cystinosis magazine

FOR FRIENDS and SUPPORTERS of the CYSTINOSIS RESEARCH FOUNDATION

SUMMER 2025

2003 — 2025

Breakthroughs begin with HOPE.

The proof is in our journey.

WE'RE BETTER TOGETHER

What it means
to experience
the benefits
of every cell
transforming.

To find community
and progress in all
our constructs
and concepts.

What it means
to describe
—such powerful
—such important
—such meaningful
developments
in a simple poem
on a trail unknown
with words alone.

We've lived our lives
witnessing this
progressive science
climbing.

We've reached
the harshest
environments
above the treeline
where it's bare.

THE CYSTINOSIS RESEARCH FOUNDATION IS A COLLECTIVE OF DONORS, RESEARCHERS,

Harnessing our
accomplishments
on this path
toward
the cure.

The winds speak,
our minds listen
traversing wisdom's peak
for a meeting
with answers
of what
we've
become.

The altitude is in us—
an alchemy mysterious
shape-shifting
into a life
sans-cystinosis.

What it means
—to look back
—to reach the top
—to approach
the next thing
as we appreciate
our growth and vitality...

which is only defined
with *a feeling.*

2003 — 2025

Breakthroughs begin with HOPE!

The proof is in our journey together. See page 10.

WE'RE BETTER TOGETHER

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 $72 million for cystinosis research in an effort to find a cure.

cystinosis RESEARCH FOUNDATION

Cystinosis Research Foundation
19200 Von Karman Ave. Suite 920
Irvine, California 92612
949 223 7610

CYSTINOSIS**RESEARCH**.ORG

CHARITY NAVIGATOR ★★★★ Four Star Charity

Platinum Transparency 2024 Candid.

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

To view this edition digitally, visit *www.cystinosisresearch.org/cystinosis-magazine.*

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

Project Management: Idea Hall
Art Direction and Design: Born Primate Co.
Printing and Distribution: Goodwork

CYSTINOSIS MAGAZINE IS A PUBLICATION OF THE CYSTINOSIS RESEARCH FOUNDATION

The entire cost to produce and distribute *Cystinosis Magazine* is underwritten by an anonymous donor.

SUMMER 2025

IN THIS ISSUE

WELCOME

ANNOUNCEMENTS

RESEARCH UPDATES

FAMILY PARTNERS

Dear Family & Friends,

A LETTER FROM
NANCY AND JEFF STACK

JUNE 2025

We love this time of the year – it is a time of renewal and hope, of looking at life with a new sense of adventure. We are grateful to all of you who have stood by our side as we blaze the path to find better treatments and a cure for cystinosis. We have come so far since 2003 when Natalie scribbled her birthday wish on a napkin: "to have my disease go away forever." Her wish was the beginning of the CRF story, but with each step forward, you have been by our side.

THE CURE IS COMING!

We have so much to be thankful for, but we have particularly exciting news to share with you about the next phase of the stem cell trial. On Friday, April 4, Novartis (who acquired the cystinosis stem cell program in May 2023) announced the opening of the next phase of the cystinosis trial for pediatric participants aged 2-5 years. The clinical trial will assess the safety, tolerability, and efficacy of the stem cell treatment.

It is with pride that we emphasize that this phase of the trial was approved because of the positive data from phase 1/2 of the clinical trial that was led by Dr. Stéphanie Cherqui at UC San Diego. We are so thankful to the five adult patients who were part of phase 1/2 and who pioneered the treatment beginning in 2019.

Since Novartis' acquisition of the cystinosis program, CRF has worked with Novartis to ensure the voices of our community were heard. We have fiercely advocated on behalf of the community every step of the way. We have reported what it is like to live with cystinosis, including the daily burden of disease and the current quality of life. We were able to advise Novartis on the clinical trial design and most importantly, we emphasized how critical it is that they move quickly to guarantee that this treatment is approved for all those with cystinosis.

The truth is the stem cell trial would not be a reality without the efforts of CRF. It was in 2007 that we funded Dr. Cherqui for the start of her work in stem cells. There were naysayers, there were hurdles and some setbacks, but in partnership with Dr. Cherqui, we persevered. CRF took the early financial risk to fund this research and as Dr. Cherqui's work progressed and proof of concept was established, other funding agencies supported her efforts, including the California Institute of Regenerative Medicine (CIRM) and the National Institutes of Health (NIH) who leveraged our early financial investments. In partnership with other stakeholders, we have successfully reached this extraordinary milestone.

We thank Novartis and their cell and gene therapy group for their commitment to our community. We are fortunate that Novartis acquired the cystinosis program and that they have so many people dedicated to ensuring a better life for our children and adults with cystinosis. We have worked together on behalf of our community, and we are grateful for the partnership. We look forward to continuing to work with Novartis during this next phase of the stem cell trial. We have included the official announcement from Novartis on page 35.

WE'RE BETTER TOGETHER

CYSTINOSIS MAGAZINE HIGHLIGHTS

We know you will enjoy this issue of the magazine. We have two in-depth interviews with CRF researchers, Dr. Sergio Catz from the Scripps Research Institute and Dr. Benjamin Freedman, from the University of Washington.

The work Dr. Catz does is focused on the immune-cell processes that underlie inflammation which is critical to understanding the pathogenesis of cystinosis. The ultimate goal of his work is to find or create new drugs to complement cysteamine that will help improve the lives of those with cystinosis. The interview with Dr. Catz can be found on page 46.

Dr. Benjamin Freedman's research is focused on kidney-related research. He is a pioneer in the field of induced pluripotent stem (iPS) cells. Dr. Freedman creates kidney organoids, which resemble small human kidneys, using iPS cells. His current study will test human stem cells in a newly engineered mouse model created in his lab. The goal of his research is to protect and restore kidney health. The interview with Dr. Freedman can be found on page 44.

In this issue you will also find heartwarming stories from families and patients about their lives and experiences living with cystinosis. Each family or patient story has a unique perspective, and each story reminds us that we are not alone; we have each other. You will also find updates about CRF research initiatives and updates on cystinosis family events.

CRF RESEARCH IS THRIVING

We have built a strong, research-driven foundation that has accomplished major milestones. As a result of your support, we have funded studies that have led to two FDA approvals, numerous clinical trials, and significant discoveries about cystinosis. Our early work has resulted in the next critical advancement of the stem cell trial. If the next phase of the trial, led by Novartis, is successful, it will likely lead to the stem cell treatment being available to all those with cystinosis.

Since 2003, CRF has funded 248 multi-year research studies in 13 countries. Our researchers have published 113 articles in prestigious journals because of CRF funding. CRF is the largest private fund provider of cystinosis research in the world. Our policy of awarding research grants twice a year guarantees that there are no gaps in funding and essential and life-saving research is prioritized. Our research program is led by our prestigious CRF Scientific Review Board (page 54), who carefully and thoroughly evaluate every research application we receive and recommend the most promising research studies to fund.

We are pleased to report that 2025 was another extraordinary year for our research program. We funded new researchers who have novel therapeutic ideas, and we have continued to fund research projects that are on track to yield new discoveries about cystinosis and lead to clinical trials for new treatments. In 2024, CRF awarded a total of 11 new research grants including three funded in the fall, totaling more than $1.8 million. The 11 research studies focus on potential new treatments, ocular cystinosis, muscle myopathy and dysphagia, and kidney disease. We are excited to share the lay abstracts of the three fall grant awards on page 51.

CRF SPONSORS THE NINTH INTERNATIONAL CYSTINOSIS SYMPOSIUM

We started the year off with our Ninth International Research Symposium held in March in Irvine, California. We were honored to work with three esteemed cystinosis experts, Stéphanie Cherqui, PhD, Francesco Emma, MD, and Julie Ingelfinger, MD, who co-chaired the symposium. The symposium provided an opportunity for CRF scientific and medical experts to share current research discoveries, explore new ideas, and create collaborations to advance cystinosis

>>>>

research. We were honored to have Melissa Wigderson, MD, from Novartis Pharmaceuticals International give the keynote address, "Onasemnogene Abeparvovec-xioi for Spinal Muscular Atrophy (SMA): Bench to Bedside." It was a fascinating presentation that illustrated how it is possible to translate bench research to the patient bedside with significant improvements in function, lifespan and quality of life. Notably, Dr. Wigderson will oversee the cystinosis clinical trials which are now open for recruitment.

The symposium highlighted the breadth of CRF-funded research from gene therapy and potential new treatments to drug repurposing and molecular research. Please read a wonderful synopsis of the symposium written by CRF Board Trustee Stephen Jenkins, MD, on page 42.

WE ARE BETTER TOGETHER - DAY OF HOPE UNITES THE COMMUNITY

In April, we were excited to welcome families from all over the world for a weekend of hope, inspiration, and community as CRF celebrated 22 years of progress and impact in the cystinosis community. The conference sessions included top CRF-funded researchers who presented their research progress on kidney disease, neurological issues, bone and muscle disease, ocular cystinosis, and clinical trial updates. We were especially thrilled to have Daniel Grant, Vice President & Global Program Head of Neuroscience & Gene Therapies Unit of Novartis, speak about the newly opened clinical trial.

The powerful relationships that are formed at the conference between cystinosis families and patients and the research community are life changing. Together we are strong, and together we will make a difference as we continue to advocate for our community.

Thank you to our dedicated Co-Chairs and CRF Board Members Jill Emerson, Clay Emerson, PhD, PE, CFM, Stephen Jenkins, MD, Kristen Murray, and Brian Sturgis, who worked to create an exceptional conference for the community. Please read more about the family conference on page 12. We know you will smile when you look at the joyful pictures of our community together!

CRF RESEARCH IMPACTS OTHER DISEASES AND DISORDERS

As we begin the next, and we hope, final phase of the stem cell trial, we recognize that the research we fund has a positive impact on other diseases and disorders. Our research has helped advance research in other diseases including Friedreich's ataxia, Danon disease, Alzheimer's disease, and other genetic and systemic diseases like cystinosis. CRF's mission was to find better treatments and a cure for cystinosis, but we are overjoyed that we have impacted other disease communities who are now creating pathways to cures for their communities. We are changing lives and giving hope to people far beyond the cystinosis community.

WITH IMMENSE GRATITUDE

We have so much to be grateful for – your unwavering support, your commitment to research, and your compassion and love for our community.

You have helped us create a global research community that is dedicated to the children and adults with cystinosis. We are committed to finding treatments that will improve the quality of life for those living with cystinosis. Our work continues and with your support, we will soar to new heights and reach new milestones.

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

With heartfelt thanks and gratitude,

Nancy and Jeff

There are many updates to be shared since last year. Although we are not even halfway through 2025, I have had a lot of changes in my life. On a positive note, in March, I moved back to Orange County, California. Though I enjoyed living in the big city of Chicago for the past two years, I am excited to be living in California again. My husband, Danny and I bought a beautiful home and love our new neighborhood. Our house has a lovely backyard for our three-year-old dog, Wesley, who enjoys running around the yard and meeting his furry friends in the neighborhood.

I recently started a new job, as an advocate supervisor, at CASA-OC (Court Appointed Special Advocates, Orange County), a non-profit organization. I worked at CASA previously before moving to Chicago, so I am thrilled to work at CASA again and advocate for children in foster care.

The most exciting news for us is that my husband and I are expecting our first child in July! Many of you know that part of the stem cell therapy clinical trial included eight rounds of chemotherapy. The reality of having chemotherapy and my current and rapid decline in kidney function over the past year led us to start a family through surrogacy. We have a wonderful gestational surrogate who is carrying our baby for us. We cannot wait to meet our daughter and become a family of three (and of course, one sweet dog!).

I never dreamed that I would have a family of my own and now that it is happening, it feels like a dream. None of this miraculous reality of becoming a mother would be possible without the medical care from talented doctors and support from my family. My goal is to be as healthy as possible for my daughter so that I can watch her grow up, graduate from college and someday if she chooses, get married. I still face medical challenges but with the support from the cystinosis community and advanced medical treatments, I have no doubt that I will be strong enough and healthy enough to watch her grow and witness her life milestones.

My medical update is always interesting! I am 34 years old, and I am doing relatively well. Because my engraftment has been slower than desired, I am on a very low dose of medication (cysteamine). I recently celebrated my "second birthday" marking three years since my stem cell and gene therapy transplant in March 2022. Overall, I feel great and I remain more hopeful than ever that the stem cell transplant will stop the progression of cystinosis.

