cystinosis magazine

TOGETHER WE SHINE BRIGHT

ROOTED IN COMMUNITY

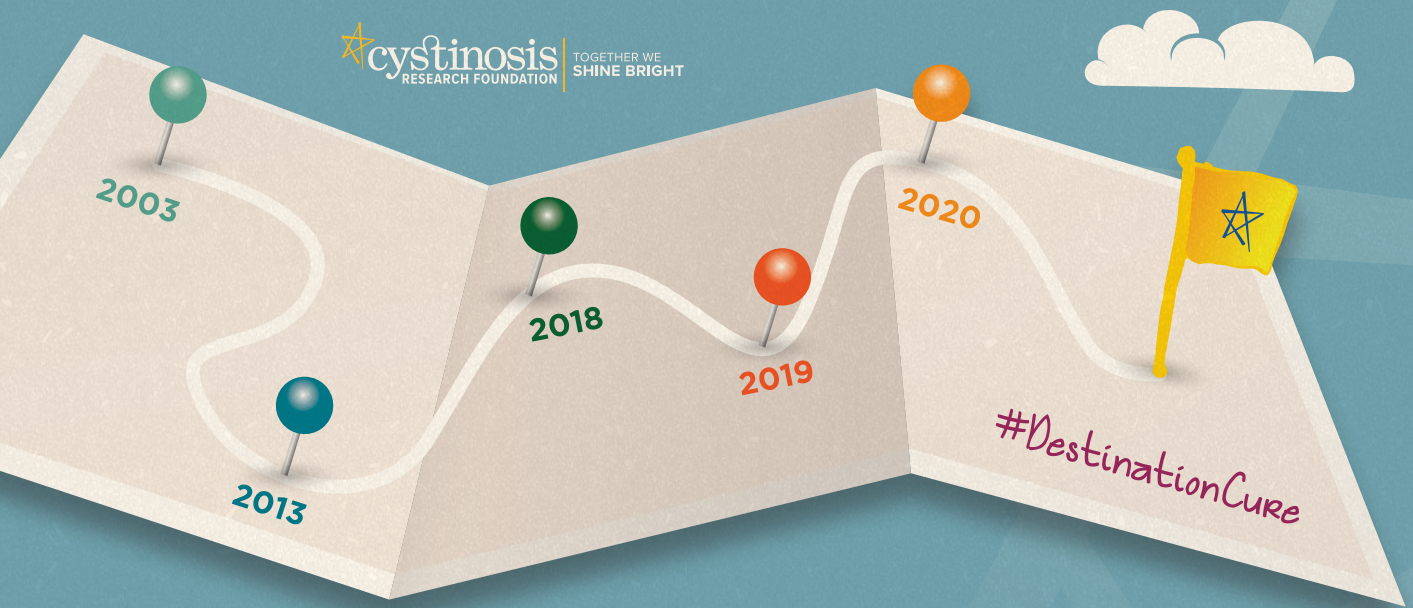
ROOTED IN RESEARCH

ROOTING FOR THE CURE

FOR FRIENDS AND SUPPORTERS OF THE CYSTINOSIS RESEARCH FOUNDATION

SPRING 2021

cystinosis RESEARCH FOUNDATION | TOGETHER WE SHINE BRIGHT



2003

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

2013

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

2018

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

2019

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

2020

- **Road to a cure!** Today, CRF is the largest fund provider of grants for cystinosis research in the world, issuing 204 grants in 12 countries.
- 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.

- CRF has raised nearly $60 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.

ROOTING FOR THE CURE

SPRING 2021

WE ARE ALL CONNECTED

From a wish comes a cure. The Cystinosis Research Foundation was founded on a wish which became a seed planted in 2003. From that seed came community. The roots have grown deep, and limbs far and wide. Today we enjoy the fruits of our active community — the collaboration of families, friends and research. Together, we are mighty, we are shining — Watch Us Blossom!

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

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

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

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cystinosis RESEARCH FOUNDATION

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CHARITY NAVIGATOR ★★★★ Four Star Charity

GUIDESTAR PLATINUM TRANSPARENCY 2021

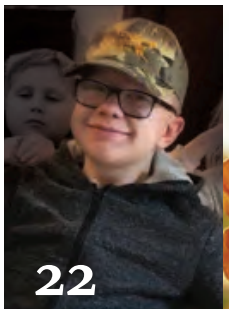
The mission of the Cystinosis Research Foundation is to find better treatments and a cure for cystinosis by supporting bench, clinical and translational research. Since 2003, CRF has raised nearly $60 million for cystinosis research in an effort to find a cure.

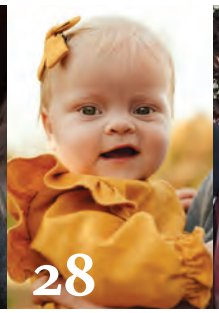
cystinosis RESEARCH FOUNDATION

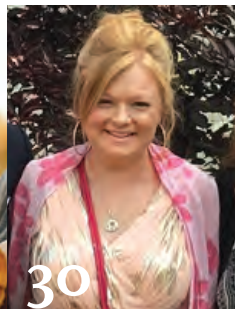
WELCOME

RESEARCH UPDATES

ANNOUNCEMENTS







FAMILY STORIES

CYSTINOSIS MAGAZINE IS A PUBLICATION OF THE CYSTINOSIS RESEARCH FOUNDATION

SPRING 2021

Dear FAMILY & FRIENDS

The past year has been a year of change, uncertainty and, for some, loss. It has been a year of adjusting to a new way of living and communicating – we have often felt ourselves isolated from family and friends. We have found creative ways to connect and stay close through virtual meet-ups, socially distanced visits and long phone calls, but nothing can replace in-person meetings, human touch and connection.

We have missed seeing you in person but we know that even though we have been apart, we are rooted together in our community. Our roots run deep, they are strong and grounded by the love and support we have for each other and the common goal we share – finding a cure for cystinosis. We are finally seeing light at the end of the tunnel; the world is opening up again. Springtime has brought renewed hope and joy to all of us.

Hope fuels our determination to find better treatments and a cure for our children and adults with cystinosis who never have a day off; the disease is chronic and relentless.

This is a year of change for our family, a year that brings Natalie's wish full circle. It was 18 years ago that Natalie made her wish, "to have my disease go away forever." Natalie's wish became a rallying cry for all those affected by cystinosis. Since that fateful day, so much has changed and in the most positive way. Our small community came together, our extended family and our friends and even strangers joined our quest to find a cure. We have formed an impenetrable bond, rooted in research and for the cure.

YOU JOINED US ON OUR JOURNEY AND YOU HELPED US START A MOVEMENT THAT BEGAN WITH A WISH AND ENDED IN AN FDA-APPROVED CLINICAL TRIAL TO TEST A TREATMENT THAT COULD BE THE CURE FOR CYSTINOSIS.

IT IS A VIRTUAL WORLD IN 2021

DAY OF HOPE FAMILY CONFERENCE

Although we could not be together in person, we were together virtually to celebrate our community! We hosted a virtual family conference that was held over two days on April 29 and May 1. The first part of the conference was science-based and was a webinar featuring presentations by five CRF-funded researchers. The second part of the family conference was geared toward children and their parents and featured break-out sessions and discussions with leading cystinosis clinicians. The conferences were well attended by a worldwide audience!

NATALIE'S WISH CELEBRATION

We have an urgent need to continue to fund research and although we cannot meet in person again this year, funding research remains a priority. On April 30 we celebrated our community virtually by hosting a series of short videos on our website that were complete with information about the research you have funded, the projects you have supported and the milestones you have helped us achieve. The videos can be viewed at any time and can be found on our website at *www.cystinosisresearch.org/natalies-wish-2021/*.

RESEARCH IS OUR PASSION

Over the course of the past year, our research program has continued forward and although there were delays with some experiments and clinical trials, the research never stopped. The pandemic taught us how to be more creative, efficient and resilient. We have built a collaborative, thriving international research community made up of the most brilliant people who have dedicated their careers to our children. They know that our hope for a brighter future hinges on their work and discoveries.

As a direct result of your support, CRF is the largest fund provider of cystinosis research in the world. CRF has funded millions of dollars of research that has led to new discoveries about cystinosis, new clinical trials and two FDA approvals. CRF has issued 204 multi-year grants, eight extension grants and awarded four equipment grants. Numerous CRF researchers have received grants from other funding sources, thereby leveraging our initial grant awards. Our targeted approach to research and our emphasis on collaboration has helped accelerate the research process and resulted in the publication of 88 research articles in prestigious journals by CRF-funded researchers.

The research we have funded has improved the quality of life for people with cystinosis and more importantly, has allowed those with cystinosis to dream of a life free of this disease. We have accomplished all of this because you have partnered with us to fund research to find a cure.

UPDATE ON THE STEM CELL AND GENE THERAPY CLINICAL TRIAL

Since 2007, we have proudly funded Stéphanie Cherqui, PhD, at UC San Diego for her groundbreaking stem cell and gene therapy work. CRF has awarded over $5.78 million in grants for her research. The seed money we provided years ago has been leveraged from other funding agencies including over $21.5 million from CIRM and the NIH.

There are times when it is hard for me to grasp the magnitude of what CRF has accomplished. We have turned research ideas into clinical trials, and along with that, have given hope for a longer and healthier life to all those with cystinosis.

THE REALITY OF THE STEM CELL TRIAL ILLUSTRATES OUR SUCCESS.

Almost a year and a half ago, on October 7, 2019, Jordan Janz became the first cystinosis patient volunteer for the stem cell study. On June 29, 2020, the second patient was transplanted and on November 16, 2020, Jacob Seachord, the third patient, was transplanted. By the end of the year, if all goes well, the remaining patients will be transplanted and then the trial will open up to more patients in different locations.

The reality is that very few research ideas make it from the bench to the bedside. The road to new treatments is long and arduous, fraught with setbacks, failures and disappointments. However, when you have a determined research community like we have, that is committed to finding better treatments and a cure, wishes and ideas become reality.

We honor and thank the first three patients for blazing the path toward the cure. One way to measure the success of the treatment is to measure cystine levels. A patient with cystinosis must take cysteamine throughout the day to control and lower cystine levels. We are so pleased to report that all three transplanted patients are doing extraordinarily well and have cystine levels low enough that they do not need to take cysteamine therapy. The genetically repaired cells are doing their job!

We have special updates on two of the transplanted patients, Jacob Seachord on page 18, and Jordan Janz on page 20.

2020 – A RECORD-BREAKING YEAR FOR RESEARCH - $3,150,914 AWARDED

In order to ensure that your donations are always at work and to keep the research cycle moving forward, CRF awards new grants biannually. We are pleased to announce that in 2020, CRF awarded 14 multi-year grants, eight research grant extensions and one new grant for lab equipment.

The grants were awarded to researchers in Belgium, France, Italy, New Zealand, Switzerland and the United States.

Please read about the four new grants awarded in the fall and learn more about the important research we are funding. The grant abstracts are listed on page 68.

We have highlighted three research projects in this issue.

SERGIO CATZ, PhD

THE SCRIPPS RESEARCH INSTITUTE

Dr. Catz's exciting and complex research is highlighted on page 52.

His work involves studying cell structure and the damage it causes in cystinosis by using sophisticated tools to examine cellular processes at the molecular level. Understanding why the cell process in cystinosis does not work correctly will hopefully lead to the development of treatments to complement current therapies for cystinosis.

MORGAN FEDORCHAK, PhD

UNIVERSITY OF PITTSBURGH

We are pleased to update you on Morgan Fedorchak, PhD's important and exciting research that involves a potential new treatment for corneal cystinosis, the painful eye condition that can lead to blindness. Dr. Fedorchak has developed SoliDrop, a delivery system for cysteamine to the eye. The goal is that SoliDrop will be a once-a-day treatment for corneal cystinosis. Dr. Fedorchak anticipates that she will meet with the FDA this summer. Please read more about her work on page 50.

JENNIFER HOLLYWOOD, PhD

UNIVERSITY OF AUCKLAND

Dr. Hollywood is focused on how she can improve the lives of those with cystinosis by collaborating to discover how well two drugs can function in tandem, creating a combination therapy with the potential to improve the lives of cystinotic patients. Her research, if successful, could result in better protection and preservation of kidney function in patients. The end goal would be to avoid kidney failure and thereby avoid kidney transplants. Please read more about her work on page 48.

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

CRF RESEARCH HELPS OTHER DISEASES AND DISORDERS

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

GRATITUDE AND APPRECIATION FOR OUR COMMUNITY

It is with enormous gratitude that we thank everyone who contributed their story to the magazine. Sharing the cystinosis journey through the eyes of our families, patients and researchers is what brings us closer together. Living with cystinosis means daily challenges; some days are harder than others but this community is resilient; we are supportive of each other.

Our cystinosis family tree has deep roots, roots that intertwine and create a strong foundation of community, research and hope.

We have faced the challenges of cystinosis together, we have overcome obstacles and we have found a path to better treatments and a cure. We cannot rest, our job is not done; there is more work to do and with your help and support, we will certainly succeed.

Thank you for embracing our community, for supporting our research efforts and for making Natalie's wish come true. You have given our community hope where there was none, you have been part of the highs and lows that we have experienced but you never let us down, you have remained by our side to lift us up and to celebrate our accomplishments.

With heartfelt thanks and gratitude,

Nancy & Jeff

A NOTE FROM NATALIE STACK

Dear Family and Friends,

Wow, what a year it has been! 2020 was a year full of stress and anxiety, but now 2021 is finally starting to give us hope for a fresh start and a new beginning. It has been over a year since the pandemic started and I am ready for things to get back to normal! I miss seeing everyone's faces at the Day of Hope weekend, I miss going out with friends and I miss seeing my co-workers in the office. I am grateful that I have not been personally affected by coronavirus; I cannot imagine what it has been like for families who lost loved ones, lost their jobs, etc. I am fully vaccinated as are most of my family members and I am ready for a new chapter in my life!

2021 has been a good year thus far. I turned 30 in February 2021 (yes, I am getting old!). I am still enjoying my job as a case supervisor at CASA Orange County (Court Appointed Special Advocates) and I still enjoy living in Irvine, California with my lovely cat, Henry. Overall, my health remains stable and I have not had a kidney transplant. Though the year of the pandemic is not what any of us had in mind, it has been a year full of reflection and growth for me.

Cystinosis is a disease no one can quite understand unless you or a loved one has it. The medications, severe fatigue, nausea, and a myriad of other complications make it an exhausting disease that one cannot escape. The older I get the more tired I become. Though it does not look like it on the outside, my body is continuously and slowly shutting down. No matter how religious I am with my medications, the disease is always one step ahead of me. Though the stem cell trial seems scary, the older I get the more I recognize that I need a better treatment. I am hoping to participate in the clinical trial in the near future - I know I am ready for this disease to no longer be a part of my everyday life.

Three patients have gone through the stem cell trial and all seem to be doing great and thriving. It has been over a year since the first patient, Jordan, had the stem cell transplant. None of the patients have needed to go back on their cystinosis medications since their transplant date - what incredible news! The progress and success of the stem cell trial so far, has made me believe that a promising future lies ahead for all of us.

The cystinosis community has given me hope through all these years that I will one day be able to live a normal life. Words cannot express how I feel about the possibility of being cured of cystinosis - it would truly be a miracle. This is all because of the community and the doctors who tirelessly fight for better treatments and never give up hope. Stéphanie Cherqui, PhD is truly our hero. She is our star that will forever shine bright in all our hearts for what she has done for our small community.

Because of the work Dr. Cherqui has done for cystinosis, I believe that my future is promising- full of life, love and happiness. I am incredibly appreciative of what the doctors, my parents and the rest of this community have done not only for me but for all those living with cystinosis. Thank you for never giving up on my wish to have my disease go away forever.

Love,
Natalie

What is cystinosis?

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

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

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

Our story

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

Today, CRF is the largest fund provider of grants for cystinosis research in the world, issuing 204 grants in 12 countries.

CRF has raised nearly $60 million, with 100% of your donations going to support cystinosis research. CRF's efforts have changed the course of cystinosis and given new energy to its investigators and scientists. CRF's commitment to research has given hope and promise to the global community of cystinosis patients and their families.

cystinosis RESEARCH FOUNDATION | TOGETHER WE SHINE BRIGHT

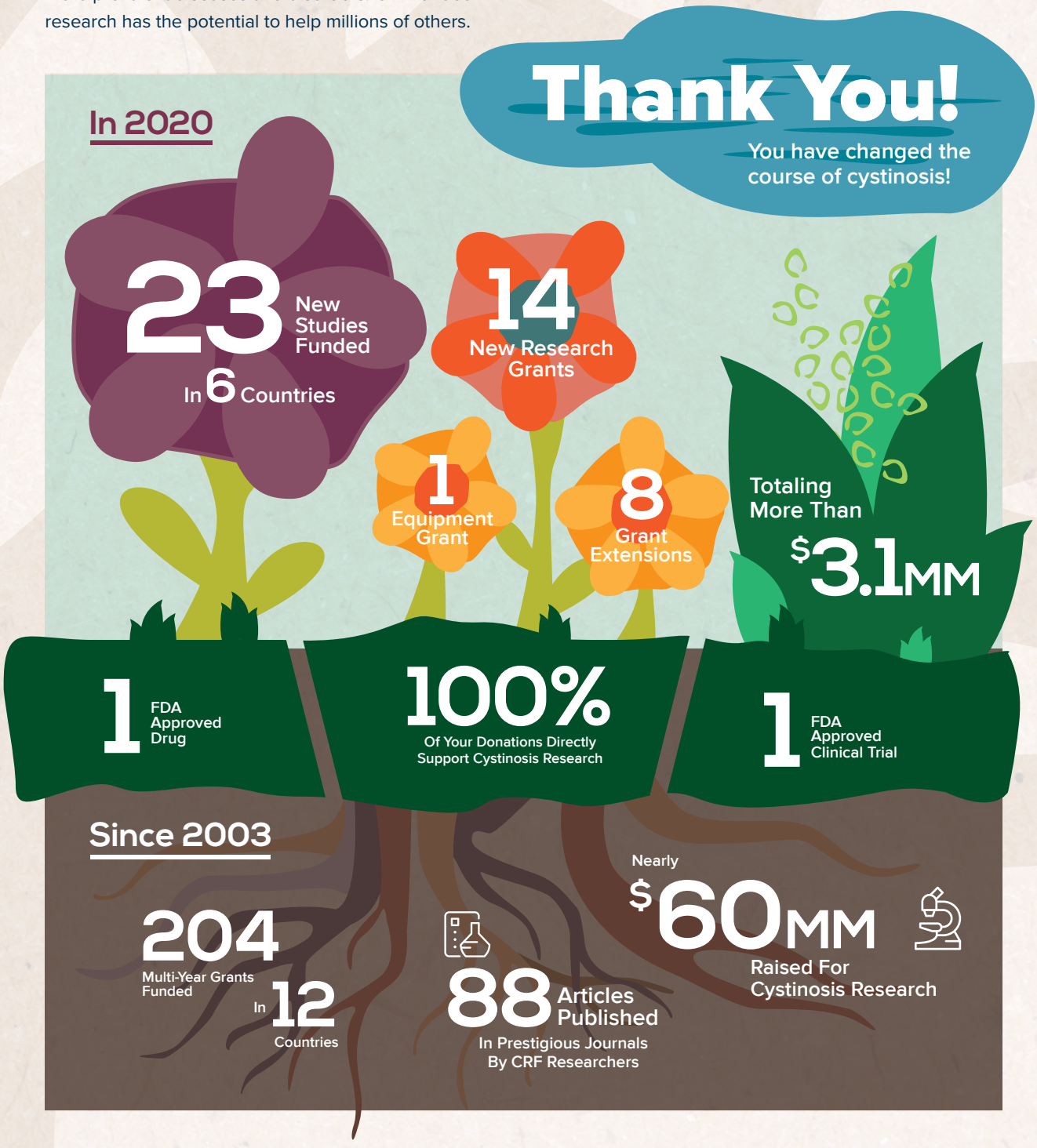
CHARITY NAVIGATOR ★★★★ Four Star Charity

GUIDESTAR PLATINUM TRANSPARENCY 2021

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.



