $2,440

EMMA GRACE SUETTA - $9,112

PEYTAN TAYLOR - $100

KADEN THOMAS - $180

ALEX WEAVER - $225

CANADA

SOPHIE'S CHAMPIONS
SOPHIE BETOURNAY - $29,550

EVA BILODEAU $266

NORA & ALAN CAMPBELL - $342

ANDREW CUNNINGHAM - $233

SETH DEBRUYN - $24,016

HOPE FOR JAMES
JAMES FEHR - $4,335

JORDAN JANZ - $545

AMANDA KUEPFER - $2,054

MARVELED BY MADDIE
MADDIE LAWRENCE - $773

MARYLYNN LEPACK - $487

OLIVIA LITTLE - $20,275

CILLIAN MCQUILLAN - $3,347

ABBI MONAGHAN - $500

KATHLEEN ROBERTS - $1,200

GABRIELLE STRAUSS - $1,040

ELROY WAGLER FAMILY - $500

MADELYN & ALIYAH WALKER - $1,770

SWEDEN

KAROLIS SCHRÖDER - $1,069

ENGLAND

ROSA BUTLER - $360

JULIETTE FOLLAIN - $15,310

AUSTRALIA

ETHAN FENN - $2,368

OSCAR MCKENZIE - $2,187

BEE ROBERTSON - $1,000

FROM FACEBOOK

FACEBOOK FAMILY AND FRIENDS FUNDRAISING EVENTS AND DONATIONS OF $69,881 ARE INCLUDED IN THE ABOVE TOTALS.

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

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

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

Since 2003, CRF:

Funded **213** Multi-Year Grants in **12** Countries

Published **100** Articles in Prestigious Journals by CRF Researchers

1 FDA Approved Drug and **1** FDA Approved Clinical Trial

Raised More Than **$63 Million** for Cystinosis Research

In 2021, CRF:

Awarded **9** New Grants: **8** Research Grants, **1** Equipment Grant

Published **10** Articles in Prestigious Journals by CRF Researchers

Totaling More Than **$2.1 Million** in **4** Countries

100% of Your Donations Directly Support Cystinosis Research

Family stories

STEM CELL AND GENE THERAPY CLINICAL TRIAL #4

TYLER JOYNT

By Tyler Joynt
CHULA VISTA, CALIFORNIA

AS a kid, I really only knew three things about cystinosis. Doctors, sickness and the San Diego Zoo. From an early age I remember throwing up often, going to the ER regularly and seeing doctors frequently. I was lucky enough to be diagnosed before I was two years old, but after cysteamine had been discovered. Living in Alabama, I had access to one of the top pediatric nephrologists in the south, someone who knew cystinosis and also happened to have a daughter that I went to school with.

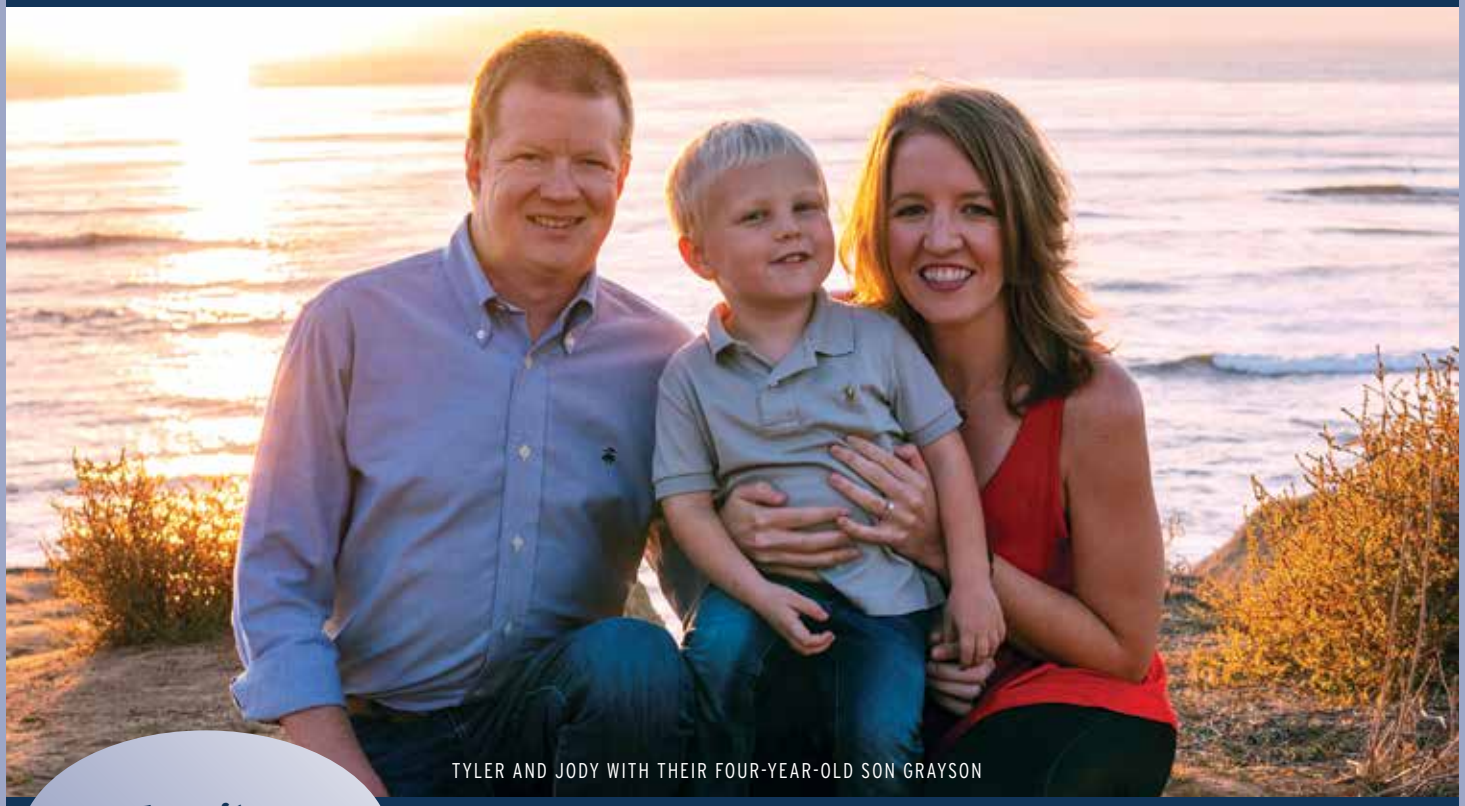
Doctors' visits to Children's Hospital of Alabama were normal for me, and I never thought about it being weird. I took a lot of medicine around-the-clock, wet the bed and vomited a lot. This was normal to me, even if it wasn't the most fun life. My parents were very supportive and for the most part allowed me to be a regular kid. That's where the San Diego Zoo comes in. For as long as I can remember, I've been doing studies all over the country in relation to cystinosis; NIH, UCSD, Stanford, Mass Gen and others, were places I was seen and was able to travel to. I didn't quite understand at first what I was doing. I just knew that I got to take fun trips, get poked and prodded, and talk to new doctors.

A trip we often took was to San Diego to go to UCSD to see any one of the amazing doctors there (Dr. Schneider should always be remembered as THE doctor who saved us). We went so often; I believe at one point we had a season pass to the zoo. If you have not been to the San Diego Zoo (or its sister, Safari Park), it is one of the most amazing experiences a kid can have and is only about 10 minutes from the UCSD Hillcrest location.

Once I was a teenager, I started to understand more about cystinosis and what these studies meant. I understood that this disease had no cure, but doctors and researchers were working tirelessly to help give us a better life. In the mid-2000s, I was "lucky" enough to be able to complete a clinical trial with Dr. Ranjan Dohil to test the first delayed-release cysteamine, or what we now know as Procysbi®. It involved a tube being put down my nose and into my GI tract, where they measured my WBC (white blood cystine) levels at different points of release of the medication. It wasn't the most comfortable or fun procedure, but it was a paying study and I was able to buy myself an electric guitar.

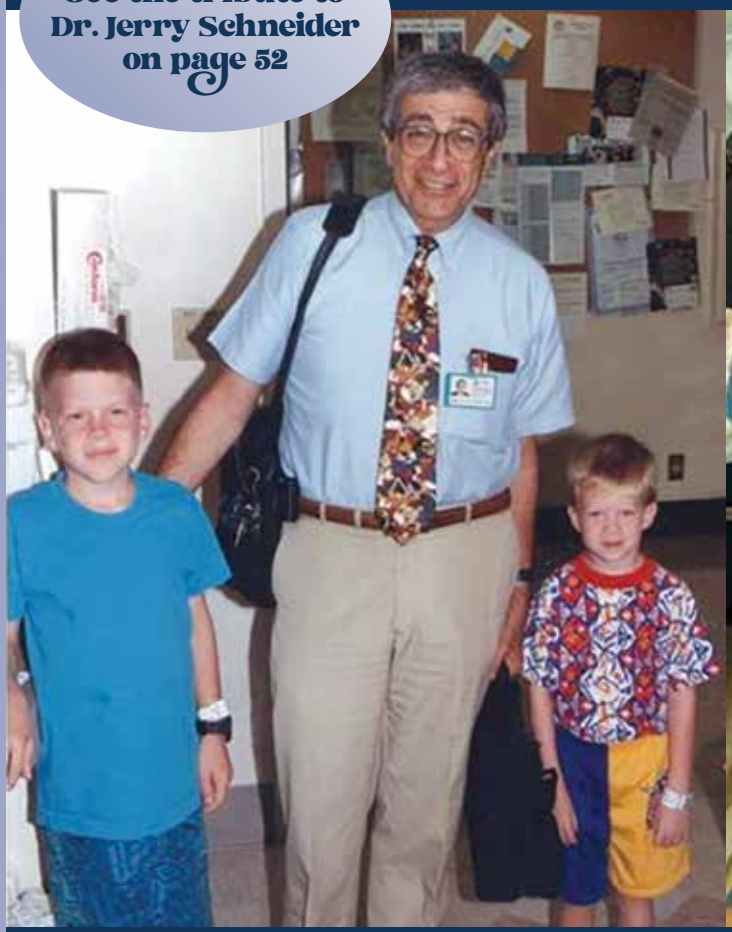
It wasn't until years later that I realized that the study was what brought us Procysbi®, and the first time I really saw the result of a clinical trial I had been a part of. Fast forward almost 20 years and, as God would have it, my wife and I were stationed in San Diego as a part of her military service. The gene therapy stem cell trial had begun just up the road at UCSD and after about a year of deciding not to throw my name in the hat, I decided that we'd never find the "perfect" time to do it. I was a little hesitant, but after seeing Jordan's success I realized that I might be a great candidate and would be able to carry the torch for those unable to participate due to age, health or location.

After months of preparation, a few small setbacks, and what felt like the longest day of my life, I was admitted to UCSD Jacobs Hospital to begin the stem cell transplant on November 9, 2021. I had four days of twice-a-day chemo, 10cc of stem cells, and 22 days later, I was back home recovering. Cystinosis has been a part of my life for over 30 years, and we have come such a long way thanks to the doctors, researchers, nurses, coordinators, parents and of course Nancy, Jeff and Natalie Stack. I am ecstatic to have been able to participate in this clinical trial for a cure, and I have so much hope for a long and healthy life for today's children (and parents) of cystinosis.