Although somewhat expected, unfortunately, last year, my kidney function really started to decline, and it continues to rapidly decline. I am currently on the kidney transplant waitlist. I expect I will need a kidney transplant in the next year. It is really difficult to accept the fact that I need a transplant, especially because for so many years, my kidney function was stable (although I was in early end-stage kidney disease before the stem cell transplant). The conditioning for the stem cell transplant likely accelerated my kidney deterioration, but I know that after a kidney transplant, my kidney function will stabilize. I know I am in good hands with the kidney transplant team, and I have a good support system.

Despite my kidney function declining, I still feel healthy. I do not take naps like I used to pre-stem cell transplant and my overall energy during the day is much better than it was prior to the stem cell transplant. I remain hopeful that my body continues to respond to the new stem cells and that my health continues to improve every day. For me, it has been a longer recovery and engraftment process than I thought it would be, but I wouldn't change a thing. The stem cell transplant was a pivotal and life-changing event for me. I hope and I wish that everyone with cystinosis will have an opportunity to have a stem cell transplant in their lifetime.

I am so thankful to the doctors and the cystinosis community for continuing to support CRF research and the foundation. There is still more to be done and with the support of our community, anything is possible. I am so blessed to be part of the cystinosis community and to have the medical opportunities available to me in my lifetime.

I am beyond grateful to each one of you who not only helped save my life but who have given hope to others who have cystinosis. Thank you for never giving up on my wish to "have my disease go away forever."

Love, Natalie

CYSTINOSIS RESEARCH FOUNDATION

OUR STORY. OUR IMPACT.

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 cystinosis grants in the world and has funded 248 grants in 13 countries.

CRF has raised over $72 million, with 100% of your donations going to support cystinosis research. CRF is the driving force of cystinosis research that has directly resulted in advances in treatment including the FDA-approval of Procysbi® and an FDA-approved stem cell and gene therapy clinical trial. We have accomplished milestones and given hope to the cystinosis community that a better quality of life and a cure for cystinosis is possible.

CRF IS SYNONYMOUS WITH HOPE

WHAT IS CYSTINOSIS?

Cystinosis is a rare, inherited, metabolic disease that is characterized by the abnormal accumulation of the amino acid cystine in every cell in the body. Buildup of cystine in the cells eventually destroys all major organs of the body, including the kidneys, liver, eyes, muscles, bone marrow, thyroid and brain. Medication is available to control some of the symptoms of this terrible disease, but cystinosis remains incurable. Cystinosis affects approximately 600 people, mostly children, in North America, and about 2,500 people worldwide.

It is one of the 7,000 rare, or "orphan," diseases in the United States that collectively 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.

CRF GLOBAL OUTREACH – 13 COUNTRIES

AUSTRALIA	GERMANY	NETHERLANDS
BELGIUM	INDIA	NEW ZEALAND
	IRELAND	
CANADA	ISRAEL	SWITZERLAND
FRANCE	ITALY	UNITED STATES

cystinosis RESEARCH FOUNDATION

CHARITY NAVIGATOR ★★★★ Four Star Charity

Platinum Transparency 2024 Candid.

WE 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 $25 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.

100% OF YOUR DONATIONS DIRECTLY SUPPORT CYSTINOSIS RESEARCH

YOU HAVE CHANGED THE COURSE OF CYSTINOSIS — THANK YOU!

SINCE 2003, CRF HAS:

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

1+1

FUNDED
248 Multi-Year Grants in 13 Countries

248

PUBLISHED
113 Articles in Prestigious Scientific Journals by CRF-Funded Researchers

113

RAISED
More Than $72 Million for Cystinosis Research

$72M

IN 2024

CRF Awarded 11 New Research Grants

Totaling More Than $1.8 Million

The Proof is in Our Journey

In 2003, the beginning of CRF, we funded two studies. Then year by year, we funded additional studies led by more brilliant scientists. We have been instrumental in unlocking the mysteries of cystinosis.

Today, in 2025, CRF has proven itself to be the leading advocate for cystinosis research, funding hundreds of researchers around the world who are working around the clock to find cures and better treatments.

Hundreds of researchers are working on this rare disease because of CRF funding.

24/7 Research

CRF is funding researchers in 13 countries. This means someone is working every minute of the day to find better treatments and a cure.

Meaningful and Lifelong Friendships

Hundreds of families connecting at the annual Day of Hope family conference. The CRF family grows every year and includes families from all over the world, confirming CRF's reach and commitment to everyone in the cystinosis community.

We're Cystinosis-Specific

CRF funds research that targets every area of the body affected by cystinosis including the kidney, eyes, brain, bone and muscle.

And now more common diseases are beginning to benefit from CRF-funded research.

Over $72 Million

raised for cystinosis research bringing hope to the community.

FDA Approval

In 2013, Procysbi®, a delayed-release medication was FDA approved. CRF funded every early bench and clinical trial.

In 2018, the FDA approved the first stem cell and gene therapy treatment in six adults with cystinosis. The study was led by Stéphanie Cherqui, PhD, at UC San Diego.

Clinical Trial Advancements

As a result of the successful adult stem cell and gene therapy trial at UC San Diego, the next - and we hope - the final phase of the trial, has recently commenced. This phase, led by Novartis, will treat young patients.

Gaining Global Exposure

113 CRF-supported, cystinosis-related published research papers to date.

Understanding Every Aspect of Cystinosis

25 clinical studies leading to new discoveries and treatments.
248 studies in all, since 2003, including critical animal models that CRF has helped create.

Biennial International Research Symposium bringing CRF-funded researchers together to accelerate research and establish collaborations.

First Canadian family conference hosted by CRF in 2022.

Establishment of the CRF Scientific Review Board comprised of the world's leading experts on cystinosis who guide the CRF research program.

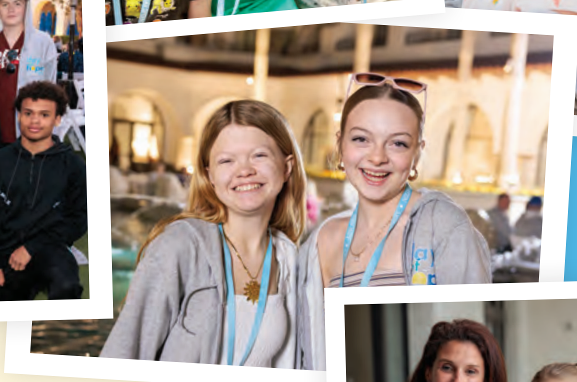
Critical seed money provided to researchers in their early stages has been leveraged by other funding sources including NIH and CIRM.

WE'RE BETTER TOGETHER

day of hope 25

Cystinosis Family Conference
HUNTINGTON BEACH, CA

by Clay Emerson, PhD, PE
Hope for Brooke
CRF Board of Trustees



In our daily lives we interact with family, fellow parents, other children and plenty of people in the medical community. However, our experience with an ultra-rare disease like cystinosis makes our journey and daily lives difficult for others to relate to. For this reason, we always look forward to the Day of Hope family conference. It provides us with an opportunity to connect with other families who share the same unique life experience that is cystinosis. The Day of Hope conference also provides us with a direct link to expert clinicians and researchers specializing in cystinosis. The conference re-energizes us with hope and informs us on progress towards improved treatments.

This year more than 60 families converged at the beautiful Hyatt Regency Resort in Huntington Beach, California, for a three-day celebration of community, progress and our common hope for a cure. The program included a fun-filled children's schedule and numerous activities for teenagers, including a trip to Dr. Albrecht's lab at UC Irvine where teens were able to get a firsthand look at cystinosis research in action.

The presentation sessions were full of the latest information from an international collection of world-renowned cystinosis experts including both clinicians and researchers. Drs. Greenbaum, Grimm, and Midgley discussed the management of cystinosis from diagnosis and Fanconi syndrome, to planning for a kidney transplant and life beyond kidney transplant. Presentations also highlighted the latest data from researchers with topics ranging from bench-level research on cellular metabolism to potential mRNA-based treatments for cystinosis by Dr. Goodyer of McGill University in Canada.

The conference also benefited from presentations directly from the community including family stories from the Alexander sisters and an especially heartfelt presentation from Natalie Stack Morgan. Natalie's original wish for her "disease to go away forever" provided the spark that has led to more than $72 million dollars of funding for research. This research has brought us to the brink of a potential cure for cystinosis, a disease for which until only recently, a cure was regarded as an unthinkable goal.

The conference also provided smaller breakout sessions giving families the opportunity to meet with each other and provide personal support in ways that only other cystinosis families can. These breakouts included spaces for parents of newly diagnosed children, teens, siblings, partners,

continued

grandparents and everyone in between to share their experiences, advice, and support. In addition to the supportive and educational aspects of the conference, Day of Hope also provided families with the opportunity to directly contribute to research. Attendees were able to participate in multiple research efforts being conducted by Dr. Stéphanie Cherqui's laboratory. Dr. Reza Seyedsadjadi of Massachusetts General Hospital, was also on-hand to recruit participants in his distal myopathy trial. Many attendees visited Dr. Donny Suh of UC Irvine who arrived in style in a complete mobile eye clinic RV and was able to examine over 40 patients right at the resort. A medical panel session enabled attendees to ask the experts all the questions that come along with a complex and multi-system disease like cystinosis. A large number of adult patients attended the conference, and many participated in an adult panel session where they generously and openly shared their life experiences and advice.

The conference came less than a week after Novartis' announcement of the current phase I/II trial for pediatric patients. As a result of this announcement, perhaps the highlight of the conference was Dr. Stéphanie Cherqui's update on the adult phase I/II stem cell gene therapy trial. Dr. Cherqui provided a detailed summary of the trial from its original foundational concept to a five-year post-stem cell transplant follow-up. She included the latest results from the patient volunteers, three of whom attended the conference. Dr. Cherqui also outlined new applications for her treatment approach that she is exploring in more common diseases including Friedreich's ataxia, Sanfilippo disease, Danon disease, and Alzheimer's. She received a well-deserved standing ovation for the multiple decades of hard work and dedication that has brought our community to the brink of a cure for everyone with cystinosis.

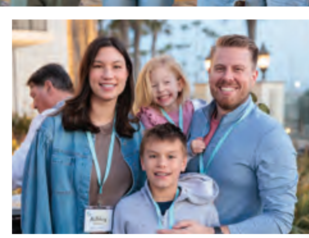
With the pediatric trial announcement hot off the press, Novartis provided an outline of the current phase I/II trial. The presentation highlighted the adaptable and flexible nature of the trial design, which we believe will result in a quick, efficient and successful trial, and will hopefully make the treatment available for our entire community.

day of hope 25

Cystinosis Family Conference

HUNTINGTON BEACH, CA

In summary, families were able to enjoy a long weekend of new and renewed connections, family support, education, and community. The conference was topped off with a Saturday night dinner where families, researchers, and clinicians celebrated family fundraising efforts and the real progress made possible by the CRF. We're already looking forward to seeing everyone in 2026!



CYSTINOSIS COMMUNITY CALENDAR OF EVENTS

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

Friday, February 28, 2025

RARE DISEASE DAY
Cystinosis Research Foundation
www.cystinosisresearch.org

Friday, March 14, 2025

10TH ANNUAL FISHING FOR BROOKE'S CURE
HOPE FOR BROOKE, IN HONOR OF BROOKE EMERSON
Contact Clay Emerson: clay.emerson@gmail.com

Month of April 2025

NATALIE'S WISH CELEBRATION
ONLINE FUNDRAISER
Cystinosis Research Foundation
Contact Nancy Stack: nstack@cystinosisresearch.org

Thursday, April 10 - Saturday, April 12, 2025

CRF DAY OF HOPE FAMILY CONFERENCE
Hyatt Regency Hotel, Huntington Beach, California
Contact Jill Emerson: jill.emerson@hotmail.com

Saturday, October 21, 2025

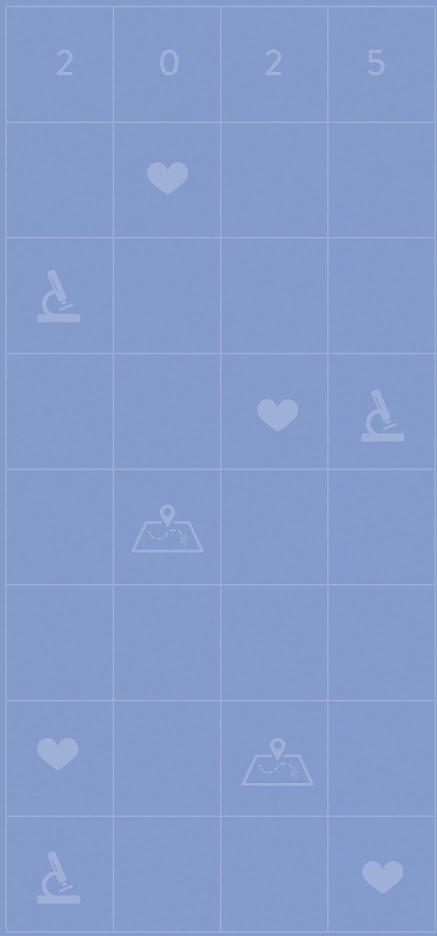
SETH'S CIRCLE OF HOPE
IN HONOR OF SETH DEBRUYN
Calgary, Alberta, Canada
Contact Kristen Murray: murraykristen@hotmail.com