CRF and Canadian Families Unite to Fund Research

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

The Cystinosis Awareness and Research Effort (CARE) has partnered with Canada Helps to establish the Canadian Cystinosis Research Foundation. This fund is administered by Aqueduct Foundation and allows for an efficient and effective fundraising process, ensuring that Canadians who donate will receive a charitable tax receipt. The link to the Aqueduct Foundation is: *www.canadahelps.org/en/charities/aqueduct-foundation*

Canadians also have the option to donate directly to CRF if they so desire, however, no charitable tax receipt will be issued. Visit the CRF webpage for Canadian Families for more details: *www.cystinosisresearch.org/canadian-families*

Since 2016, **Canadian families have directly funded CRF research with $875,512** in grant payments through the Aqueduct Foundation. CRF is incredibly grateful for the support of our Canadian cystinosis families and friends. Grant funding in the first quarter of 2021 included:

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

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

Liang Feng, PhD
Xue Guo, PhD
Stanford University
"Molecular Mechanism of Cystinosis"
$37,500

To learn how to donate, visit our CRF Canadian Families webpage at www.cystinosisresearch.org/canadian-families. If you would like to learn more about how to fundraise in Canada please contact: Zoe Solsby at zsolsby@cystinosisresearch.org.

Cure Cystinosis
International Registry

CRF is excited to announce that the Cure Cystinosis International Registry (CCIR) is open for enrollment!

The Cystinosis Research Foundation has partnered with CoRDS (Coordination of Rare Diseases at Sanford) to create the only international cystinosis patient registry in the world. CoRDS supports and enables rare disease communities to build robust registries to help accelerate research. Enrolling in the cystinosis patient registry is one of the most effective ways to help support research and advance clinical treatments for those living with cystinosis.

CCIR is an online, confidential database of standardized information about individuals with cystinosis. By sharing your diagnostic and treatment history, you can help provide researchers with the data necessary to conduct informed research and clinical trials which ultimately will lead to improved treatment options and outcomes for patients.

The comprehensive questionnaire contains 135 questions about cystinosis that include questions about diagnosis and treatment, as well as all areas affected by cystinosis including the eyes, kidneys, muscle, bone and neurological complications. Designing the questionnaire was a collaborative effort by leaders in the cystinosis community including researchers, clinicians, adults with cystinosis, and parents of children with cystinosis. View our CCIR collaborators at the web page listed below.

Our goal is 100% participation by our international cystinosis community. The sooner we reach our goal, the more useful our data will be for researchers working around the world to find better treatments and a cure for cystinosis.

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

Day of HOPE

RECONNECTING FRIENDS...

UPLOADING RESEARCH...

TRANSFERRING EXCITMENT...

The First Ever

Virtual Day of Hope Conference was a huge success! The conference featured five CRF-funded researchers including Stéphanie Cherqui, PhD, Francesco Emma, MD, Morgan Fedorchak, PhD, Paul Grimm, MD, and Reza Seyedsadjadi, MD. Each live presentation was followed by an interactive Q&A session. Including a special Q&A session with Jordan Janz and Jacob Seachord, both patients in Dr. Cherqui's stem cell transplant study. Jordan and Jacob shared their experiences and answered your questions about the trial.

A highlight of the event was our Children's Day of Hope program which brought our families together for a fun meet-up and lots of conversation! The Saturday program included a welcome and introduction, an easy-to-understand presentation about cystinosis by Stephen Jenkins, MD, breakout sessions for parents of children with cystinosis, including a private teen breakout session, and then a surprise interactive session with all of the children! We were pleased to include cystinosis experts and clinicians Paul Grimm, MD, Julian Midgley, MD, and Joshua "JJ" Zaritsky, MD, PhD.

Natalie's Wish

Thank you to everyone who joined us for a virtual celebration of our CRF community and the brilliant researchers fighting to create better treatments and a cure for cystinosis!

Over the past 18 years, you have shared in the highs and lows that we have experienced along our journey toward a cure and together we celebrated 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 cannot be together in person this year, we will always be united in our hope for a cure.

FAMILY *Fundraising*
FROM AROUND THE WORLD

In 2020, our global community helped raise over $2.2 million for cystinosis research!

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

UNITED STATES

KATIE AHNEN - $270

HADLEY ALEXANDER - $19,793

ISAAC ANDREWS - $1,280

LILY BEAUREGARD - $7,228

EVA BILODEAU - $266

JACKSON BLUM-LANG - $420

OLIVER BRITTEN - $7,521

NOAH BROWN - $760

ROSA BUTLER - $378

CHASE CHODAKOWSKY - $715

JOSHUA CLARKE - $10,000

CHARLOTTE COE - $497

MIA COPELAND - $2,330

ADDISON COX - $100

BAILEY DEDIO - $500

ELEANOR DICKS - $525

BROOKE EMERSON - $24,024

JAMES 'DREW' ENDSLEY - $580

TINA FLERCHINGER - $40,619

CALEB GOWAN - $2,555

HOLT GRIER - $26,738

NICOLE HALL - $11,391

SHEA HAMMOND - $818

LANDON HARTZ - $3,780

MARY HEAD - $258

SAM & LARS JENKINS - $4,554

JESSICA JONDLE - $870

JOEY JORDAN - $425

JOSIE KANUPKE - $6,689

SHANNON KEIZER - $350

AARAV KHALASI - $6,706

HAYDEN KIRCHHOF - $44,208

JAKE KRAHE - $4,933

KENZIE LAWATSCH - $835

KALEB LAWSHE - $3,140

LOLA LONG - $3,315

LACEY LOWERY - $400

PRESTON LUKE - $315

AYLA & OTTO MAHER - $29,062

KEEGAN MANZ - $2,700

STELLA GRACE MILLER - $1,715

BRADY MURDOCH - $2,066

AIDAN O'LEARY - $50,539

EMMA & GRACIE PATTERSON - $2,045

JENNA AND PATRICK PARTINGTON $75,491

MORGAN PEACHMAN - $3,665

ABEL & PAUL PRUITT - $25,000

FRANK & ZACK RITCHIE - $258

GRACE SEVEL - $1,228

CHARLIE SIMPSON - $1,497,607

ZYLAR SMETHURST - $330

MITCHELL SMITH - $3,095

HENRY STURGIS - $75,628

EMMA GRACE SUETTA - $15,941

PEYTAN TAYLOR - $420

EVERLY TURNER - $1,349

BRADEN & DAX TYNER - $7,505

2020 FAMILY EVENTS AND FUNDRAISING AROUND THE WORLD

CANADA

SOPHIE'S CHAMPIONS
SOPHIE BETOURNAY - $33,815

TODD BRAYE - $374

ELSIE BUCK - $345

ANDREW CUNNINGHAM - $12,750

SETH DEBRUYN - $15,030

HOPE FOR JAMES
JAMES FEHR - $13,992

JORDAN JANZ - $2,434

MARVELED BY MADDIE
MADDIE LAWRENCE - $711

OLIVIA LITTLE - $18,150

JENNY RAYCRAFT - $500

KATHLEEN ROBERTS - $2,730

GABRIELLE STRAUSS - $2,600

FROM FACEBOOK

FACEBOOK FAMILY AND FRIENDS FUNDRAISING EVENTS AND DONATIONS OF $88,577 ARE INCLUDED IN THE ABOVE TOTALS.

NORWAY

DENIS LILLAND - $149

ANDREAS ROTH - $2,030

SWEDEN

ISABELLA KÜHNEL - $1,030

KAROLIS SCHRÖDER - $4,006

SWITZERLAND

NATHANAEL BELL - $1,000

ALICE JEANRICHARD - $2,587

AUSTRALIA

ETHAN FENN - $3,873

BEE ROBERTSON - $650

IN MEMORY

LYNDSEY BEELER - $300

SAMANTHA GROVER - $50,637

SARAH MELANG - $1,000

SHANNON PAJU - $200

ROOTED IN COMMUNITY

THE NO-HANDS ALL-HANDS PIE-EATING CONTEST

Each year at Halloween, **CRF Board Trustee Bruce Crair** and the team at Boingo Wireless host a pie-eating contest for the occasion. This year, on October 30, the event was held virtually and was a huge success! Bruce was challenged to participate and agreed to do so, on the condition that each member of the Boingo executive team make a $100 donation to CRF. Following the event, the team had donated $1,150, and to sweeten the success, Bruce and his wife Cathy matched those contributions, **raising a total of $2,300 for CRF.**

Thank you to Bruce, Cathy and the entire Boingo Wireless team for joining CRF on our road to a cure!

Lessons Learned

During our Year in COVID Lockdown

This year has been a whirlwind for us; while the three of us have literally been in our home together for a year because of COVID-19, we have had so much on our plate, it seems.

With Brooke in virtual school, and both Clay and I working from home, we have given new meaning to the phrase "family time." But as much as we have gone stir crazy at times, I have learned the following important lessons this year, which will serve us well in the future:

I AM NOT MEANT TO BE A TEACHER (AND KIDS NEED SPACE TO LEARN)!

Brooke started 1st grade as a full-time virtual student. It was challenging to say the least. What we figured out early on is that Brooke thrives at and prefers in-person learning, as much for the social development as the academic benefits. We also learned that I am not cut out for teaching! (I suspect I am not the only parent in the world to feel this way right about now.)

Teaching our children is difficult work, and it takes a certain personality and level of patience to do it well. I quickly realized that I don't understand what a 1st grader should and shouldn't know, and what they should and shouldn't struggle with. That, combined with my need to make everything okay for Brooke, made teaching a difficult undertaking. As her "teacher", I wasn't properly pushing her to independently work on lessons, make mistakes and learn from them, all things which are necessary to learn and grow as a six-year-old student. I never thought I could "help" too much, but I did! While I always knew I was overprotective, it wasn't until virtual school that I realized how much.

EVEN DURING COVID, PEOPLE ARE STILL HERE TO HELP!

While in lockdown, I began to feel like I was stuck on an island in terms of Brooke's education.

But what I learned is to unapologetically reach out for help. Once I reached out to Brooke's IEP team, I quickly received assistance, and her team has been phenomenal during all of this. Even though our communication and Brooke's PT therapy sessions looked different the first half of the year, she still received tremendous support, and her IEP team jumped in to modify that support to accommodate the virtual aspect of services and even added additional services. Her IEP team and school district have been amazing during the lockdown, and I couldn't be more grateful for the assistance and guidance they have given not only to Brooke but also Clay and me.

WHAT IT MEANS FOR BROOKE TO LEAD A "NORMAL" LIFE

When we first started our cystinosis journey, several people we spoke to encouraged us to treat Brooke the same way we'd treat a child without cystinosis. I always assumed I knew what this meant and that I was doing just that. But during lockdown, I realized that I need to work on this, for my sake as well as Brooke's sake. It's natural for parents to want to protect their children, and since I couldn't "fix" cystinosis, I have been trying to fix other things in life. By doing everything for her, I haven't afforded her the opportunity to grow into an independent six-year-old. Now that I recognize and am working on this, I realize that this, by far, is the best piece of advice we received.

As much as the past year has been stressful and stifling for all of us, there are some good things to come out of it. Brooke started back to school in-person in January. She attends school four days per week and takes the bus to school (apparently her favorite part of school!). She is thriving and is progressing well academically and socially.

She is also doing well in her school-based physical therapy, and has met all of her annual goals! Her IEP team, having worked with us throughout this entire year, as well as her beloved 1st-grade teacher, are helping Brooke prepare for 2nd grade, which will be here before we know it. Even though it's a big transition (2nd grade is in a new school and her IEP team will be made up of all new people), Brooke is definitely up for the challenge! Most importantly, I am working on letting go, and giving Brooke more space to be a normal kid. This year has solidified for me the importance of allowing her to be bored, make mistakes, not always get what she wants, and become more responsible and independent because that is "normal" life.

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

Learn about the fundraisers in honor of Brooke on page 44.

Next-Level Hero

Jacob Seachord downplays his role as a pioneering patient of the stem cell transplant, but his experience provides new layers of hope to cystinosis families.

Not much fazes Jacob Seachord, and yet sometimes it all just hits him. While cystinosis affects about 2,000 people in the world, he is one of three to receive a stem cell transplant procedure that may be the cure.

"I don't think about being special, but every now and then I'm like, maybe I'm paving the way for more people to test this, and that's pretty cool," Seachord says.

On November 16, 2020, Seachord became the third person to receive the stem cell treatment, developed by Dr. Stéphanie Cherqui at UC San Diego. The transplant procedure is anticipated to be a one-time treatment performed with the hope that it will stop the progression of cystinosis or even be the cure.

In 2018, the FDA approved the clinical trial for six patients to test the safety and efficacy of the stem cell treatment. Since 2007, the Cystinosis Research Foundation (CRF) has supported Dr. Cherqui's groundbreaking research, and thanks to the generosity of CRF friends and allies from around the world, CRF has funded nearly $6 million in grants to Dr. Cherqui for this study.

Though he downplays his role as a pioneer of the transplant procedure, Seachord holds a special place in the hearts of cystinosis patients and their families. He has heard from many of them in the weeks and months since he received a transplant of his own stem cells after they were modified to correct the cystinosis gene.

As Seachord, 23, has been responding to emails and social media posts full of gratitude, he and his family have come to understand the full depth of the community's support.

Receiving the online messages as well as cards and letters "has touched his heart and mine," says Seachord's mom,

Rocky Seachord, writing in the blog she launched to keep cystinosis families and friends informed about Jacob's journey. "I almost cried each time we received a letter. It is so thoughtful for people to take time out of their busy day for him. Thank you!"

More than four months after Jacob's transplant, the Seachords report that he is feeling great, taking four-mile walks near the family's home in Bremerton, Washington, and enjoying the chance to finally have some contact with friends.

Jacob continues to build his muscles back after the chemotherapy that accompanied the procedure as well as the inactivity of his hospital stay and post-procedure convalescence. But he's achieving numerous milestones of normalcy, including a return to work at the family fencing business. So far, that work is all outside and only with his dad to reduce exposure during this time of continuing COVID-19 restrictions.

The pandemic has necessitated special accommodations, of course, especially given Jacob's immune-system vulnerabilities after the procedure. He wasn't allowed visitors during his 3-1/2-week hospital stay in San Diego for the transplant, so his parents and others would assemble outside his room to wave amid displays of balloons and posters of support.

Video chats full of love and online games of Yahtzee helped family and friends stay connected.

"It was stressful because we couldn't be there with him, but the nurses and others took such good care of him," Rocky says.

As memories of the procedural stresses recede, more hopeful signs replace them. A recent follow-up trip to San Diego for post-transplant testing brought more good news.

Everything checked out well; Jacob's platelet levels are back in the normal range, indicating that his immune system has recovered. That means fewer restrictions, including to Jacob's diet.

"They said I could get takeout," Jacob says with a smile. "That was exciting."

There are lots of smiles in the Seachord household these days. Jacob is off cysteamine, vastly changing his daily regimen and eliminating lots of side effects. Without the twice-daily doses of cysteamine, there are 16 fewer daily pills

Jacob Seachord

BREMERTON, WASHINGTON

by Dennis Arp

in his life. Likewise, he no longer is burdened by hourly applications of eye drops to clear away cystine crystals. These and other daily and hourly requirements, as well as the financial costs that come with them, may actually be things of the past.

"It's really nice, especially since one of my doses of Procysbi® (cysteamine) was coming at 4 in the morning," Jacob says. "I'm really happy to eliminate that."

The prospect that the transplant might be a cure for him and other cystinosis patients is a joyful thought, of course, he says. But he retains a resilient perspective that has helped sustain him through two decades of treatment for the disease.

"Yes, for sure I'm excited," he says. "The first two (transplant recipients) are doing pretty well right now, and I feel great. I know there's a small possibility that I might have to go back on (cysteamine), but I'm also used to that life – taking lots of medicine, making lots of adjustments. But it sure would be nice to be able to stay off it for the rest of my life."

Rocky, her husband Mike and the rest of their family also revel in the transplant's possibilities.

"It's really like a reset – like he's been born again," Rocky says. "Now he has three birthdays – his regular one, his kidney transplant birthday, and a third one for the stem cell transplant."

As the post-procedure transition continues, Rocky's two biggest concerns are for Jacob's transplanted kidney, which is now 11 years old, and for possible lost time on cysteamine if the procedure turns out not to be a cure.

"It sounds like when they do the six-month visit we'll have more of a definitive answer, so we're looking forward to that," she says.

In the meantime, she maintains a mode that's familiar to cystinosis parents.

"I'm always watching him, and so is his dad. Is he a little more tired today? Does he look OK to you?" she says. "Then it's no, take a step back. Who doesn't have a day when they're a little more tired?"

As the good days accumulate and the signs grow ever more positive, the transplant procedure's life-changing possibilities become all the more tangible for Jacob and the entire cystinosis community.

Jacob shrugs at his role in making this history happen, so it's up to his mom to put this moment in perspective.

"I know he's a hero," Rocky says. "My husband and I were just talking about this – you know when you live it day-to-day, it's easy to make like it's not a big deal. But it is a big deal. It's a really big deal."

THOUGHTS ABOUT JORDAN

Julian Midgley, BM, BCh (MD)
Alberta Children's Hospital
Calgary, Alberta, Canada

I first met Jordan when he was nine months old fairly soon after the initial diagnosis of cystinosis that, curiously, was made in Winnipeg (although Jordan's family lived in Alberta - but that is another story...). Now that Jordan is 22 years of age it must be that I have seen him in clinic over 80 times!

It is clear that cystinosis makes for resourceful families. When I first heard about a stem cell transplant to treat cystinosis I was puzzled - how does this work for a disease that affects every cell of the body? I learned about this new treatment alongside Jordan (and his family) mainly at the CRF Day of Hope family conference. When it became clear that Jordan was considering this stem cell trial all sorts of new ideas and possibilities came over the horizon. (Got to give kudos to Barb, Jordan's mother, for getting Jordan's name on Dr. Cherqui's list!)

I remember talking to Jordan at one clinic about the possibility of "being the first patient" in the stem cell trial. Real groundbreaking (pioneer spirit) stuff. Not sure that we knew at the time that Jordan would be first! The journey began and Jordan's ability to be relatively stoic and unexcitable has clearly helped him navigate the twists and turns of the journey.

One of the many impressive things about Jordan is that he has been open about his participation in the trial. There were lots of people/families wanting to know how the trial was going - particularly since he was the first patient. This reflects Jordan's bravery and willingness to let others know of his progress. It wasn't all easy and there are still challenges ahead - but Jordan is up to these challenges with the big support of the big cystinosis family, his own family and the teams in San Diego and at the Alberta Children's Hospital in Calgary.

When I see Jordan now in clinic, compared to when he was nine months old, I see a mature young man who rolls with the punches, rarely gets upset and has taken life head on, achieving more than any young man could possibly expect. Jordan even has two jobs and his own house! He also looks fit and well with, curiously, now darker hair and, much to my chagrin, may be taller than me! One of the biggest pleasures of being a paediatric nephrologist is witnessing a nine-month-old growing up to become a young man that everyone can be proud of.

Jordan and his mom, Barb.

Jordan and his niece, Drew.

By Barb Kulyk, Jordan's mom
CONSORT, ALBERTA, CANADA

LIFE v2.0

JORDAN'S NEXT CHAPTER BEGINS

When I was first asked to write something for the CRF Magazine, I really struggled not knowing what I wanted to say or how I felt.

Since the last year and eight months that Jordan has been off Cystagon®, and the last year and five months since his transplant, life has been a whirlwind of emotions.

I went from feeling like cystinosis was lurking, always ready to pounce, to feeling guilty that my son was the only one that had the stem cell transplant, to acceptance of our new way of life and immense gratitude to CRF, Stéphanie, my family support and God for this opportunity.

I found that even though Jordan and I talked every day for his entire life, and I thought I knew everything about him, I realized that we mostly only discussed his health. Once I was able to stop asking him how he felt every day - if he was tired, what he ate, if his legs were sore, did he drink enough water - I was able to replace those conversations with so many other topics.