TYLER AND JODY WITH THEIR FOUR-YEAR-OLD SON GRAYSON

See the tribute to Dr. Jerry Schneider on page 52



TYLER DURING HIS STEM CELL TRANSPLANT

Olivia Little

Our classroom's spirit

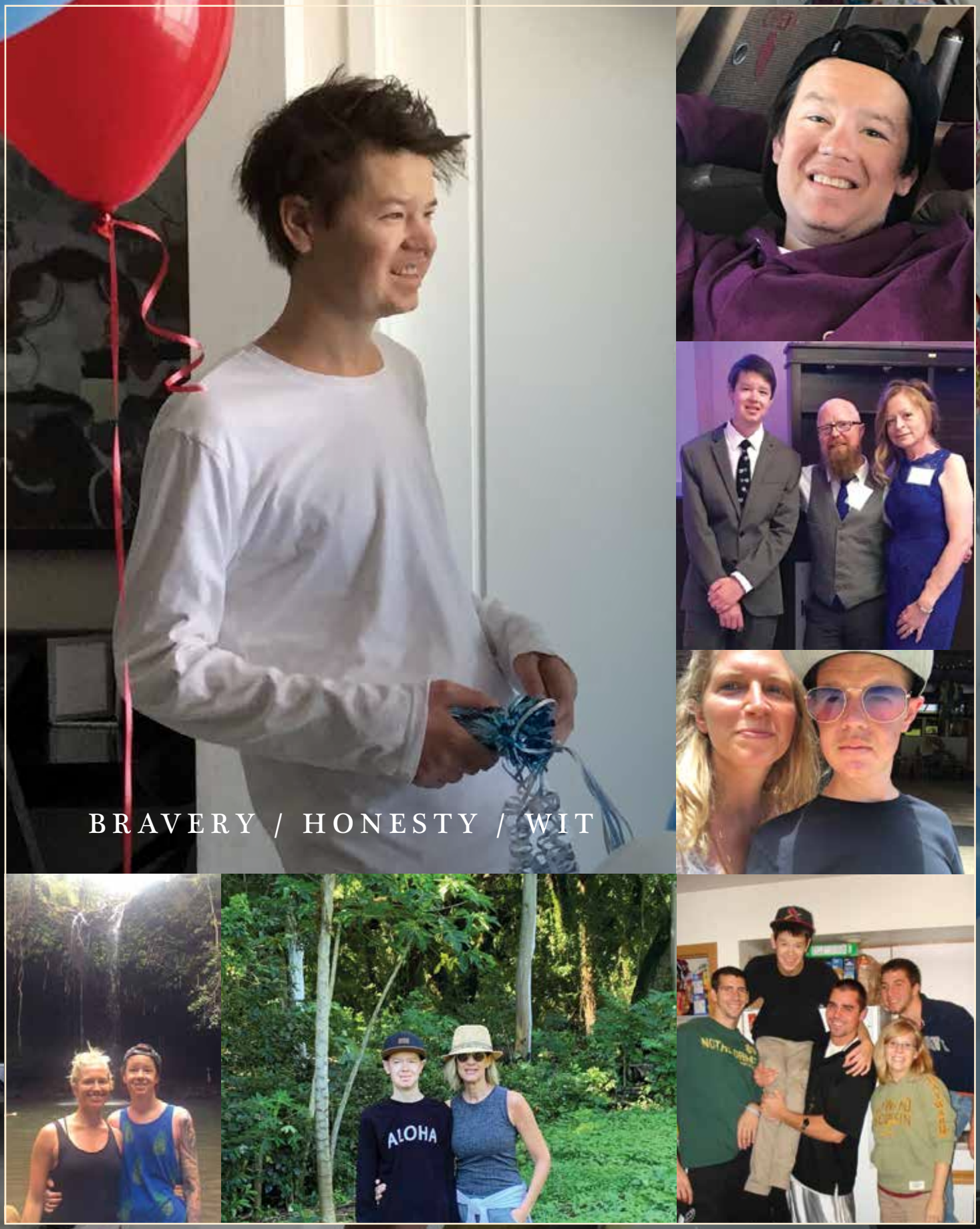
As a Waldorf sixth grade teacher at Edge Hill School, I met Olivia in September of 2021. Olivia had been homeschooled because, as her mother wisely noted, building a strong physical body was a priority, given her cystinosis diagnosis. Olivia arrived trailing and emanating all the sweetness that a homeschooled child in a strong and loving family carries. She also arrived with an eagerness to meet new friends, an open-minded capacity to pay attention and learn, and a commitment to completing her best work.

Olivia's family has not put cystinosis "first" for Olivia. Thus, in the classroom, she took her "vitamins," not pills, at a specific time. Her fellow students didn't take much notice but, as children do, they watched and deduced. Some of them understood that the vitamins were related to a physical illness, but the class did not crave details, simply an acknowledgment that there was a need for medical care. And when Olivia was absent for a relatively short time, as she quickly recovered with such determination, the students understood that her surgery had to do with an illness, and they simply waited for her return, sending wishes, and being delighted when she reappeared. Even the toughest character in the class was charmed by her kindness.

Olivia has shared with us the magic of her innocence. She has shared her sincerity. She speaks the truth, softly. She has shared her generosity, offering compliments to other students and occasionally, surprising them beautifully in doing so. She has shared her desire to work and play and accomplish in a way that is fresh and creative. Her progress in all areas of the curriculum has been remarkable, and she works diligently at home to finish all her daily work, bringing in beautiful main lesson pages.

By Ms. Lise Gunby, Olivia's teacher
DURHAM, ONTARIO, CANADA

Having taught Waldorf classes for more than twenty years, one comes to care deeply for the craft of teaching. That craft is, of course, the curriculum. It is also looking respectfully and intensively into the character, needs and desires of the individual, and it is forming a group of young humans into a whole that possesses humanity, care, reflection, kindness, curiosity, and compassion – all the nouns we want to make into active adverbs. We call this "the spirit" of the class. As an admired colleague of mine said recently, Waldorf teachers strive to acknowledge the magnificence of life. Because of Olivia, that magnificence shines especially brightly in our little classroom.


BRAVERY / HONESTY / WIT
ALOHA

IN MEMORIAM: TANNER EDWARDS

By Traci Gendron, Tanner's mom
FORT COLLINS, COLORADO

When I think of Tanner, two words come to mind, brave and honest. He always told you what you needed to hear, not what you wanted to hear.

He had such a great sense of humor and wit and always made me laugh. I will miss that about him.

Tanner had cystinosis and fought it on his terms. He didn't want or expect anyone to feel sorry for him, "it is what it is," he would always say to me, which was very hard for me to accept. But he was wise beyond his years.

He often had difficulty tolerating his medication (phosphocysteamine, Cystagon®, and Procysbi®); they all gave him severe GI issues, so he could never handle a full dose. Imagine not being able to take the only drug that will slow down the progression of your illness.

When Tanner was first diagnosed, we didn't know anyone with cystinosis. It was a terrifying experience because we had no support system, but somehow, we always made it through. Luckily, we found CRF, which gave us hope and introduced us to many people battling the same disease. Thanks to CRF, we could connect with families facing similar situations and share ways of managing cystinosis.

But the disease finally won on November 13, 2021, and Tanner passed away peacefully with his dad and me by his side.

I recognized over the past year that he wasn't doing very well. From the conversations we had, I think he knew he was dying. But he told me he had no regrets, that he had been happy and enjoyed his life. I prayed continuously for God to let me keep him as long as possible. I'll never forget when he was six years old, he told me that he would have a new heavenly body when he died, and now he does without the struggles of being an adult with cystinosis.

Even though he was fighting for his life, he still found a way to enjoy the simple things in life. He was an avid sports fan, like his dad, and you could ask him anything about most teams, and he would have an answer. He had such a big heart for kids and admired how some players helped sick children. He even met Shaq before his first kidney transplant. He was also a big sneaker connoisseur. His collection was awe-inspiring, and every time he got a new pair, he was thrilled.

Tanner also had a deep love for travel. His favorite place in the world was Hawaii. He would go for a month at a time, and if it were up to him, he would have lived there. He said it felt healing to him, and I'm so grateful that he took the time to explore and experience the island, and I was lucky enough to experience it through his eyes.

I don't know what Tanner would have done without his dog, Smee. He was always by his side. Smee now lives in Illinois with Tanner's dad; they bring each other comfort.

I'm amazed at how Tanner dealt with his sickness; he didn't complain about it once. He was undoubtedly my hero. I cannot express the profound loss I feel every day, but I know he is at peace now. He was so deeply loved and is missed by many.

"Hope is belief in the plausibility of the possible as opposed to the necessity of the probable."

Maimonides
12th century philosopher

A Mother's Journey

By Erin Finucane, Sofie's mom
PHILADELPHIA, PENNSYLVANIA

In October 2019, I was sitting in Children's National Hospital in Washington, D.C., with my husband Matt and our 14-month-old daughter Sofie. The day is seared in my brain — the sterile smell of yet another hospital wing. The ceaseless knot in my stomach after a six-month medical mystery tour. The uncomfortable realization that they never send the chief nephrologist in with good news. Matt paced and I bounced Sofie on my hip and tried to take notes as the doctor whirled through a Grey's Anatomy-style lecture complete with renal tube diagrams scribbled on the hospital bed paper. I captured three phrases from that appointment: lysosomal storage disorder; rare genetic condition; no cure. As parents, we all expect to have to advocate for our children. However, this was an entirely different level.

Advocacy comes naturally to me after a nearly 20-year career in social change. I studied peace in Ireland; led anti-poverty campaigns in Brussels; and managed global health efforts (among others) in Washington, D.C. It never dawned on me what a luxury it was to choose the issues I was working on until that October when the issue chose me. In some ways, it felt like my life's work had prepared me for this moment.

I'd like to tell you that when we got this diagnosis, I immediately put on my strategist hat and began to plot how our family was going to fight for a cure. Instead, I found myself in a dark wilderness of grief, fear and uncertainty. The months that followed were terrifying. We started treatment right away and Sofie couldn't orally tolerate the onslaught of medication, so we had to place a g-tube in her belly. We were on a constant nausea rollercoaster, trying to get her to absorb the nutrition and supplements she needed. Oral eating became more elusive. The care she required was relentless. I was so afraid that the beautiful life we had worked so hard for was gone, fear that was only amplified by a global pandemic.

> life may be more complex, but it is no less beautiful

Finding our family's new equilibrium was a slow and iterative process. Sofie's nausea finally stabilized with various GI interventions including homemade g-tube blends instead of shelf-stable formula. We bought a home in Philadelphia, a city we love, where we are closer to family. We transferred Sofie's care to Joshua Zaritsky ("Dr, JJ"), the Chief Nephrologist at St. Christopher's Hospital for Children, who connected me to CRF's Jill Emerson. And we began to engage more with the Cystinosis Research Foundation, a consistent source of hope and light. As I write this, I am en route to my first Day of Hope, what I'm sure will be another milestone in the journey.

We talk about hope a lot in our family. My favorite definition of hope is by Maimonides, a 12th century philosopher who says, "hope is belief in the plausibility of the possible as opposed to the necessity of the probable." It is always probable that Goliath will win; but sometimes David does. I learned in my social change work and now as a mother confronting the complexity of cystinosis, hope is central to everything. It's how we continue to put one foot in front of the other. It's how our community raises critical resources. It's how we bring more researchers and doctors into the fight. It's how we conquer fear. It's how we win the fight for a cure and we're lucky because there are so many reasons to be hopeful.

Without a doubt, my greatest source of hope is Sofie. She was born on the 4th of July and is every bit the firecracker, joyful and mischievous, with a legendary belly laugh. At three and half years old we are getting ready for pre-K in the fall. She is doing well but like most kiddos with cystinosis, there are challenges, and the care is intense. On a daily basis, I am blown away by her resilience. She is a living example of one of our family values: life may be more complex, but it is no less beautiful.

And so, our journey continues. As we continue to find our way, I am so grateful to the Stacks, the Cystinosis Research Foundation and the broader CRF community who inspire us every day to keep fighting. Matt and I are both honored to be on this adventure with you.

WALK by FAITH

when opportunities happen, we must make the move

By Bryan and Alex Stout

CHERRYVILLE, NORTH CAROLINA

To say our lives have been busy since we were married would be an understatement. That was in October of 2017 and here we are in the spring of 2022. We bought a home, started a family, and became foster parents all in just the last few years. We are definitely a busy little family and hoping to grow even more.

Kayne is our two-and-a-half year-old. He is all boy, and his nickname is "Wildman" which he lives up to every single day. He is obsessed with tractors, trucks, banjos, guitars, and his cousins. If he doesn't play some sort of instrument later in life, we will be shocked. His mawmaw, popa and nana say he is well-loved, not spoiled. We both never expected to have children, but prayers do work, miracles happen, and God has more than blessed us. We thank Him every single day for Kayne. He started preschool this year where Alex is the director.

As far as our health goes, we are both doing well. We fight the everyday struggles of cystinosis; but, like the rest of the community, you live with it and move on. We try to stay positive and look on the bright side of it all. For example, these stem cell transplants and all the amazing news they bring. It's so hard to imagine waking up and not having to slam 40 plus pills down throughout your day, especially when it is what you've done your whole life. It is extremely difficult to put into words what being disease-free would mean for us. Raising a child without all our "baggage" would seem like a dream.

A big goal of ours after getting married was becoming foster parents. We were licensed a few years ago and really enjoy it. Too many children suffer with rough home lives, and we just wanted to make a difference in any way possible. In January of this year, we received a very surprising phone call. A two-week-old little boy needed a home. Now with one toddler already running the house, our preference was three or older. We just didn't want to take on more than we could handle,

but after a lot of talking and prayers, he joined our home. God works in crazy ways and when opportunities happen, we must make the move. Did we have to make sacrifices, and is it crazy at times? Absolutely, but we simply wanted this child to have the best chances at life. Needless to say, he has a special place in our hearts already and Kayne loves being a big brother.