Tuesday, December 2, 2025

GIVING TUESDAY – FUND A CURE FOR CYSTINOSIS!
GIFT CHALLENGE
Cystinosis Research Foundation
www.cystinosisresearch.org

December TBD, 2025

THIRD ANNUAL PICKLEBALL TOURNAMENT
IN HONOR OF ISLA MCALLISTER
Contact Duncan McAllister: duncanmcal@yahoo.com



COMMUNITY UPDATES

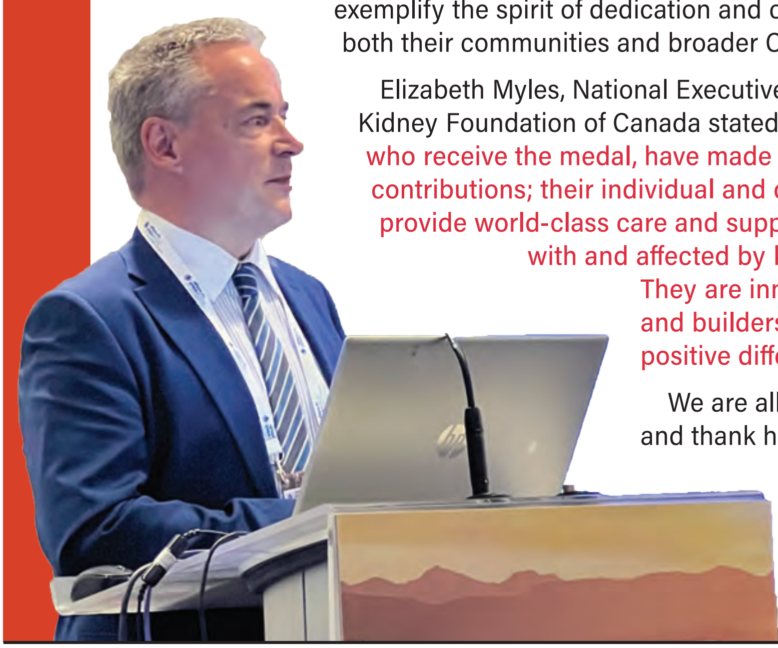
FAMILY STORIES

BREAKTHROUGHS BEGIN WITH HOPE

DR. JULIAN MIDGLEY —

A POSITIVE IMPACT

Congratulations to Julian Midgley, MD, who was recently awarded the prestigious King Charles III Coronation Medal. The Coronation Medal recognizes significant contributions, whether in public service, arts, education, science, or other areas, that have advanced Canadian society or brought international recognition to the country. The recipients exemplify the spirit of dedication and commitment to both their communities and broader Canadian society.



Elizabeth Myles, National Executive Director of The Kidney Foundation of Canada stated that individuals who receive the medal, have made "exemplary contributions; their individual and collective efforts provide world-class care and support to those living with and affected by kidney disease. They are innovators, disruptors and builders who make a positive difference every day."

We are all proud of Dr. Midgley and thank him for his dedication and commitment to children and adults with cystinosis.

THANK YOU, CANADA —

FOR YOUR PARTNERSHIP AND FRIENDSHIP!

When it comes to finding a cure, there are no borders between Canada and the United States. Cystinosis families from Canada are committed CRF partners who are dedicated to funding research that will lead to better treatments and a cure for all our children and adults with cystinosis.

Fundraising is hard work, but it is incredibly gratifying, too! When you plan an event, you are uniting your community in the quest to find better treatments and a cure for cystinosis. Thank you to the Canadian families who continue to organize and plan events to raise money for research. Since 2016, Canadian families have funded more than $1,321,762 in CRF research grant payments.

OUR STRENGTH IS IN OUR PARTNERSHIP!

HOW IT WORKS:

The Cystinosis Awareness and Research Effort (CARE) has partnered with Canada Helps to establish the Canadian Cystinosis Research Foundation. Aqueduct Foundation administers this fund and allows for an efficient and effective fundraising process to ensure Canadians who donate will receive a charitable tax receipt. When you donate through Aqueduct Foundation be sure to select the Canadian Cystinosis Research Foundation from the dropdown menu after entering your donation amount.

www.canadahelps.org/en/charities/aqueduct-foundation

If you are Canadian and would like to donate or raise money for CRF-sponsored research, contact:

Barb Kulyk at *Barbara_Kulyk@hotmail.com* or

Kristen Murray at *murraykristen@hotmail.com*

TOGETHER, WE ARE one

COMM UNITY FUND RAISING

1 PURPOSE.
1 JOURNEY.
1 CURE.

Cystinosis Research Foundation – Irvine, California

THANK YOU FOR CELEBRATING 20+ YEARS OF GROUNDBREAKING RESEARCH!

Your incredible generosity has raised over $1,070,000 for cystinosis research! Every dollar brings us closer to a cure and the discovery of more effective treatments. We are changing lives and giving those affected by cystinosis hope for a brighter future. It's never too late to help fund life-saving research!

It all started with one girl's wish "to have my disease go away forever." More than two decades later, Natalie Stack's wish for a cure has evolved from one girl's dream into the rallying cry of an entire worldwide community. It is our collective drive to find a cure that has changed lives and given hope to those living with cystinosis. Today, the cure for cystinosis is within reach, thanks to your commitment to our children and adults with cystinosis.

While we began as a small community of separate families scattered across the world, we have now evolved into a united global community, a research powerhouse, and a movement dedicated to turning our hope for a cure into reality.

We have made progress, but much remains to be discovered. Our relentless pursuit of a cure requires us to continue to fund cystinosis research with the greatest potential.

RAISED
OVER
$1,070,000

Natalie's wish for a cure is our wish. It fuels our determination to find better treatments and a cure for cystinosis, and we won't stop until we do. Please join us to celebrate over 22 years of impact, ring in a new era of progress, and continue the momentum for all born with cystinosis, today and in the future.

Natalie's WiSh 25
~The~ WISH that is CHANGING LIVES

RARE DISEASE DAY®

RAISED

$38,600

Cystinosis Research Foundation – Irvine, California

THANK YOU FOR CELEBRATING RARE DISEASE DAY WITH CRF

With your generous support, we were able to continue giving a voice to our rare cystinosis community on Rare Disease Day 2025! We thank you for continuing to show your commitment to our small but mighty community through your generous donations. We are excited to announce that we raised $38,600 on Rare Disease Day. Every dollar goes directly to fund research for better treatments and a cure for cystinosis.

Without you, we would not be where we are today. We have made progress, but there is much more research to fund and more milestones to reach. While we believe the stem cell treatment will be a treatment for all people with cystinosis, we must continue to find better treatments for our children and adults with cystinosis. Our work is not done! Thank you for your participation on Rare Disease Day – you have made a difference; the proof is in the research!

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

10TH ANNUAL FISHING FOR BROOKE'S CURE

It's been ten years since Brooke was diagnosed with cystinosis. That diagnosis turned our lives upside down. Just two months after her diagnosis we decided to hold a fundraiser for CRF. Like the diagnosis, our attempt at fundraising was a venture into the relative unknown. However, we found that fundraising provided a much-needed opportunity for direction, community, and hope to enter the otherwise bleak picture; and, with that, the Fishing for Brooke's Cure Fundraiser was born.

The tenth annual Fishing for Brooke's Cure Fundraiser was held on March 14th. Despite the colder than average conditions, the fishermen were able to catch (and release) 505 fish and even made time to rescue a capsized kayaker from the 48°F water. Between the "per fish" pledged donations supporters made, additional direct donations and a single donor's generous total fundraiser match, those 505 slimy, scaley and shiny fish led to a haul of almost $70,000 for cystinosis research! We are eternally thankful to our dedicated fishermen and hundreds of generous donors, many of whom have supported our event from day one.

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

2ND ANNUAL PICKLEBALL TOURNAMENT IN HONOR OF ISLA

In December 2024, the McAllister family organized their second annual fundraising tournament for CRF to raise money in honor of their daughter Isla and support cystinosis research. This year, the pickleball tournament was held at Lifetime Athletics in Oklahoma City. Their generous Oklahoma and Texas community of family and friends joined in the fun to support Isla. Participants enjoyed playing pickleball and the opportunity to purchase jewelry that supported CRF. A pickleball tournament is always competitive, but courts were also available for the children to play and enjoy. Following the event, Isla's supporters contributed over $14,475 for cystinosis research! Thank you to the McAllister family for hosting their unique and successful pickleball tournament for CRF. We are grateful for your commitment and support of our mission to fund research for better treatments and a cure for all those with cystinosis. We are better together!

Fera at Five

By Vanessa Bonneau, Fera's mom
QUEBEC, CANADA

My daughter Fera is five years old. She's energetic, imaginative, impetuous. She's learning her letters, how to use superlatives, and not to bite (I hope). She has cystinosis. When I have to explain her health condition to someone who doesn't know her, I always begin with: "She's mostly a typical kid, but..." I'm desperately eager for that to be true. She goes to a small preschool, she dabbles in sports and activities. She laughs, she cries, she goes to bed too late sometimes.

I let her take the lead on making sense of her health condition. So far, she doesn't seem to see herself as different from her peers. I think that's because, like all five-year-olds, she's taking in so much about the world. Once in a while, she'll stun me with a pronouncement or question related to cystinosis: "Not every kid gets the needle." (Referring to her nightly growth hormone injection.) Or, "Did you have a g-tube when you were a kid?" Our family friend donated a kidney in Fera's honour, and after we discussed this in front of Fera, she later asked, "Why did R____ give away her collarbone?"

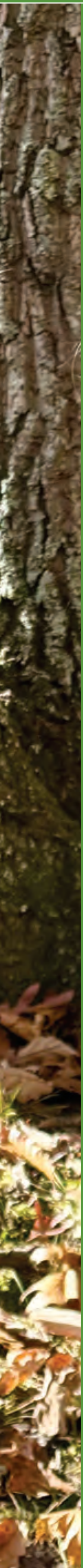
It took us a good two years to stabilize Fera – to limit her vomiting, get her eating, and to figure out a reasonable medication schedule. Travel is still tricky, but definitely easier. We have had to reckon with the fact that Fera does not seem to respond as well as hoped to cysteamine in terms of preserving her kidneys. Sadly, her function has deteriorated much more quickly than many other children in this community. In some ways, this slow revelation echoed her diagnosis: the questions, confusion, worry, guilt, and the sense of failure. But we've always given her her meds and followed directives from her doctors. For me it's a reminder of the little control I have over Fera, or anything, really. I can only love her and take care of her as best I can. I've learned I can feel more than one thing at a time. I'm sad and bitter about cystinosis, but at the same time, I'm grateful there is a treatment, even though it's imperfect, and that we have access to it. I'm grateful for the circumstances in my life that allow me to more or less care properly for Fera. I'm grateful for Fera. Since she was little, we've referred to her as a light bulb, for the way her sweet face breaks into joy at the slightest thing. (Other times a storm comes over it.)

I can't deny the toll her care takes on me. When I wake in the night to give Fera her meds, I can only describe how I feel as homesick. I'm so far from where I set out. I'm not exactly sure how I got here or where I'm going. Still, unlike Fera, I chose this. The fatigue and logistics don't help me to be the present and equanimous mother I admire. I aim for nonchalance. I pretend not to watch Fera eat. I offer her her water bottle and then look away as she chugs.

We never found the right moment to give Fera a sibling. She makes up for it with a rolling cast: currently her brothers are Broccoli and Pickle, and her sisters are Stripe and Aleda. She also has a real baby cousin she told me she loves twice as much as me.

Around the time of Fera's diagnosis, a mother of a teenager with cystinosis told me: "We never think about cystinosis!" For years I found that puzzling. But I've started to see what she means. If we're out for a picnic or a bike ride or on some excursion enjoying ourselves, other than alarms set for meds, and hauling water bottles, no one is thinking about cystinosis. Fera is infinitely more than her health condition.

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



Advice from Ten Years In...

Reflecting on the past decade, it's hard to believe how far we've come and how much we've accomplished. Over these years, we've hosted 10 Fishing for Brooke's Cure fundraisers, raising almost $400,000 for CRF in the fight against cystinosis. Ten years ago, our journey toward a diagnosis began, and today, Brooke is 10 years old and in her final year of elementary school.