I learned that he loves to tend to his yard, and we talk endlessly about plants and trees. I also learned that he wants to go to college, he had never said this to me before. He never thought that he would get to go, he thought he would be dependent on his family and not be able to live too far away from us. He was always in a rush to move out, buy a house and get a job like he was trying to beat the clock.

In October, after Jordan came back from his one-year checkup in San Diego, he had to isolate for two weeks and when the quarantine was over, he had applied to three different colleges.

I am happy to report that Jordan has rented out his house and is heading to Calgary in the fall for Butchery and Charcuterie Management at SAIT Polytechnic College. I could not be more proud of him. As we scrolled through his classes and took virtual tours of his residence, I couldn't help but think about the night he signed the consent for the trial and all the mixed emotions that came with that action. I remember silently praying for him to have choices and a normal life of a 22-year-old. I prayed for the burdens of this disease to be lifted. Something so simple as a college application symbolized that all these prayers had been answered.

My hope and wish for the next steps of the trial is that everyone with cystinosis has an opportunity to participate and get to live with so many choices that they don't know how to pick just one. I want our children to outlive us and want every parent to be able to wake up without having cystinosis be the first thing they think of.

Forever grateful, Barb

Big Days Ahead

By Caleb Gowan, Age 17
KARLSTAD, MINNESOTA

I was diagnosed with cystinosis later than most people, around the age of 6. When my doctor sent me to the Mayo Clinic, the pediatric nephrologist didn't know very much about the disease and when my parents googled it, they were heartbroken.

At the Mayo Clinic, they wanted to put in a g-tube but instead, I learned very fast how to swallow pills! My mom said "no" to the g-tube. My mom can be bossy but she says it is a sign of leadership. I can say that with her persistence I usually don't ever miss a dose of medicine. Because the doctors at Mayo knew very little about cystinosis, we went to the CRF Day of Hope conference and there my mom realized I needed to start taking Cystagon® after listening to a lecture given by Dr. Grimm about two sisters in Canada years apart in age and the positive effect the younger sister had by starting Cystagon® shortly after birth.

Luckily, Teresa Partington gave my mom information about Dr. Langman who is a top cystinosis doctor in the Midwest. He was looking for more study subjects for the delayed-release cysteamine, RP103 clinical trial. We traveled to Chicago every other week and met Dr. Langman and his amazing team! Heather Price was the person in charge of giving us RP103, now known as Procysbi®. Heather said I was the first person to take RP103 who had never been on Cystagon®. She also said I reminded her of Jordan Janz because he was in the study too but is older than me.

The children's hospital was close to a Lego store at Water Tower Place shopping mall which made the trip fun. We visited the store and that helped erase the memory of awful flights with turbulence and barf bags. Has anyone ridden in a cab in Chicago? Barf! My grandma took me on one trip, and I vomited in the container in the cab and the driver still made my grandma pay a $50 fee even though she had everything cleaner than when we were in the cab. She is the grandma who carries disinfectant wipes (even before COVID) and wipes down our seats in the airplane to embarrass us. Pretty sure my devout Catholic grandma dropped the f-bomb at that cab driver or maybe wanted to. She was hurt and upset. I remember my mom was at work back in Minnesota and tried to calm Grandma down over the phone after the interaction with the unfriendly cab driver.

I'm sure many people with cystinosis have had a similar struggle but we need to just pray for people who do not understand our struggles in life. I know I am a much more understanding and patient person when it comes to understanding other's differences. Don't worry, my grandma went to confession and God forgave her the way he does all of us in our daily struggles.

I really hope we can still go to California for the Day of Hope after everyone with cystinosis is cured!

After starting the Cystagon® and growth hormone, I felt more like a normal kid! I had the energy to throw a baseball and had a much better quality of life. My baseball coach was amazed at how I could run with less stiffness after starting the medicine and how I had even more energy after my kidney transplant. If there are younger kids with cystinosis reading this, I want them to know how important it is to take their growth hormone shot and medicine correctly every day. It hasn't always been easy, but I want a bright future and the only way to do that is by taking my pills and shot every day. I rarely forget to take my pills, but I often can be overwhelmed with the rigorous dosing and GI pain but…I will not let cystinosis win. My mom, step-mom and grandma are crazy and make sure I never miss my medicine. I get annoyed but I know they are trying to help because they love me.

Right now, I am playing basketball, have a part-time job and I am taking 12 college credits this semester as a junior in high school. There are definitely challenges in my life right now with family and school that go beyond cystinosis, but I am eagerly awaiting the stem cell transplant for everyone suffering from cystinosis. I am grateful for Jordan Janz and others who have paved the way for a cure and better treatments. I really hope we can still go to California for the Day of Hope after everyone with cystinosis is cured! The Stack family can sure put on a good party and make everyone feel welcome! Zoe and Stacy are pretty amazing too!

My faith in God has gotten me through a lot of hard things in life including cystinosis. The hardest part about the disease is that sometimes people don't understand why my short-term memory isn't great and why I want to sleep in or don't have the energy to do things. My nine-year-old brother Noah is a pretty persistent kid and even though I'm tired or don't feel well he usually is able to talk me into whatever his plans are. I'm trying to get better at explaining what the disease is because my family who advocates for me, will not be around forever.

Right now, I am seen at the University of Minnesota Children's Hospital and the nurse practitioner I see in the pediatric nephrology department, Tracy Moe, quizzes me on the pills I take and what they are for. I can fill my own pills (with some help from my mom) and am working towards independence. I feel this is very important for all teenagers with cystinosis. One of the nurses told my family after my transplant and post-transplant lymphoma treatments, she could tell I am a fighter. This makes me happy to know I can do anything I set my mind to in this life and I will not let cystinosis define me. Someday, I hope to be a Division 1 basketball coach, so look out Coach K at Duke!

What drink should I use to take Procysbi®?

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

When Sam was two years old, we were able to enroll in a phase 4 trial for Procysbi®, then called RP103. He was one of the first children to get the medication through a gastrostomy tube, along with Henry Sturgis. We started the trial the same day.

I'll never forget the disaster of the first morning on Procysbi®. We mixed the beads in some orange juice and tried to inject them through the g-tube, immediately clogging it. Over the next few weeks, we had serious doubts about the new drug and thought about switching back to Cystagon®. But after a lot of trial and error, we perfected the art of giving Procysbi® through a g-tube, and Sam stopped throwing up all the time.

When Sam was older, he started taking pills by mouth. Sam hates anything fruity, so he insisted on taking his Procysbi® with water. We noticed his cystine levels went up after he made the switch. We figured it was because we were no longer mixing his Procysbi® beads in apple sauce and orange juice.

Procysbi® beads are designed to bypass the stomach where the pH is low (acidic) and dissolve in the small intestine, where the pH is high (basic). If you take the medicine with something acidic (like orange juice), it should theoretically delay absorption. If you take it with something basic, the beads could dissolve prematurely, which may cause more rapid absorption with higher peak levels, which can cause more side effects. The drug could also be metabolized faster, which can cause higher cystine levels 12 hours after taking the medication.

Because Sam was no longer taking his medicine with orange juice, we had to increase his dose by a capsule or two to get his cystine levels back down. Sam's brother Lars started Procysbi® when he began pre-school.

Lars loves anything with sugar and was happy to take his medicine with juice. He's the same size as Sam now, but he doesn't have to take as many Procysbi® capsules (Sam takes 11 twice a day and Lars takes nine twice a day).

Now, this is all speculation; I can't prove that Sam needs a higher dose because he takes it with water instead of juice. But we decided to do a little experiment with the boys to test the pH of different drinks and measure how long it takes for Procysbi® beads to dissolve in them. Our hypothesis was that Procysbi® beads would dissolve faster in drinks with more base and would not dissolve in drinks with acid. We bought some pH test strips that tell you a liquid's pH based on color change.

Here are the results of our experiment:

Drink	pH	30 minutes	60 minutes	120 minutes
Coca Cola	3	Not dissolved	Not dissolved	Not dissolved
Orange Juice	2	Not dissolved	Not dissolved	Not dissolved
Apple Juice	3	Not dissolved	Not dissolved	Not dissolved
Milk	6	Not tested	Not tested	Not tested
Smart Water	7	Not dissolved	Not dissolved	Not dissolved
Kirkland Water	7	Not dissolved	Not dissolved	Not dissolved
Tap Water	8	Not dissolved	Not dissolved	Not dissolved

We were surprised that the pH of milk was actually more acidic than water. We didn't test whether the beads dissolved in milk because it would've been hard to see the white beads in a white liquid. Also, even though milk is acidic, you shouldn't use it to take Procysbi® because the fat and protein can diminish the absorption of the drug.

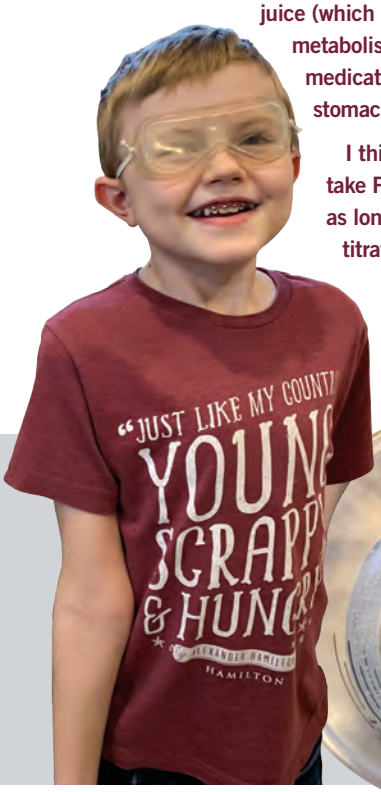
We were also surprised that our tap water was more basic than bottled water. This is what Sam uses to take his Procysbi® every day. We did try adding a couple of drops of lemon juice to the tap water, which immediately brought the pH down to about 5.

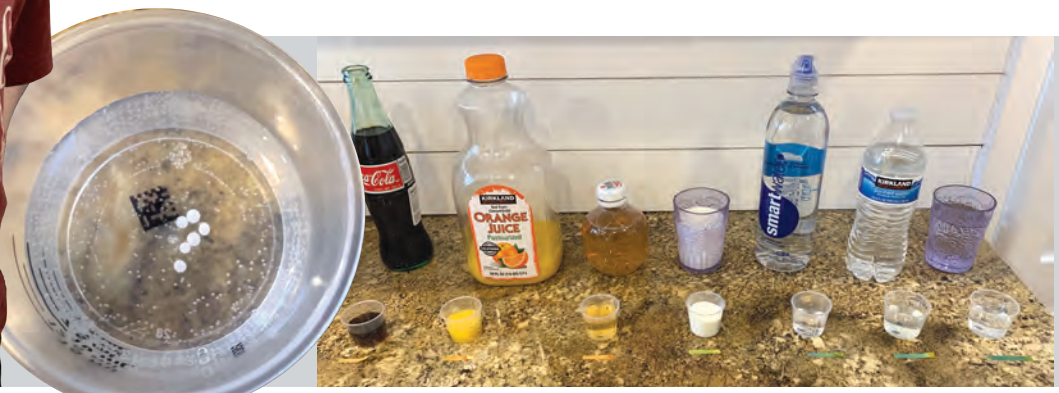
We were surprised that none of the beads dissolved in any of the liquids, including tap water, which had a pH of about 8. I will say that the beads were starting to swell at the 120-minute mark, which may be signs of early dissolution. This was done in little glass bowls, however, and not the stomach, which has a significant amount of mechanical digestion from muscular contractions. Maybe if we had continuously stirred the beads in the tap water they would've eventually dissolved. Another experiment for another day!

According to the package insert, in the original trials, there was no difference in the mean plasma peak and area under the curve in people that took it with orange juice or water.

The package insert does say to avoid taking Procysbi® with grapefruit juice (which actually interferes with the drug's metabolism) and to avoid taking it with medications that increase the pH of the stomach (bicarbonate or carbonate).

I think the moral of the story is that you can take Procysbi® with whatever drink you prefer, as long as the dose of the medication is titrated to appropriately reduce your cystine levels, and you take it the same way every time.





EXTENDED FAMILY
Extending Love

By Jim Flerchinger, Tina's uncle
PORTLAND, OREGON

My memory of the dates and times may not be totally accurate; however, the thoughts and feelings are true. We knew how much Mark and Denice wanted another child to join their two beautiful girls, so we were so happy for them when darling Tina was born into a large, loving, extended family a few years after the turn of the century.

Our granddaughter Jennifer was just a few months younger than Tina, and we enjoyed seeing the two babies together. Tina was happy, if a very quiet baby, but we noticed she was lagging a bit behind Jennifer. Shortly after she began on solid food, she began to develop symptoms that caused her to end up in the emergency room at the hospital. The ER doctors would run blood tests to find Tina's blood electrolytes out of balance. As soon as they rebalanced her blood electrolytes Tina would perk up and she would be ready to go. After numerous trips to the ER and their pediatrician, Denice and Mark were directed by their pediatrician to seek care and a diagnosis at the University of Washington or at Oregon Health Science University (OHSU).

My wife Debbie and I live in the Portland area, so they chose to bring Tina to OHSU. Tina was only about 18 months old when they brought her to OHSU. Our extended family would check in often with Denice offering words of encouragement and prayers. Denice stayed at the hospital for around six weeks with all three girls, and Debbie would make the trip to OHSU almost daily during that time. I would accompany Debbie on my days off work, and I remember Denice saying how she appreciated Debbie listening to the doctors as her extra set of ears given all that was happening.

I remember occasionally taking Tina's two sisters for a walk-off of "pill hill" to get some fresh air and ice cream in downtown Portland. During this time, a diagnosis of cystinosis was made. Dr. Al-Uzri championed Tina's care from that time until the present. Tina was finally released from OHSU and she and her family went back home to eastern Washington with many medications and a continuous testing schedule.

Denice and Mark would come down to the Portland area many times over the years to OHSU and stay with us while Tina underwent her healthcare updates. These visits allowed us to be a very close part of their family. Mark is my youngest brother of a family with 10 siblings, and we have always had a special connection. With Tina's care, we were able to keep closer than the six-hour drive that separated us. I remember playing pranks on the nieces during their visits, and they on us. I placed a rubber mouse in their bed on one such prank. On our next visit to their house, the nieces stuffed our bed with toilet paper. The next morning, I came down to breakfast with toilet paper coming out of my pockets and shirt collar.

Sometime after Tina was diagnosed with cystinosis, Denice and Mark became Tina's fiercest advocates. Denice especially sought out any information on this genetically inherited disease and got in contact with the Cystinosis Research Foundation (CRF) and Nancy and Jeff Stack. Denice and Mark started having a spring fundraiser for the CRF. At first it was a few hors d'oeuvres and wine. Over the years it grew into a major fundraiser as 'food from around the world' as well as wine and beer. Denice and Mark became major contributors to CRF, and the rest of our family always came to help at these fundraisers because that is what extended, loving families do. We became event set-up specialists, waitstaff, bartenders and auction runners. We watched Denice be transformed from Tina's mom to a polished, gifted public speaker and board member of CRF. Over the years we have watched as CRF has had one success after another with medications and treatments for those affected by cystinosis, improving their lives. Cystinosis robs the health of those affected by it, and CRF is the magic that transforms the health of those affected by it.

CRF IS THE MAGIC THAT TRANSFORMS THE HEALTH OF THOSE AFFECTED BY [CYSTINOSIS].

In early 2019, Tina's kidney function started declining. The doctors had told us that Tina would probably need a kidney transplant by age nine, so although it was not totally unexpected, it was discouraging news. More trips to OHSU and more testing, including possible donors. Tina's dad, my brother Mark, was found to be the perfect match. It was hard to believe that a really ancient 50+-year-old kidney was a match for my beautiful 16-year-old niece.

Denice, Mark and Tina moved to our house for a month during this time. I must admit I was a little surprised by how many suitcases of 'stuff' they packed into our house, taking over two bedrooms and the majority of our refrigerator, but so happy they were here! After settling in for a few days, they checked into the hospital at OHSU.

The operations, removal for Mark, transplant for Tina, was an intense time. Denice stayed with Tina at OHSU in the Pediatric unit, and I stayed with Mark in the Surgical Recovery unit. This was a very emotional time for all of us. Debbie's sister died the same day as the kidney transplant, which only added to our appreciation for the gift of life Mark was able to provide for Tina. When life gets down to extreme basics, you develop a different sense of what is really important for the years here on earth. To say it is life-altering is cliché and is an understatement at best.

Through it all, we have been so very impressed and proud of this family. Mark and Denice have somehow managed to balance fighting hard for the best care and research for Tina while raising their two older daughters to be caring, compassionate, fun, loving women. And "our" Tina is a feisty, loving teenager with a hopeful future. She has been a blessing to the entire family, opening our eyes to appreciate the joy in every moment we can share with her.

HENLEY J PARSEL

By Melissa Parsel, Henley's mom // GILBERT, ARIZONA

Henley Jordan Parsel was born on February 25, 2020, four days early, at the beginning of a pandemic when the world was starting to shut down, grocery store shelves were bare, and we worried about our health and jobs. It was already a stressful year full of uncertainty, and just when we felt we were finding our new normal, we heard our six-month-old daughter might have a very rare genetic disorder called cystinosis. Since we knew how rare it was, we didn't want to believe it could be true. We had known something was wrong. She had feeding issues and reflux since she was born. Her growth chart percentages were dropping each month and at her six-month check-up, she had lost 10 ounces and was in the 5th percentile for weight.

On October 6, 2020, her diagnosis was confirmed, and our world came crumbling down! We began to mourn the life we once dreamed of for our family and daughter. She stopped breastfeeding and wouldn't even take a bottle or food by mouth anymore. She was constantly crying in the middle of the night. Would she ever be able to eat by mouth? Will she grow strong enough to play normally with her sister? Will she live a long life? How are we going to manage all of this? We had so many worries and were absolutely devastated. The first few months were the most difficult and challenging times of our lives. She was given all her food and medications through a g-tube. We set alarms to go off almost every hour, reminding us of a medication, feeding or some type of therapy she needed. We were having a hard time seeing the light at the end of the tunnel and didn't know if it would ever get better. As we started learning more about cystinosis and Fanconi syndrome, we knew how important it was to get her electrolytes and white blood cells (WBC) stable. We tried to remain positive and hopeful that she would one day eat by mouth again and that our daily routine would get easier.

Within four months of Henley being hospitalized, she stopped throwing up and started to slowly show interest in solids and a bottle again. When we received the news, her WBC was in the normal range for the first time, we couldn't be happier. We started a new medication recently that helps her hold onto more of what she is taking in and she finally gained 1.8 pounds in less than a month! Even though it is easier than when she was first diagnosed, every day is a new day and comes with different challenges. She is still struggling to eat on her own, but we celebrate the wins of her having more time playing, crawling all over, standing, growing and always being happy!

When we look back to when this all started, we'll never forget the day we were told it might be cystinosis. The genetic counselor came into our hospital room late at night and discussed the potential diagnosis. Before he left, he gave us hope for a cure someday. At the time, we were so overwhelmed that the word "someday" seemed so far away or would never happen. After learning about the stem cell and gene therapy trials and how well the three patients are doing, "someday" is a lot closer than we could have ever imagined! It gives us hope that cystinosis can be cured in the next few years and our daughter has the potential to live a long and healthy life. The dreams we once had can and will become a reality!

For the new parents out there reading this, all of us know how devastating, overwhelming and difficult this disorder can be. The best advice we ever received was to not compare your child to others, every patient is different. Take one day at a time; eventually, it will get easier.

We will be forever grateful for the knowledge and support we have received from the doctors, specialists, cystinosis community and our family and friends. We wouldn't have been able to get through the darkest days without all of you… Thank You!

H J P

AFTER LEARNING ABOUT THE STEM CELL AND GENE THERAPY TRIALS AND HOW WELL THE THREE PATIENTS ARE DOING, "SOMEDAY" IS A LOT CLOSER THAN WE COULD HAVE EVER IMAGINED!