Bryan - So these days I am pretty much a stay-at-home dad. Which I do enjoy but it's a hard job. My sisters like to tease me about it. I do still work my regular job but with the two kids now, and Alex's director position, I am needed more at home. I never imagined I would be a dad especially not at 41 with a two-month-old. But in all honesty, I would never change it. I'm so thankful I found Alex and I'm so happy we were able to start a family. It's hard to believe we will be married five years this October.

Alex - I never imagined I would have the blessed, crazy life I have with being married, being a mom and working at a preschool. I honestly never thought I would ever become a mom because of having cystinosis, but God had other plans for me. There are days that I wonder where I am going to find the energy to keep up with two children under the age of three years old, but when I see their faces and I know they are relying on me and Bryan to love them, guide them through life, and play with them, it pushes me through the "rough days." I am beyond grateful for these two little blessings from God, but I am even more grateful for the extraordinary, supportive, strong-willed husband that God has blessed me with. We are a happy little family that is praying one day cystinosis can be something in our past and not in our present.

I couldn't write this article without mentioning Tanner. He was a close friend, who always had a good inside joke, a big heart, and I think of him a lot. Losing him, in a way, has reminded me to slow down, enjoy the small moments in life, and the people in your smaller circle. No one knows what our future holds. You will never be forgotten buddy.

A Grandparent's Journey Through Cystinosis

By Carol Guess Stevens, Collins' grandmother
STATHAM, GEORGIA

I'll never forget the day I heard the word, cystinosis. My son said, "Don't look it up, Mom. It's probably not what Collins has. It'll just scare you." So of course, like anyone would do, I googled, "cystinosis."

After reading and trying to comprehend this unheard-of word, I fell to my knees, praying that surely, this isn't what our baby has. The odds are in our favor, it's so rare, not us, not our Collins. After a multitude of tests and waiting (Oh the pain of waiting…) the diagnosis came back, "Collins has cystinosis." The news came during the Christmas holidays and during COVID-19. So, add isolation to the pain of worrying about our baby's prognosis and the worry about my baby—Collins' dad.

That's the added pain about cystinosis, or any lifelong condition, how the stress of this condition affects the patient and the caregiver. The double whammy of worry.

As a grandparent of a child with a rare disease, your immediate reaction is, "how can I help? I want to make it better." As you become more aware of the condition, watching your child take care of their child, the stress increases. It takes a while for the family to figure out how to deal with this disease, and its side effects, and the side effects of the medication. The administering of the medication — loads of it! (It's still hard for me to wrap my mind around it.) The responsibility is enormous.

The bottom line for us as grandparents is to provide support. Support for our children, the parents, and support for our grandchildren. Our road is a different path. Support for our children means to learn how to help care for the cystinosis patient. Learning how to administer medication and food. Providing support by allowing the parents to take a break. The parents need time to rest and take a break from the day and night grind of taking care of their child. Support during the ups and downs and the hurdles. And there are many keeping the faith that a cure is on the horizon. Praying that the promise of a bright and normal future is ahead for our children and especially, our grandchildren. It's a new way of life, and a new normal. A normal, happy life.

The Green Ribbon Campaign

The Green Ribbon campaign is a fundraiser created by some friends in Collins' neighborhood. It's a simple concept that promotes cystinosis awareness, as well as raises funds for the research. We advertised the Green Ribbon Campaign in a neighborhood newsletter, and the word spread quickly. A small donation like $10 buys the bow, but most people contributed more money than that. We purchased the ribbon material and wire at the local craft store. The ribbons were placed on mailboxes, fence post and front porch columns. We raised approximately $10,000 with very little effort. Our hope this year, is to start early and sell more green ribbons. Give it a try. Let's go nationwide!


Collins'
Cure
Please accept and wear this
ribbon to raise awareness and
help find a
cystinosis.

PARENTING A CHILD WITH CYSTINOSIS,

IT'S ONE FOR THE AGES

By Lauren and Jimmy Hartz, Landon's parents
PITTSBURGH, PENNSYLVANIA

AGE 2

Preschool Director
"Mrs. Hartz, Landon threw up. We had to evacuate the classroom and you'll have to take him home. I'm so sorry."

Me
"Ok. He isn't sick. He had a feed this morning and he was crying so hard, because I left the room, that he threw up."

I sat in the hallway, with Landon on my lap, and cried along with him. I knew, in that moment, that my need to advocate for him and explain, over and over again, was just beginning, and to be honest, I wasn't sure that I had the capacity.

AGE 5

T-ball Coach
"Okay Landon, you're up to bat."

T-ball Coach
"Go Landon! Run to first base!"

Jimmy
"Do you think he's okay? Do you think this is too much?"

Lauren
"I don't know."

AGE 6

Lauren
Hello (Teacher),

My name is Lauren Hartz. My son, Landon, will be in your class this year. I wanted to share some information about Landon. He has a disease called cystinosis. He was diagnosed with cystinosis when he was 14 months old. He has a g-tube in his belly and this is how he gets his medication. He does a great job at protecting it so it isn't something that you would have to worry about. He will need to get medication daily with the nurse. He usually gets his medication at 1pm but we can shift it a bit to accommodate his school schedule so to be as minimally disruptive as possible. He also needs unlimited access to water as he is prone to dehydration. This also means that he will use the bathroom more often. He needs to be given permission when he asks and not told to wait.

Please let me know if you have any questions or concerns.

Thank you,
Lauren Hartz

AGE 7

Lauren
"Landon, come here honey. I have to give you meds."

Landon's friend
"What's that?"

Landon
"It's my mic key button."

Friend
"What's it for?"

Landon
"I get meds because I have cystinosis."

Friend
"Oh."

AGE 9

Jimmy
"Hi coach, I'm Landon's dad. I just wanted to let you know that he has a disease called cystinosis. It makes it a little harder for him to keep up with running and it's important that he has water whenever he asks for it."

Head Coach
"Ok, no problem. Thanks for letting me know."

AGE 10

Lauren
Hello (Teacher),

I am Landon Hartz's mom. I'm not sure if you knew this but Landon has a disease called cystinosis. Because of this, Landon is more prone to dehydration and drinks more water than you typically see in kiddos. He told me that he forgot to bring his cup to your class today and that he was told that he couldn't go and get it. I talked to him about ways that he can make it easier to remember to bring his cup, but if this happens again, it's important that he is either allowed to get his cup or is given permission to go to the water fountain.

Teacher
Hello Mrs Hartz,

I did not know this and am very sorry. Thanks for letting me know. I will make sure that it doesn't happen again.

AGE 11

Peer
"Why do you run so slow?"

Landon
"I really have flat feet and when I run, I start with my heel, so it's like I'm putting the break on as I am running. I'm working on it."

Landon just turned 12. It feels like, in many ways, we are entering into a new chapter. We see his curiosity about the world, about people, and about himself expanding. He is maneuvering through what his values are, who he connects with, and honoring and moving through his emotions. It's never been easy to "fix" his problems because we weren't just presented with a skinned knee that would heal or a belly ache that could be relieved with bright colored liquid in a small plastic cup. The benefit to that is that we have had practice in moving through hard situations and have become stronger for it.

Our job, as his parents, in his new chapter is to continue to provide the resources that we can for him based on his needs and desires. We can have some conversations with people but ultimately, he is beginning to advocate for himself more. We spent most of his life walking a step ahead of him, leading him, guiding him and making decisions for him. In this chapter, we are walking next to him and supporting him. I didn't know that I had the capacity to advocate for him, as I sat in the hallway of that preschool crying along with him, but I did it. Landon has demonstrated strength and resiliency beyond what I ever could, so I am certain that he's got this.

Cheers to a great summer!

By Tricia Simms, Henry's mom
SANDPOINT, IDAHO

It was so refreshing to attend the Day of Hope this year. Meeting in person was so motivating, memorable and fun. Being able to talk with everyone during the multi-day conference really brought back the feeling of connection. Our cystinosis community is so special and kind, we are so grateful to be part of such a wonderful group of people. Henry really enjoyed the presentations given by Dr. Grimm and Dr. Cherqui this year. A big thank you to the Stack family and CRF for all that they do for cystinosis. We miss everyone already and can't wait to attend next year.

This has been a very eventful time in Henry's life, he is now 15 years old but will turn 16 on July19. Henry has had a few challenges, changes and adventures this past year. He had an ATV accident at the end of summer in August that crushed his left hand, shortly thereafter he started ninth grade at Sandpoint High School and is currently taking driver's education, and will hopefully be driving this summer.

Henry had a wonderful care team of specialized doctors who worked on his hand. He would like to give a very big thank you to his hand and wrist surgeon, Dr. Erin Miller from UW Medicine. She was very helpful and comforting in the hospital. He had many surgeries and grafts, and the level of expertise and care was amazing. We feel so grateful. Henry has been doing hand therapy with Jared Rattray three times a week after school and has worked very hard at gaining back his strength and mobility.

henry sturgis

Henry has done well in his first year of high school and we are so proud of him! He is getting great grades. Although math is a challenge for him, he studies hard and does well in all his other classes. He is done with Algebra I, so he tackled his math for the year. He is interested in a lot of different career choices and is taking advantage of different programs the school has to narrow down what he wants to do.

With all the changes and new things in Henry's life, there are still regular things that never change and never get old. He still enjoys snow skiing, playing video games and hanging out with friends.

Henry plans on boating a lot this summer and wake surfing, as well as working a part-time summer job.

Henry has such a positive attitude and mindset; he can accomplish anything he sets his mind to.

Here's to a great summer!

Good-bye G-tube!

By Stephen Jenkins and Samuel Jenkins
SALT LAKE CITY, UTAH

Samuel was diagnosed with cystinosis when he was 12 months old. Like many children with cystinosis, one of his main issues was growth failure and vomiting. Once he tasted water, he refused to nurse or take formula anymore. Shortly after his diagnosis the doctor told us he would probably need a feeding tube. We were terrified by the idea. It sounded so permanent, and what if it got yanked out?

Two months after his diagnosis, Sam was going to the operating room to get a surgically placed button-style gastrostomy tube. His post-operative recovery was a little rough, complicated by fluid and electrolyte disturbances. Surgeons are really good at doing surgery, but not always so great at the complexities of pediatric nephrology. Sam was in the hospital for a whole week to make sure he tolerated feedings through the tube.

Sam was connected to the feeding tube almost 24 hours a day. We were always adjusting the rates and timing based on his complicated medicine schedule and what he could tolerate. There was still a lot of vomiting, but we quickly saw the benefits of the feeding tube. He started to gain weight, and it was a lot easier to give him his electrolytes and cysteamine. He continued to drink a lot of water, and he stopped taking in any nutrition by mouth. He was completely dependent on the feeding tube for nutrition for about three years. We wondered if he would ever eat.

There were many nights when he would roll around and the tube would kink, setting off the alarm. Or he would roll around and the sideport would open, and all the feeds would soak the mattress. "Fed the bed," we'd say. One night he got so wrapped up in the tubing, it pulled the gastrostomy tube right out. We panicked and ran around the house looking for the backup kit. Luckily, we were able to put a new button in and that's when we learned you have to swap the tube out periodically, and make sure the balloon was still full of water. Something that was scary at first became very routine.

When Sam was two years old, he was enrolled in the phase IV trial for Procysbi®. Henry Sturgis and Sam were the first kids with cystinosis to receive Procysbi® through a g-tube (they started the trial the same morning.) The first attempt was a disaster. We clogged the button immediately with all the beads and had to swap out the tubing. It took a while to perfect the art of suspending beads in apple sauce and flushing everything with orange juice, but we became pretty good at it.

When our second son, Lars, came around, Sam started to try eating foods. Lars also has cystinosis, but got on cysteamine right away, and

Sam was excited to compare battle scars with Henry at the Day of Hope family conference.

he's always been a good eater. I think watching Lars eat gave Sam the motivation he needed to try different foods. Soon he was taking in all sorts of solids. Over time we were able to reduce the number of boxes of formula he got each day, and eventually we were only doing night feeds. We continued night feeds for several years, until he was regularly eating enough on his own.