Throughout this journey, we've learned countless lessons — and I know many more are ahead as we navigate life with a tween and look toward the future of cystinosis research. As we look back over the past decade, here are some key lessons we've learned that have made all the difference for us — and for Brooke:

01 Overshare with Your Child's School from the Start

When we first attended Brooke's PreK orientation, we made sure the school understood our reality: cystinosis, with all its tough truths, even though it didn't apply to Brooke at that moment. While it may have been overkill, it was critical that those responsible for her care understood how to support her. Being transparent from the beginning helped establish a foundation of trust. While we still advocate for Brooke's needs at school, the empathy and commitment from her teachers and staff have made a world of difference.

02 Advocate for Your Child — Loudly and Often

Over the years, we've often had to push for Brooke's needs, whether with doctors, teachers, or other professionals. There were times we feared coming off as overbearing, but in the end, advocating for your child's health and well-being is non-negotiable. As Brooke has gotten older, she's learned to advocate for herself, and we're proud to see her speaking up for her own rights now.

03 Treat Your Kids Like "Normal" Kids — *Because They Are*

Cystinosis is part of Brooke's story, but it doesn't define her. It's easy to fall into the mindset that her condition makes her different, but the reality is that she is just a regular kid. She deserves to be treated as such, without the label of "sick" overshadowing her. This has been a key lesson for us: don't let cystinosis take away the joy of being a kid, or the responsibilities of growing up.

04 Incorporate Your Kids into Their Medical Care When They're Ready

There's no rush. Every child's journey is different, and it's okay not to share everything about cystinosis with them right away. For us, this was a delicate balance. We spoke with other parents who had shared everything with their kids early on, and I wondered if I was doing something wrong by waiting. But as Brooke showed signs of medical anxiety, we realized she wasn't ready either. We didn't hide the truth from her, but we waited until she was mature enough to understand. Now, we have open conversations about her medications, diet, and what her treatments mean. She's even begun sharing her story with friends at school.

05 Lean into the Community

What you're going through, someone else has likely experienced too. Take advantage of the support systems around you. Whether through online cystinosis support groups or conferences hosted by CRF, connecting with other families can be incredibly comforting and empowering. Brooke has found tremendous comfort in developing friendships with other kids who have cystinosis, and I know these relationships will continue to be important to her as she grows and learns to manage cystinosis on her own.

06 Find Something, Anything, That Gives You a Sense of Control

For us, that was fundraising. Right after Brooke's diagnosis, we began organizing events — and we haven't stopped since. We don't raise huge sums every year, and our events aren't extravagant, but they are authentic to us. Fishing has always been a passion for Clay and his friends, so transforming a regular day of fishing into a competitive event for cystinosis research has become something we all look forward to. It gives us a sense of purpose and allows us to make a difference in a situation where we often feel powerless.

07 Don't Forget to Take Care of Yourself

You can't pour from an empty cup. Make sure you take time for yourself. Self-care looks different for everyone. For Clay, it's fishing. For me, it's working (yes, I truly love my work!). Whatever it is, carve out time to do those things — and remember, it gets easier as your kids get older. And never underestimate the power of sleep!

08 Have Faith

At times, this journey can feel overwhelming. But our faith in the researchers, doctors, and the mission of CRF has been our guiding light. Their tireless work toward a cure gives us hope, and that hope has carried us through some of the toughest days. Even when things seemed bleak, we've always known that we're not alone in this fight.

A lot has happened over these 10 years, and we are excited for the changes that the next 10 years are sure to bring. While we don't wish away the time, we recognize how close we are to a cure for all with cystinosis. We also know that without Natalie's wish — and her parents' determination to make it a reality — our journey would look very different. For that, we will forever be grateful.

As we look toward the next decade, uncertainties remain. But one thing is certain: CRF will always be part of our family, fighting alongside all those who share our goal — to make a cure and better treatments for cystinosis a reality.

We are different people than we were a year ago.

Sierra Thrives

By Mariah and Ryan Hub, Sierra's parents FORT WASHINGTON, MARYLAND

Sierra Shines

Our first child Sierra was born in June of 2022, and by all accounts she was a typically developing little girl. She was born full-term, 7lbs. 7 oz., 21 in., and passed all initial screenings. We had no reason to believe there was anything atypical in her development. We were sent home and ready to start our new adventure together as a family of three.

Things started to change at about 9-12 months when we noticed she started developing feeding difficulty, either refusing food/milk or eating and throwing up daily. She was referred to a GI specialist at Children's Hospital in Washington, D.C., thinking maybe it was a GI issue. Lab work revealed Sierra had Stage 3 CKD. She was admitted to the hospital for a full work up.

As first-time parents, we were terrified. We knew something was wrong, but when every physician was telling you it's normal and "she's just a picky eater," you start to believe them. We remember sitting with her, meals taking 3-4 hours to eat a tablespoon of yogurt. We tried everything we could think of—a high chair, sitting on the ground or couch, lights on, lights off, music, TV, no distractions, eating with family, eating with one parent, different textures, temperatures—everything.

We spent two weeks in the hospital learning everything Sierra didn't have and finding very few answers as to why she was categorized as failure to thrive. We met with every discipline and finally nephrology had an answer: cystinosis. We could feel the tension as we sat in a family support room with every member of the care team from medical students to social workers. We were advised that our daughter had a rare disease that approximately only 2,000 people worldwide have. We were told our journey would be difficult, her quality of life would be poor, she would need hourly medications and a kidney transplant in her early teens, and she would have a shorter life span than her peers without the disease. We had no words. We felt isolated and alone and had all these emotions with few people that truly knew how we felt.

It has been 18 months since Sierra's diagnosis. While there are still challenges, life has gotten immensely better for Sierra and dealing with the disease. The medicines become routine, and her energy levels are the same as a normal toddler. We know there will be new challenges in the future, but we are fortunate for every day we have with Sierra and know she will be able to handle anything new like when she first did 18 months ago.

We are different people than we were a year ago. We are at a point where Sierra is thriving. She happily takes her medicine and eye drops, and talks about becoming a doctor one day. A year ago, we never thought this would be possible. We couldn't leave the house because she would vomit daily, sometimes multiple times a day. We had to cancel plans and decline party invitations because each day was a toss-up on whether she would be sick or not. Now we are at a point of stability. We see her personality shine. She's goofy and playful and has a way with words.

We are thankful for the entire CRF community. These were some of the first people we were connected with post-diagnosis and stories like this in the CRF magazine were some of the first things we read. For new parents with children with cystinosis, it may seem hard to believe (as it was with us), but things do get better.

By Ashley, Duncan and Graham McAllister, Isla's family OKLAHOMA CITY, OKLAHOMA

So Grateful

for our small *but mighty* village

Our story with cystinosis began like so many others in the community. A routine well child check up with our pediatrician showed a sharp drop off in height and decrease in weight. We began the journey of doctor appointments with various specialist visits. That ultimately led us to a pediatric genetics specialist who ordered full genetic testing for our daughter Isla. We received our official diagnosis in February 2022.

The first year was certainly the hardest. From the g-tube placement to formulating Isla's medicine and eating schedule all while trying to maintain the everyday aspects of our lives. The world does not stop spinning when your child receives a diagnosis that completely changes what their life and your life will look like. We were able to battle through the ups and downs of those early months and eventually ended up with our first hospitalization in November 2022 due to multiple viral illnesses and dehydration.

We decided from an early stage that cystinosis was not going to define who our sweet Isla is and that we are going to do everything we can to not let this limit her. Looking back, it almost seems like that hospitalization marked a turning point for us. Isla was able to bounce back and continue to catch up on her growth through the following year. Isla started preschool in the fall of 2024. School was a big change, but she has been thriving. She enjoys music class and, of course, recess. Isla played on a soccer team in the fall, and she is also in ballet and tap dance class with a recital coming up this May. We understand that challenges lie ahead, but we are committed to providing Isla with as many positive experiences as possible.

We attended our first CRF conference in 2023 and were blown away by the community of families. The often-summarized description of this amazing group of people, "small but mighty" could not be more precise. Scientific research is a long process, and we left the conference knowing that we wanted to do our part in carrying the torch for those that come after us. We now host an annual pickleball tournament in Oklahoma City that will be in its third year this winter. The fundraiser has seen two years of growth coming almost entirely from family and friends. While we have learned many things in the first few years of what will be a long road, advocating for Isla and those in the cystinosis community is our top priority.

Raising children truly takes a village and having a child with cystinosis makes that statement even more evident. We are so thankful for our family, friends, teachers, health care team and cystinosis community.

We want to do our part in carrying the torch for those that come after us.

By Amelia Wesselink and Tim Maher, Ayla and Otto's parents ROSLINDALE, MASSACHUSETTS

positivity & creativity

In writing this piece, we relied on two of our kids' strongest traits: Ayla's positivity and Otto's creativity. We want to share the positive and hopeful things that have happened in our lives and in our family since our kids' cystinosis diagnoses (Ayla at age 2 and Otto at 11 months).

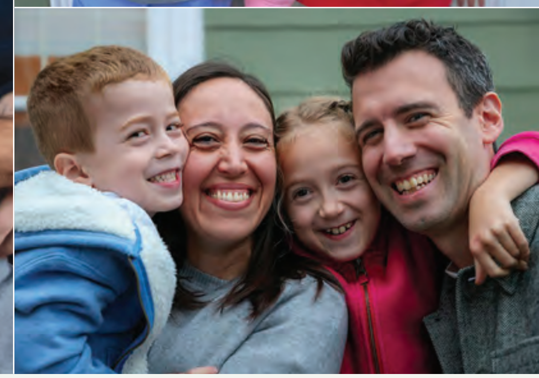
Our kids have so much compassion for others. Their experience with cystinosis has allowed Ayla and Otto to develop a wonderful ability to recognize others' feelings and empathize with them. Whether they are consoling a classmate, helping their cousins do their medicine, or reminding us to take deep breaths when we are upset, their emotional intelligence is next level.

They are the most medically savvy kids. Otto walks into the phlebotomy lab at Boston Children's like he owns the place, sits down in the chair, and rolls up his sleeve. Ayla has started to explain cystinosis to her friends. They ask questions about their medicines and what they do. We can talk to them about scientific research and clinical trials.

They know their bodies and know how to advocate for themselves. They are great at listening to their bodies. At the end of dinner, they ask, "Belly, are you really all done?" They appreciate their bodies and all that their bodies can do. Talking about cystinosis has also led to conversations about body positivity and diversity – that all bodies work in different ways, and that all bodies are wonderful.

Their love for each other is boundless. They help each other through the parts of cystinosis that are hard – the medicine, the eyedrops, the doctor's appointments, the hospital visits. Otto recently had his tonsils out, and he spent much of his recovery on the couch snuggling with Ayla while she read to him. We love hearing stories from their school nurse about when their paths cross in the nurse's office and they chat and joke with each other for a while. They love teasing their nephrologist, Dr. Traum, together – they have an ongoing joke about how he is (or is not) secretly Batman.

Just take a deep breath.



They will get to chart their own path without the weight of their parents' expectations.

We met so many wonderful families through CRF. We went to the CRF family meeting for the first time last year. We were nervous, but the connections we have made through CRF have been invaluable. We exchange regular emails with Nancy, Clay, and Jill about ongoing cystinosis research. We met up with the Emersons in New Jersey last summer. Ayla recently told me that her favorite thing about having cystinosis was meeting new friends – she loves to talk about Brooke, Emma S., Emma D., and Josie. We can't wait to see everyone at this year's meeting.

Cystinosis has changed how we think about our kids' future. That may sound grim, but we do not mean it in a negative way. As a parent, it is easy to fall into patterns of having set ideas or expectations about what our kids' lives will look like – what activities they will do, what their jobs will be, what their future families will look like. But cystinosis has allowed us to shed some of these expectations. We hope that this will be a good thing for Ayla and Otto: that they will get to chart their own path without the weight of their parents' expectations.

Our family is stronger because of our cystinosis journey. Dealing with the challenges of parenting kids with a chronic illness has forced us to strengthen our communication – a skill that has tremendously benefited our marriage. Our family has had to build trust with each other and an openness and honesty about our physical and emotional well-being in ways that perhaps we would not have without a challenge like cystinosis. And we have found unbelievable strength and resilience in our community – our extended family, our friends, our medical teams, and other cystinosis families.

It is not all sunshine and rainbows over here. The tough times tend to come in waves: sometimes cystinosis feels all consuming, whereas other times it is very much in the background. As our family battles through the ups and downs that come with cystinosis, we'll take the small victories where we can.