Surrounded by Support

By Jenny Raycraft
CALGARY, ALBERTA, CANADA

Cystinosis has affected my life in a way that I consider to be both a blessing and a demanding obstacle. Cystinosis has made me realize how precious life is and to never take anyone or anything for granted. What I have been through in the past 26 years of my life, most people don't encounter in their entire lifetime.

I try to remain positive and resilient every day and having a strong support structure around me has been the key. My family, friends, a very cute little dog named Minnie and my fiancé have been the big reasons why I continue to remain positive. Not only do I have all of them, but I have the world's greatest doctor, Dr. Julian Midgley, and his staff who, I believe, have had a positive impact on my overall health. Without these individuals in my life, I don't believe I would be doing as well as I am today.

I have the world's most supportive parents who have always been by my side and continue to give me unconditional love which has helped me in a bigger way than words can even begin to explain. I would not be where I am today or who I am today, without their love and support.

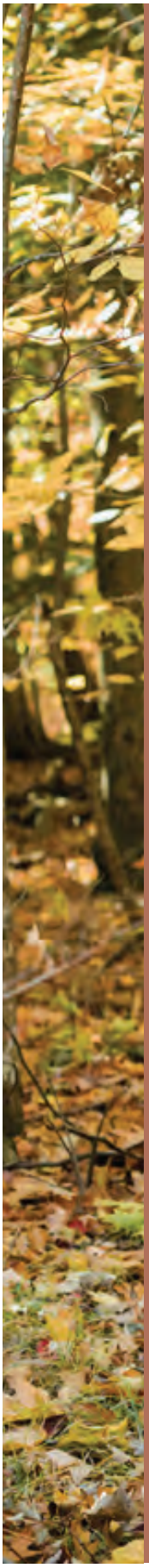
Not only do I have the most supportive parents, but I also was blessed to meet Steven, who is now my fiancé. We met when I was 21 years old. Nearly five years later we are now engaged and plan on getting married in the summer/fall of 2022! Steven proposed in Banff, Alberta on November 22, 2020. He has been my rock during the pandemic and words can't begin to express how lucky I am to have such a supportive person by my side through everything, especially with cystinosis.

The Cystinosis Research Foundation continues to give me hope that we are getting closer to a cure for cystinosis. I feel very fortunate to be a part of such a wonderful and supportive community. The stem cell trial gives me hope that one day soon we will all have a better quality of life for those living with cystinosis. I am very interested in participating in the stem cell trial, not only to improve my health and overall quality of life, but to help others with cystinosis. I have always wanted to help others and if I am part of the trial, I would be able to help in some way. The opportunity to participate would mean more to me than I can begin to put into words - I hope all of us have that opportunity very soon.

I feel very fortunate to be a part of such a wonderful and supportive community.

"Knowing Jenny has been a great privilege and a blessing, even more so because she has agreed to marry me! Proposing to Jenny was the easiest decision I have ever made. She has shown time and time again how strong she is, especially during these trying times. The fear of the unknown has weighed on her mentally, but she has persevered and it has only made her stronger in my eyes."

– Steven Flory, Jenny's fiancé



Curious Aidan

By Erin and Jim O'Leary, Aidan's parents

CHICAGO, ILLINOIS

It's been four years since our cystinosis journey began and there's certainly never a boring day. One of the biggest gifts for our family was welcoming our beautiful baby girl, Maeve Isabelle O'Leary, in November 2019. She has brought so much love, laughter and chaos to the O'Leary household. Aidan is a very proud big brother, and it is absolutely wonderful to see them play, learn and grow together. We feel thankful as our family's bountiful blessings outweigh the many challenges associated with having a child afflicted by a chronic disease.

Just when our sea had settled a little bit, a pandemic was thrust into our reality. 2020 was an "interesting" year - COVID-19 created new challenges and rattled our fragile ecosystem. Being stuck at home with two young children during the Chicago winter is not for the faint of heart! We struggled to find the right balance of protecting Aidan's health and also letting him and Maeve just "be kids." We initially defaulted to being very conservative but are now cautiously branching out and living our lives.

It's hard to believe that Aidan just turned five years old. He is currently finishing up his Junior Kindergarten year with pod learning and will be attending Kindergarten in the fall. He aspires to be an astronaut, paleontologist and singer when he grows up. His current interests include dinosaurs, everything that has to do with the movie *Aladdin* and going skiing. He is such a bright light with an unbelievable imagination and an insatiable thirst for knowledge. He can be shy when he's outside of his comfort zone, but once he settles in, his energy and endless questions will make your head spin! He is our hero, and hands down, the strongest person we know.

Life with cystinosis is hard, and the endless worry of what's going to happen next is scary.

There are so many factors completely outside of your control, and the medication burden is a beast. We've found a schedule where Aidan almost never gets sick, but it is quite laborious starting at 6:00 in the morning and ending at 11:30 at night. Our family tends to just pour ourselves into the present, trying to keep Aidan as happy and healthy as possible until better treatments are available. This can be exhausting at times, but we are very blessed to have wonderful family, friends and medical professionals supporting us.

Overall, his health is very stable and his growth has been fantastic — reaching nearly the 50% percentile for height. He truly is thriving, and we are extremely hopeful with all of the impressive research and medical advancements being funded by the Cystinosis Research Foundation. We have always believed that one day Aidan would be cured of this terrible disease, and we know the CRF is going to make that a reality. Thank you to the Stack family for your unyielding leadership, and thank you Stéphanie Cherqui for your tireless efforts in finding a cure.

For everyone in Aidan's Army, we cannot wait to get back in full swing with you in 2022 with our annual charity event. Thank you to all of our amazing donors for your generosity and for helping cultivate better treatments for all those afflicted by cystinosis. Our family is forever grateful for your support.

AIDAN IS SUCH A BRIGHT LIGHT WITH AN UNBELIEVABLE IMAGINATION AND AN INSATIABLE THIRST FOR KNOWLEDGE.

BUSY

A journey through cystinosis from a grandparent's point of view.

By Amanda Kelly, Bee's Grandmother
BRISBANE, AUSTRALIA

After two premature grandchildren, we expected the same for our third. However, Bee decided that she liked where she was and was born a week overdue on exactly the same day as her older sister four years previously.

For the first few months, it was the usual problems with juggling three small children. Then at around nine months, we noticed Bee would always be thirsty, trying to grab the tap every time it was turned on. She was vomiting and losing weight. She could not shed tears and did not perspire even though Brisbane (Australia) is hot and humid in summer.

Our daughter, Erin, took her to the doctor many times. I would be there to support her when I could, and we took the older siblings to our home when Bee needed to go to the hospital. Erin's husband is wonderful. He is very supportive, but he has to work.

The doctor and hospital visits became more frequent. We knew there was something terribly wrong. I called it, "failure to thrive." The frustration of not knowing what was causing her symptoms was incredibly painful and the feeling of helplessness was overwhelming.

Meanwhile, we did (and still do) our best to keep Bee's siblings happy and give them lots of attention while Bee was having her many hospital visits and tests. Living at our place for a couple of weeks at a time, getting them to school, etc. I'd forgotten how busy a young mum's life could be (exhausting!). We are on call 24/7. My phone is beside my bed.

At 14 months old, finally, after "every test known to man," a doctor advised that she thought the problem may be renal related. Further tests proved positive for Fanconi Syndrome and cystinosis. It was a bittersweet result. Finally, we had a diagnosis.

And we were devastated.

Suffice to say, we devoured everything we could about cystinosis. Even though at the time of diagnosis, it was incurable, my husband and I have made it our mission to do everything we can to help cure our Bee, and to highlight this rare disease.

We attended the Cystinosis Research Foundation Day of Hope family conference in Newport Beach, California in 2019, and were so incredibly humbled by the work that has been done to find a cure and the support and love in the cystinosis community. As 'Team Bee' we attended every lecture and function and networked our hearts out. We are eternally grateful to Natalie, Nancy and Jeff. We were also (through our Uncle and Aunt who live in San Diego and who attended the conference with us), able to tour the UC San Diego facility where the "magic" to find a cure is being done. We were also able to meet Stéphanie Cherqui, our hero.

Bee is now four years old. She is still on multiple medications a day, and she has just started at Kindy two days a week.

Bee is "as tough as old boots," as we say here in Australia. She is the Boss Baby. Her imagination and capacity to play and talk are beyond belief! She takes her meds, her blood tests, her many specialist appointments and trips to the hospital with bravery beyond her years. She looks after her babies, the dozens of baby dolls that she loves. She is "Doctor Bee" and gives them their medications and needles. It's incredible to see how she copes with an extraordinary childhood.

But the bravest and hardest working person I have known is our daughter. I have the utmost respect for parents of cystinosis children, especially those with other children.

The endless, round-the-clock care and attention that is required just to give their children a "normal" life is awe-inspiring. I don't think she has had more than three hours of sleep in four years.

My husband and I have always believed that one day, in Bee's lifetime, there would be a cure. We now believe with all our hearts that with the magnificent efforts of the Cystinosis Research Foundation and the rest of the cystinosis community it will happen in OUR lifetime and we are even more hopeful that we will see our granddaughter Bee grow into a beautiful, healthy adult.

FINDING BALANCE

By Katie Monaghan, Abbi's mom

ST. CATHARINES, ONTARIO, CANADA

I started this on my phone in the waiting room of another appointment because during a pandemic, between work, schooling, family time and preparing for my daughter's kidney transplant, I'm not sure where else I'd find the time.

Abbi was diagnosed with cystinosis in October of 2007. When I think about that exact day, I still feel that paralyzed feeling and the lump in the back of my throat. At diagnosis, we knew Abbi would eventually require a kidney transplant. It's something that was on our minds and discussed at every appointment.

I feel as though we have been preparing for this for the last 13 years. This past year, Abbi's kidney function took a drastic drop. Could it be the blips of noncompliance with medications? Abbi is a 14- (almost 15-) year-old teenage girl taking over 40 doses of life-sustaining medications daily that are prolonging her life; however, they also have some pretty significant side effects. There are many days that this amount of medication is very unrealistic. I question myself frequently, is Abbi "Surviving or Thriving?"

Could the drop in kidney function be due to the significant growth she's had over this past year - which is what we have been working toward? Along with growth, a kidney has to work harder and a kidney that is failing will fail more. Could it just be the progression of cystinosis? Or could it be a combination of everything?

Whatever it is, no amount of planning, even 13 years of planning, prepares you for your child needing a life-saving organ donation. Over the past few months, Abbi has been prepping for a kidney transplant.

It's a very involved process to ensure that her body as a whole is healthy enough to endure this major surgery. Abbi has had scans, x-rays, blood tests, physical tests, booster shots of immunizations, and ongoing appointments to track levels. There have been many days that I think to myself, *I feel like I'm torturing her.*

Abbi is at approximately 13% kidney function and we had a donor come forward. It's a "Big Ask" to have someone donate a major organ. Yes, you can definitely live with one kidney but how do you just ask someone to donate it to your child? From the very beginning as Abbi's mom, I just assumed I would be a match. However, we are not the same blood type. We then assumed Abbi's father would be a match, but health complications prevented that from happening. We had a close friend step forward before we even asked who completed all of the required testing. However, in the final round of testing, there was a small issue that would not allow our friend to donate. We have since had multiple people step forward

ABBI HAS GROWN TO BECOME HER VERY OWN ADVOCATE

requesting more information on being a living donor and willing to hop on this emotional roller coaster with us.

As much as we have prepared for this moment for the last 13 years, it's now happening faster than I can think. The goal right now is to have Abbi receive a kidney before requiring dialysis. With all of this going on, life is still happening too. The most important thing we have learned over the past 13 years and especially this last year is Balance. There is always "A Silver Lining."

Abbi has grown to become her very own advocate; she speaks up for herself during all appointments and she sets her limits and boundaries. We have learned what is most important to us and we know the importance of prioritizing it.

Both Abbi and her brother are bright, inquisitive and kind. There are days when it is important to complete all schoolwork and tasks, and there are days when it's important to go for a drive and share a bucket of fried chicken and a great conversation.

"This Too Shall Pass" is a phrase I often say in my head... and while this passes, we will continue to Thrive.

"IT'S NOT THE LOAD THAT BREAKS YOU DOWN; IT'S HOW YOU CARRY IT."

— LENA HORNE

By Crystal Walker, Madelyn, Aliyah and Sarah's mom
CALGARY, ALBERTA, CANADA

For the longest time, I believed rare meant something extraordinary, something precious, and therefore something entirely likely to pass me by in life. I associated it with a rare gem, or other object - something unusual, and usually extremely valuable. Or it could mean a rare event, like being struck by lightning - unlikely to happen to anyone I knew. Solar eclipses are rare events we celebrate. Until our doctor told us that our daughter had a rare disease, rare in our life had mostly positive connotations.

And then joined the rare unfortunate few to have been struck by lightning. Twice.

When our second daughter Aliyah was diagnosed with cystinosis at 11 months old, our nephrologist told us that we would have to become the experts on this rare disease. He told us that some doctors might not like being less informed than we were on this strange disease that they would rarely, if ever, encounter and that we needed to be confident in our knowledge and expertise as we walked this cystinosis journey. This both encouraged and terrified us. We, with no medical training and no science background between us, had to be experts on a disease? How would we understand what was happening to Aliyah (and later, Madelyn, who was diagnosed at six weeks old), and make sense of strange symptoms and medical jargon and pharmaceuticals?

In those first weeks Nancy Stack and then Karen McCullagh, another Calgary cystinosis mom, found us, and suddenly we had a new home and family in which to plant our feet. On social media, our newfound "cystas" shared their insights and questions, and we could compare our children's symptoms, finding solace in their commonalities and other cysta-advice. Rare our daughters were, but we had found a rare gem in the cystinosis community and CRF - connection, comfort and understanding. For years, we did not realize that this community soothed the challenges of living with this rare disease, which included delayed diagnosis, few or inaccessible treatments (if any), limited resources for research and development, and the loneliness of walking a road that few understand.

In November 2019, we were struck by lightning a second time when Madelyn, then six years old, started experiencing new symptoms. These led to a diagnosis of moyamoya, and her condition spiraled quickly into bilateral strokes, of which she suffered five. The treatment, brain surgery, came too late to save her from becoming severely disabled and losing her ability to sing, dance, tell stories, run and play. During Madelyn's rehabilitation in the hospital, her sister Aliyah who also has cystinosis, received the diagnosis of moyamoya as well, leading to a barrage of questions. So far, there is no known connection between the two.

Cystinosis and moyamoya are unlikely bedpartners - and terrible ones. People with cystinosis dehydrate quickly and are constantly thirsty, drinking gallons of water. People with moyamoya require extra hydration to maintain a healthy blood flow. Madelyn, diagnosed at six weeks old, did not drink water with the same exuberance as her sister. She had the consistent dehydration of cystinosis combatting the extra hydration needs of moyamoya. Both girls have added

RARE OUR DAUGHTERS WERE, BUT WE HAD FOUND A RARE GEM IN THE CYSTINOSIS COMMUNITY AND CRF - CONNECTION, COMFORT AND UNDERSTANDING.

aspirin to the daily medication regime; Madelyn also has a plethora of anti-seizure medications. Because she can no longer swallow, her cystinosis meds plus food and lots of water now go through her new g-tube. Cystinosis has become, rather than her primary challenge, a complicating factor to her disability, but we know that as time passes, cystinosis will create challenges that are enormous.

Aliyah's brain surgery in May 2020 went smoothly and she was home three days later. But we have entered a whole different world - a new experience of rare disease. Suddenly, we realized the gift we had been given by CRF and our cystinosis family. It softened the edges of living with a rare disease so much, in fact, that we didn't really even realize we were rare. We always had somewhere to turn with questions, with sadness, with new medications. Moyamoya was a dramatic departure from this cystinosis journey. Suddenly, we feel adrift without a life-line, lost in a sea of questions. Is this or that symptom related to cystinosis? Or moyamoya? Or maybe stroke? How can I share with a cystinosis family some of our cystinosis wisdom - will we frighten you now that Madelyn's circumstances are so changed? Are we relevant in this community?

As we navigate our daughters' new challenges, we are endlessly grateful for our friendships with you, for your care and support and prayers and love. We have been made stronger because of you, and your courage, resilience and ability to find silver linings. The Cystinosis Research Foundation has offered such a unique security net for all of us - a place to connect, to belong, to share, to understand and be understood. We are never-endingly grateful for all that you do - for all that your families have done to raise awareness and funds for a cure.

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

TOGETHER, WE ARE one

1 PURPOSE. 1 JOURNEY. 1 CURE.

Internet

CYSTINOSIS FAMILIES AND FRIENDS SUPPORT RESEARCH THROUGH FACEBOOK FUNDRAISING

We are forever grateful to all those who have set up fundraisers to support the important research being done to improve treatments and ultimately find a cure for cystinosis. And now, with Facebook Fundraiser, it is even easier! Just type in the link on your browser to get started. *www.facebook.com/fund/CystinosisResearchFoundation*

In 2020, our Facebook Community continued to grow **raising $88,577 to support cystinosis research.** Since Facebook doesn't charge fees on fundraisers for nonprofits, the money you raise for CRF will go directly to cystinosis research. Since January 2021 our Facebook Friends have raised over $6,000. CRF will put your contributions to work immediately when the 2021 Spring Research Grant Awards are announced at the end of June!

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In Honor of Grace Sevel – Willoughby, Ohio

NO SHAVE NOVEMBER

The Willoughby Police Department does an annual "No Shave November" where officers do not have to shave for the entire month of November. In return, the officers pay a "fee" to participate. The money raised is then donated to a charity. This year it was decided the money raised would go to support cystinosis research. **CRF received a portion of the proceeds, $870, from The Willoughby Police Department in honor of Grace Sevel.**

Mike Sevel, an officer with the department, and his wife Kristina became part of the cystinosis community when their daughter, Grace, was diagnosed with cystinosis on May 15, 2020.

Although times were challenging the first several months, Grace is now doing very well. She is tolerating her medications, gaining weight and her levels are all within the acceptable range. Grace smiles almost all day long and is becoming an avid music/dance fan.

Mike and his family feel blessed to be in their situation because before now, so many families had no hope of a better future free from cystinosis. They did the best they could, coping with the challenges that cystinosis brings. Today, because of CRF and cystinosis research, treatments are improving, and a cure for this terrible disease is no longer a dream but a very real possibility.

Grace's diagnosis was the first time anyone at the police department had ever heard of cystinosis. However, because of Grace and the cystinosis community, more people are learning about cystinosis and striving for the day when Grace will tell people in the future that she had a rare disease as a child.

We are grateful to Mike and his fellow police officers in the City of Willoughby for choosing to support CRF and joining our quest for the cure!

In Honor of Aarav Khalasi – Sacramento, California

IT TAKES A VILLAGE

Thank you Minaxi, for sharing Aarav's Time To Shine fundraiser on Instagram for Rare Disease Day which contributed **$1,686 for cystinosis research!**

Aarav's Time to Shine started with the hopes to raise awareness and funds to cure our son's disease. It has become so much more with the support of loved ones and our cystinosis community. Most of you have probably already heard the saying it takes a village to raise a child and for us that couldn't possibly be more true. We are amazed by how many people have supported us by helping us raise funds, encouraging us and helping us stay hopeful. Cystinosis is a part of our journey and the cure will always be our main motive. With the support that we have, I truly believe that one day our village will succeed. We have made so much progress, and we are not ready to stop in the hopes of improving the lives of those with cystinosis in so many ways.

The Kalasi Family – Minaxi, Mukund, Aarav, Isha, and Rani

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1 CURE.