Sam started taking some pills by mouth when he was five or six. Over time he started taking most of his pills by mouth, but there were always a handful that he refused to take because they tasted bad. We had to keep using his g-tube to give him potassium chloride and potassium citrate. Then our pharmacy found a waxy potassium chloride that didn't taste bad, and Sam started taking it by mouth. That left potassium citrate. For years, we continued using the g-tube primarily to give him potassium citrate. We had a huge supply of potassium citrate pills in the cupboard that he had tried before, but he couldn't swallow them. We didn't pressure him. We were so used to the g-tube, it didn't really bother us, and we barely thought about it.

One day when he was twelve years old, Sam decided he wanted the g-tube out. He decided he was going to take those potassium citrate pills, even if they tasted bad, and he did! He took all his pills by mouth for several months, and we were finally convinced he didn't need the g-tube anymore. We brought him back to his surgeon at Primary Children's Hospital and scheduled a surgery date.

In January 2022, we took Sam in for the same-day procedure. Here's how Sam described it:

"I was nervous, but also excited. It would be the first time I didn't have a g-tube in 11 years. When we got to the hospital, we were waiting in the waiting room for about 30 minutes and in the actual room for around three hours.

"After a while they were ready for me. My bed was wheeled into a large room that felt like a freezer. There was a platform with a pillow in the center. It had a big light over it. I climbed on the platform, and they put a warm blanket on me. After that they gave me a laughing gas mask. I put it on, and it wasn't long before I felt tired. I fell asleep a little while afterwards.

"Then I woke up and the surgery was over. My g-tube was gone. I had some pain in my stomach and the nurse gave me a pain pill. When I was feeling well enough, I checked out and went home."

Sam was pretty sore after the procedure, but the surgical site healed up quickly, and now he has a nice pink line where the hole used to be. He was excited to compare battle scars with Henry Sturgis at the Day of Hope family conference.

We are so proud of Sam for his perseverance and courage, and for the way he took responsibility for his health and decided he was ready to move forward. There's nothing I could've done to convince him to start taking all his pills by mouth. It was a decision he had to make, and when he did it, he didn't look back. The g-tube was a big part of his life and our lives for many years, but we are ready for this new phase!

Emerson Family Update

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

It's been six years since Brooke's diagnosis. Looking back, I marvel at how much she has grown and where we are now as compared to then, so much has changed!

Brooke is currently wrapping up 2nd grade, and to people who don't know much about cystinosis and what Brooke deals with behind closed doors, she looks and acts like a typical seven-year-old. She is growing and gaining weight well and is blossoming into an independent and unique girl. We are so proud of the academic progress that she has made, while virtual learning during the pandemic was certainly a challenge, she has bounced back nicely and loves school and her friends. Her favorite subjects are social studies and Spanish. She has come out of her shell and has turned into quite the social butterfly!

Over the past year, she has become increasingly more aware of her situation, and has many questions about her medications and why she takes them. She is also beginning to understand the role she has in her care. During the school day, Brooke goes to the nurse for supplementary tube feeds if she hasn't had enough breakfast or lunch orally. Recently, Brooke has decided that she no longer wants to visit the school nurse multiple times per day, and she has taken it upon herself to eat more orally so that she doesn't need tube feeds. Since committing to this, Brooke has gained weight more quickly than she has in a long time! She also wants to get rid of her g-tube by the time she is ten years old (her timeline) and is actively working on what needs to be accomplished to make that a reality. While Brooke doesn't understand and know everything about cystinosis, she is old enough to participate in parts of her care and is taking ownership of what she can. She has embraced that her growth hormone shots are necessary for growth and strength, her eyedrops, while unpleasant and disruptive as a every waking hour treatment, are necessary for her eyes, and eating more orally and swallowing pills is a requirement in order to have her g-tube removed. We couldn't be prouder of the growth that she has made in such a short period of time.

That's not to say that the past six years have been without challenges. As with any progressive condition, we have hit bumps in the road here and there. Brooke deals with nausea and stomach pain on and off, and we continually work to find ways to decrease the negative side effects of her medication. This summer, we struggled to find an appropriate summer camp given her aversion to extreme heat and her photosensitivity. We still have Brooke in physical therapy and occupational therapy to proactively address issues we expect to arise as cystinosis progresses.

Often, we are hit with the realization that time isn't a luxury you feel like you can afford when living with a progressive condition, and even when things are going well, there is often a race against the clock mentality. So, we look forward to the advances that CRF-funded researchers continue to make and are grateful that during these past six years so much progress has been made. Six years ago, when we received the diagnosis, Clay and I could never have imagined that five people would have received the stem cell therapy, and we are so hopeful that Brooke might be able to receive the therapy soon. In the meantime, we continue to fundraise so that we may have better eye treatments available so that Brooke doesn't have to take eye drops every waking hour and doesn't have to seek out indoor camps and activities because of her photosensitivity. We fundraise so that research on muscle wasting and Fanconi syndrome can continue so that hopefully the progression of cystinosis can be slowed, stopped, and potentially reversed. We fundraise in the hope that treatments are identified without all the side effects caused by those currently available.

We look forward to the next six years, and where we will be then. We are anxious for the therapy to be available to pediatric patients as we race against the clock, and we hope that the stem cell therapy is approved and available to all cystinosis patients. We hope that perhaps six years from now Brooke will have been "cured."

Brooke is old enough to participate in parts of her care and is taking ownership of what she can.

Partington Photo Journal

2021 – 2022

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

NYC STUDY

During her spring break week, I took Jenna to participate in the CRF-funded cognitive study at Albert Einstein College of Medicine in The Bronx, NY. We enjoyed our stay in Manhattan, fitting in a Broadway show, walks in Central Park and shopping between study visits!

(Almost) KIDNEY TRANSPLANT

Jenna was scheduled to receive a kidney transplant in March. She was admitted to Stanford's Lucile Packard Children's hospital two days prior to surgery to receive IV fluids and supplements to prepare for surgery.

Her blood chemistry improved so dramatically during this time, her transplant team suggested holding off. Jenna's medications have been adjusted to try to match the improved kidney function that Jenna experienced while on IV Fluids. She is having weekly blood draws to check her blood chemistry and it's going okay. I remember an attending ICU physician calling Jenna an "electrolytic marvel" when she was just a baby. She still is.

Jenna and Patrick will both still need kidney transplants. The timing is TBD.

SEVENTEEN

As I write this, Jenna and Patrick are at Six Flags Theme Park in Vallejo, CA. Patrick drove. They are stopping at Starbucks on the way. Heaven knows what kind of music DJ Jenna, in the passenger seat, is streaming for the ride. They are experiencing "normal" and "17" and being out and about and social after the long couple of years the world has experienced. Spring break has been a good time for the two of them to spend time together. It's unreal to think that next year at this time, they'll be making plans for life beyond home and high school.

It's unreal to think that next year at this time, they'll be making plans for life beyond home and high school.

GRANDPA DOUG

A startling and devastating event was the passing of my Dad, Doug Batt "Grandpa Doug" on January 19.

We had a wonderful Christmas with him and my mom. The first week of January saw him actively building a fence in our yard. He became ill very quickly, and the last six days of his life were difficult. We are still adjusting to the loss of such an important person in our lives. My dad's spirit is at work in so much of what we do. I love that Jenna and Patrick were able to know and love him so well, and hope they always trust that he is the butterfly, hummingbird, song and beauty that follows them throughout their lives.

LOOKING FORWARD

We are thrilled to know that Natalie and the other transplanted patients are doing so well!

The Day of Hope was a bonding, enlightening time, as always, and we are encouraged by the large body of research into cystinosis that continues to be funded by CRF. We live for news of new knowledge, improved drugs, and potential cures, just as we wonder how cystinosis will shape Jenna and Patrick's late teens and early 20's and beyond. Patrick and Jenna agree that cystinosis is not what shapes them. They are shaping their lives around their disease, more independently all the time. Kevin and I agree it is a freeing feeling after so many years of caring for their unique needs. Yet: there are still more than 20 prescriptions to fill each month (how long will I be in charge of that? Isn't it the least I can do?), doctor visits to manage and show up to, specialty lab kits to be ordered and shipped, transplants to consider and more. While we don't lament the disease during our day-to-day… it hovers over us. Making sure it doesn't consume any of this family of four is the goal. Everyone has difficulties to rise above. Grandpa Doug has reminded us that life is for living. Now.

Love,
Teresa, Kevin, Patrick & Jenna

The Day of Hope was a bonding, enlightening time, as always, and we are encouraged by the large body of research into cystinosis that continues to be funded by CRF.

GIVING TUESDAY

MATCHING **$50,000** GIFT CHALLENGE

Your generosity on Giving Tuesday exceeded our goal, raising **more than $230,320** for the CRF research program.

Thank you for making Giving Tuesday the most successful in CRF history! Your support will allow us to accelerate research that will lead to new treatments and a cure for cystinosis.

One hundred percent of your contributions will go directly to research. Thank you for being part of the Cystinosis Research Foundation community – we are changing lives together!

SAVE THE DATE

TUESDAY, NOVEMBER 29, 2022

TOGETHER, WE ARE one

1 PURPOSE. 1 JOURNEY. 1 CURE.

COMMUNITY NEWS

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

TOGETHER, WE ARE one

1 PURPOSE.
1 JOURNEY.
1 CURE.

In Honor of Emma Suetta – Etna, California

90-MILE BIKE RIDE FOR THE CURE

Sara Kennedy trained for months to complete the self-imposed 90-mile bike ride for the CDA Fondo race around Lake Coeur D'Alene. She paired her training for the race with a fundraiser in honor of her friend, Shelly Suetta, and her adorable daughter Emma, to support cystinosis research. Race day brought a wet ride in the rain and created challenges on the downhill sections of the course, slowing her progress, but her 6-hour and 41-minute journey generated donations of $1,738. Thank you, Sara, and all those who participated for your commitment to cystinosis research!

In Honor of Collins Galloway – Cumming, Georgia

FIRST ANNUAL WINDERMERE CHARITY GOLF CLASSIC

Thank you to the Galloway family for hosting their first annual Windermere Charity Golf Classic in December in honor of their daughter, Collins. Community and friends enthusiastically supported the event with 64 golfers registered to participate in the tournament to support CRF and cystinosis research. Following a fun-filled day of golf, nearly 100 people gathered for dinner at the country club. A big thanks to the Windermere Country Club staff, Adam Brown, Eddie Rundle, Josh Nichols, Clint Erickson, Joe Yagey and Bobby Hutchinson, who helped make the event a success. At the end of the evening, an incredible $7,000 was raised for cystinosis research! We are grateful to the Cumming community for their generosity and support for Collins.

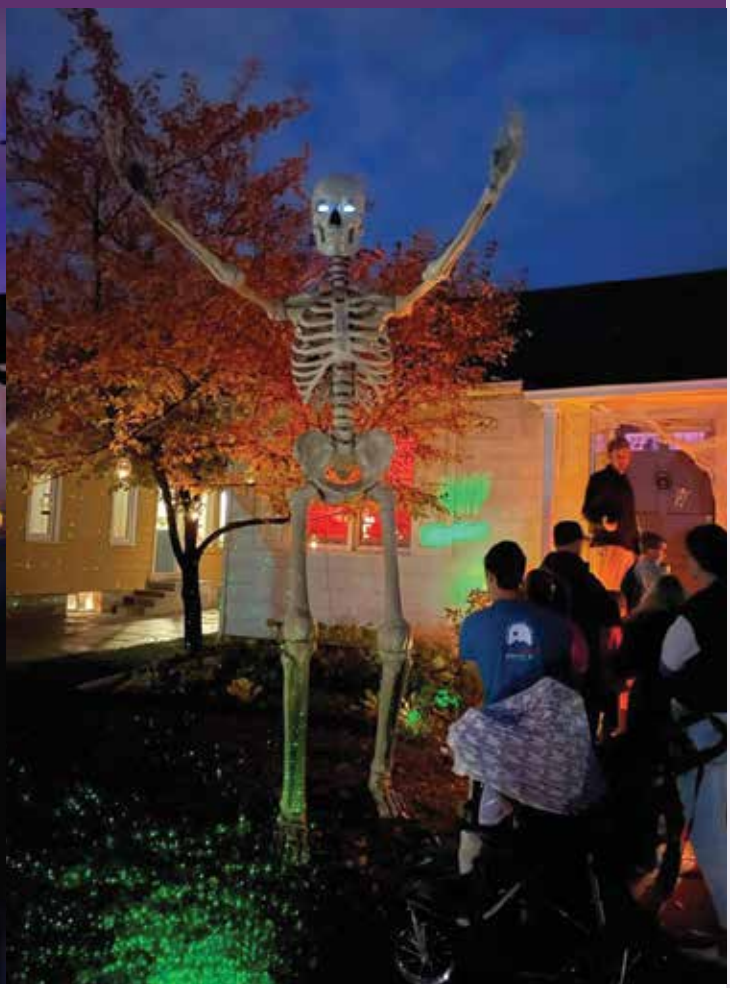
In Honor of Lily Beauregard – Swansea, Massachusetts

THIRD ANNUAL CHILI COOK-OFF

The 3rd Annual Chili Cook-off held in honor of Lily Beauregard was organized as a fundraiser for CRF by Shelli Pereira, a dear friend of the Beauregard family. The community enthusiastically participated in the event. There were awesome chili cooks, dedicated volunteers, entertaining musicians and generous donors. The Eagle Event Center and the Dunny crew provided beautiful space and wonderful service. At the end of the festivities, more than $5,279 was raised for CRF and cystinosis research. Courtney, Kevin and Lily are grateful to their friends and neighbors for their generosity and support in joining their quest for a cure!