MY NEW BEGINNINGS

Hello Cystinosis Community,

Since my last update a few years ago, I completed my nursing classes as an LPN (Licensed Practical Nurse) in June 2023. After I completed my classes, I moved provinces in Canada from Alberta to British Columbia (BC) to live closer to my family on Vancouver Island.

It's always 'fun' moving – especially dealing with the unexpected medical mysteries that are unknown on the other side. For instance, what drugs are covered in another province? How do I find a cystinosis specialist in my area now that I am an adult? And what about a kidney transplant doctor?

As I had guessed and hoped, all the unknowns seemed to work themselves out in time. Even my pharmacist at the Alberta Children's Hospital told me she wasn't worried about me because she knew that I was resourceful and that I am a good advocate for myself and will find the right answers. I believe the key to success for all adult cystinosis patients is that we learn in our own time.

At times, it feels like a long journey, but over the past year and a half, I feel like I finally have my bearings. I have my new doctors and my new career as an LPN – things feel established now. However, working full time and with a constant nursing rotation of 4 days on and 2 days off, I only have one real weekend (Saturday and Sunday) off a month! That schedule did not leave much room for work/life balance.

So, I am changing jobs! Beginning the first of April, I started a new job. The job is on the other side of the island in Sidney BC. I will work as an LPN at a retirement community. I am looking forward to having the weekends off!

I am also moving into a condo that is near where my sister lives. It is also close to my new job, so that is very nice and handy.

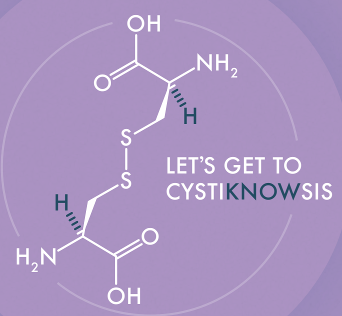
I am looking forward to attending the Day of Hope Conference in April, too!

–Heather Wegerif

all the unknowns seemed to work themselves out in time.

FOLLOW YOUR HEART

RESEARCH UPDATES



THE REWARD OF COMMITMENT

BECAUSE OF **YOU,** WE ARE ONE STEP CLOSER TO A CURE FOR EVERY PERSON WITH CYSTINOSIS!

We are thrilled to share news about the next phase of the stem cell and gene therapy trial. This phase of the trial will bring us closer to a cure for all children and adults with cystinosis. The CYStem Phase I/II clinical trial is open to children aged 2 to 5 years with nephropathic cystinosis.

Make no mistake, the road to the cure has required hard work, millions of dollars, and the unwavering commitment of families, patients, friends, and researchers. Without CRF's early and continued financial commitment to Stéphanie Cherqui, PhD, this extraordinary news would not be a reality today. Since 2007, CRF has funded over $6.6 million in grants to Dr. Cherqui and because of our support, other funding agencies including the California Institute for Regenerative Medicine (CIRM) and the National Institutes of Health (NIH) have supported Dr. Cherqui's work leveraging CRF's early research dollars.

Dr. Cherqui has dedicated her career to finding a cure for our children and adults with cystinosis. It is CRF's partnership with Dr. Cherqui that has brought our wish for a cure from a possibility to reality. She has been our guiding light - our beacon of hope - and we are incredibly grateful.

A very special thanks to the five adults with cystinosis who pioneered this treatment. They risked so much on behalf of this entire community, and their participation and the successful data from their phase of the trial led to this important phase of the stem cell trial.

It is with gratitude that we thank Novartis and their cystinosis stem cell and gene therapy group for their commitment to our community, for listening to our voices about the burden of disease, quality of life, and clinical trial design, and most importantly, our plea to move quickly to ensure this treatment is approved for all those with cystinosis. We look forward to continuing to work with them during this next and critical phase of the stem cell trial.

See the important COMMUNITY UPDATE *from* NOVARTIS on the next page. >

Novartis CYStem Phase I/II Clinical Trial in Cystinosis

Dear Cystinosis Community,

We are pleased to share details about the CYStem clinical trial, which was recently published on *ClinicalTrials.gov.*

What is CYStem?

CYStem is an open-label, multi-center, Phase I/II study to assess safety, tolerability and efficacy of DFT383 in pediatric participants with nephropathic cystinosis. Novartis has partnered with cystinosis patients, their caregivers and patient organizations to guide the design of this trial and have included their feedback wherever possible.

How will the trial work?

The purpose of the study is to investigate if DFT383 is safe and effective in children aged 2-5 years who have nephropathic cystinosis. DFT383 is a cellular gene therapy. A standard of care (SoC) group will also be enrolled, in which children will not receive study treatment, and will continue treatment with standard of care (i.e. cysteamine). The information from this SoC group will be used to better understand the disease and the results observed in the children receiving DFT383. The two groups will be run at the same time. Investigational sites may participate in one or both groups.

Who can participate?

- The trial aims to include approximately 30 participants.
- Approximately 15 participants will receive treatment with DFT383 in 3 groups (1A, 1B and 1C) dosed in a staggered approach. The total study duration for a participant in Group 1 will be up to 32 months for the primary study period.
- Approximately 15 participants meeting similar inclusion/exclusion criteria and receiving SoC will be enrolled. The Schedule of Activities will be reduced for this Group 0. Group 0 is not a direct control but will provide essential context for interpreting the results observed in the participants receiving DFT383. The total duration for a participant in Group 0 will be up to 24 months.
- Recruitment will start in the second quarter of 2025.
- There will be various trial locations which continue to be added over the next several months.

What are the key criteria for participation?

- Key Inclusion Criteria:
  - Informed consent in writing from parent(s) or legal guardian(s) must be provided
  - 2 to 5 years of age (including 5 years and 364 days old) at Screening
  - Weight-for-stature is ≥ the third percentile and is ≥ 10 kg
  - Oral cysteamine therapy for at least 6 months
  - Clinical diagnosis of nephropathic cystinosis
  - Laboratory evidence of renal Fanconi syndrome (RFS)
  - Preserved kidney function (eGFR ≥ 90mL/min/1.73m2)
  - Received all age-appropriate vaccinations

>>>>

Dr. Stéphanie Cherqui, *Pioneer of Stem Cell and Gene Therapy Clinical Trial for Cystinosis, University of California, San Diego*

Daniel Grant, *Vice President & Global Program Head, Novartis Global Drug Development, Neuroscience & Gene Therapies Unit*

Dr. Melissa Wigderson, *Global Program Clinical Head, Novartis Pharmaceuticals*

What are the key criteria for participation? *(continued)*

- Key exclusion Criteria for Group 1 and 0:
  - A history of kidney transplantation
  - A prior or planned bone marrow or stem cell transplantation or prior treatment with gene therapy
  - History of malignancy
  - A severe or uncontrolled medical disorder
  - Major surgery within 90 days
- The following exclusion criteria only apply to Group 1 only as they are important for procedures related to DFT383 treatment:
  - Indomethacin within 2 weeks prior to Screening

What are some of the key things the study is looking to assess?

- Key criteria for both Group 0 and Group 1:
  - Adverse events and serious adverse events
  - Physical exam, blood and urine test, electrocardiogram, vital signs
  - Caregiver interview
  - Cystine levels in white blood cells and in the cornea
  - Oral and ophthalmic cysteamine use
- Key criteria for Group 1 only as they are related to DFT383 treatment:
  - Blood cell count normalization
  - Lentivirus in blood
  - Malignancies
  - Reversal of Renal Fanconi Syndrome

Patients and caregivers interested in enrolling in the study should reach out to their primary physician. In the meantime, we look forward to a successful start to this important trial and will be in touch with any further relevant updates.

Kind regards,

The Novartis CYStem Cystinosis Study Team

Novartis Pharmaceuticals
1-888-NOW-NOVA
(1-888-669-6682)
novartis.email@novartis.com

This statement is not intended to establish any legally enforceable rights, obligations, or commitments on Novartis.

CELL AND GENE THERAPY (CGT) CLINICAL TRIALS

Drug Development Explained

BY BETTY CABRERA, MPH

DIRECTOR OF RESEARCH ENGAGEMENT AND OPERATIONS
UNIVERSITY OF CALIFORNIA, SAN DIEGO — GENE THERAPY INITIATIVE

THE WORLD IS ON THE VERGE OF ENTERING PHASE 3 CLINICAL TRIALS FOR A GROUNDBREAKING CELL AND GENE THERAPY (CGT) TREATMENT FOR CYSTINOSIS.

Considering that CGT products often take 5-10 years longer to develop than traditional drugs, it is remarkable that the timeline for the early stages of cystinosis CGT, led by Dr. Stéphanie Cherqui at the University of California, San Diego, has closely aligned with that of traditional drug development.

This achievement is a testament to the unwavering hope and support of the cystinosis community, a well-executed long-term strategy, and a plan for accelerated approval. These factors will be key in making it possible to achieve a medical breakthrough for patients sooner.

We hope this information provides insight into the drug approval process and highlights the remarkable progress made in developing cystinosis CGT.

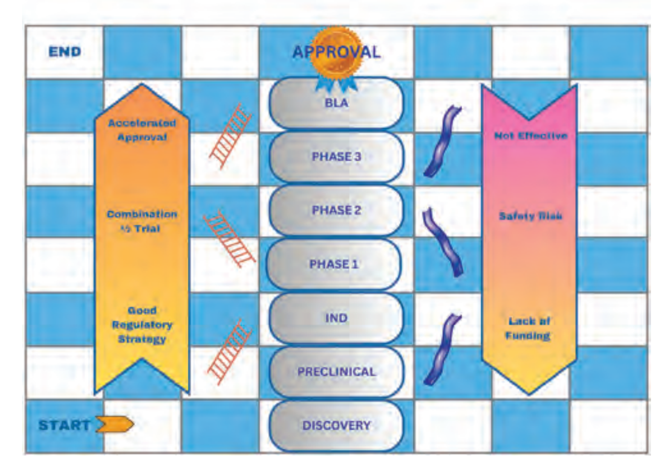
WHY DOES IT TAKE SEVERAL YEARS FOR A DRUG TO FIND ITS WAY TO PATIENTS?

The development pathway for drugs can be confusing and lengthy, especially where CGT products for rare disease are concerned. What follows is a break down to explain what happens along the way.

Drug developers collect different types of data or evidence that a drug is a) safe or not harmful, and b) effective, or that it cures a disease or reduces symptoms in most people who might take it. They submit the collected data to the Food and Drug Administration (FDA) several times along the way. For instance, they submit data in an Investigational New Drug (IND) application to gain approval to test the drug in people, and in a Biological License Application (BLA) to gain approval for the drug to be prescribed to patients. The FDA reviews evidence to determine if a drug's potential benefits outweigh its risks.

The development process from drug discovery to approval can be visualized using the classic children's board game Chutes and Ladders. Each space on the board represents a step that drug developers must take to demonstrate a drug's safety and effectiveness. They must pass through ordered stages or phases of testing and FDA evaluation to advance a drug candidate to the next level. Information about what must happen at each stage can be found in the table.

Setbacks can send a drug candidate down a "chute", requiring additional work and delays. Short chutes, such as the requirement to add a sub-study and collect data not originally planned for, can be minor setbacks. However, long chutes, such as a FDA clinical hold that can be issued when significant safety concerns exist about the drug or how the trial is being conducted, are major setbacks and make advancement very difficult. It is critical for drug developers to strategize carefully not only to avoid the chutes, but also to arrive at "ladders" that bypass spaces or steps and accelerate passage. [More on ladders in the next Q&A.]



CGT products and rare diseases pose unique challenges, making the development process riskier and longer. Rare diseases require case-by-case evaluation to determine the best suited tool in the gene therapy toolbox that should be used. The FDA's standards for judging CGT safety and effectiveness are still evolving, and manufacturing these products can be complex and expensive. Selecting the optimal dose range and finding suitable sites to conduct the trial can also be challenging. Clinical trial sites must have specially trained personnel with experience handling and delivering CGTs. Sites also need the appropriate medical expertise to monitor safety and treat patients for any negative responses to CGTs. Additionally, patient enrollment can be slow due to the limited number of people with the condition and the even smaller pool of people who meet the strict entry or eligibility criteria.

AREN'T THERE WAYS TO SHORTEN THE PATHWAY TO DRUG APPROVAL FOR RARE DISEASES?

There are certainly "ladders" that can accelerate the passage to approval. The variety of ladders can include a well-designed clinical trial, a strong strategy for navigating the FDA rules and regulations, and a plan for adequately funding all aspects of drug development.

Phase 1 and Phase 2 trials are often combined in CGT trials for rare diseases to minimize patient exposure and reduce the risk of long-lasting effects. Phase 1/2 trials can accelerate the development process, but they also pose a challenge: selecting a dose range that is neither too low nor too high based on limited available information. If the dose is too low, it may not be effective, while a dose that is too high may cause severe side effects in vulnerable patients. Careful planning is required to avoid these possible "chutes."