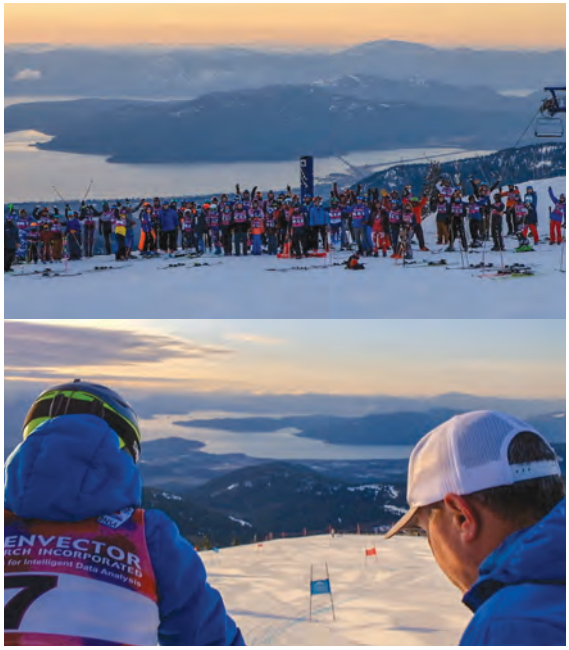
In Honor of Nicole Hall – Richardson, Texas

KINDFEST USA 2020

We are pleased to share that KindFest USA 2020 was a huge success with over 100 attendees, 14 headline speakers and dozens of table hosts. The virtual space was bursting with kindness and insightful conversations about spreading joy and thoughtfulness in the workplace and beyond. An enormous thank you to Becca Smith, the event organizer and longtime friend of the Hall Family, and to the attendees and sponsors who **together raised over $3,652 for the Cystinosis Research Foundation.** CRF was honored to be part of KindFest USA and your mission to make every day a kindness day!

In Honor of Henry Sturgis – Sandpoint, Idaho

2400 FEET OF SCHWEITZER MOUNTAIN - SANDPOINT, IDAHO



The weather was perfect for the 13th annual 24 Hours for Hank ski event held in honor of Henry Sturgis. With clear skies and nearly a full moon, participants were able to watch the moon set and the sun rise as they waited for their turn to start the 2400 vertical foot giant slalom! Hank was the first to start the race, skiing in perfect snow conditions. Everyone's legs were burning by the time they finished the 2.4 mile course, which took the fastest skiers nearly 3.5 minutes to finish. Racers then had an hour break before they had to take their second race run. The combined time of both runs determined the winners and the competition between the age groups was very competitive. The 79 racers attacked the mountain at 6 a.m. and were finished at noon. Everyone had a great time while **raising $100,000 for cystinosis research!**

CRF is grateful to Brian Sturgis and the 24 Hours for Hank team for organizing another successful ski event. Thank you to everyone who participated for your generosity and for supporting cystinosis research.

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1 CURE.

In Honor of Braden and Dax Tyner – Milton, Florida

THANK YOU SIMPLIFIED AND EMILY LEY

More than 11 years ago, Emily Ley started a stationery and paper business that has grown into a very successful company, Simplified. Emily has generously shared her success by donating to CRF for many years. The donations, in honor of her dear friend Christi Tyner and Christi's boys, Braden and Dax who both have cystinosis, have helped fund critical research to find a cure. **Emily recently donated $3,620 to CRF** bringing the total donated by Simplified to an astounding $32,000! We are grateful to Emily and the Simplified community for providing hope for a brighter future to those with cystinosis.

In Honor of Tanner Edwards – Fort Collins, Colorado

BIRTHDAYS ARE FOR FUNDRAISING! WOODWARD INC. CELEBRATES TOM GENDRON

Tom Gendron, president and CEO of Woodward, Inc., hit a milestone birthday in February 2021. He probably never thought this would be in the middle of a worldwide pandemic, where working remotely was the norm and celebrating birthdays, work anniversaries and holidays were all very different.

How do you celebrate a special birthday when you can't be together? What do you get someone when you aren't supposed to travel and leaving your house is even a rarity? Tom's staff members wanted something different and unique for Tom. They had just acknowledged his 30 years at Woodward with a gourmet wine basket and celebration via a Zoom meeting. What else could they do?

Tom and his wife Traci, whose son Tanner has cystinosis, have experienced the ups and downs of living with cystinosis. The team came up with the idea of a fundraising birthday campaign for the Cystinosis Research Foundation. A page was created on CRF's website for members of Tom's staff to donate in honor of his birthday. The foundation means a lot to the family, with Tom and Traci serving on the Board of Trustees. The team surprised Tom at a Zoom staff meeting and presented him with birthday gifts typical for someone getting older: a cane, compression socks, multivitamins and more. The best gift was a note acknowledging the generosity of his team that **raised $17,725 for cystinosis research.** Tom was surprised and very appreciative of what the staff had done for him. Thank you to everyone who helped make this donation possible and for helping celebrate Tom's milestone birthday!

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1 CURE.

In Honor of Brooke Emerson – Hammonton, New Jersey

SIXTH ANNUAL FISHING FOR A CURE FRIDAY, APRIL 16, 2021

Six years ago, our world was turned upside down when finally, after a long battle to arrive at a diagnosis, the word "cystinosis" entered our lives. Between all of the confusion, uncertainty and fear, those were unquestionably the hardest days of our lives. However, only two months after Brooke's diagnosis we were having our first fundraiser. Organizing the fundraiser the first year provided a much-needed distraction at a time when they were hard to come by. More importantly, the realization that we had the ability to proactively do something to benefit Brooke and other families was truly empowering. The first year was a huge success and before the day was over, we all knew we had to do it again. We have had a fundraiser each year since then and, thanks to our generous co-workers, friends and families, we have raised more than $140,000 for cystinosis research.

The concept of our fishing fundraiser is simple: the fishermen (and their significant others) reach out to co-workers, friends and family and ask for them to make a pledge. The pledge represents an amount that they will donate per fish caught. The fishermen then fish one full day from dawn to dusk catching as many fish as possible. We specifically fish for shad, and we fish in places and at times when the fishing can be extremely good. These fish live in the ocean and swim into rivers and streams in the spring to spawn. In tough years some fishermen may fish all day and only catch 10 shad while in better years an angler may catch more than 100. The fish are quickly released to go about their important business.

It is amazing to reflect on what has happened over the past six years. There have been major advances in research related to improved treatments and a potential cure for cystinosis. It is reassuring to know that we have played a part in the progression of that research. So, just like the shad, we returned to the river on April 16th with renewed focus, **caught 382 fish and raised over $33,000!**

— Clay Emerson, Brooke's dad

In Honor of Brooke Emerson – Hammonton, New Jersey

MUSIC BY N5MD AND MIKE CADOO

The album, Twenty Years Away, was released in November with proceeds from sales and downloads donated to CRF in honor of Brooke Emerson. One of the tracks is by Loess, a duo with Clay Emerson, Brooke's dad and Ian Pullman. The music label n5MD was founded by Mike Cadoo who has spearheaded the fundraising efforts. We thank Mike, n5MD and all the artists who contributed their time and talent to support Brooke and cystinosis research. **CRF received over $3,000 from the direct sales** of the initial release and will receive ongoing royalties in January and July for sales in future years. Learn more about n5MD: *http://n5.md/twenty*

TOGETHER, WE ARE one

1 PURPOSE.
1 JOURNEY.
1 CURE.

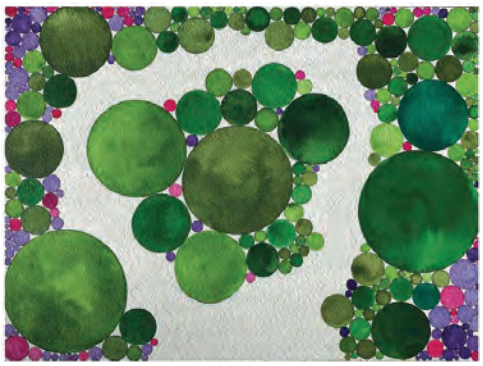
In Honor of Andrew Cunningham – Langdon, Alberta, Canada

FORE FATHERS GOLF CLASSIC

The ninth annual JCFG Memorial Golf Classic held on September 12 was formed because four families, impacted by the loss of a father to heart disease, wanted to make a difference. Each of the dads shared a passion for golf, so a golf tournament was established in their honor. John McCullagh, Conway Cameron, Frank Halluk and Gordon Cunningham, aka "The Fore Fathers," became the inspiration for the fundraising. **This year $3,750 was raised to fund cystinosis research.** Since 2012, the families have honored the "Fore Fathers" and their legacy by raising more than $108,400 for cystinosis research. Thank you to the Fore Father families and especially Karen McCullagh whose son, Andrew Cunningham, has cystinosis and is the grandson of two of these great men. Your support has made a difference in the lives of our children and adults with cystinosis!

In Honor of Jenna and Patrick Partington – Sacramento, California

PAULETTE'S GARDEN



This winter, we lost one of Land Park's finest when Paulette Bruce succumbed to lung cancer. We were humbled to learn, after her passing, that her family wished for Jenna & Patrick's Foundation of Hope to receive memorials in her honor. The adoration that people had for Paulette was evidenced in the outpouring of gifts that were made to JPFH in the weeks following her death. Our friend and local artist, Whitney Lofrano, was inspired to create and donate a piece of art entitled "Paulette's Garden"; silk scarves created from this work were created and sold for donations to JPFH. Thank you to Paulette's sons, Mike, Kevin and Rob and their families, to Whitney, and to the many friends and family who contributed so generously in the name of Paulette. We will miss her dearly, and thank her for her support of Jenna & Patrick's Foundation of Hope over the years. **Over $4,200 was donated in Paulette's name.** Her memory will live on in the promising research being done by the Cystinosis Research Foundation.

ROOTED IN RESEARCH

SPRING 2021

PUBLISHED STUDY

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.

Congratulations to Stéphanie Cherqui, PhD, and Corrine Antignac, MD, PhD, for their recently published study in the PLOS One (Public Library of Science Journal). The article, "Non-invasive intradermal imaging of cystine crystals in cystinosis" is a result of data collected from cystinosis patients, many of whom volunteered while attending CRF Day of Hope family conferences. Thank you to all of the patient volunteers who helped us learn more about a potential new bio marker for cystinosis to monitor long-term disease control and medication compliance. CRF awarded a grant to UCSD to purchase the equipment and has funded $618,827 in research grants for this important study.

PROGRESS REPORTS

NON-INVASIVE INTRADERMAL IMAGING OF CYSTINE CRYSTALS IN CYSTINOSIS *published March 2021 in the* ***PLOS One (Public Library of Science Journal)*** *by* ***Stéphanie Cherqui, PhD,*** *University of California, San Diego, and* ***Corrine Antignac, MD, PhD,*** *Imagine Institute (Inserm U1163) Paris, France*

Testing a New Combination to Unlock Treatment Options

by Dennis Arp

Dr. Jennifer Hollywood knows all about the benefits of working in tandem to solve a problem. For seven years, she and Dr. Alan Davidson have teamed up in search of better treatments for cystinosis.

By teaming the medication everolimus with the proven effects of cysteamine, Dr. Jennifer Hollywood hopes to better protect kidney function and avoid the need for transplant.

Now Dr. Hollywood and her colleagues are collaborating to discover how well two drugs can function in tandem, creating a combination therapy with the potential to improve the lives of cystinosis patients.

In the team's research lab in New Zealand, Dr. Hollywood is investigating new possibilities for the drug everolimus, which is typically used to target organ rejection and cancer. They have found that everolimus has therapeutic potential to treat cystinotic cells and kidney organoids grown in their lab, especially when the drug is combined with cysteamine.

Thanks to grant support from the Cystinosis Research Foundation (CRF), Dr. Hollywood will test whether the drug combination can prevent the onset of Fanconi syndrome and kidney damage in their rat model of cystinosis.

The ultimate goal for the combination therapy is better protection and preservation of kidney function in cystinosis patients so they don't progress to kidney failure, eliminating the need for a transplant.

"While cysteamine does a very good job of treating cystinosis by entering the lysosomes and removing cystine buildup in cells, Fanconi syndrome isn't reversed and kidney damage isn't completely prevented," says Dr. Hollywood, postdoctoral research fellow in molecular medicine and pathology at the University of Auckland. "This suggests there are other factors that need targeting, and we think the combination of cysteamine with everolimus may solve this shortcoming of cysteamine."

"… better protection and preservation of kidney function … eliminating the need for a transplant."

If successful, the study will provide the first pre-clinical evidence in a new animal model that cystinosis can be more effectively treated with a combination drug therapy. The data collected will justify advancing a clinical trial in patients with cystinosis.

The project builds on Dr. Hollywood's background in gene editing, first developed in Ireland, to both study and correct genetic diseases. Her work on cystic fibrosis mutations using CRISPR gene-editing technology led to her partnership with Dr. Davidson in Auckland. A CRF grant helped bring the researchers together.

"The addition of CRISPR-generated cystinosis iPS lines with isogenic controls made a very strong model to characterize and study cystinosis," Dr. Hollywood says. "Once we started characterizing these lines, I found that there was an autophagy pathway defect in both patient and gene-edited lines."

The iPS in the gene-edited lines stands for induced pluripotent stem cells – adult cells that can be reprogrammed to a state similar to that of embryonic stem cells.

"These cells allow for personalized medicine because you can make iPS lines from a patient's own skin cells and test drugs for toxicity in a particular tissue – for example, kidney organoids," Dr. Hollywood says. "Because we're using this human-based source of cells, any advances we make will be more relevant."

The iPS cells have proved immensely helpful in the team's research because they provide a renewable source of cells that carry the cystinosis mutation. The team can readily turn them into kidney tissue, which is vital since that is the organ of interest in cystinosis.

"These cells provide a human-based platform for testing new drugs that hold potential as cystinosis treatments," Dr. Hollywood says.

RESEARCH UPDATE

JENNIFER HOLLYWOOD, PhD

University of Auckland, Auckland, New Zealand

The team is focusing on everolimus as a new drug for cystinosis because it has proved effective in removing blockages in the autophagy pathway, which plays an important role in cell health. Autophagy provides proteins and energy to cells as it also serves as the recycling center of the cell.

"When the pathway is blocked, toxic bodies build-up, causing cells to die," Dr. Hollywood says. "We found that when we treated the cystinotic cells with everolimus, the block in autophagy was removed, and the amount of cell death decreased."

Of course, adding a new drug to create a combination therapy means also dealing with the possibility of new side effects. As a chemotherapy drug, everolimus is typically prescribed at high doses and taken every day. In use with cysteamine to treat cystinosis, the drug will be delivered at a lower dose and less frequently – probably twice weekly – which should reduce the risk of side effects, Dr. Hollywood says.

The pre-clinical trial should answer a lot of questions about dosing and side effects as it also provides data on effectiveness, she adds.

"We will begin our everolimus dose optimization in the coming months and should know the effects of the combination by summer 2022," she says.

If the research proves successful, the project would go directly to phase 3 trials, which would greatly accelerate the translation to clinical use, Dr. Hollywood notes. That's a big benefit of testing drugs that already have FDA approval for other uses.

"With the funding support from the CRF, we would have the necessary in vivo data to progress straight to humans," she says.

CRF funding has been integral to the lab's success throughout its research journey, Dr. Hollywood notes.

"We have generated three new models of cystinosis – iPS, kidney organoids and now a rat model," she says. "We've discovered a new treatment and are now performing a pre-clinical drug trial. Without the support of cystinosis charities such as the CRF and Cystinosis Ireland, we would not have been able to do this, and for that, we are so grateful."

If the research proves successful, the project would go directly to phase 3 trials...

Now Dr. Hollywood is eager to see that support turn into more real-world impact that changes the lives of cystinosis patients.

"What we're hoping to see from this work is that we can prevent Fanconi syndrome, and if that's the case, cystinosis patients won't need to take a multitude of pills to replace their electrolytes due to the severe loss of nutrients," she says. "I don't want to promise anything now, but that's the idea – prevent Fanconi syndrome and prevent kidney damage."

If that's what this tandem treatment makes possible, "we'll all be very happy," she says.

> "… prevent Fanconi syndrome and prevent kidney damage … that's the idea."

‘I Refuse to Accept That This Is the Only Reality’

by Dennis Arp

Dr. Morgan Fedorchak is driven to provide cystinosis patients an alternative to the pain of hourly eye drops. Thanks to CRF's support, her breakthrough gel drop technology moves a step closer to clinical trial.

Dr. Morgan Fedorchak is in the problem-solving business. So when she learned in 2016 that many cystinosis patients have to readminister eye drops every waking hour, she knew her lab was ready-made to restore some normalcy to their lives.

“It’s difficult for me to adequately express just how difficult hourly administration is,” says Dr. Fedorchak, assistant professor of ophthalmology at the University of Pittsburgh School of Medicine.

The Fedorchak Lab already had been working to apply a new technology to solve a similar dilemma faced by glaucoma patients, who were having to reapply eye drops two or three times a day.

“I would stand before a group of scientists and try to help them understand the depth of this problem we had to fix. How can patients be asked to administer this many eye drops every day for the rest of their lives?” she says. “Then to find out there were patients being asked to administer every hour? All of a sudden, it made glaucoma look like a walk in the park.”

In addition to the alarm, Dr. Fedorchak felt excitement.

“I saw that this was an area where we could potentially make a big difference with our technology,” she says.

Thanks to ongoing support from the Cystinosis Research Foundation (CRF), Dr. Fedorchak has been making progress ever since. Now her research offers cystinosis patients the very real possibility of a once-a-day application to protect their eyes from the buildup of cystine crystals on their corneas.

The most recent grant support from the CRF is funding rigorous new testing of Dr. Fedorchak’s novel drug-delivery system. She and her team hope to show that SoliDrops, their controlled-release technology, will allow for less-frequent dosing, less eye irritation and increased shelf stability of cysteamine drops.

“I think at a minimum, that’s what everyone deserves – to treat a disease with a drug that works, and to feel comfortable while you’re doing it,” says Dr. Fedorchak, who in addition to ophthalmology is a professor of bioengineering, chemical engineering and clinical and translational science.

“What is this tradeoff we’re asking? It’s crystals in your cornea or just horrible irritation of your ocular surface. I refuse to accept that this is the only reality that exists for cystinosis patients.”

The vessel for this new reality is provided by polymers, or a biodegradable plastic. The cysteamine used to treat corneal cystinosis goes into the eye suspended in a gel drop, along with polymer microparticles. In the eye, the gel turns into a solid when it reaches body temperature, then it breaks down slowly, releasing the drug to protect the cornea without having to readminister drops.

“Essentially, we’re building a brick wall around the polymer materials,” Dr. Fedorchak says. “Then, over time, that brick wall turns into more of a chain-link fence, where the drug can start to escape through little pores, following a timed-release pattern.”

After a full day of drug release, the microspheres are flushed out, “and you’re ready to go (with a new application),” she says.

Dr. Fedorchak notes that the terms “solid” and “brick wall” refer to the stability of the technology. Patients shouldn’t think that the gel drops will be uncomfortable.

RESEARCH UPDATE

MORGAN FEDORCHAK, PhD

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

"SoliDrops will allow for less-frequent dosing, less eye irritation and increased shelf stability of cysteamine drops."

"It is a solid, but it's pliable and soft. I have kids, and other parents will probably understand this – it's a lot like slime," she says with a smile. "It loves water, so it keeps nice hydration on the ocular surface. It allows your eye to move independently of that 'solid slime,' if we can call it that."

Comfort is a major reason Dr. Fedorchak saw her technology as the perfect solution for cystinosis patients.

"The goal here is to deliver just the right amount of drug so those crystals can be resolved without causing any other type of irritation or adverse event," Dr. Fedorchak says. "We want to solve all the problems in a way that's easy, safe and convenient."

During this new phase of CRF-funded research, the Fedorchak Lab is seeking to confirm the dosing of the gel drops using the cystinosis mouse model. The team also hopes to determine the reduction of crystal density compared with Cystaran® eye drops, one of the current treatments.

During the testing, team members have seen no signs of discomfort in the mice. They're finding "this is a safe method and we can keep the gel where it needs to be for as long as we want," Dr. Fedorchak says.

In addition, the lab is examining drug distribution throughout the body in testing with healthy rabbits. In March, they were wrapping up these studies, "and the combination of these two models will give us a really good sense of how this is going to work in a person," she says.

If the findings continue to look good, Dr. Fedorchak anticipates a possible call with the Food and Drug Administration by early summer as a first step in proceeding to human trials.