TOGETHER, WE ARE one

1 PURPOSE.
1 JOURNEY.
1 CURE.



In Honor of Sam and Lars Jenkins – Salt Lake City, Utah

SECOND ANNUAL HAUNTED HOUSE

The evening of Saturday, October 23, was a scary night in the Jenkins' neighborhood as the family hosted their second annual Haunted House to raise money for CRF and cystinosis research. Together, the family masterfully redecorated the living room and kitchen in a super spooky motif and built a terrifying path into the backyard employing their nieces and nephews to be ghosts and goblins. Sam scared unsuspecting people by popping out of a cardboard box. The grand finale took place in a closed chamber embellished with a fog machine, strobe light and Lars in a terrifying mask scaring and delighting the more than 200 visitors who at the end of the night raised over $3,000! Thank you, Ashton, Stephen, Sam and Lars, for sharing your haunted house to support cystinosis research and a cure!

TOGETHER, WE ARE one

1 PURPOSE.
1 JOURNEY.
1 CURE.

In Honor of Brooke Emerson – Hammonton, New Jersey

SEVENTH ANNUAL FISHING FOR BROOKE'S CURE

Those participating in the 7th Annual Fishing for Brooke's Cure fundraiser were up against some terrible conditions this year, freezing weather and a lack of fish! But undeterred, they fished their hearts out and caught 121 fish. Despite the challenges, it was another successful fundraiser for the Emerson family, with a record 200 individual donations/pledges raising $28,861, with contributions still coming in! Thank you, Jill, Clay and Brooke, for hosting and organizing this extraordinary fundraiser. We are grateful to your friends, family and community for the overwhelming support for Brooke and cystinosis research. Since your first fishing event, CRF has received $168,981 in honor of Brooke to help fund cystinosis research and find a cure. Thank you all for joining our quest for the cure!

In Honor of Henry Sturgis – Sandpoint, Idaho

14TH ANNUAL 24 HOURS FOR HANK SKI EVENT

The 2400 Feet of Schweitzer Mountain held on March 26, was the 14th annual 24 Hours for Hank Ski event. The skiing conditions were perfect, with clear skies and firm snow. The racer's legs were burning by the time they finished the 2.4-mile course, taking the fastest skiers nearly four minutes to finish. There were 69 racers who participated, and they made the event a tremendous success, raising over $104,000 for cystinosis research!
A special thank you to Brian Sturgis and his committee, the Schweitzer Mountain team, as well as everyone who participated. CRF is grateful for your dedication and commitment in honor of Henry and cystinosis research!

CYSTINOSIS COMMUNITY CALENDAR OF EVENTS

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

Saturday, July 9, 2022

5TH SHOOT FOR CYSTINOSIS
IN HONOR OF ABBI MONAGHAN
Decew Gun Club, Thorold, Ontario, Canada
Contact Katie Monaghan: k8tmonaghan@yahoo.ca

Monday, August 8, 2022

KEGS 4 KAUSE
HEARTS FOR HADLEY
IN HONOR OF HADLEY ALEXANDER
Payette Brewing Co., Boise, Idaho
Contact Marcu Alexander: hearts4hadley@gmail.com

Friday, August 12, 2022

SHOOTING FOR A CURE
HOPE & WISHES
IN HONOR OF JAKE KRAHE
Hill 'n Dale Club, Medina, Ohio
Contact Jeremy Krahe: jdkrahe25@gmail.com

Thursday, Sept. 2 – Sunday, Sept. 4, 2022

CAPITAL CUP GOLF TOURNAMENT
IN HONOR OF JENNA & PATRICK'S
FOUNDATION OF HOPE
Sacramento, California

Saturday, October 15, 2022

9TH ANNUAL
HEARTS FOR HADLEY BENEFIT
IN HONOR OF HADLEY ALEXANDER
Jump, Boise, Idaho
Contact Marcu Alexander: hearts4hadley@gmail.com

Thursday, October 21, 2022

SETH'S CIRCLE OF HOPE
IN HONOR OF SETH DEBRUYN
CALGARY, CANADA
Contact Kristen Murray: murraykristen@hotmail.com

Tuesday, November 29, 2022

GIVING TUESDAY
HELP FUND A CURE FOR CYSTINOSIS!
CYSTINOSIS RESEARCH FOUNDATION
www.cystinosisresearch.org

Spring 2023

10TH ANNUAL SWING GOLF EVENT
JENNA & PATRICK'S FOUNDATION OF HOPE
In honor of Jenna and Patrick Partington
Catta Verdera Country Club, Lincoln, California
Contact Kevin Partington: kevin.partington@cushwake.com

Dr. Jerry Schneider was a pillar of the cystinosis community, he will never be forgotten.

Dr. Dohil, Dr. Trauner, Morton Kondracke and Dr. Schneider

Elaine, Jerry, Jane and Danielle Schneider

Dr. Jerry Schneider: In Memoriam

Our community mourns the loss of Dr. Jerry Schneider who passed away on December 28, 2021. Dr. Schneider dedicated his entire career to ensuring that those affected by cystinosis would get the best care and treatment possible. Dr. Schneider along with his colleagues discovered cysteamine treatment, and he later became the Co-Principal Investigator that discovered the delayed-release form of cysteamine (Procysbi®). He was passionate about finding a cure for cystinosis and was amazed and proud when the stem cell trial was approved by the FDA in 2019.

"I admired Jerry during all my career for his amazing contribution to the cystinosis field. As a student, I so admired his work and his outstanding publications on cystinosis. When I met him for the first time while he was visiting our lab in Paris, I was amazed by his intelligence but also his goodness and kindness. Jerry was a strong supporter of my work and advised me all along. He was such a great person with who I loved to talk science but also laugh; he had a great sense of humor. He supported my transition to the University of California San Diego, and I am so proud to consider him as a mentor and role model." - Stéphanie Cherqui, PhD

Dr. Schneider was the chair of the CRF Scientific Review Board and as the chair, he guided the early CRF research strategy which has now grown exponentially into a global research community. We fondly remember Dr. Schneider as a kind, gentle and loving person, and we are grateful for his dedication to our community. Dr. Schneider was a pillar of this community; we will miss him.

Cystinosis Cure Foundation

RESEARCH UPDATES

The Wish is alive

Venturing Inside Cells to Rescue Bone Health

A new study made possible by CRF support could ultimately help reverse cystinotic skeletal disease.

by Dennis Arp

For cystinosis patients and their families, the prospect of organ failure is familiar and ominous. What often starts with the kidneys seldom stops there; it seems inevitable that other organ failures will follow.

Now, thanks to support from the Cystinosis Research Foundation (CRF), researchers are working to eliminate a critical link in that chain of inevitability. Their study may help protect the long-term bone health of those living with cystinosis.

A CRF grant is funding a pioneering bone research project led by Dr. Andrea Del Fattore, who for more than 20 years has studied the physiopathology of bone ailments. He is joined on the project by Dr. Giulia Battafarano, with unique expertise in how cystinosis affects bone health.

Their research explores how cystinosis causes primary defects of bone cells. The study may ultimately illuminate pathways to treatments that restore normal bone function.

"Cystinosis patients don't have such specific treatment. When that can be developed, it will have a direct effect on their quality of life."

The project dovetails with previous research shedding light on the prevalence of bone ailments in cystinosis patients and how the disease disrupts the development of healthy bones.

Research led by Dr. Pablo Florenzano found that 27% of cystinosis patients reported one or more long-bone fractures, while 46% experienced a reduction of bone mineral density.

To date, it's been thought that these skeletal effects of cystinosis were caused by a depletion of phosphate, which is crucial for bone growth and mineralization. Patients often develop bone ailments without sufficient phosphate, including Rickets, a childhood disease characterized by soft or distorted bones.

Recent research by Dr. Del Fattore and his team has found that bone complications in cystinosis patients have roots beyond the breakdown in kidney function, causing phosphate depletion.

"We recently demonstrated that bone alterations and decreased mineralization are also due to primary defects in bone cells," said Dr. Del Fattore.

This discovery of reduced bone metabolism unrelated to kidney impairment was revealed by studying the specialized cells responsible for new bone formation. These cells, called osteoblasts, showed increased expression of cathepsin D, an enzyme that degrades proteins.

"With this new study, we hope to understand the changes in cystinotic osteoblasts better and to evaluate whether inhibiting cathepsin D in these osteoblasts can restore the bone remodeling in cystinosis," said Dr. Battafarano.

To test their hypothesis, Dr. Del Fattore and Dr. Battafarano will treat the affected cells with a cathepsin D inhibitor and evaluate the effects on their differentiation and activity.

"Moreover, osteoblasts maintain the integrity of the skeleton also by regulating the differentiation and activity of bone-resorbing cells called osteoclasts," Dr. Del Fattore said. "So, we will also analyze the potential of treated cystinotic osteoblasts to regulate the osteoclast function to restore the physiological bone remodeling in cystinosis."

In this phase of their research, Dr. Del Fattore and his team perform in vitro and in vivo experiments.

"Ultimately, we will seek to confirm the results using human cells, but it's difficult to obtain these cells because it requires an invasive procedure," said Dr. Del Fattore.

"The primary goal of the project is to provide results the scientific community can use to continue expanding the body of knowledge on cystinosis and bone health," said

RESEARCH UPDATE

ANDREA DEL FATTORE, PhD and GIULIA BATTAFARANO, PhD

Bambino Gesù Pediatric Hospital, Rome, Italy

Dr. Battafarano. "Cystinosis patients don't have such specific treatment. When that can be developed, it will have a direct effect on their quality of life."

Dr. Del Fattore expressed that the means for inhibiting cathepsin D might end up being a drug infusion, but multiple agents are still being studied and developed, so there are many variables to be worked through before the best delivery agent emerges.

There are no guarantees, of course, but if progress continues and the impediments to normal bone health can be reversed, cystinosis patients may be able to match the growth patterns of their healthy age-group peers, with less bone fragility and far fewer deformities.

"If, as someone affected by cystinosis, you can move like those who are unaffected by the disease, then there's no question but that you can live a better life," said Dr. Battafarano.

The chance to be agents of change on behalf of cystinosis patients and their families motivates the researchers in the lab.

"It's important to create a deep connection between the researchers, clinicians, and patients," said Dr. Del Fattore. "We want to understand what they go through every day so we are able to do all we can to improve the quality of their lives."

It's all made possible by support from the Cystinosis Research Foundation.

"We're so grateful because, without that support, we wouldn't be able to increase our knowledge," said Dr. Del Fattore. "That's very important to us, but also the whole community."

Understanding the Course of Cell Correction

By going inside the metabolic process, a new study aims to maximize stem cell transplantation.

by Dennis Arp

When Shawn Davidson was a PhD student at the Massachusetts Institute of Technology in 2010, he became deeply interested in the targeting cellular metabolism to treat cancer. His approach to profile the alterations in metabolism provided a broad framework to understand how to target metabolic vulnerabilities or how to target metabolism to improve cellular health.

His fascination in targeting metabolism evolved to identifying specific targets in other diseases, including neurodegenerative ailments and genetic diseases like cystinosis.

The armamentarium to study metabolism is evolving, "I've spent a lot of time over the past 12 years building new tools for studying metabolism," said Davidson, PhD, now an associate research scholar at Princeton University. "We need new ways to look inside cells and tissues and then we need to study the application to treat these diseases across the board."

During his research journey, Dr. Davidson got the opportunity to attend Cystinosis Research Foundation's (CRF) annual Day of Hope Conference, during which he met cystinosis patients and learned about how the disease impacts their lives.

Grant support from the CRF is keeping the project on track.