The FDA Accelerated Approval (AA) pathway is a ladder that allows for conditional approval of products for devastating, progressive rare diseases. This pathway accepts data about predictors of clinical outcomes or of disease improvement, called surrogate endpoint and biomarker data, enabling patients to access potentially helpful products sooner. However, drug developers must still collect and submit long-term data to obtain

continued on next page >

full FDA approval and answer the pivotal question in the Phase 3 trial: does the treatment give the desired clinical outcome? The reason AA is needed is that the ideal period for collecting pivotal trial data from a patient in Phase 3 is one to two years, yet it often takes longer than that to see sufficiently significant improvements in a patient's physical condition or clinical outcome.

Given that a rare disease may affect patients with the same diagnosis differently, determining the most reliable, easily measured outcomes that provide the earliest possible information about drug effectiveness can be difficult. If the outcomes chosen for measurement are not solid, a chute could lead back to square one. Alternatively, if the outcome chosen is reliable and indicates marked improvements, there may be a ladder to the jackpot – FDA approval. The conditional approval allows drug developers who struggle to manage the high cost of conducting CGT clinical trials to defer certain development costs, get a drug temporarily across the finish line and recoup funds.

WHY ARE ONLY CERTAIN PATIENTS ELIGIBLE TO PARTICIPATE IN A CLINICAL TRIAL?

Clinical trials often have strict eligibility rules or criteria to minimize risk and ensure consistent data. The "golden rule" in clinical research is to enroll the fewest number of patients necessary to obtain required data. This means that patients with advanced disease and tissue damage may be excluded because certain aspects of the disease are unlikely to improve in a significant and measurable way during the short course of the trial. The aspects of a rare disease can also show up differently among patients making collection of consistent data difficult and leading to a decision to narrow eligibility criteria to a sub-group with certain disease characteristics. The FDA or Institutional Review Board (IRB) at a particular trial site may also require testing in adults before children for safety reasons.

While this narrow eligibility approach may seem exclusive, it can lead to approval in a sub-group of patients and provide an opportunity for drug developers to replenish resources and build upon successful operations. A win can be literally game-changing in the sense that the next round of drug development or approval applications will be on a slightly different game board with the number of ladders outnumbering chutes. This approach can ultimately lead to more inclusive trials and access to the drug for a broader range of patients.

IS DRUG DEVELOPMENT OF THE CGT CALLED CTNS-RD-04 FOR CYSTINOSIS MOVING AT AN ACCELERATED PACE?

There have been several accelerating ladders at different stages for CTNS-RD-04 drug development that are summarized in the table below. The funding from the Cystinosis Research Foundation was crucial for Dr. Stéphanie Cherqui to determine which CGT tool would work best for cystinosis. It also helped her find out why it worked (called the mechanism of action) which would be important for approval of the IND application to test it in people. This was equally important for securing funding through grant applications that would cover the high expenses to conduct the complex Phase 1/2 trial proposed. The strategy to combine the Phase 1 & 2 trials and select the proper dosing, eligibility criteria and measurable outcomes was critical for collecting data on safety and effectiveness that would be compelling enough for pharmaceutical companies to be interested in developing Phase 3 of the trial.

Ultimately, the pharmaceutical company Novartis will make sure that the final product to be included in the BLA for FDA approval will be manufactured in a way that meets industry standards and is more accessible to patients across the country. Steps taken up to this point may also help secure AA for the cystinosis CGT product. This is key for speeding up the approval process and paving the way for availability of this therapy to many more cystinosis patients.

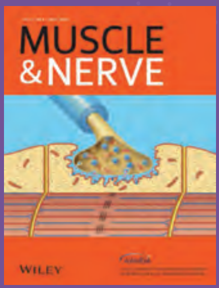
See important "ladders" and their impact on next page. >

The funding from the Cystinosis Research Foundation was crucial for Dr. Stéphanie Cherqui to determine which CGT tool would work best for cystinosis.

LADDER	IMPACT
CRF funding of Proof of Concept studies	- Provided critical funding when none was available from other sources - Laid the foundation for a gene therapy approach that could make a competitive grant from a government funding agency
CRF funding of Cystinosis Patient Registry for natural history data that help determine clinical outcomes, surrogate endpoints and biomarkers for trial	- Provided compelling data to include in the IND application that the outcomes selected for testing in the Phase ½ trial would be acceptable to the FDA
CIRM funding for Preclinical and Phase 1/2 trial conducted at the University of California, San Diego	- Trial conducted at an academic center with a CIRM designated Alpha Clinic, which was a positive feature to take into consideration for CIRM funding for the trial - Helped to de-risk the trial and attract pharmaceutical companies with the required resources to conduct a larger Phase 3 trial
Sub-licensing of product to industry	- Allowed an expert team to develop the regulatory strategy for a Phase 3 trial that could lead to Accelerated Approval - Expanded the age range to test drug in children

RECENTLY PUBLISHED STUDY

We are proud of CRF-funded researchers who have published 113 articles in prestigious research journals since 2003.



MUSCLE AND NERVE
VOL. 71 / NO. 4 / **APRIL 2025**

By Reza Seyedsadjadi, MD
Department of Neurology
Massachusetts General Hospital
Boston, Massachusetts

PROSPECTIVE DYSPHAGIA ASSESSMENT IN ADULT PATIENTS WITH NEPHROPATHIC CYSTINOSIS

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 Dr. Reza Seyedsadjadi and his colleagues for this publication and for his dedication to the children and adults with cystinosis.

To access all articles published, visit:
www.cystinosisresearch.org/published-studies

Ninth International Cystinosis Research Symposium

SPONSORED BY cystinosis RESEARCH FOUNDATION

by Stephen L. Jenkins, MD
Sam & Lars Hope for a Cure
CRF Board of Trustees
CRF Scientific Review Board

On March 6 and 7, 2025, more than 40 researchers from seven countries gathered in Irvine, California, for the 9th Cystinosis Research Symposium. It was exciting to see new researchers joining the field and to witness the progress being made in translating research from the lab to patient care.

Dr. Melissa Wigderson from Novartis Pharmaceuticals gave the keynote address on the development onasemnogene abeparvovec-xioi, a gene therapy for spinal muscular atrophy. This gene therapy uses an adeno-associated virus (AAV) to deliver functional copies of the mutant gene to motor neurons. This gene therapy was approved by the FDA in 2019, and since that time more than 4,000 patients have been treated. Importantly, Novartis Pharmaceuticals purchased the cystinosis gene therapy program, and Dr. Wigderson will oversee the clinical trials of gene therapy for cystinosis.

Dr. Stéphanie Cherqui presented her research on the Phase 1/2 clinical trial of autologous hematopoietic stem cell gene therapy for cystinosis. Six participants, ages 20-46 years, were transplanted, and Dr. Cherqui now has follow-up data up to 63 months on the first patient. White blood cell cystine and tissue cystine crystals in skin and rectal mucosa have decreased compared to baseline. Patients 1 and 3 have experienced improvement in muscle strength and motor coordination. Patients 4 and 5 have low vector copy numbers and have restarted a low dose of cysteamine therapy. She is applying the same gene

Dr. Melissa Wigderson, Keynote Speaker

therapy design to other rare genetic diseases, like Friedreich's ataxia and Danon disease, as well as much more common diseases like Alzheimer's.

Beyond gene therapy, other regenerative medicine approaches are in development. Dr. Paul Goodyer discussed mRNA therapy, pioneered by Moderna for vaccines, as a potential way to restore cystinosin production. Transfecting patient-derived cells with normal cystinosin mRNA resulted in increased protein production, reduced cystine levels, and improved autophagy. Moderna is already advancing mRNA therapies for other rare diseases in Phase 2 trials.

Dr. Benjamin Freedman's research on induced pluripotent stem cells (iPSCs) and kidney organoids showed promising results. By using CRISPR to correct the CTNS gene in iPSCs derived from cystinosis patients, he created kidney organoids that integrated into mouse kidneys, potentially paving the way for future organ regeneration.

Repurposing FDA-approved drugs for cystinosis treatment is a promising strategy. Dr. Alessandro Luciani and Dr. Olivier Devuyst used artificial intelligence to identify drug candidates. MTORC1 inhibitors like sirolimus showed potential but had significant side effects. SGLT-2 inhibitors such as dapagliflozin, already approved for adults with chronic kidney disease and proteinuria, improved lysosomal function and proximal tubule health in preclinical models.

Dr. Francesco Emma and Dr. Esther De Leo tested genistein, a supplement that lowered cystine levels in cystinosis knockout mice but failed in rats, suggesting limited human applicability. Dr. Sergio Catz screened drug libraries and identified candidates that enhance autophagy, including an FDA-approved drug for kidney disease. His lab is also studying chronic inflammation's role in cystinosis and potential anti-inflammatory therapies.

Dr. Bruce Barshop is investigating different prodrug versions of cysteamine. Prodrugs are designed to be activated within the target cell or organ so that there are fewer systemic side effects. One of the prodrugs he studied successfully lowered cystine levels in fibroblasts, but it had toxic side effects and killed the cells. Dr. Herbie Newell and Dr. Jennifer Hollywood are investigating another cysteamine prodrug called CF10 that is safe and effective in animal models.

Dr. Liang Feng studied cystinosin protein conformations and proposed using small molecules to enhance its open state for better cystine transport. Dr. Ming Li identified a rare cystinosis mutation

Cystinosis Research Foundation's Scientific Review Board at the Ninth International Cystinosis Research Symposium (L-R): *Francesco Emma, MD; Larry Greenbaum, MD, PhD, FAAP; Benjamin Freedman, PhD; Olivier Devuyst, MD, PhD; Stéphanie Cherqui, PhD; Sergio D. Catz, PhD; Stephen L. Jenkins, MD; Julie R. Ingelfinger, MD; Aude Servais, MD, PhD;* Not Pictured: *Paul C. Grimm, MD*

causing rapid protein degradation and successfully stabilized it with a chaperone drug, potentially enabling precision medicine for similar mutations.

We talk a lot about new medications for cystinosis, but what about dietary approaches? Dr. Francesco Bellomo shared an update on the use of ketogenic diet in cystinosis, which they have studied in both knockout mice and rats. If started early, the ketogenic diet could prevent the development of Fanconi syndrome. The diet also increased production of proteins involved in muscle regeneration, suggesting there may be a role for muscle disease as well. The diet has yet to be studied in humans with cystinosis, but Dr. Francesco Emma plans to do a trial soon.

Dr. Lauren Albrecht is studying the way different lysosomal metabolites may affect the pathogenesis of kidney and bone disease in cystinosis, and whether restoring normal levels of these metabolites outside the lysosome may improve cell function. Dr. Olivia Pagliarosi and Dr. Andrea Del Fattore examined Pepstatin A, a cathepsin D inhibitor, which increased bone mass and density in cystinosis knockout mice. They also found that cysteamine is toxic to osteoblasts, potentially explaining bone fragility in patients.

Dr. Maren Leifheit-Nestler shared an update on her lab's research on musclin, a muscle-derived myokine that impedes muscle atrophy and is highly expressed during exercise. They measured musclin levels in 35 patients with cystinosis, and they are significantly reduced compared to healthy controls. Musclin could be used as a biomarker to assess treatments for myopathy, or it may be a target for treatment itself.

Dr. Aude Servais and her team used whole-body MRI to assess 47 muscles in cystinosis patients, identifying tongue, trapezius, deltoids, forearm extensors, soleus, and gastrocnemius muscles as the most affected. MRI findings correlated with swallowing and respiratory issues, providing a valuable tool for assessing future treatments.

Dr. Reza Seyedsadjadi is conducting a clinical trial to improve swallowing function in cystinosis. He is recruiting 30 adults for randomized interventions, including respiratory therapy, tongue muscle exercises, and behavioral feedback training, aiming to identify tailored therapies for dysphagia.

The symposium showcased the remarkable scope of cystinosis research. From gene therapy to dietary interventions and drug repurposing, scientists are pursuing multiple avenues to improve patient outcomes. Despite political challenges to research funding, the Cystinosis Research Foundation continues to support these efforts, thanks to dedicated fundraisers and generous donors. The progress being made gives families like mine hope for a brighter future.

NEW INSIGHT FOR THE FIGHT

USING HUMAN STEM CELLS AND SPECIALLY ENGINEERED MICE, DR. BENJAMIN FREEDMAN SEEKS MORE "AMAZING PROGRESS" IN THE BATTLE TO PROTECT AND RESTORE KIDNEY HEALTH.

by Dennis Arp

Researchers know all too well that cystinosis packs many tools of destruction as it targets patients' kidneys. So why does Dr. Benjamin Freedman exude confidence as his lab pursues breakthroughs?