As Dr. Fedorchak reflects on all the progress her team has made, including during a year of pandemic-related challenges, her thoughts center on the profound difference CRF funding has made. Early support was particularly transformational.

"The support said that our platform had merit – that there was a group of people who had reviewed my work and believed in me and my team. That makes all the difference in the world," she says. "As we've progressed, the CRF continues to say, 'We're here to do what's needed to make your project successful.' It allows me to focus exclusively on the experiments that are going to get us to a clinical trial."

With that trial now on the horizon, Dr. Fedorchak's excitement continues to grow. As each testing hurdle is cleared, she gains clarity that her gel drop technology is ideally positioned to improve the lives of cystinosis patients.

"If we had one-third of the reasons for reformulating cysteamine with this technology, it would be enough to want to pursue this project," she says. "But we have three reasons – the chance to reduce dosing frequency, to reduce the irritation of administering the eye drops, and the stability of the drug in solution. Put them all together and it's a no-brainer."

New Pathways to Solutions

by Dennis Arp

CRF's support and sophisticated tools help Dr. Sergio Catz uncover mechanisms that lead the way for the development of complementary cystinosis therapies.

Because cystinosis travels multiple cellular pathways, so does the research of Dr. Sergio Catz. He and his team go deep inside cellular structures to find where the disease wreaks havoc, and to identify new ways to repair this damage.

For cystinosis patients and doctors, Dr. Catz's research means a greater foundational understanding of disease mechanisms as well as a growing potential for new treatments to improve cell and kidney function.

Thanks to vital support from the Cystinosis Research Foundation, Dr. Catz is making steady progress on his multiple research tracks.

"We expect that these studies will help develop treatments to complement current therapies for this devastating disease," says Dr. Catz, professor in the Department of Molecular Medicine at the Scripps Research Institute in La Jolla, California.

It's well known that lysosomes, which consume old or broken parts within the cell, are dysfunctional in cystinosis. But there's still much that isn't known about the disease.

"Autophagy means 'self-eating,' and it's a process that allows cells to get rid of damaged components and at the same time recycle some of the building blocks of those cells," Dr. Catz says. "But why doesn't this process function properly in cystinosis patients? That is one of the key questions at the heart of our research. The second part is that once we find what isn't working properly, can we repair it, and if so, how?"

Dr. Catz and the six colleagues on his lab team use sophisticated tools to examine cellular processes at the molecular level. Using a technique called super-resolution microscopy, they observe nanometric biological events with a great level of detail.

"We are one of the few research groups using this technique to study lysosomal disease, which is not easy to do in part because the data processing requires very powerful computational analysis," Dr. Catz says. "We have a very strong team."

> "Autophagy is a process that allows cells to get rid of damaged components and at the same time recycle some of the building blocks of those cells."

Building on decades of research experience, Dr. Catz has discovered that a specialized recycling mechanism called chaperone-mediated autophagy is defective in cystinosis. Combining the cutting-edge microscopy techniques and complementary functional assays, Dr. Catz's group generates a diverse type of data and uses the new knowledge of autophagy pathways to develop better treatments not just for chronic kidney disease but Fanconi syndrome as well.

Another key pillar of the team's research examines neutrophil-mediated inflammation in cystinosis. Neutrophils are the most abundant white cell in human blood, and they represent an essential part of the human immune system. Neutrophils lead the fight against bacterial and fungal infections.

"These cells have granules with toxins sent to kill bacteria," Dr. Catz explains. "But when these cells are activated in the absence of an infection, the toxins can damage otherwise healthy tissue. Neutrophil-mediated inflammation can also be seen in diseases like arthritis and cardiovascular disease."

In studying cystinosis, Dr. Catz and his team learned that these cells depart their quiet and reactive state to become hyperactive in releasing these toxins.

"We're studying what causes this activation of neutrophils in cystinosis and how they can be controlled," Dr. Catz says. "Our research shows that cysteamine does not prevent neutrophil hyperactivation, so we are exploring alternative drugs to treat this aspect of the disease."

The work is intensive and time-consuming, but with CRF support, Dr. Catz is determined to find out where the system is going wrong and to design new pharmacological approaches to rectify the problem.

"We implement a pipeline called high-throughput screening of different compounds so we can see which one has an effect on the problem," he adds.

RESEARCH UPDATE

SERGIO CATZ, PhD

The Scripps Research Institute, La Jolla, California

super-resolution microscopy

Meeting the patients and their families provides our greatest motivation...

In search of drugs to complement cysteamine, the lab team combs through a library of thousands of compounds that already have regulatory approval for use in humans. Their search is systematic, but in some ways also "kind of a fishing expedition," Dr. Catz says. "We do this in cellular studies first, and then we take the studies to in vivo studies for proof of concept for cystinosis in animals (mice)."

So far, the research team has identified promising drugs that have proved effective at correcting autophagy. Some of these drugs are now being analyzed using the mouse model of cystinosis.

"Once new potential compounds are identified, we design experiments to narrow it down to those that are the most effective," Dr. Catz says.

Throughout Dr. Catz's multi-track research journey, his work has benefited from collaboration with colleagues from all over the world, including Dr. Corinne Antignac in Paris and Dr. Stéphanie Cherqui in San Diego. Dr. Catz serves with both on the Cystinosis Research Foundation Scientific Review Board.

"We help others in shaping their hypothesis, and they help us in shaping ours," Dr. Catz says. "Our research benefits greatly from genetic studies such as those performed by Corrine Antignac and obviously transplantation studies by Stéphanie Cherqui. We have complementary expertise. An example is how we started to characterize neutrophil function utilizing Stéphanie's model of transplanted mice, and the approach is helping us understand how transplantation may help reduce neutrophil inflammation."

Those connections wouldn't be possible without the CRF, Dr. Catz notes.

"When we come together, we see that our research can take completely different approaches but still be interdependent," he says.

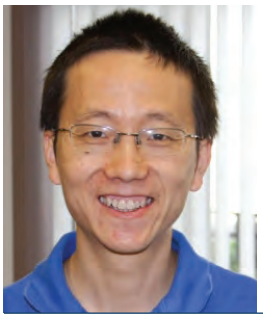
During the global COVID-19 pandemic, those connections are maintained virtually, but they have never been more important. The CRF is the hub of a community that provides many layers of support, Dr. Catz says. Early and sustained CRF grant support has allowed his team to show progress that now also attracts institutional funding from agencies such as the National Institutes of Health (NIH).

"Funding from the Cystinosis Research Foundation remains essential for us to continue basic and applied research that is not supported by our NIH grants," Dr. Catz says.

The CRF also connects researchers to those whose lives are changed by their breakthroughs, which is equally sustaining, Dr. Catz adds.

"Meeting the patients and their families provides our greatest motivation. It helps keep us focused on translating our research into discoveries that improve people's lives," he says. "We appreciate all the hard work of the families and allies. We are honored to be part of the community. If we can come up with therapies that directly affect the lives of patients, that would be spectacular."

Molecular mechanism of cystinosis



Liang Feng, PhD
Research Mentor
Stanford University, Palo Alto, California

Objectives:

In this study, our goal is to decipher the molecular mechanism of membrane transporters found on lysosomes that play critical roles in the pathogenesis of and therapy of cystinosis. We aim to understand how these membrane transport proteins work at the molecular level.

Executive overview of progress:

Membrane proteins play critical roles in many aspects of cystinosis, such as its cause and therapeutic interventions. Membrane proteins are challenging to characterize due to their hydrophobic nature (their relative instability when extracted out of the native membrane environment) and their dynamic properties. We have taken multiple approaches to overcome these barriers. We systematically applied and evaluated a variety of strategies and reagents, which led to much improved biochemical behaviors of these membrane proteins. We also developed new reagents that can specifically recognize the target proteins and may help to stabilize the protein in a defined conformation. These provided critical tools to facilitate efforts in figuring out how these proteins work at the molecular level. In addition, we have made significant progress towards understanding the dynamic properties of these proteins, which are essential for their functions. Together, we have developed enabling tools for this challenging project and made substantial progress in multiple fronts, which have laid a solid foundation for deciphering molecular mechanisms of membrane transporters that play important roles in cystinosis.

RESEARCH

PROGRESS REPORT

Development of a once-daily subcutaneous injection of cysteamine bitartrate

Michael Sekar, PhD
Principal Investigator
AMMA Therapeutics, Inc.

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

In the spring of 2020, CRF awarded a grant to Amma Therapeutics for $304,064, to study the *Development of a once-daily subcutaneous injection of cysteamine bitartrate*, led by Michael Sekar, PhD, Principal Investigator, and Laura Rita Rega, PhD, Co-Principal Investigator. The project is comprised of three specific AIMs conducted over a one-year time period.

Aim #1 includes formulation development and compatibility, and in vitro drug release and syringe injectability which are now complete.

Read about their progress, and the goals for Aim #2, despite the challenges of Covid-19 related disruptions.

In Summary:

AIM #1 (6 months): formulation development and in vitro testing

AIM #2 (3 months): small animal pharmacokinetic ("PK") testing

AIM #3 (3 months): small animal efficacy and safety testing

Accordingly, the first six months have been dedicated to completing AIM #1. We faced significant Covid-19 related disruptions to workflows and higher costs, but we have managed to stay within the projected timelines and budgets.

For AIM #1, we screened and assessed physiochemical properties for numerous BAIT formulations comprising different BAIT constructs. While our primary goal has been to develop a BAIT formulation of cysteamine bitartrate, we also evaluated another form of cysteamine that may allow us to deliver greater amounts of cysteamine in smaller injection volumes. AIM #1 activities have been largely completed and we selected the most promising BAIT formulations to advance to Aim #2.

AIM #1 Goals

1. Evaluate the solubility, chemical, and physical stability of cysteamine bitartrate in BAIT NPT formulation excipients.
2. Screen BAIT constructs that may comprise formulations that achieve optimal drug delivery profiles, stability, and applicable as subcutaneous injections.

Status

1. Solubility – **Completed**
2. Compatibility – **To be completed**
3. In vitro drug release - **Completed**
4. Syringe injectability - **Completed**

The goal of AIM #2 is to select a single BAIT formulation, based on rodent PK studies, to advance to a longer-term efficacy study in AIM #3. Upon more comprehensive discussions and planning for AIM #3 with our scientific and project collaborators, Dr. Rega and Dr. Emma, it became apparent that two important unknowns could pose a challenge towards a successful AIM #3:

- The plasma cysteamine levels needed to achieve the desired efficacy in the cystinosis rodent model
- The proper dosing regimen (dosage, frequency) for cysteamine BAIT that achieves therapeutic plasma cysteamine levels

To elucidate these unknowns, AIM #2 has been expanded to include additional rodent PK and pharmacodynamic studies. It is our intention to stay within the project timelines and budgets despite the expansion of Aim #2. The first of these studies, a single dose PK study at AMMA, was initiated in early February and we are awaiting bioanalysis results.

Newborn screening for cystinosis

Objective

This final progress report summarizes the completion of milestones and activities during the funding period from September 2017 to August 2020. Below are the original milestones and our progress with regards to each.

SUMMARY OF PROGRESS IN ACHIEVING RESEARCH GOALS, OBJECTIVES AND AIMS

The primary objective of this project is to develop and validate a specific and quantitative assay for newborn screening (NBS) of cystinosis (CN) using dried blood spots (DBS). To date, we have been able to achieve progress in both of our proposed specific aims.

Specific Aim 1:

Enhance the sensitivity and specificity of the existing immuno-SRM assay for Cystinosis (CN) by adding additional marker peptides of cystinosin (CTNS).

A high affinity monoclonal antibody (mAb) was successfully produced to the sequences CTNS 115 and SHPK 363. The CTNS 115 mAb enriches the target peptide sequence from DBS of both patients and healthy controls for quantification by liquid chromatography tandem mass spectrometry (LC-MS/MS). Because of the existence of a co-enriched contaminating peptide discussed below, additional mAb productions were undertaken. Peptides CTNS 120 and CTNS 194 failed to derive high affinity mAbs. The sequence CTNS 274 generated an antibody that successfully isolated standard peptides but failed to enrich endogenous CTNS 274 from DBS. This indicates that the sequences may be difficult to extract from human blood or digest into the target sequence.

When utilizing CTNS 115 mAb for enrichment of this sequence, a contaminating peak was consistently present in the analysis. This contaminant has an identical mass and a very similar retention time to the biomarker CTNS 115 sequence. This necessitated extended runtimes to allow for separation of the two peaks and accurate quantification. Changes to the enrichment process, including aggressive washing, salt washes, and heating, were unable to remove the contaminating sequence. A final antibody production is ongoing that will raise an mAb specifically to the CTNS 115_2 sequence is underway and discussed below under Ongoing Efforts.

Important aspects of CTNS 115 immuno-SRM analysis have been studied over the course of the grant period. The limits of detection, intra-day (within day) coefficients of variation (CV), and inter-day (between day) variation were studied to determine whether they would allow for successful translation. Acceptable CVs are < 20%. Variations were measured by conducting triplicate full process assays (including DBS extraction, digestion, and capture) across five different days. Intra- and inter-day variations were < 11.4% and 4.83% across five days, respectively. The limits of detection and quantification for CTNS 115 were 3.4 and 7.8 pmol/L. All these parameters are within acceptable ranges for clinical translation.

Sihoun Hahn, MD, PhD
Principal Investigator
Seattle Children's Hospital Research Institute

Specific Aim 2:

Assess the ability of a multiplexed immuno-SRM assay to correctly identify patients with CN in a large set of clinical samples and proven carriers from a broad spectrum of mutations.

Normal control DBS were screened to establish normal control ranges and tentative diagnostic cutoffs. When analyzed by immuno-SRM, over 95% of DBS samples from CN patients were below these cutoffs. In the CTNS cohort, over 50% of patients had levels of CTNS 115 which were at or near the limits of detection, i.e., undetectable. Normal controls sample were collected by fingerstick while patient DBS were spotted from whole blood collected during routine clinical course. One third of patients with non-detectable SHPK were found to be homozygous for the 57-kb deletion mutation. In addition, SHPK levels were found to segregate patients with homozygous 57-kb deletions, heterozygous for the 57-kb deletion and another mutation, and heterozygous for two other distinct mutations. Combined, the results indicate the multi-plex quantification of CTNS and SHPK peptide in DBS effectively identify Cystinosis patients with high sensitivity and specificity.

During the grant period we discovered that the use of certain anticoagulants will significantly affect the measured concentrations of CTNS biomarker peptides. The use of Sodium Heparin as an anticoagulant for blood collection is comparable to the analysis of blood collected from fingerstick or with no anticoagulant. We found that in patient samples as well as controls, blood collection in K2EDTA reduced the measured CTNS 115 concentrations. This is not an issue for NBS as these DBS are collected by heel stick methods. In a clinical setting, however, it will now be important to collect CN DBS samples utilizing fingerstick or a specified anticoagulant.

ONGOING EFFORTS

Our study opened the feasibility of newborn screening for cystinosis using Immuno-SRM. Majority of confirmed patients presented with either absent or low signature target peptides and overall, the performance of the assay was acceptable for clinical use. The only but significant caveat was the interference peak which necessitated extended runtime to separate it from endogenous peak. This extended runtime makes the assay not yet suitable for high throughput newborn screening. Here, we are currently working on producing the antibodies that can help eliminate the contaminant in the sample preparation.

ANTIBODY PRODUCTION:

Since the no cost extension, the peptide sequence contaminating CTNS 115 analysis has been identified. This allowed us to initiate an mAb production project that provides us multiple avenues to produce a successful NBS assay for CN. This project aims to generate antibodies against both the target sequence and the contaminating sequence. After this initial production, mAbs that bind both sequences will be removed by negative selection. This step should lead to mAb sequences that bind only CTNS 115_2 with no co-isolation. Successful production of a CTNS 115_2 specific antibody is an ideal solution that will be readily adaptable to our current workflows and eliminate the issue of interference. This assay will allow for rapid screening of CN patients as an extended analysis is no longer necessary to separate contaminants. Generation of an antibody against contaminant peptide gives the project a secondary solution. In this case, we can include depletion of contaminant peptide as an initial step in our analysis and utilize the current CTNS 115 mAb for isolation of CTNS 115 alone. This project gives two viable paths toward a rapid screening assay for CN.

PATIENT SAMPLE COLLECTION:

We continue to work with our collaborator (Dr. Gahl) at the NIH to collected patient samples in multiple anticoagulants so that the differences between them can be studied and appropriate diagnostic ranges can be established depending on the collection conditions.

Dissect the protein turnover mechanism of cystinosis mutants

Overview

In this proposed research, we hypothesize that a group of pathogenic Cystinosin mutants are selectively ubiquitinated by an unidentified human lysosome protein quality control system and degraded prematurely in the lysosome. In our preliminary study, we have identified a pathogenic CTNS mutant, ΔITILELP (hereafter referred to as CTNS7Δ), as a fast degrading mutant in humans. We plan to pursue two specific aims to test the central hypothesis. For Aim 1, we planned to measure the half-lives of all pathogenic Cystinosin mutants to identify more fast-degrading mutants using cycloheximide (CHX)-based chase assay. For Aim 2, we planned to identify the corresponding E3 ubiquitin ligase and downstream degradation machinery. We will use a CRISPR- and flow cytometry-based high throughput screening method to determine the E3 ligase and the downstream machinery.

PROGRESS IN THE FOURTH SIX-MONTH PERIOD

Our lab is still running on a limited capacity in the past six months of the funding period due to COVID-19 pandemic. My lab members are working in shifts to maintain social distancing. So, we focused our efforts on 1) developing a new screening system to isolate fast-degrading CTNS mutants, 2) analyzing the subcellular localization of CTNS7Δ-GFP, 3) generating the HRD1 knockout (KO) and HRD1 GP78 double KO cell lines.

Aim1a:

Screening for new CTNS mutants that are quickly degraded by the lysosome protein quality control system

In our previous efforts to identify fast-degrading CTNS mutants, we used a low throughput method by testing all reported disease-causing CTNS mutants one by one. This way, we only identified one mutant (CTNS7Δ) out of 41 tested mutants. For the last six months, we decided to take a more direct approach. Instead of screening the reported Cystinosin mutants for fast degrading mutants, we used PCR-based random mutagenesis to create a CTNS mutant library (Fig. 1). The library will be fused to a GFP-mCherry tag. If a CTNS mutant is recognized by the lysosome membrane quality control system, it will be constitutively degraded inside the lysosome lumen. Consequently, the GFP to mCherry ratio will be low because GFP is sensitive to the lumenal proteases, but mCherry is resistant. In contrast, if the mutant is stable, the GFP-mCherry tag will be localized to the cytoplasmic side of the lysosome membrane, and the GFP/mCherry ratio will be high. We will then use flow cytometry to sort mutants with a low GFP/mCherry ratio and determine their coding sequences by Illumina sequencing (Fig1A).

So far, we have finished the construction of the phage-based CTNS library for transfecting the HEK293 cells (Fig. 1B). We are in the process of evaluating the library by determining the mutation rate for each Kb DNA in the CTNS coding region, as well as testing the transfection efficiency with HEK293 cells.

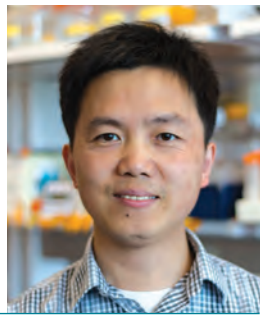
Aim1b:

Determining the subcellular localization of CTNS7Δ-GFP mutant

In our previous study, we have shown that CTNS7Δ-GFP appears as five distinct bands on a Western Blot. While band 5 is a breakage product of free GFP falling off CTNS7Δ-GFP, bands 1-4 are localized to the membrane fraction, either at the lysosome membrane or at the ER membrane. Using the lysosome immunoprecipitation (IP) experiment, we have shown that band 2 and band 4 are localized to the lysosome membrane. We suspected that band 1 and band 3 are localized to the ER membrane and rapidly degraded through the ER-associated degradation pathway. In support of this hypothesis, knocking down P97, an essential AAA ATPase involved in the ERAD pathway, stabilized both bands 1 and 3 (Figure 3C). However, the direct evidence to support their ER localization is still lacking. When we checked the CTNS7Δ-GFP under the fluorescence microscope, the mutant protein appeared to localize to both ER and lysosomes.