"That was really moving and inspiring," he said. "I became extremely committed to doing something different and important to improve the lives of patients."

His chance to make a transformational difference has now arrived in the form of a new metabolic study supported by a grant from the CRF.

The goal of Dr. Davidson's novel research project is to develop methods to measure the degree of metabolic correction provided by stem cell transplantation. In addition, he will test the effects of multiple drugs and natural substances on the performance of transplanted stem cells.

"We're eager to see if we can improve transplantation outcomes," he said.

It's a particular joy for Dr. Davidson, that his project will have a chance to enhance the breakthrough stem cell research that could well be the cure cystinosis patients have been seeking. That research, made possible by the CRF, shows how transplanted stem cells correct the metabolic defect in cystinosis.

"The stem cells send out long, thin filaments (projections known as tunneling nanotubes) that connect to surrounding cells," Dr. Davidson explained. "Metabolites, lysosomes, and mitochondria are exchanged between cells via those filaments."

The first phase of his study will try to visualize the process of metabolism, using a new technology called tissue Imaging Mass Spectrometry (IMS). In so doing, Dr. Davidson hopes to measure levels of cysteamine, cystine and related compounds in mouse tissues at the single-cell level.

In the second phase of the study, he will use IMS to characterize the metabolic profile of tissues in three different kinds of mice – normal, those with cystinosis, and those that have had cystinosis corrected by stem cell transplantation.

"We're hoping to get additional insights into the mechanisms by which stem cells influence the surrounding cells," he said.

The study's third phase will use a drug-delivery microdevice to individually administer compounds to different tissues of cystinosis mice transplanted with healthy stem cells. A combination of conventional fluorescence microscopy to visualize how these agents alter tunneling nanotubes and IMS will be used – this time to measure the effect of the compounds on the quantity of lysosome transfer and degree of metabolic correction.

"I was really inspired by the work of Dr. Stéphanie Cherqui and others, showing that you can have these donor cells contribute healthy lysosomes to sick cystinosis cells," Dr. Davidson said. "I want to be able to measure and

RESEARCH UPDATE

SHAWN DAVIDSON, PhD

Princeton University, Princeton, New Jersey

quantify the consequences of these interactions. I think our technology really lends itself to quantitatively determining the impact of this therapy, which will help in evaluating the efficacy and generate hypotheses about paths toward further improvement."

Those questions include: How durable will the stem cell treatment prove to be? How efficient is the transfer of the lysosomes between cells? Which cell types receive lysosomes from the donors? What other metabolic changes are happening in the process?

"More importantly, can we get healthy cells to donate more lysosomes?" Dr. Davidson adds.

In the process of pursuing those answers, the new technology emerging has a chance to change the nature of metabolomics – the study of processes within cell metabolism.

"In contrast to conventional metabolomics assays where one needs an input of as many as 100,000 cells," he said. "We're getting very close to getting all the information from single cells."

The advances in technology open new possibilities for even more breakthroughs.

"If we can understand how the donor cells act once they're inside the host, I think it will lend itself to a number of interesting opportunities on how to improve this therapy," Dr. Davidson said.

As for the timeline of the project, Dr. Davidson hopes to have a pilot up and running within the next few months, with substantial data being generated within a year.

Grant support from the CRF is keeping the project on track.

"It has allowed me to hire an extra person and to get materials with a specific application for this project," he said. "The support has given me an analytical edge and the ability to have a focused effort on a developing broadly applicable methods to measure chemical classes of compounds (thiols and disulfides)."

Being welcomed into the cystinosis community has also left an indelible impression.

"One thing that stood out about the Day of Hope was hearing the kids say that they look forward to it more than Christmas," Dr. Davidson said. "That told me a lot about this community. The whole experience was incredibly motivating."

Seeking Important Insights on Neuromuscular Damage

A CRF grant supports foundational research to discover the long-term effects of skeletal and respiratory decline in cystinosis patients.

by Dennis Arp

Often it starts with muscle weakness in the hands. Jar lids and twist-off bottle tops just won't budge anymore. Eventually it becomes impossible to dress in the morning without some assistance. In rare cases when muscle weakness progresses to hamper breathing and swallowing, the effects can be devastating.

For years, cystinosis patients, families and doctors have known about the potential for muscle complications as patients age and the effects of the disease advance. But little is known about the rate of muscle failure, nor about the long-term consequences and natural history of symptoms.

Now these questions will be explored in depth. Thanks to a grant from the Cystinosis Research Foundation (CRF), experienced research physicians in France are launching a study to thoroughly investigate the neuromuscular complications of cystinosis, focusing on skeletal and respiratory muscle weakness.

For more than two decades, Pascal Laforêt, MD, PhD, and Hélène Prigent, MD, PhD, have been working to better understand neuromuscular disorders and treat patients to lessen the effects.

"It confirms for us that the energy we put into this is well invested"

"I evaluate neurological and neuromuscular patients almost every day, so I know very well how people's lives are impacted," Dr. Prigent said.

Laforêt and Prigent have collaborated on research for many years at the medical center Hôpital Raymond Poincaré in Garches, France. Joining them on this cystinosis research project is Aude Servais, MD, PhD, a nephrologist who treats adult cystinosis patients at Hôpital Necker, a hospital in Paris that specializes in the treatment of rare diseases.

"We are very experienced in searching for the predictive factors of disease," Dr. Servais said.

The goals for this new observational cystinosis research study are to learn more about the root causes and pathways of neuromuscular involvement in patients. They will also seek to translate their findings into applications of care that optimize disease management and target quality of life.

About 20 adult cystinosis patients are being recruited in France for the study, which is on track to begin this summer.

Dr. Laforêt and Prigent, as principal investigators on the project, have assembled a cross-disciplinary team that in addition to clinical experience includes experts in pulmonology and radiology, as well as physical and occupational therapy.

The partners in the project "are specialists in exploring the muscles," Dr. Laforêt said. "We're all very excited because little is known about neuromuscular involvement with cystinosis."

The research will be performed at the Raymond Poincaré Hospital Neuromuscular Center, using standardized tools to assess muscle strength and function in each patient. Whole body Magnetic Resonance Imaging (MRI) will be performed to better describe the pattern of skeletal muscle involvement. In addition, respiratory muscle damage will be investigated with specific pulmonary function explorations and systematic evaluation of its consequences on breathing efficiency.

"We will also analyze the swallowing function in patients complaining of difficulties as well as those who have a significant impairment rating after they complete a questionnaire on swallowing," Dr. Laforêt said. "Clinical tests will be performed at baseline and after one year."

The researchers plan to correlate their findings with other complications of cystinosis, such as reduced kidney function, transplantation, leukocyte cystine levels and inconsistent compliance with treatment.

Dr. Laforêt and Prigent note that they have some foundations for insight from their previous work investigating Pompe disease, another rare lysosomal storage condition.

"We have done a lot of research on this disease, including an academic registry that goes back 15 years, so we've been able to analyze very precisely the effects of the disease such

RESEARCH UPDATE

PASCAL LAFORÊT, MD, PhD and HÉLÈNE PRIGENT, MD, PhD

Raymond Poincaré University Hospital, Garches, France

as its potential for severe respiratory failure," Dr. Laforêt said. "The registry has allowed us to monitor overtime response of muscle function to treatment."

With their cystinosis research project, the doctors are just beginning to capture data. Still, the team is beginning with some hypothetical awareness.

Because the treatment regimen for cystinosis has proved generally effective, Dr. Prigent suspects that they may see complications related to noncompliance.

"Sometimes patients get fatigued with following the regimen of treatments, so one thing we'll be looking at is whether complications are more frequent when we have disruptions in the treatment," she said.

Dr. Laforêt added that experience with Pompe disease suggests that "some treatments are less efficient in targeting muscles," he said. "With Pompe disease, we have a treatment that we know improves the heart very quickly, but it is less effective with the skeletal muscle and even less with the diaphragm. So perhaps [with cystinosis], it's a matter whether current treatment targets the muscle, less than the kidney."

Dr. Servais said that early results seem to support a hypothesis that where there are neuromuscular complications, fat replaces lean muscle mass.

With more MRI and functional test results, "we should be able to see if there's a direct correlation," she added.

All three doctors are eager to gather more widespread results so they can improve the overall understanding of how to tailor care "that has a direct impact on quality of life," Dr. Prigent said.

The grant support from CRF helps make it all possible, the doctors say.

"Now we're able to accelerate the process of collecting and analyzing data," Dr. Prigent said.

The support also tells the doctors that this area of research is important to the cystinosis community.

"It confirms for us that the energy we put into this is well invested," Dr. Laforêt said.

CRF Funded Research DISCOVERIES from Bench to Bedside

Clinical Trials Underway

UC San Diego Stem Cell and Gene Therapy Trial for Cystinosis.

The Stem Cell and Gene Therapy clinical trial is underway. Recruitment for Phase I/II is almost complete. The trial is available to individuals worldwide, though priority will be given to U.S. patients. If you are a patient with cystinosis and are interested in participating in the Phase III trial or would like more information, please email Anne Sawyers at *amsawyers@health.ucsd.edu* or call Anne at 858-246-4986. For additional inclusion or exclusion information, visit the CRF website. This study is currently funded in part by the Cystinosis Research Foundation (CRF). *www.cystinosisresearch.org/current-clinical-trials*

Cystinosis Patients - Are you interested in learning more about how the brain functions?

This CRF funded study by Sophie Molholm, PhD, is now recruiting patient volunteers. The project aims to gain a better understanding of how brain function is affected by cystinosis, focusing on auditory and visual processing and memory. Contact Ana Francisco for more information *ana.alvesfrancisco@einsteinmed.org* or call 718-862-1824. This study is currently funded by the Cystinosis Research Foundation (CRF). *www.cystinosisresearch.org/current-clinical-trials*

Characterization of Distal Myopathy and Dysphagia in Nephropathic Cystinosis and Evaluation for Muscle Regenerative Capacity Research Study.

Now Open to Adults 18+ Years

Dr. Reza Seyedsadjadi and Dr. Florian Eichler of the Massachusetts General Hospital (MGH) Center for Rare Neurological Diseases are conducting a study to learn more about muscle weakness and swallowing difficulties in Nephropathic Cystinosis and the ability of these muscles to regenerate (rebuild themselves). For more information contact Natalie Grant at 617-643-3799 or *nrgrant@mgh.harvard.edu*. This study is currently funded by the Cystinosis Research Foundation (CRF). *www.cystinosisresearch.org/current-clinical-trials*

A new study funded by the Cystinosis Research Foundation at the Bambino Gesù Children's Hospital, in Rome, Italy, could ultimately help reverse cystinotic skeletal disease.

CRF is funding a pioneering bone research project led by Dr. Andrea Del Fattore, who for more than 20 years has studied the physiopathology of bone ailments. He is joined on the project by Dr. Giulia Battafarano, a research fellow with special expertise in how cystinosis affects bone health. Their study may help protect the long-term bone health of those living with cystinosis.

Improving characterization of neuromuscular involvement in adults with cystinosis. A research study funded by the Cystinosis Research Foundation at the Hôpital Raymond Poincaré, in Garches, France.

Neurologist Pascal Laforêt, MD, PhD, and Pulmonologist, Hélène Prigent, MD, PhD, will explore the neuromuscular complications of cystinosis focusing on skeletal and respiratory muscles weakness in a cohort of patients followed in Necker-Enfants-Malades Hospital Center for inherited renal disorders (Dr. Aude Servais, Nephrologist).

Twenty patients will be recruited and evaluated at the Raymond Poincaré Hospital Neuromuscular Center by Dr. Laforêt to assess muscle strength and function with standardized tools. A full-body muscle MRI will be performed to describe the pattern of skeletal muscle involvement. Dr. Prigent will investigate respiratory muscle damage with specific pulmonary function explorations and systematic evaluation of its consequences on breathing efficiency. They will also analyze the swallowing function in patients complaining of swallowing difficulties, or with significant impairment rating after having completed a swallow questionnaire.