It turns out Dr. Freedman is developing potent weapons of his own in the fight against cystinosis.

"We're applying a suite of powerful next-generation research tools to get a deeper understanding of the disease and expand treatment options that improve the lives of cystinosis patients," says Dr. Freedman, Associate Professor of Medicine in the Division of Nephrology at the University of Washington.

For more than 17 years, Dr. Freedman has focused on kidney-related research, drawing inspiration from his uncle's brave battle with nephrotic failure – a journey that included two kidney transplants.

Energized by transformational funding provided by the Cystinosis Research Foundation (CRF), Dr. Freedman is blazing promising pathways into research realms full of possibility. He's finding insights in kidney organoids that resemble small human kidneys while he also mines the potential of regenerative cells.

"We've made some amazing progress," Dr. Freedman says.

Powering his lab's cutting-edge work are formidable advancements like mouse mutants, CRISPR gene editing and human induced pluripotent stem (iPS) cell lines. His latest project will build on the lab's seven years of CRF-supported research by testing to see if a new form of programmed cell death is causing cystinosis.

"We want to know if treating these cells with gene therapy can alleviate debilitating symptoms," Dr. Freedman adds.

BIG HOPES FOR THERAPY

He's focused on two paths to therapy. The first seeks insights by studying the disease in patients' cells – essentially using the cells as avatars in hopes of testing out new treatments. The second line of inquiry pursues the potential to regenerate healthy new tissue using patients' own stem cells.

"So, it's a two-pronged approach, but the centerpiece of both is these amazing stem cells," Dr. Freedman says.

On the regenerative side, Dr. Freedman and his lab team are implanting cystinosis cells into the kidneys of a new type of cystinotic mouse – one capable of accepting human tissue grafts. Those grafts then will be examined for signs of new healthy kidney tissue as well as for any lingering symptoms of cystinosis.

"The biggest finding we've observed so far is that the host animals can send blood vessels into these human tissue grafts and form chimeric structures – tissue that resembles vital kidney filtration units called nephrons," the professor says.

A key facet of his research progress is its move from a petri dish to a living host animal.

"We need this new context for the stem cells to mature and form kidney tissue," he notes.

To gain the knowledge that might lead to better treatments, Dr. Freedman and his colleagues also need the cells in a condition that allows them to become loaded with cystine, which can damage cells over time.

"From studying the 20 or so individual patient lines we now have, we can see these cells get sick if they have the mutations that cause cystinosis," he says.

IN PURSUIT OF THERAPEUTIC RESPONSE

There's an overarching upside to amassing such insight. In this case, it empowers the researchers to develop a potentially powerful therapeutic response based on a gene-editing methodology.

"Because we're exploring the potential of putting a healthy copy of the cystinosis gene back into these cells, I sometimes think about this as a three-step plan," Dr. Freedman says. "It starts with us making cells that come from a person, and those cells all have cystinosis. Then we introduce a second piece of the plan – a healthy copy of the cystinosis gene. Finally, we can implant the improved cells into the kidneys, where they have a chance to form new healthy tissue that restores function."

WE HAVE A VIBRANT GROUP OF DIFFERENCE MAKERS IN MY LABORATORY WHO ARE WORKING EVERY DAY ON CYSTINOSIS, WITH LONG CAREERS AHEAD OF THEM, AND THAT WOULD NOT BE POSSIBLE WITHOUT CRF.

Dr. Freedman has already seen enough positive results to get him excited about the project's long-term success. The team has engineered a special mouse that accepts human cells. Plus, he's extremely impressed with how seamlessly the cell structures form inside the kidneys.

"These advances are all on top of how well we can now get cystinosis to happen in a dish," he adds.

However, the researchers are still hotly pursuing their ultimate breakthrough: functional rescue of cystinosis.

"That's the holy grail," Dr. Freedman says.

NEW VISTAS OF OPPORTUNITY

But beyond his lab's work to protect and restore kidney health, their research is opening new boundary-stretching opportunities.

"The engineering of an immune-tolerant animal is big because it can also be used as a general tool," the professor says. "In fact, all of these advances – the mouse strains, the cell lines, even the gene therapy tools – are resources the wider research community can use. Maybe someone else wants to try a different type of cell, or to study the eyes instead of the kidneys."

Dr. Freedman notes that there is still much to be learned about the mechanisms of cell death in cystinosis and other diseases.

"It's a very generalizable topic; it's believed those mechanisms contribute to a wide variety of disorders but especially to the Fanconi syndrome that is observed in cystinosis," he says. "I think the lessons we take from the research on cystinosis can be a power multiplier for those who study other disorders."

In a similar way, CRF support has "monumentally" amplified the impact of his lab's investigations over the past seven years, Dr. Freedman says.

"We have a vibrant group of difference makers in my laboratory who are working every day on cystinosis, with long careers ahead of them, and that would not be possible without CRF," he enthuses. "It's also been extremely rewarding to meet the community of people CRF brings together."

Though the work can be complicated, the source of inspiration is not.

"I try to put a bit of pressure on our team because folks are waiting for us to help cure this disease," Dr. Freedman says. "Everyone in the lab feels that sense of urgency."

Benjamin Freedman, PhD
Associate Professor, Department of Medicine, Division of Nephrology
UNIVERSITY OF WASHINGTON — SEATTLE, WASHINGTON

INVESTIGATING THE MYSTERY OF THE INFLAMMATORY RESPONSE

REVEALING THE SECRETS OF MOLECULAR MECHANISMS TAKES POWERFUL INTRACELLULAR TOOLS AND A RESEARCH TEAM DEDICATED TO TURNING DATA INTO EFFECTIVE THERAPIES.

by Dennis Arp

Behold the vigorous but vexing ways of the neutrophil.

Born in bone marrow and flowing through our bloodstream, these most abundant of the white blood cells deploy powerful microbial molecules to help us fight off infection. But sometimes there's collateral damage, as neutrophils errantly aim their destructive toxins at healthy tissue. The resulting neutrophil-mediated inflammation is the bane of patients with diseases like arthritis, cancer, and cystinosis.

Welcome to the research world of Dr. Sergio D. Catz.

Perhaps no one is diving deeper into the immune-cell processes that underlie inflammation than Dr. Catz. He and his lab team have invested years exploring the connection between molecular mechanisms and the inflammatory response. Now, they are focusing on how cystinosis patients experience the debilitating effects.

As with his other cystinosis research work, this new project is supported by funding from the Cystinosis Research Foundation (CRF). "I expect to identify new dysregulated mechanisms in cystinosis," says Dr. Catz, professor in the Department of Molecular and Cellular Biology at the Scripps Research Institute in La Jolla, California.

"We anticipate that by manipulating upstream sensors that track lysosomal damage, we'll be able to reduce neutrophil-mediated inflammation in cystinosis mouse models," he adds.

DEPLOYING THE POWER OF MICROSCOPY

The ultimate goal is to find or create new drugs to complement cysteamine and other therapies that improve the lives of cystinosis patients. But the journey starts with fundamental cellular research using sophisticated super-resolution microscopy.

Those muscular microscopes allow Dr. Catz and his 10 lab colleagues to explore at an intracellular level. When coupled with thorough computational analysis, imaging yields insights about the fundamental pathology of cystinosis – from autophagy to transporters and beyond.

"To resolve a problem, we have to look at the details, and to do that we have to use tools and techniques that make them visible," Dr. Catz says. "I think there's now a wide understanding in the cystinosis community about the small but very important organelle that is the lysosome."

It's critical to also understand the body's cellular recycling machinery and the transporters that move nutrients into cells and building-block components out of lysosomes to maintain or restore the balance called cellular homeostasis, the researcher adds.

"Basically, we are studying to find which of the small parts of molecules are involved in this very exquisitely controlled transport, and how we can protect the organism as we clear the traffic jam when processes break down," Dr. Catz explains.

Growing evidence suggests that the inflammation triggered by cellular breakdown is a pathogenic factor in the development of cystinosis symptoms. Because he has studied the sources and pathways of inflammation throughout his research career, Dr. Catz says it's a natural next step for his cystinosis research to focus on neutrophils and inflammatory response.

"We know that neutrophils are the first line of cellular defense protecting us from bacterial infection," he says. "Through our cystinosis research, we are learning that when the cystinotic gene is not expressed in cells, an altered lysosome gets activated even when there's no pathogen whatsoever."

FINDING THE TRIGGERS OF INFLAMMATION

Dr. Catz and his lab colleagues are investigating why the cells have been activated and how the lysosome accumulates cystine, which then triggers an inflammatory response.

"If we can follow the chain of response so that we can identify exactly which molecules are being activated and in what order, we can intervene and prevent the exposure of cells to toxic components," he explains.

It's a painstaking approach that requires uncommon technical proficiency using state-of-the-art microscopy techniques, high throughput screenings, and chemical biology approaches complemented with lab tests such as ELISA (enzyme-linked immunosorbent assay), flow cytometry, immunoblotting and immunofluorescent staining.

"We're being extra meticulous and systematic in studying these mechanisms for very good reasons," Dr. Catz says. "We want to come up with a translational approach for treating the disease even as we try to complement treatments that are already being used."

As the researchers identify and understand specific cellular mechanisms, "we will look for drugs that can be aimed at those specific targets without getting off target," the doctor adds.

Ideally, the research will point to drug therapies that are already on the market.

"When we find an existing drug that fits the profile we need, it's like a shortcut," Dr. Catz says. "All the toxicology analysis, all the pharmacokinetics, all the studies of the drug will have been performed, and it will have FDA approval."

The team has already identified one compound that improves autophagy, and they are starting in-vivo experiments with an FDA-approved drug that's being used to treat other kidney diseases.

These examples of research progress reflect the monumental support provided over the years by CRF, Dr. Catz says.

COLLABORATIVE SPIRIT FUELS DISCOVERY

"The field is growing based on the contributions of numerous labs, with each having an independent and original view on how to approach different problems," he adds. "We find that the scientists who belong to the Cystinosis Research Foundation have a collaborative spirit that's conducive to new discoveries. That long-term commitment is invigorating, and it's very important as we advance with our research."

Dr. Catz's own work is becoming more prominent and influential, leading to papers in high-profile publications and funding from a variety of sources, including the National Institutes of Health (NIH). Nonetheless, he says, "without CRF support, I probably wouldn't even be a cystinosis researcher."

In the beginning, he was studying cellular mechanisms in cystinosis he thought might be important, but it was all still speculative.

"CRF funding was immensely important, although it was just as important that they provided the right environment for a scientist who was coming from a different mindset," Dr. Catz says. "If you look at the CRF scientific community, you see chemists, computational biologists, clinicians, cell biologists and others, and everybody fits in because it's a complex disease that requires all these contributions."

These days, Dr. Catz is completely comfortable navigating all the complexities of his intracellular research world.

He sees breakthroughs on the horizon.

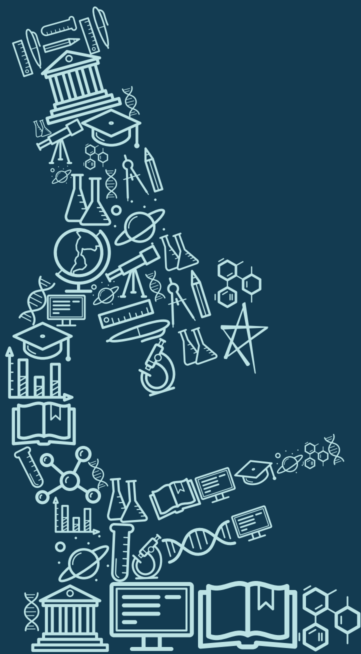
"I'm optimistic that in the relatively short term, we'll find out more about inflammation and whether these drugs have potential," he says. "Then, we will keep searching for more therapies, and always with the same urgency."

CYSTINOSIS RESEARCH STAR

Sergio D. Catz, PhD

Professor, Department of Molecular and Cellular Biology

SCRIPPS RESEARCH — LA JOLLA, CALIFORNIA



THE IMPACT *of* CRF RESEARCH

SINCE 2003, THE CYSTINOSIS RESEARCH FOUNDATION HAS RAISED AND COMMITTED MORE THAN $72 MILLION FOR CYSTINOSIS RESEARCH, MAKING CRF THE LARGEST PROVIDER OF GRANTS FOR CYSTINOSIS RESEARCH IN THE WORLD. OUR DEDICATED RESEARCHERS AND SCIENTISTS ARE WORKING IN 13 COUNTRIES AROUND THE WORLD TO FIND BETTER TREATMENTS AND A CURE FOR CYSTINOSIS.