To provide further evidence of the ER-localization for bands 1 and 3, we are developing other biochemical approaches. So far, we have tried two methods, including immunoprecipitation of the microsome vesicles and differential centrifugation. Unfortunately, both methods have failed. As shown in Figure 2A-B, we tested IP with antibodies against two different baits (Sec61β-3HA and HRD1). Although we were able to pull-down ER microsomes, there was no difference between the control and the antibody reaction, suggesting that the observed pull-down was due to non-specific binding to resins. We then tested differential centrifugation and Oxiprep density gradient to enrich ER microsomes (Figure 2C-D). Under these conditions, however, lysosomes are also enriched together with the microsomes.

We are now testing if we could use FACS sorting to separate the ER microsomes from the lysosome fraction. We plan to label Sec61β with a very bright fluorophore PE/Dazzle and sort the ER microsomes by flow cytometry. Following the FACS sorting, we will use Western Blotting to check if bands 1 and 3 are enriched in the microsome fraction.



Ming Li, PhD
Principal Investigator
University of Michigan, Ann Arbor, Michigan

Aim2:
In search of the E3 ubiquitin ligase that ubiquitinates CTNS7Δ-GFP

As stated above, we hypothesized that bands 1 and 3 of CTNS7Δ-GFP are degraded through the ERAD pathway. However, knocking out either GP78 or HRD1, the two major E3 ubiquitin ligases that function in the ERAD pathway, did not slow down the degradation of the CTNS7Δ-GFP (Figure 3A-B). We also knocked down HRD1 in the GP78 knockout background and observed minimal CTNS7Δ-GFP degradation. These results strongly suggest that a novel ER-localized E3 ligase might be involved in the degradation of CTNS7Δ-GFP.

We plan to perform a whole-genome CRISPR screening to identify this new E3 ligase. To do this, we need to generate a HEK293 strain with the double knockout of HRD1 and GP78. This double knockout strain was successfully generated two weeks ago (Figure 3D, DKO-5, and DKO-6). We will perform the CRISPR screening soon.

CLOSING

We wish to thank the CRF for the generous support. This project did not work as we initially hypothesized. We proposed that CTNS7Δ-GFP was degraded by an unidentified quality control system on the lysosome membrane. After extensive investigation, we now believe that CTNS7Δ-GFP is degraded at the ER by the ERAD pathway. Our results suggest that a novel ER E3 ligase might be involved in the turnover of CTNS7Δ-GFP. We will use the CRISPR screening to identify this E3 ligase.

The other unexpected result was: out of 41 disease-causing CTNS mutants, we only identified one fast degrading mutant (CTNS7Δ-GFP). We are now using a more direct approach to create the fast degrading CTNS mutants. Finding these mutants will enable us to study the mechanism of the lysosome protein quality control, a completely unexplored question in the field.

Figure 1

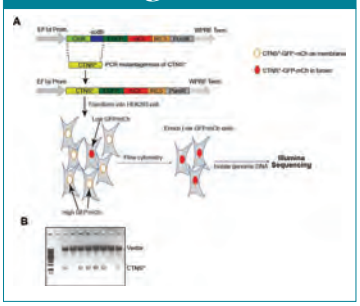


Fig. 1 *A more direct method to screen for the fast-degrading/constitutive CTNS mutants.* ***A)*** a flow chart describing the steps to isolate the constitutive CTNS mutants. ***B)*** Completion of the CTNS-eGFP-mCherry expression construct for mammalian cell transfection.

Figure 2

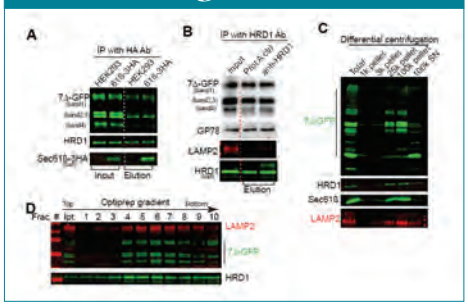


Fig. 2 *Developing a method to purify ER microsomes (in progress).* ***A-B)*** ER microsomes non-specifically bind to agarose resin during immunoprecipitation experiments. Two different baits (Sec61β and HRD1) have been tested. ***C)*** ER microsomes are enriched in the same fractions as lysosomes (labeled by LAMP2) during a differential centrifugation. ***D)*** ER microsomes are enriched in the same fractions as lysosomes (labeled by LAMP2) during a Optiprep gradient centrifugation.

Figure 3

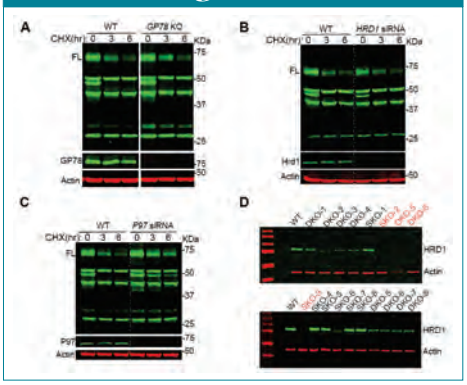


Fig. 3 *Bands 1 and 3 of CTNS 7Δ-GFP are degraded by the ERAD pathway via a new E3 ligase.* ***A)*** GP78 alone is not important for the degradation of CTNS 7Δ-GFP. ***B)*** HRD1 alone is not important for the degradation of CTNS 7Δ-GFP. ***C)*** P97 is important for the degradation of CTNS 7Δ-GFP. ***D)*** Generation of HRD1 single knockout and HRD1 GP78 double knockout lines in HEK293 cells. SKO: single knockout of HRD1. DKO: double knockout of HRD1 and GP78.

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

Overview

The overall **goal** of this project is to conduct preclinical therapeutic drug intervention studies in *Cystinosin (Ctns)* knock-out (KO) rats to determine whether a combination treatment of cysteamine and everolimus ameliorates the cystinosis-like phenotype. To achieve this, we proposed the following Aims:

Aim 1: Determine the optimal dose of cysteamine that achieves a 50% rescue of the cystinotic phenotype in *Ctns* KO rats (yr 1)

Aim 2: Determine the optimal dose and schedule of everolimus delivery (yr 1)

Aim 3a: Evaluate cysteamine and everolimus drug-drug interactions in *Ctns* KO rats (yr 1-2)

Aim 3b: Evaluate whether treating *Ctns* KO rats with cysteamine and everolimus provides greater therapeutic benefit than cysteamine alone (yr 2)

PROGRESS TO DATE

Aim 1: *Determine the optimal dose of cysteamine that achieves 50% rescue of the cystinotic phenotype in the Ctns KO rat*

Overview of aim:

We set out to determine the optimal dose of cysteamine which would result in a 50% reduction in cystine levels in our Ctns rats in order to ensure that we can detect a beneficial effect of everolimus when we use them in combination. The original doses selected based on other studies were 30, 60 and 120mg/kg. To avoid possible high levels of variability in delivering the drug in drinking water we deliver cysteamine in an edible jelly pill that is fed to the rats twice a day.

We first sought to determine the optimal dose of cysteamine that the rats can tolerate by feeding the rats three doses of cysteamine over the course of 10 days and recording the percentage of jelly eaten to completion (Figure 1). Next, we measured the amount of cystine in white blood cell, polymorphonuclear leucocytes (PMNs) and kidney tissue using HPLC-MS/MS (Figures 2 and 3). The dose that maintains tissue cystine levels at 50% will be used for combination studies.

Results of aim 1:

1) Determining the optimal dose of cysteamine that the rats can tolerate

Cysteamine containing jellies were made by adding 1g Raspberry jelly powder and 1g Gelatine with 10 ml of milliQ water and heating to 50 °C to dissolve. The mixture is cooled to 40 °C before addition of cysteamine to avoid heat effects. Vehicle jellies contain no cysteamine. Rats are pre-conditioned to eat jellies by feeding them with jellies containing no drug weekly for three weeks prior to initiation of drug study. During the experiment, rats were fed cysteamine containing jellies twice daily, (6am and 6pm) over the course of 10 days and the percentage of jelly eaten was recorded. We found early on that 120 mg/kg was too toxic for the rats and they refused to eat it, therefore, we reduced the concentration of the highest dose to 90 mg/kg. In order to detect a measurable reduction in cystine levels we need the rats to eat the majority of the jellies containing cysteamine. As can be seen in figure 1, there was a high degree of aversion to eating the jelly containing cysteamine at the higher concentrations of 60 and 90 mg/kg with rats eating 50% or less of the jelly as the experiment progressed most likely due to the gastrointestinal toxicity induced by cysteamine. We saw good compliance at 30 mg/kg in the majority of animals and chose this concentration as the upper limit of cysteamine to be used.

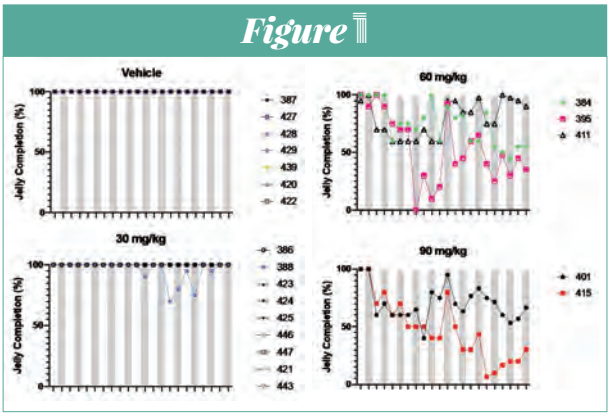


Fig. 1 ***Determining optimal dose of cysteamine***

Graphs showing the percentage of jelly with or without cysteamine that was eaten to completion over the course of 10 days. Numbers indicate individual animals. White bar = 6 am feed. Grey bar = 6 pm feed.

RESEARCH

PROGRESS REPORT

CRF has granted research funding to the University of Auckland since 2009, awarding $805,143 for the important research conducted by Dr. Hollywood and Dr. Davidson.

Jennifer Hollywood, PhD
Principal Investigator
University Of Auckland,
Auckland, New Zealand

Alan Davidson, PhD
Co-Principal Investigator
University Of Auckland,
Auckland, New Zealand

2) Measuring cystine levels in PMNs and kidney tissue following treatment with cysteamine

In order to determine whether the cysteamine is having a therapeutic effect on the cystine levels in the Ctns rats we first measured the amount of cystine in Polymorphonuclear leucocytes (PMNs) with and without cysteamine treatment. Animals were fed three doses of cysteamine (7.5, 15 and 30 mg/kg) based on the results from the previous experiment. Blood was collected from each animal before treatment (baseline) and following 10-day treatment with cysteamine or vehicle only jellies. Following extensive optimisation of the protocol to isolate PMN cells, we found that the levels of cystine in the PMNs did not reduce as expected (figure 2). This is most likely due to the timing of the experiment where the blood was collected 5 hrs after the final treatment and the fact that polymorphonuclear leucocytes harbouring cystine are short living cells (≈12 hours); therefore, we may have missed the therapeutic effects of cysteamine. To overcome this we are now performing a specific time course experiment whereby we will measure cystine in PMNs at 0, 15, 30, 60, 120, 240, 480 mins post-treatment (see future work for more details).

We next measured the level of cystine in the kidney tissue of these animals. Importantly, as seen in figure 3 there is a reduction in the amount of cystine in males at 30 mg/kg following 10 days of treatment however, due to animal outliers, this was not significant. The effects were less obvious in female animals however there is a trend towards reduction at all doses. It is worth noting that 10 day treatment may not be long enough to see a significant reduction in the kidney tissues and longer treatment may result in better reduction.

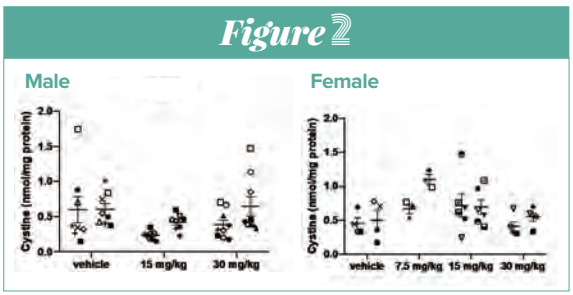


Fig. 2 *Amount of cystine (nmol/mg of protein) in PMNs at baseline and after 10 days of dosing. Each unique symbol represents one animal. Two-way ANOVA performed all data are plotted mean ± SEM. No significance was found.*

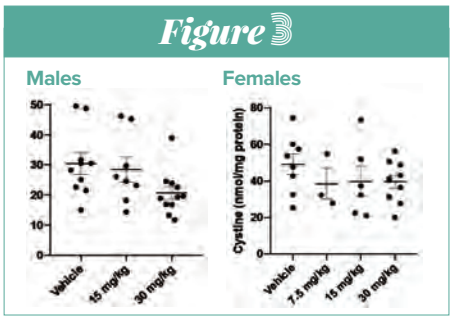


Fig. 3 *Amount of cystine (nmol/mg of protein) in kidney tissue following 10 days of dosing. Two-way ANOVA performed all data are plotted mean ± SEM. No significance was found.*

FUTURE WORK

Based on the results gathered so far a maximal dose of 30 mg/kg of cysteamine will be used going forward. At this dose we do see a reduction in cystine levels in the kidney tissues of Ctns rats which is promising. To better understand whether delivery of cysteamine in jelly pills is reaching sufficient levels in the blood of these animals to be therapeutic we are in the process of performing a time course PK study in the Ctns rats. Blood will be collected at 0, 15, 30, 60, 120, 240, 480 mins post-treatment and cysteamine levels measured using HPLC-MS/MS. We will also measure the level of cystine in the PMNs in parallel and this information will allow us to determine how much cysteamine is in the blood following treatment in both sexes and whether the animals are reaching a desired therapeutic threshold in the blood to lower cystine when cysteamine is delivered in jelly pills. If the results show that delivery with jelly pills is insufficient then we will repeat this study using subcutaneous injection of cysteamine.

Aim 2 is to determine the optimal dose and schedule of everolimus delivery and this will begin shortly. To determine whether everolimus is having a therapeutic effect on mTOR signalling we have optimised a western blot readout to measure the level of a downstream target of mTOR, p70S6K in kidney tissue and are optimising a similar readout in blood (figure 4).

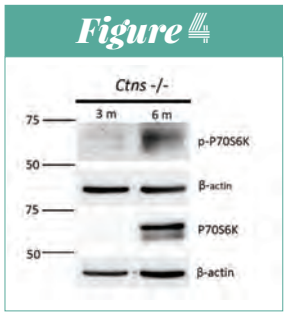


Fig. 4 *Western blot of total and phosphorylated p70S6k in 3- and 6-month-old Ctns rat kidney tissue.*

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

EXTENDED

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

Kidney Research

22 GRANTS

Robert Chevalier, MD
UNIVERSITY OF VIRGINIA,
CHARLOTTESVILLE, VIRGINIA

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

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

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

Benjamin Freedman, PhD
UNIVERSITY OF WASHINGTON,
SEATTLE, WASHINGTON

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

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

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

Philip Newsholme, PhD
CURTIN UNIVERSITY,
PERTH, WESTERN AUSTRALIA

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

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

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

Skin, Muscle and Bone

16 GRANTS

Justine Bacchetta, MD, PhD NEW
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

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SCHOOL OF MEDICINE,
PALO ALTO, CALIFORNIA

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SAN DIEGO,
LA JOLLA, CALIFORNIA

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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 NEW
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

CONTINUED ON NEXT PAGE

CONTINUED FROM PAGE 63

Molecular Study of Cystinosis in the Yeast Model

3 GRANTS

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

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

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

Genetic Analysis of Cystinosis

5 GRANTS

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

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

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

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

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

Neurological

16 GRANTS

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

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

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

Florian Eichler, MD
MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS

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

33 GRANTS

EXTENDED

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

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

Bruno Gasnier, PhD
PARIS DESCARTES UNIVERSITY, PARIS, FRANCE

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

Patrick Harrison, PhD
UNIVERSITY COLLEGE CORK, CORK, IRELAND

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

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

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

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

Cellular and/or Molecular Studies of the Pathogenesis of Cystinosis

57 GRANTS

EXTENDED

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

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

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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
Yann Terras, MSc
PARIS DESCARTES UNIVERSITY, PARIS, FRANCE

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

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

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

Alessandro Luciani, PhD
UNIVERSITY OF ZÜRICH, ZÜRICH, SWITZERLAND

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

Norbert Perrimon, PhD
HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

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

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

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

Lab Equipment for Cystinosis

4 GRANTS

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

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

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

CRF RESEARCH

GRANT AWARDS

TOTAL 2020 RESEARCH GRANTS AWARDED **$3,150,914**

Fall Grants Awarded **$521,424**

GRANT EXTENSIONS

Corinne Antignac, MD, PhD, *Principal Investigator*
Imagine Institute, Paris, France
"Intra-Dermal Imaging of Subjects with Cystinosis Using Confocal Microscopy"
$31,306 ONE-YEAR EXTENSION #2

Corinne Antignac, MD, PhD, *Principal Investigator*
Imagine Institute, Paris, France
"Intra-Dermal Imaging of Subjects with Cystinosis Using Confocal Microscopy"
$31,306 ONE-YEAR EXTENSION #3

Stéphanie Cherqui, PhD, *Principal Investigator*
University of California, San Diego, La Jolla, California
"Intra-Dermal Imaging of Subjects with Cystinosis Using Confocal Microscopy"
$102,755 ONE-YEAR EXTENSION #2

Stéphanie Cherqui, PhD, *Principal Investigator*
University of California, San Diego, La Jolla, California
"Intra-Dermal Imaging of Subjects with Cystinosis Using Confocal Microscopy"
$102,755 ONE-YEAR EXTENSION #3

Pierre Courtoy, MD, PhD, *Principal Investigator*
de Duve Institute, Brussels, Belgium
Laura Rita Rega, PhD, *Co-Principal Investigator*
Bambino Gesù Children's Hospital, Rome, Italy
"Secondary Treatment of Ctns-/- Mice with Dibasic Amino-Acids: Safety, Efficacy and Mechanism(s)"
$46,174 ONE-YEAR EXTENSION

Olivier Devuyst, MD, PhD, *Principal Investigator*
University of Zürich, Zürich, Switzerland
"Development and Characterization of a Rat Model of Cystinosis"
$115,500 ONE-YEAR EXTENSION

Francesco Emma, MD, *Principal Investigator*
Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
"Development and Characterization of a Rat Model of Cystinosis"
$105,996 ONE-YEAR EXTENSION

Laura Rita Rega, PhD, *Co-Principal Investigator*
Bambino Gesù Children's Hospital, Rome, Italy
"Secondary Treatment of Ctns-/- Mice with Dibasic Amino-Acids: Safety, Efficacy and Mechanism(s)"
$16,170 ONE-YEAR EXTENSION

EQUIPMENT GRANT

Stéphanie Cherqui, PhD
University of California, San Diego,
La Jolla, California
HRT3-RCM
$82,320 PURCHASE TOTAL

SEE 2020 FALL
LAY ABSTRACTS
STARTING ON PAGE 68

Indicates Fall Grants

Justine Bacchetta, MD, PhD, *Principal Investigator*
Irma Machuca-Gayet, PhD, *Co-Principal investigator*
Hospices Civils de Lyon and INSERM

"Pathophysiology of Bone Disease in Nephropathic Cystinosis" (CYSTABONE – 2020)

$108,000 ONE-YEAR STUDY

Sergio Catz, PhD, *Research Mentor*
Raquel Carvalho Gontijo, PhD, *Research Fellow*
The Scripps Research Institute, La Jolla, California

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

$150,000 TWO-YEAR STUDY

Sergio Catz, PhD, *Research Mentor*
Farhana Rahman, PhD, *Research Fellow*
The Scripps Research Institute, La Jolla, California

"Molecular Trafficking Regulators of Dynamic Organelles in Cystinosis"