THE IMPACT OF CRF RESEARCH

AREAS OF RESEARCH FOCUS & GRANTS AWARDED SINCE 2002

New Drug Discovery Cysteamine, New Medications and Devices

30 GRANTS

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

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

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

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

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

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

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

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

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

Michael Sekar, PhD
AMMA THERAPEUTICS, INC., HAYWARD, CALIFORNIA

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

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

Eye-Corneal Cystinosis Research

10 GRANTS

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

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

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

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

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

Cystine Measurement and Cysteamine Toxicity Study

10 GRANTS

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

Shawn Davidson, PhD
PRINCETON UNIVERSITY, PRINCETON, NEW JERSEY

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

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

Cellular and/or Molecular Studies of the Pathogenesis of Cystinosis

60 GRANTS

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

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

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

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

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

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

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

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

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

Bruno Gasnier, PhD NEW
Yann Terras, MSc
CNRS/UNIVERSITÉ DE PARIS, PARIS, FRANCE

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

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

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

Alessandro Luciani, PhD
UNIVERSITY OF ZÜRICH, ZÜRICH, SWITZERLAND

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

Norbert Perrimon, PhD
HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

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

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

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

Bruno Vogt, MD
Daniel Pouly, PhD
UNIVERSITY HOSPITAL OF BERN, BERN, SWITZERLAND

Skin, Muscle and Bone

18 GRANTS

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

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

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

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

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

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

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

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

Thyroid

1 GRANT

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

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AREAS OF RESEARCH FOCUS & GRANTS AWARDED SINCE 2002

Molecular Study of Cystinosis in the Yeast Model

3 GRANTS

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

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

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

Genetic Analysis of Cystinosis

5 GRANTS

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

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

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

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

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

Neurological

17 GRANTS

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

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

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

Florian Eichler, MD
MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS

NEW

Pascal Laforêt, MD, PhD
Hélène Prigent, MD, PhD
RAYMOND POINCARÉ UNIVERSITY HOSPITAL, GARCHES, FRANCE

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

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

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

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

Cure Cystinosis International Registry (CCIR)

1 GRANT

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

Rat Model for Cystinosis

3 GRANTS

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

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

THE IMPACT OF CRF RESEARCH

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

34 GRANTS

NEW

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

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

Bruno Gasnier, PhD
PARIS DESCARTES UNIVERSITY, PARIS, FRANCE

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

Patrick Harrison, PhD
UNIVERSITY COLLEGE CORK, CORK, IRELAND

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

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

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

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

Kidney Research

23 GRANTS

Robert Chevalier, MD
UNIVERSITY OF VIRGINIA, CHARLOTTESVILLE, VIRGINIA

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

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

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

NEW

Benjamin Freedman, PhD
UNIVERSITY OF WASHINGTON, SEATTLE, WASHINGTON

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

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

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

Philip Newsholme, PhD
CURTIN UNIVERSITY, PERTH, WESTERN AUSTRALIA

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

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

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

Lab Equipment for Cystinosis

9 GRANTS

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

Corinne Antignac, MD, PhD
IMAGINE INSTITUTE, PARIS, FRANCE

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

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

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

2021 CRF RESEARCH GRANT AWARDS

TOTAL 2021 RESEARCH GRANTS AWARDED $2,152,223

FALL GRANTS AWARDED $1,539,980

RESEARCH GRANTS

Francesco Bellomo, PhD
Principal Investigator
Francesco Emma, MD
Co-Principal Investigator
Bambino Gesù Children's Hospital, Rome, Italy

"Vanin-1 as therapeutic target in nephropathic cystinosis"

$181,874 TWO-YEAR STUDY

Stéphanie Cherqui, PhD
Principal Investigator
University of California, San Diego, La Jolla, California

"Advancing the understanding of renal Fanconi syndrome in cystinosis"

$329,908 TWO-YEAR STUDY

Andrea Del Fattore, PhD
Principal Investigator
Giulia Battafarano, PhD
Co-Principal Investigator
Bambino Gesù Children's Hospital, Rome, Italy

"Analysis of the impact of Pepstatin A/Cysteamine combined treatment on bone remodeling activity of cystinotic mice"

$225,500 TWO-YEAR STUDY

Benjamin Freedman, PhD
Principal Investigator
University of Washington, Seattle, Washington

"Developing a therapeutic strategy for nephropathic cystinosis with iPS cells"

$283,490 TWO-YEAR STUDY

2021 CRF RESEARCH GRANT AWARDS

Indicates Fall Grants

Bruno Gasnier, PhD
Principal Investigator
CNRS / Université de Paris, Paris, France

"A critical role for cystinosin during embryo development"

$265,000 TWO-YEAR STUDY

Pascal Laforêt, MD, PhD
Principal Investigator
Hélène Prigent, MD, PhD
Co-Principal Investigator
Raymond Poincaré University Hospital, Garches, France
Aude Servais, MD, PhD
Co-Principal Investigator
Necker Hospital, Paris Descartes University, Paris, France

"Improving characterization of neuromuscular involvement in adults with cystinosis"

$139,323 THREE-YEAR STUDY

Robert Mak, MD, PhD
Principal Investigator
University of California, San Diego, La Jolla, California

"Dietary glycine supplementation attenuates infantile nephropathic cystinosis-associated muscle wasting and adipose tissue browning"

$296,759 TWO-YEAR STUDY

Bruno Vogt, MD
Principal Investigator
Daniel Pouly, PhD
Co-Principal Investigator
University Hospital of Bern, Bern, Switzerland

"Early events of cystinosis pathogenesis: pro-apoptotic signals and mRNA translation"

$196,090 ONE-YEAR STUDY

EQUIPMENT GRANT

Sergio Catz, PhD
The Scripps Research Institute, La Jolla, California

Celldiscoverer CD7 Zeiss Microscope

$234,279 PURCHASE TOTAL

SEE 2021 FALL
LAY ABSTRACTS
STARTING ON NEXT PAGE

Advancing the understanding of renal Fanconi syndrome in cystinosis

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

OBJECTIVE/RATIONALE:

Although cystinosin, the protein involved in cystinosis, is expressed in all the organs, renal Fanconi syndrome is the first manifestation of cystinosis that presents early in the 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 functions of cystinosin in the kidney beyond cystine transport explain the early renal 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 of the cause of the renal Fanconi syndrome in cystinosis. The transporter is the Na+/H+ exchanger (NHE3), a major absorptive sodium transporter that expresses the apical membrane of the kidney's proximal tubules 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. Therefore, our working hypothesis is that cystinosin has a role in the cellular localization and function of NHE3 in the kidney proximal tubules, and in its absence, NHE3 is dysregulated, participating in the renal Fanconi syndrome in cystinosis. Thus, this project aims to investigate the role of cystinosin in NHE3 localization and the impact of its absence in proximal kidney tubules. The analyses will be conducted in vitro in the yeast and human kidney cell models and in vivo mice.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The elucidation of the NHE3 transport regulation, expression and function mechanism in the 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 cystinosis.

Analysis of the impact of pepstatin A / Cysteamine combined treatment on bone remodeling activity of cystinotic mice

Andrea Del Fattore, PhD, *Principal Investigator*
Giulia Battafarano, PhD, *Co-Principal Investigator*
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

OBJECTIVE/RATIONALE:

Patients affected by cystinosis develop hypophosphatemic rickets. We proved that skeletal alterations in cystinotic mice are due to primary defects of bone-forming cells, known as osteoblasts. Cystinotic osteoblasts are characterized by increased protease cathepsin D (CtsD) expression. We demonstrated that treatment with CtsD inhibitor, pepstatin A, restores the physiological bone remodeling activity but does not reduce the levels of intracellular cystine content. This project investigates the effects of a combined pepstatin A/cysteamine treatment on the bone phenotype.

PROJECT DESCRIPTION:

This project aims to evaluate whether a combined pepstatin A/cysteamine could restore the physiological bone remodeling activity in cystinosis. We will analyze in vitro the effects of the treatment on cystinotic osteoblasts to restore physiological bone formation. Since to maintain the integrity of the skeleton, osteoblasts regulate the differentiation and activity of bone-resorbing cells osteoclasts; we will also analyze the osteoclastogenic potential of treated cystinotic osteoblasts. Moreover, in vivo experiments will evaluate whether the combined treatment can prevent the somatic growth defect and bone loss in growing cystinotic mice and correct the bone defect in postpubertal mice.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The project proposes whether pepstatin A could restore the osteoblast function impaired in cystinosis, counteracting the detrimental effect that cysteamine could have on bone. Although cysteamine represents a cystine-depleting treatment, it worsens the mineralization ability of cystinotic osteoblasts and decreases osteoclastogenesis, mainly when administered at high doses. This study will be essential to identify a new treatment for skeletal alterations in cystinosis with the long-term goal to translate the results into benefits for patients.

ANTICIPATED OUTCOME:

The in vitro study will evaluate the effects of the pepstatin A/cysteamine combined treatment on cystinotic bone pathology. We expect to discover if cathepsin D inhibition induced by pepstatin A into bone cells can restore the physiological bone remodeling that could also be affected by cysteamine treatment. The in vivo experiments will be essential to assess whether the treatment could rescue the bone growth of growing animals or the bone mass in post-pubertal animals.

Developing a therapeutic strategy for nephropathic cystinosis with iPS cells

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

OBJECTIVE/RATIONALE:

This proposal aims to utilize human stem cells to understand nephropathic cystinosis and develop therapeutics. The kidney is a susceptible organ in cystinosis, leading to kidney failure early. 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. Furthermore, we will test whether stem cells treated with gene therapy can form healthy kidney tissue in a recipient with cystinosis.

PROJECT DESCRIPTION:

We will take vital stem cells from patients with cystinosis and reproduce classic cystinosis symptoms in a petri dish. We will figure out what is happening inside these cells to cause the disease through detailed analyses. 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 first create a new type of cystinotic mouse capable of accepting human tissue grafts. We will then 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 any residual symptoms of cystinosis.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

This project will provide new insight into the mechanisms and determinants of cystinosis in kidneys, specifically in human kidneys, which remain poorly understood; pave new roads to discover therapeutics, including regenerative therapies and gene therapies, which require further development; and establish a suite of powerful tools 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 symptoms can appear in organoids in a petri dish under the right circumstances. This will teach us which factors in our bodies and environment contribute most to these symptoms. Gene therapy will help us restore proper levels of functional cystinosin protein, which is expected to benefit kidney cells dramatically and result in longer-lasting grafts that are free of symptoms. The new cystinosis mouse will be handy for studying human cells and tissues in a more realistic environment that simulates a patient with cystinosis.

A critical role for cystinosin during embryo development

Bruno Gasnier, PhD, *Principal Investigator*

CNRS / UNIVERSITÉ DE PARIS, PARIS, FRANCE

OBJECTIVE/RATIONALE:

Cystinosis results from the genetic inactivation of the lysosomal membrane protein, cystinosin. In preliminary studies, we discovered a strong, unexpected genetic interaction between cystinosin and another lysosomal protein during the mouse model of cystinosis. This interaction, which manifests as an embryonic lethality when both genes are inactivated, reveals a hitherto unsuspected role of cystinosis during embryo development. We aim to identify the underlying mechanisms to improve our understanding of the biology of cystinosis and the tools at work in cystinosis.

PROJECT DESCRIPTION:

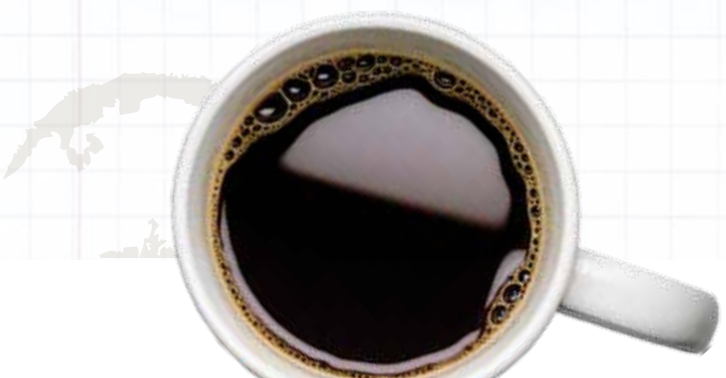
Our preliminary studies have implicated an extra-embryonic tissue, the yolk sac, as a site for the synergy between cystinosis and its genetic interactor. This tissue ensures the nutrition of post-implantation mammalian embryos before the onset of placental function. In this process, maternal proteins secreted by uterine glands are internalized and degraded in yolk sac lysosomes to produce amino acids and other nutrients required for embryonic growth. Our research will develop with three specific aims. The first aim will probe the causal link between the yolk sac and embryo defects by selectively re-expressing cystinosis in the yolk sac epithelium using a transgenic mouse line. In the second aim, we will explore the potential implication of another embryonic organ, suggested by preliminary metabolomic studies, using biochemical and histological techniques. Finally, we will evaluate a candidate mechanism for the synergy between cystinosis and its genetic interactor and the interplay between the yolk sac and the embryonic organ using cellular and physiological approaches.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Our study may help reveal novel mechanisms at work in cystinosis. On the one hand, the similarities between the yolk sac epithelium and the proximal kidney tubule, the primary target of infantile cystinosis, may help trace disease mechanisms common to these protein-absorptive tissues. On the other hand, the potential crosstalk between two organs affected by the loss of cystinosin and its genetic interactor in our experimental model may suggest unanticipated hypotheses about the role of inter-organ communication in the disease mechanism.