TO SEE EACH AREA OF RESEARCH FOCUS & GRANTS AWARDED IN DETAIL, VISIT:

WWW.CYSTINOSISRESEARCH.ORG/IMPACT

AREAS OF RESEARCH FOCUS & GRANTS AWARDED SINCE 2003

Cystine Measurement and Cysteamine Toxicity
10 GRANTS

Thyroid
1 GRANT

Cellular and/or Molecular Studies of the Pathogenesis of Cystinosis
68 GRANTS

Skin, Muscle and Bone
22 GRANTS

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

Molecular Study of Cystinosis in the Yeast Model
3 GRANTS

New Drug Discovery Cysteamine, New Medications and Devices
32 GRANTS

Genetic Analysis of Cystinosis
5 GRANTS

Neurological
17 GRANTS

Cure Cystinosis International Registry (CCIR)
1 GRANT

Eye-Corneal Cystinosis Research
12 GRANTS

Rat Model for Cystinosis
4 GRANTS

Kidney Research
29 GRANTS

Lab Equipment for Cystinosis
9 GRANTS

AUTUMN 2024

$419,732.00

RESEARCH AND FELLOWSHIP

GRANT AWARDS

Cystinosis Research Foundation is the largest fund provider of grants for cystinosis research in the world, issuing 248 grants in 13 countries since 2003.

Andrew Hall, MD, PhD
Principal Investigator
University of Zurich, Zurich, Switzerland

"Illuminating Lysosomal Defects in Cystinotic Kidney Disease."

$140,000 ONE-YEAR STUDY

Feodor Price, PhD *(Mentor)*
Lee Rubin, PhD *(Mentor)*
William Chen, PhD *(Fellow)*
Harvard University, Cambridge, Massachusetts

"Characterizing Both the In Vitro and In Vivo Myogenic Potential of Skeletal Muscle Progenitors from Cystinosis Patients."

$150,000 TWO-YEAR FELLOWSHIP

Donny Suh, MD, FAAP, MBA, FACS
Principal Investigator
University of California, Irvine, California

"Assessment and Improvement of Corneal Involvement in Cystinosis."

$129,732 TWO-YEAR STUDY

SEE LAY ABSTRACTS STARTING ON NEXT PAGE

Illuminating Lysosomal Defects in Cystinotic Kidney Disease.

Andrew Hall, MD, PhD, *Principal Investigator*

UNIVERSITY OF ZURICH, ZURICH, SWITZERLAND

OBJECTIVE/RATIONALE:

Cystinosis causes kidney disease and ultimately kidney failure, which imposes huge medical and psychological burdens on patients and substantially shortens life expectancy. The proximal tubule is the major site of injury in cystinotic kidney disease. Proximal tubular cells have a highly developed endo-lysosomal system that reabsorbs and degrades proteins filtered by the glomerulus. Cystinosis occurs due to genetic defects in the lysosomal protein cystinosin, but exactly how these affect endo-lysosomal function in the proximal tubule is not well understood.

PROJECT DESCRIPTION:

We have developed cutting-edge intravital imaging techniques using two-photon microscopy and targeted fluorescent probes to visualize the endo-lysosomal system working in kidney tubules in living mice. With this technique, we can directly assess the consequences of manipulating endo-lysosomal genes that cause kidney diseases.

In this project, we will apply this approach to investigate how endo-lysosomal function is altered in cystinosin deficient mice, which develop a phenotype closely resembling that of human cystinotic kidney disease. We will evaluate several key dynamic processes, including protein uptake and trafficking, vesicular acidification, calcium uptake/release, lysosomal protein degradation and lysosomal exocytosis. This will enable us to better understand what cystinosin normally does and what happens when it is missing.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Identifying the consequences of cystinosin loss on endo-lysosomal function in the proximal tubule is a critical step in elucidating the pathogenesis of cystinotic kidney disease. In the longer term, this new knowledge might lead to the development of new treatment strategies. Moreover, it may have relevance for understanding how cystinosis damages other organs.

ANTICIPATED OUTCOME:

We expect to shed new light on where and how cystinosin depletion impacts on the endo-lysosomal system in kidney proximal tubules in vivo. This information will help to explain how cystinotic kidney disease arises, and could generate new ideas concerning processes that might be targeted therapeutically in the future.

Characterizing Both the In Vitro and In Vivo Myogenic Potential of Skeletal Muscle Progenitors from Cystinosis Patients.

Feodor Price, PhD, *Mentor*
Lee Rubin, PhD, *Mentor*
William Chen, PhD, *Fellow*
HARVARD UNIVERSITY, CAMBRIDGE, MASSACHUSETTS

OBJECTIVE/RATIONALE:

Cystinosis patients experience muscle wasting in the limbs and neck. To date, it remains unclear whether this muscle wasting is caused by problems during muscle repair, at the level of stem cells (satellite cells) or progenitors (myoblasts), or fully mature muscle. Recent studies show that mature muscle in cystinosis patients look histologically healthy, suggesting the possibility that functional issues in the satellite cell or myoblast populations exist. Our goal is to investigate these cell populations to determine whether functional differences exist and if they lead to muscle wasting in cystinosis patients.

PROJECT DESCRIPTION:

In healthy muscle cells, we are able to turn large numbers of myoblasts back into a satellite-cell-like state, capable of regenerating muscle when transplanted. We term these cells in vitro derived satellite cells (idSCs). We have successfully generated cystinosis patient-derived myoblast lines, with preliminary results comparing cell growth rates, their ability to differentiate into muscle, and their expression of stem cell genes. However, our data requires additional biological replicates to draw meaningful conclusions. To investigate the regenerative potential of cystinosis cell lines, we aim to identify the morphological and behavioral differences between cystinosis and healthy myoblasts. We also aim to use a mouse model for cystinosis to determine the capacity of satellite cells/myoblasts to drive muscle repair. Finally, we aim to determine whether we can generate cystinosis idSCs and further, whether they can regenerate muscle when transplanted.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

Our findings will increase the field's understanding of muscle wasting and repair in cystinosis patients. Specifically, we will learn how each cell population, from satellite cells, myoblasts and on through to differentiated muscle, is affected between healthy relative to cystinosis patient samples. We hope to improve the quality of life for cystinosis patients through the development of new drugs and cell therapies to treat muscle wasting using our newfound understanding of muscle biology in cystinosis patients.

ANTICIPATED OUTCOME:

We expect to learn how myoblast and idSC cell lines differ between cystinosis and healthy patients in terms of growth and muscle formation. These findings will shed light on how muscle wasting occurs in cystinosis patients. Given the improved regenerative capabilities of idSCs, we are curious to know whether cystinosis idSCs are capable of repairing muscle unaided, or with small molecule treatment.

Assessment and Improvement of Corneal Involvement in Cystinosis.

Donny Suh, MD, FAAP, MBA, FACS, *Principal Investigator*

UNIVERSITY OF CALIFORNIA, IRVINE, CALIFORNIA

OBJECTIVE/RATIONALE:

Cystinosis is a rare genetic condition that causes cystine crystals to build up in the eyes, leading to significant vision problems like sensitivity to light, pain, and vision loss. Current systems to monitor corneal involvement are limited and do not fully capture the progression of the disease, making treatment decisions difficult. This project aims to improve how we monitor and treat corneal involvement in cystinosis by refining a new grading system and exploring innovative therapies, such as combining eye drops with punctal plugs.

PROJECT DESCRIPTION:

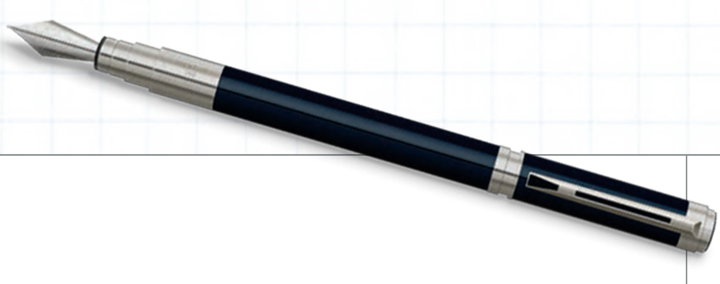
Our team will validate the University of California, Irvine Cystinosis Corneal Crystal Scoring (UCI CCCS) system, which better captures disease progression through five stages. We will use advanced imaging tools like a Pentacam camera to assess how accurately this system reflects disease severity and symptoms patients report. Additionally, we will explore combining standard cysteamine eye drops with punctal plugs to improve treatment outcomes. Punctal plugs help keep the medication on the eye longer, potentially reducing the number of doses needed and improving comfort. We will work with cystinosis patients and their families to gather data on symptoms, medication use, and quality of life to refine our approach.

RELEVANCE TO THE UNDERSTANDING AND/OR TREATMENT OF CYSTINOSIS:

This project addresses critical challenges in cystinosis care, including the difficulty of monitoring disease progression and low patient adherence to treatment. By improving how we assess and treat corneal involvement, we aim to enhance the quality of life for children and young adults with cystinosis. This work will provide clinicians with better tools to monitor the disease and offer more effective, patient-friendly treatment options.

ANTICIPATED OUTCOME:

We expect to validate the UCI CCCS as a reliable tool for monitoring corneal changes in cystinosis and demonstrate that punctal plugs can improve treatment effectiveness by reducing the need for frequent eye drop administration. These advancements will lead to better management strategies, improved vision outcomes, and enhanced independence for patients living with this challenging condition.



CYSTINOSIS RESEARCH FOUNDATION

SCIENTIFIC REVIEW BOARD

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

CHAIRPERSON

Stéphanie Cherqui, PhD
Professor, Department of Pediatrics, Division of Genetics
University of California, San Diego
SAN DIEGO, CALIFORNIA

THANK YOU FOR THE YEARS OF DEDICATION TO THE CYSTINOSIS COMMUNITY.

BOARD MEMBERS

Sergio D. Catz, PhD
Professor, Department of Molecular and Cellular Biology
Scripps Research
LA JOLLA, CALIFORNIA

Olivier Devuyst, MD, PhD
Professor, Institute of Physiology
Group Leader of Mechanisms of Inherited Kidney Disorders
University of Zurich
ZURICH, SWITZERLAND

Francesco Emma, MD
Head of Pediatric Nephrology, Director of Nephrology Laboratory
Bambino Gesù Children's Hospital
ROME, ITALY

Benjamin Freedman, PhD
Associate Professor, Department of Medicine, Division of Nephrology
University of Washington
SEATTLE, WASHINGTON

Larry Greenbaum, MD, PhD, FAAP
Division Director of Pediatric Nephrology Bernard Marcus Professor of Pediatric Nephrology, Emory School of Medicine
Executive Director, Children's Healthcare of Atlanta
ATLANTA, GEORGIA

Paul C. Grimm, MD
Professor of Pediatrics
Medical Director, Pediatric Kidney Transplant Program
Stanford University School of Medicine and Stanford Children's Health
PALO ALTO, CALIFORNIA

Julie R. Ingelfinger, MD
Deputy Editor of the New England Journal of Medicine
Professor of Pediatrics
Harvard Medical School
BOSTON, MASSACHUSETTS

Stephen L. Jenkins, MD
Assistant Professor, Hospitalist, Department of Internal Medicine
University of Utah Hospital
SALT LAKE CITY, UTAH

Aude Servais, MD, PhD
Senior Nephrologist, Department of Adult Nephrology
Necker Hospital, Paris Descartes University
PARIS, FRANCE

LEADERSHIP.
GUIDANCE.
COMMITMENT.

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 $72 million with 100% of your donations going to support cystinosis research.

EDUCATION

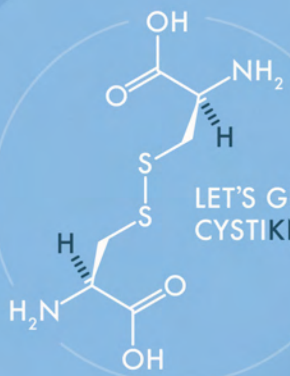
CRF is dedicated to educating the medical and public communities about cystinosis to ensure early diagnosis and proper treatment.

cystinosis RESEARCH FOUNDATION

CHARITY NAVIGATOR ★★★★ Four Star Charity

Platinum Transparency 2024 Candid.

Zoe R. Solsby
Vice President



LET'S GET TO
CYSTIKNOWSIS

Our collective of donors, researchers,
and community partners unite for
a future free from cystinosis.

SCAN TO DONATE

HELP
ACCELERATE
OUR
RESEARCH
TODAY!

WE'RE BETTER TOGETHER

cystinosis
RESEARCH FOUNDATION