$150,000 TWO-YEAR STUDY

Pierre Courtoy, MD, PhD, *Principal Investigator*
Christophe Pierreux, PhD, *Co-Principal Investigator*
de Duve Institute, Louvain University Medical School, Brussels, Belgium ($5,500)

Laura Rita Rega, PhD, *Principal Investigator*
Bambino Gesù Children's Hospital, Rome, Italy ($37,301)

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

$42,801 SIX-MONTH STUDY

Andrea Del Fattore, PhD, *Research Mentor*
Giulia Battafarano, PhD, *Research Fellow*
Bambino Gesù Children's Hospital, Rome, Italy

"Cathepsin D Inhibition to Rescue Osteoblast Function in Cystinosis"

$75,000 ONE-YEAR STUDY

Shawn Davidson, PhD, *Principal Investigator*
Princeton University, Princeton, New Jersey

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

$160,244 ONE-YEAR STUDY

Olivier Devuyst, MD, PhD, *Principal Investigator*
Alessandro Luciani, PhD, *Co-Principal Investigator*
University of Zürich, Zürich, Switzerland

"New Model Systems for Integrated Drug Discovery in Cystinosis"

$290,000 TWO-YEAR STUDY

Morgan Fedorchak, PhD, *Principal Investigator*
Kanwal Nischal, MD, FRCO, *Co-Principal Investigator*
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

"Development of a Topical Controlled Release Cysteamine Eye Drop"

$410,810 TWO-YEAR STUDY

Liang Feng, PhD, *Research Mentor*
Xue Guo, PhD, *Research Fellow*
Stanford University, Stanford, California

"Molecular Mechanisms of Cystinosis"

$150,000 TWO-YEAR STUDY

Jennifer Hollywood, PhD, *Principal Investigator*
Alan Davidson, PhD, *Co-Principal Investigator*
University of Auckland, Auckland, New Zealand

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

$200,530 TWO-YEAR STUDY

Sophie Molholm, PhD, *Principal Investigator*
John Foxe, PhD, *Co-Principal Investigator*
Albert Einstein College of Medicine, Bronx, New York

"The Development of Neuromarkers of Cognitive Disfunction in Cystinosis"

$333,164 TWO-YEAR STUDY

Giusi Prencipe, PhD, *Research Mentor*
Marianna Nicoletta Rossi, PhD, *Research Fellow*
Bambino Gesù Children's Hospital, Rome, Italy

"Role of DNA Methylation in Cystinosis"

$75,000 ONE-YEAR STUDY

Michael Sekar, PhD, *Principal Investigator*
AMMA Therapeutics, Inc., Hayward, California
Laura Rita Rega, PhD, *Co-Principal Investigator*
Bambino Gesù Children's Hospital, Rome, Italy

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

$304,064 ONE-YEAR STUDY

Reza Seyedsadjadi, MD, *Principal Investigator*
Florian Eichler, MD, *Co-Principal Investigator*
Massachusetts General Hospital

"Optimizing Dysphagia Assessments Using MBSImP in Adults with Nephropathic Cystinosis"

$67,019 ONE-YEAR STUDY

Pathophysiology of bone disease in nephropathic cystinosis: the CYSTEABONE-2020 project

Justine Bacchetta, MD, PhD, *Principal Investigator*
Irma Machuca-Gayet, PhD, *Co-Principal investigator*
HOSPICES CIVILS DE LYON AND INSERM

OBJECTIVE/RATIONALE:

Bone impairment has been recently described in patients with nephropathic cystinosis, with international recommendations for diagnosis and management published in 2019; the concept of "cystinosis metabolic bone disease" is currently emerging. Even though its exact pathophysiology remains unclear, this complication has a significant impact on patients' quality of life, because of an increased frequency of bone pains, deformations and fractures occurring in late teenage and early adulthood. It is therefore of utmost importance to understand the underlying mechanisms of such bone impairment.

PROJECT DESCRIPTION:

We have three main objectives at this stage of the project, based on our previous results obtained with a previous CRF grant:

- we have shown that there is an impaired communication between cells that build bone (i.e., osteoblasts) and cells that resorb bone (i.e., osteoclasts), and we want to fully dissect the underlying mechanisms of this abnormal cross-talk.

- we have data showing that inflammation may play a role in the excess of osteoclasts. Thus, we want to confirm that inflammation pathways (e.g., interleukin 1) are clinically relevant for bone complications in cystinosis.

- we have data showing genotype/phenotype correlations in osteoclasts; we want to confirm these data by implementing the CRISPR technology on cell lines carrying representative mutations of the identified phenotypes.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

If our hypothesis of deregulation of the interleukin 1 pathway in the bone disease of patients with nephropathic cystinosis is proved to be true, we will be able to propose new therapeutic perspectives such as therapeutic modulation of the interleukin 1 pathway so as to improve pain and deformations, and therefore the quality of life. In the long term, our results may provide a strong rationale for a clinical trial in the field; drugs targeting the interleukin 1 pathway already exist for inflammatory diseases.

ANTICIPATED OUTCOME:

The CYSTEABONE-2020 project aims to better understand the underlying mechanisms of bone impairment and to identify novel therapeutic approaches to improve (or prevent the onset of) bone symptoms in cystinosis. We will perform experiments both in murine models and in cells from patients recruited in different French and European centers.The result that would be the most relevant for patients in daily life would be the confirmation of abnormal inflammation pathways in our models of bone impairment, since they may have direct clinical effects.

Cathepsin D inhibition to rescue osteoblast function in cystinosis

Andrea Del Fattore, PhD, *Research Mentor*
Giulia Battafarano, PhD, *Research Fellow*
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

OBJECTIVE/RATIONALE:

Patients affected by cystinosis develop hypophosphatemic rickets. We demonstrated that skeletal alterations and decreased mineralization in cystinotic mice are also due to primary defects of bone-forming cells, osteoblasts. Particularly, cystinotic osteoblasts showed increased expression of the protease cathepsin D. Since it was reported that the administration of cathepsin inhibitors improves bone mineralization in hypophosphatemic cells, this project aims to understand the effects of the cathepsin D inhibition in cystinotic osteoblasts and to evaluate whether it could restore the physiological bone remodeling in vivo.

PROJECT DESCRIPTION:

This project aims to evaluate the role of cathepsin D in the reduced osteoblast differentiation and activity observed in cystinosis. We will analyze in vitro the effects of cathepsin D inhibition on cystinotic osteoblasts in order to rescue physiological bone formation. To test our hypothesis we will treat osteoblasts with cathepsin D inhibitor and we will evaluate the effects on their differentiation and activity. Since osteoblasts regulate the differentiation and activity of bone-resorbing cells osteoclasts to maintain the integrity of the skeleton, we will also analyze the osteoclastogenic potential of treated cystinotic osteoblasts. We will evaluate, by in vivo experimental models, the effect of cathepsin D inhibition on bone remodeling. These experiments will be important to understand whether cathepsin D inhibition could re-establish the correct bone remodeling lacking in cystinosis.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

The project aims to characterize the role of cathepsin D in the cystinotic skeletal disease and to understand whether cathepsin D inhibition could restore the osteoblast differentiation and mineralization impaired in cystinotic cells. This study will be important to identify a potential target for the treatment of skeletal alterations occurring in cystinosis with the long-term goal to translate the results into benefits for patients.

ANTICIPATED OUTCOME:

This study will allow us to better understand the role of cathepsin D in cystinotic bone pathology. By in vitro study, we expect to discover if cathepsin D inhibition into cystinotic osteoblasts can restore the normal functions such as differentiation, mineralization and cross-talk with osteoclasts. The in vivo study will allow us to understand whether cathepsin D inhibition could rescue the physiological bone remodeling in an animal model of cystinosis and correct the cystinotic bone defects.

Role of DNA methylation in cystinosis

Giusi Prencipe, PhD, *Research Mentor*
Marianna Nicoletta Rossi, PhD, *Research Fellow*
BAMBINO GESÙ CHILDREN'S HOSPITAL, ROME, ITALY

OBJECTIVE/RATIONALE:

We recently demonstrated that the protein NLRP2 is highly expressed in cystinosis and drives the production of pro-inflammatory and pro-fibrotic factors. Interestingly, recent studies demonstrated that NLRP2 expression is regulated by DNA methylation. DNA methylation is a modification of DNA that exerts a strong impact on gene expression and has been found altered in many diseases, including acute and chronic kidney diseases. Our preliminary results showed a global DNA hypomethylation in kidneys from cystinotic mice and in proximal tubular epithelial cells from cystinotic patients. Based on these results, we hypothesize that in cystinosis dysregulation of DNA methylation could affect signaling pathways contributing to the development and progression of kidney damage.

PROJECT DESCRIPTION:

To evaluate alterations of DNA methylation in cystinosis, we propose to:

1) study DNA methylation in the tubular and glomerular portion of kidneys isolated from cystinotic and wild type (WT) mice by using a wide range technique. This approach will give us the possibility to identify gene networks and signaling pathways contributing to cystinosis development and/or progression that are specifically regulated by this mechanism.
2) evaluate the effects of hypermethylating compounds on cystinotic PTEC, with the aim to understand if modification of DNA methylation levels can ameliorate the cystinotic phenotype.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Our research on DNA methylation will contribute to a better comprehension of the mechanisms and pathways involved in the pathogenesis and progression of this disease. Indeed, the evidence that cysteamine does not cure cystinosis, even after cysteine levels normalization, highlights the need to explore the contribution of other mechanisms, including epigenetics. The results obtained will contribute to providing the rationale for translational research studies aimed at implementing conventional therapies used in presently available approaches.

ANTICIPATED OUTCOME:

We expect to obtain data supporting the role of alterations of DNA methylation in cystinosis disease, by regulating genes and pathways involved in the initiation, progression and end-stage renal failure.

Optimizing dysphagia assessments using MBSImP in adults with nephropathic cystinosis

Reza Seyedsadjadi, MD, *Principal Investigator*
Florian Eichler, MD, *Co-Principal Investigator*
MASSACHUSETTS GENERAL HOSPITAL

OBJECTIVE/RATIONALE:

Swallowing difficulty is a major concern in patients with nephropathic cystinosis. So far, more traditional swallow studies have failed to help us understand swallowing mechanics in affected patients. Some patients even had normal testing despite swallowing difficulties.

PROJECT DESCRIPTION:

We propose applying a modern computerized technique to swallow studies we have already obtained from patients who participated in a longitudinal study. We already have obtained 60 studies from 20 patients over a course of a one-year study. We will apply these techniques to these studies and compare measurements in patients with different degrees of swallow issues and weakness.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Results of this study will help us better understand how swallowing is affected in patients with nephropathic cystinosis and yield better potential targets for the treatment of patients. It will also help us find better outcomes to monitor responses to future studies.

ANTICIPATED OUTCOME:

We expect to better understand the mechanics of swallowing and detect abnormality in earlier stages. We also hope to define more sensitive markers to allow us to monitor disease status over time.

Q + A WITH

AVROBIO

Fernanda Copeland, MS, RD, CDE	*Executive Director, Global Head Patient Advocacy & Engagement*

AVROBIO is a lentiviral gene therapy company headquartered in Cambridge, Mass., with an office in Toronto, Ontario. Our vision is to bring personalized gene therapy to the world. We aim to prevent, halt or reverse disease throughout the body with a single dose of gene therapy designed to drive durable expression of therapeutic protein, even in hard-to-reach tissues and organs including brain, muscle and bone. Our ex vivo lentiviral gene therapy pipeline includes clinical programs in Fabry disease, Gaucher disease type 1 and cystinosis, as well as preclinical programs in Hunter syndrome, Gaucher disease type 3 and Pompe disease. AVROBIO is powered by our industry leading plato® gene therapy platform, our foundation designed to deliver gene therapy worldwide. For additional information, visit avrobio.com, and follow us on Twitter and LinkedIn.

AVROBIO supports the cystinosis community through shared goals such as increasing disease awareness, educating and empowering those living with rare conditions, developing advanced therapies and enabling access to those therapies. We also partner with the community to highlight the patient's voice and provide education and information.

1 *Does AVROBIO need to wait for the UCSD phase 1/2 study to be complete before starting the next trial? (Does the FDA or other regulatory agencies need to review the data from the first six patients before AVROBIO can begin the next clinical trial?)*

We expect the UCSD phase 1/2 study to fully enroll by the end of the year and, in the coming months, we plan to engage the FDA on the design of our next trial. Some safety data from the pediatric patients in the phase 1/2 study will be needed prior to initiating this trial, and the data will also help inform the trial design.

2 *When will you start phase 3? What is the timeline?*

We expect the UCSD phase 1/2 study to fully enroll by the end of the year and, in the coming months, we plan to engage the FDA on the design of our next trial.

3 *Where will the new sites be located? Will there be one new site for phase 3 transplants or multiple sites?*

We are still early in the planning phase, and site locations are still to be determined.

4 *Will there be international sites? Canada? Europe?*

We are still in the early planning phase, but we expect to have sites globally.

5

What ages will phase 3 be open to? What is the patient demographic you are looking for?

We are planning to engage the regulatory agencies, medical experts in cystinosis and potential study investigators, as well as the patient advocacy leadership community to help inform our inclusion and exclusion criteria.

6

How many patients do you anticipate you will enroll in phase 3?

We anticipate discussing the design of the next trial, including the number of patients, during our regulatory interactions in 2021.

7

How will the protocol differ from what Stéphanie Cherqui has done in the phase 1/2 trial?

Dr. Cherqui's phase 1/2 clinical study was designed to assess safety. The next trial will assess safety and efficacy; therefore, the design will depend on our interactions with the regulatory agency in 2021.

8

Can you explain the difference between Stéphanie Cherqui's vector and AVROBIO's vector?

Both vectors are lentiviral vectors. AVROBIO's vector is designed to accommodate larger-scale production.

9

Will patients in the next trial have to pay for the transplant? Will insurance cover it?

We appreciate the importance of understanding the costs associated with clinical trial participation. Patients do not generally pay for procedures that are part of clinical trials. Clinical trial participation protocols vary from site to site, and interested participants should discuss the details with a study site coordinator.

10

Will AVROBIO provide housing for the post-hospitalization follow-up? What costs will be covered?

We appreciate the importance of understanding the costs associated with clinical trial participation. Reimbursement may be available for costs associated with travel to the study site, such as airfare, hotel, mileage, parking and meals. Clinical trial participation protocols vary from site to site, and interested participants should discuss the details with a study site coordinator.

11

Who do I contact if I am interested in participating?

You should discuss your treatment options, including potential participation in clinical trials, with your healthcare provider.

The phase 1/2 clinical study is being conducted by UCSD and contact information can be found at clinicaltrials.gov with the following clinical trial identifier: NCT03897361

Information about the future clinical trial will be shared on clinicaltrials.gov and will be found by searching for AVROBIO.

12

Will Dr. Cherqui be involved with phase 3 and beyond?

Dr. Cherqui is an important member of the cystinosis community and we look forward to working together to advance therapies for the cystinosis community.

AVROBIO's gene therapies are investigational, which means that they have not been proven safe or effective or approved by the FDA or any other regulatory agency. Patients should discuss all treatment options, including potential clinical trial participation, with their healthcare provider.

CALL FOR RESEARCH PROPOSALS

When Nancy and Jeff Stack established the Cystinosis Research Foundation in 2003, they were committed to aggressively funding cystinosis research to ensure the development of new and improved therapies and a cure for cystinosis. But never in their wildest dreams could they have imagined what has been accomplished in 18 short years. Since its inception, CRF has funded 204 multi-year research studies in 12 countries. Our researchers have published 88 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 2021 call for research proposals and fellowship grants. The grant awards will be announced at the end of July 2021.

In 2020, CRF issued a total of 23 grants, which included 14 new grants, eight grant extensions and one equipment grant totaling over $3.1 million which brings us closer to better treatments and a cure. All research applications received by CRF are evaluated by CRF's Scientific Review Board (SRB), composed of the leading international experts in the field of cystinosis. The SRB provides independent, objective reviews and recommendations for each research proposal submitted based on the NIH scale of standards. Additionally, the SRB follows grant review guidelines established by CRF and advises the foundation on the scientific merits of each proposal.

In 2010, CRF established the Cure Cystinosis International Registry (CCIR) to serve as a hub of information about cystinosis and its complications.

Cure Cystinosis
International Registry

CRF is proud to announce the new Cure Cystinosis International Registry (CCIR) opened for enrollment on April 1, 2021. CRF has partnered with Sanford CoRDS (Coordination of Rare Diseases at Sanford) to create the only international cystinosis patient registry in the world. The site will include a Professional Research Portal so that researchers and scientists who register can access and view de-identified, aggregate cystinosis patient information. The registry will 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.

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.

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 our adults and children with cystinosis. Thank you!

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Imagine Institute (Inserm U1163)
PARIS, FRANCE

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Nephrology Department, Senior Physician
Necker Hospital
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THANK YOU FOR YOUR DEDICATION TO THE GLOBAL CYSTINOSIS COMMUNITY

CYSTINOSIS COMMUNITY CALENDAR OF EVENTS

2021

Friday, June 4, 2021

LOTS OF LOVE FOR LANDON CHARITY GOLF OUTING
IN HONOR OF LANDON HARTZ
Black Hawk Golf Course, Beaver Falls, Pennsylvania
Contact Jimmy Hartz: lotsofloveforlandonCRF@gmail.com

August 2021

PAINT THE TOWN PURPLE
IN HONOR OF OLIVIA LITTLE
Port Elgin, Ontario, Canada
Contact Erin Little: Erin.Little@livalittlefoundation.com

Thursday, October 21, 2021

SETH'S CIRCLE OF HOPE
IN HONOR OF SETH deBRUYN
Calgary, Alberta, Canada
Contact Kristen Murray: murraykristen@hotmail.com

Tuesday, November 30, 2021

GIVING TUESDAY FUNDRAISER
Cystinosis Research Foundation

2022

Monday, February 28, 2022

RARE DISEASE DAY
Cystinosis Research Foundation

March 2022

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

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

March 10 – 11, 2022

CRF INTERNATIONAL CYSTINOSIS RESEARCH SYMPOSIUM
Beckman Center, National Academies of Science, Engineering, and Medicine, Irvine, California
Contact Nancy Stack: nstack@cystinosisresearch.org

March 31 – April 2, 2022

CRF DAY OF HOPE FAMILY CONFERENCE
(IN-PERSON MEETING!)
Balboa Bay Resort, Newport Beach, California
Contact Nancy Stack: nstack@cystinosisresearch.org

Saturday, April 2, 2022

NATALIE'S WISH CELEBRATION CRF FUNDRAISER
(IN-PERSON GALA EVENING!)
Balboa Bay Resort, Newport Beach, California
Contact Zoe Solsby: zsolsby@cystinosisresearch.org

April 2022

7TH ANNUAL FISHING FOR BROOKE'S CURE
IN HONOR OF BROOKE EMERSON
Hammonton, New Jersey
Fishing locations to be determined
Contact Clay Emerson: clay.emerson@gmail.com

Monday August 8, 2022

AIDAN'S ARMY GOLF TOURNAMENT
IN HONOR OF AIDAN O'LEARY
Orchard Lake Country Club, Orchard Lake, Michigan
Contact Erin O'Leary: erinkmccarthy33@gmail.com

September 2022

LILLYANNA'S LEMONADE AND BAKE SALE FOR A CURE
IN HONOR OF EMMA GRACE
Etna, California
Contact Shelly Suetta: shellysuetta@hotmail.com

LEADERSHIP. GUIDANCE. COMMITMENT.

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MISSION

The mission of the Cystinosis Research Foundation is to find better treatments and a cure for cystinosis by supporting bench, clinical and translational research. Since 2003, CRF has raised nearly $60 million with 100% of all your donations going to support cystinosis research.

EDUCATION

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

CHARITY NAVIGATOR Four Star Charity

GUIDESTAR PLATINUM TRANSPARENCY 2021

From a dream
came rays of hope
which bear more
fruit than it could
ever imagine as
its blossoms
became stronger
and mightier
toward
the cure
by earth
by seed
by sun
by water
into tree
we are reminded
of our roots
through
the dream.