ANTICIPATED OUTCOME:

Our study will also unveil novel biological roles of cystinosin. The existence of functional synergy between cystinosin and another lysosomal protein and the elucidation of the underlying mechanism will help put these roles in a broader context and at multiple scales, from the intracellular level to the inter-organ level. This basic knowledge should, in turn, suggest novel hypotheses about disease mechanisms.



Improving characterization of neuromuscular involvement in adults with cystinosis

Pascal Laforêt, MD, PhD, *Principal Investigator*
Hélène Prigent, MD, PhD, *Co-Principal Investigator*
HÔPITAL RAYMOND POINCARÉ, GARCHES, FRANCE

Aude Servais, MD, PhD, *Co-Principal Investigator*
NECKER HOSPITAL, PARIS DESCARTES UNIVERSITY, PARIS, FRANCE

OBJECTIVE/RATIONALE:

Besides the consequences of renal failure, the long-term prognosis of cystinosis appears to be related to neuromuscular complications. The primary manifestations of neuromuscular involvement have been described in previous studies, highlighting hand muscle weakness, respiratory insufficiency and swallowing impairment. Yet, the long-term outcomes and natural history of these symptoms remain an important issue, and in the era of early cysteamine treatment and new treatment formulations, muscular and lung evolution of adult patients with cystinosis remains unknown.

PROJECT DESCRIPTION:

Throughout this project, we will thoroughly examine the neuromuscular complications of cystinosis, focusing specifically on skeletal and respiratory muscle weakness, in a well-characterized cohort of patients followed in Necker-Enfants-Malades Hospital Reference Center for inherited renal disorders (Aude Servais, MD, PhD). Using standardized tools, twenty patients will be recruited and evaluated in Raymond Poincaré Hospital Neuromuscular Center to assess muscle strength and function (Pascal Laforêt, MD, PhD). A whole-body muscle MRI will be performed to identify the pattern of skeletal muscle involvement and will be studied with specific pulmonary function explorations and systematic evaluation of its consequences on breathing efficiency (Hélène Prigent, MD, PhD). We will also analyze the swallowing function in patients complaining of difficulties swallowing or with significant impairment rates after completing a swallowing questionnaire. Also, clinical tests will be conducted at baseline and after one year. We will relate clinical and morphological neuromuscular complications with the other complications of the disease, renal function or transplantation, leukocyte cystine level, age at initiation of treatment and adhesion to treatment.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

This exploratory analysis of all dimensions of neuromuscular involvement in patients with cystinosis should provide further insights into the pattern of skeletal muscle involvement, severity and the determinants of neuromuscular complications of this lysosomal disease and improve patient care. The respiratory and sleep evaluation results will provide the opportunity to offer appropriate management when such disorders are identified. With the systematic intervention of an occupational therapist, the extensive functional motor evaluation can provide personalized rehabilitation support and care for patients and then provide guidelines for detection and assessment of neuromuscular manifestations in cystinosis. The same conclusions may be anticipated for the swallowing function assessment.

ANTICIPATED OUTCOME:

We hope this study will enhance our knowledge of neuromuscular manifestations in cystinosis. Increased awareness and characterization of these potentially disabling symptoms should improve the care of the patients by leading us to better and more specific management of these difficulties. This study should also help identify outcome measures that are useful in future clinical trials to assess the response of skeletal muscles to innovative therapies.

Dietary glycine supplementation attenuates infantile nephropathic cystinosis-associated muscle wasting and adipose tissue browning

Robert Mak, MD, PhD, *Principal Investigator*

UNIVERSITY OF CALIFORNIA, SAN DIEGO

OBJECTIVE/RATIONALE:

Muscle wasting in patients with infantile nephropathic cystinosis (INC) is an important long-term complication with a major impact on the quality of life. Cysteamine is the only approved therapy for INC but does not prevent or reverse INC-associated muscle wasting. We previously showed that glycine-enriched diet can improve muscle wasting when given to cystinosis mice (2 to 9 months of age), at the early stages of these comorbidities in infantile nephropathic cystinosis (INC). We now aim to test whether glycine-enriched diet can slow progression of muscle wasting and kidney disease at a later and advanced stage in cystinosis mice, from 6 to 12 months of age.

PROJECT DESCRIPTION:

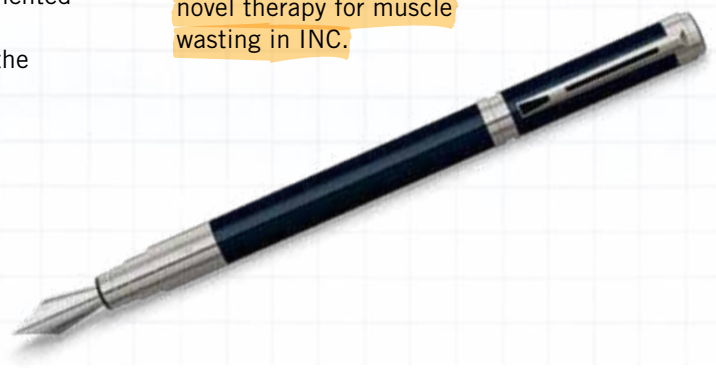
Six-month-old cystinosis mice and control wild type mice will be fed with various diets, containing different amounts of glycine supplementation for six months. Mice will be studied, including lean body mass, muscle function and kidney function and then sacrificed at 12 months of age. Various tissues will be harvested for subsequent investigation of molecular mechanisms.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

In our published study, we characterized muscle wasting and adipose tissue browning in one-, four-, nine-, and 12-months old cystinosis mice. Profound muscle wasting and adipose tissue browning was evident in 12-month-old cystinosis mice. In this proposal, we aim to study whether glycine supplemented diets can slow the progression of muscle wasting and adipose tissue browning at the stage of advanced disease.

ANTICIPATED OUTCOME:

Our hypothesis is that dietary glycine supplementation will slow progression of muscle wasting at an advanced stage of cystinosis. Such dietary supplements may become novel therapy for muscle wasting in INC.



CALL FOR SPRING 2022 GRANT APPLICATIONS

JOIN OUR RESEARCH LEGACY

When Nancy and Jeff Stack established the Cystinosis Research Foundation (CRF) in 2003, they were committed to aggressively funding cystinosis research to ensure the development of new and improved therapies and a cure for cystinosis. But never in their wildest dreams could they have imagined what has been accomplished in 19 short years. Since its inception, CRF has funded 213 multi-year research studies in 12 countries. Our researchers have published 100 articles in prestigious journals as a result of CRF funding. Every dollar donated goes directly to support cystinosis research.

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

In March, CRF announced $2.5 million was available for the spring 2022 call for research and fellowship applications. The grant awards will be announced in early July 2022.

In fall 2021, CRF issued six new grants totaling $1,539,980 that will bring us closer to better treatments and a cure. All research applications received by CRF are evaluated by CRF's Scientific Review Board (SRB), composed of the leading international experts in the field of cystinosis. The SRB provides independent, objective reviews and recommendations for each research proposal submitted based on the NIH scale of standards. Additionally, the SRB follows grant review guidelines established by CRF and advises the foundation on the scientific merits of each proposal. CRF has created a thriving and collaborative international research community. If you are a scientist or researcher and would like to apply for a grant, please visit our website for more details.

Cure Cystinosis
International Registry

In 2021, CRF updated the registry questionnaire to include questions that are relevant to recent scientific advancements, new medications and patient care. CRF partnered with CoRDS *(Coordination of Rare Diseases at Sanford)* creating a new Cure Cystinosis International Registry (CCIR), the only international cystinosis patient registry in the world. The site includes a professional Research Portal so that researchers and scientists who register can access and view de-identified, aggregate cystinosis patient information. The registry will connect all of the stakeholders in the cystinosis community – the scientists, researchers, clinicians, pharmaceutical companies, patients, and families – and provide them with resources that have never been available in one place before, all to accelerate better patient care.

We encourage every family and patient to enroll today. Your information is essential to advancing cystinosis research. If you have already enrolled, thank you!

Visit the CRF website to learn more about CCIR and enroll.

WWW.CYSTINOSISRESEARCH.ORG/CURE-CYSTINOSIS-INTERNATIONAL-REGISTRY

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

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

NEWLY PUBLISHED STUDIES

SPRING 2022

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.

LYSOSOMAL CYSTINE MOBILIZATION SHAPES THE RESPONSE OF TORC1 AND TISSUE GROWTH TO FASTING, *published February 18, 2022, in Science by* ***Matias Simons, MD, and Zvonimir Marelja, PhD,*** *INSERM Imagine Institute, Paris, France.*

CENTRAL NERVOUS SYSTEM COMPLICATIONS IN CYSTINOSIS: THE ROLE OF NEUROIMAGING *published February 15, 2022, in Cells by* ***Aude Servais, MD, PhD,*** *Hospital Necker, Paris, France*

NEPHROPATHIC CYSTINOSIS: PATHOGENIC ROLES OF INFLAMMATION AND POTENTIAL FOR NEW THERAPIES *published January 6, 2022, in Cells by* ***Giusi Prencipe, PhD,*** *Bambino Gesù Children's Hospital, Rome, Italy.*

DRUG REPURPOSING IN RARE DISEASES: AN INTEGRATIVE STUDY OF DRUG SCREENING AND TRANSCRIPTOMIC ANALYSIS IN NEPHROPATHIC CYSTINOSIS *published November 27, 2021, in the International Journal of Molecular Sciences, by* ***Francesco Bellomo, PhD, Anna Taranta, PhD, and Francesco Emma, MD,*** *Bambino Gesù Children's Hospital, Rome, Italy.*

BENEFITS AND TOXICITY OF DISULFIRAM IN PRECLINICAL MODELS OF NEPHROPATHIC CYSTINOSIS *published November 24, 2021, in the Cells by* ***Anna Taranta, PhD, Francesco Bellomo, PhD, and Francesco Emma, MD,*** *Bambino Gesù Children's Hospital, Rome, Italy.*

HEMATOPOIETIC STEM CELL GENE THERAPY FOR CYSTINOSIS: FROM BENCH-TO-BEDSIDE *published November 2021, in the Cells by* ***Stéphanie Cherqui, PhD,*** *University of California, San Diego.*

DEFICIENCY OF THE SEDOHEPTULOSE KINASE(SHPK) DOES NOT ALTER THE ABILITY OF HEMATOPOIETIC STEM CELLS TO RESCUE CYSTINOSIS IN THE MOUSE MODEL *published November 2021, in the Molecular Genetics and Metabolism Journal, by* ***Stéphanie Cherqui, PhD,*** *University of California, San Diego.*

A SUSTAINED RELEASE CYSTEAMINE MICROSPHERE/THERMORESPONSIVE GEL EYEDROP FOR CORNEAL CYSTINOSIS IMPROVES DRUG STABILITY *published October 2021 in the Drug Delivery and Translational Research Journal by* ***Morgan Fedorchak, PhD and Ken Nischal, MD, FRCO,*** *University of Pittsburgh, Pittsburgh, Pennsylvania.*

DYNC1LI2 REGULATES LOCALIZATION OF THE CHAPERONE-MEDIATED AUTOPHAGY RECEPTOR LAMP2A AND IMPROVES CELLULAR HOMEOSTASIS IN CYSTINOSIS *published October 2021 in the Journal of Autophagy by* ***Sergio Catz, PhD,*** *The Scripps Research Institute, La Jolla, California*

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!

CHAIR

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Professor
Laboratory of Hereditary Kidney Diseases,
Imagine Institute (Inserm U1163)
PARIS, FRANCE

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Division of Genetics
University of California, San Diego
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Director of Nephrology Laboratory
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The mission of the Cystinosis Research Foundation is to find better treatments and a cure for cystinosis by supporting bench, clinical and translational research. Since 2003, CRF has raised over $63 million with 100% of your donations going to support cystinosis research.

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

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CYSTINOSIS
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The road seemed so far.
Almost never-ending.
Sometimes unseeable.
But a wish
was the difference.

In our story with cystinosis,
a collective dream was born.
It colored in the lines,
defining the light
inside us.

We are alive.
We are light.
Together, we shine bright.

A wish was the difference.
A wish that is living,
and we are breathing it.

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