

Cystinosis is a rare metabolic disease that afflicts approximately 2,000 people, mostly children, worldwide and approximately 500 in the United States. It is a rare genetic disorder that causes the amino acid cystine to accumulate in the organs. Cystine is trapped in the cell and forms crystals causing cell death as its concentration increases. Over a period of years, the cystine slowly destroys various organs in the body including the kidneys, liver, muscles, white blood cells, eyes and central nervous system. Other complications occur that include muscle wasting and difficulty swallowing.

The earliest abnormalities are seen in the kidney. Cystinosis is a common cause of Fanconi Syndrome, a renal tubular disease. Cystinosis is most common and most severe in young children. By about one year of age, patients have large volumes of urine and lose large amounts of salt and other minerals in their urine.

Without specific treatment, children with cystinosis experience kidney failure at nine years old on average. Before dialysis and kidney transplants this was fatal. Now these patients can receive renal dialysis or renal transplantation. However, even with successful renal transplantation, these children develop abnormalities in other organs.

TREATMENT

Fortunately the drug cysteamine (Cystagon™), which was developed in the 1980s, slows the progression of cystinosis by removing the cystine from the cells. In order for the drug treatment to be effective, it must be taken every six hours around the clock, daily. Because of the offensive smell and taste of cysteamine some patients cannot tolerate it. For those who can cysteamine has led to a much better future. But cysteamine is a treatment, not a cure.

SYMPTOMS

There are three clinical forms of cystinosis. Infantile (nephropathic) cystinosis; late-onset cystinosis; and benign cystinosis. Infantile cystinosis is the most severe and the most common type of cystinosis. Children with nephropathic cystinosis appear normal at birth but by 9–10 months of age, have symptoms that include excessive thirst and urination and failure to thrive. Children often appear pale and thin and have short stature. The abnormally high loss of phosphorous in the urine leads to rickets.

After one year of age, cystine crystals appear in the cornea and causes severe sensitivity to light (photophobia). Children with

cystinosis also have an increased level of cystine in their white blood cells. In time, patients can develop problems such as hypothyroidism, severe muscle weakness and central nervous system complications. These children have normal intelligence, but have an unusual defect in short-term visual memory. Many have poor GI motility. Cysteamine causes hyper secretion of gastric acid, resulting in gastric distress.

HOW IT IS INHERITED

Cystinosis is an autosomal recessive genetic disease. This means that both parents are carriers of the abnormal gene that leads to this condition. The parents do not exhibit any of the symptoms of cystinosis. In such couples, the odds are that one-in-four children will have cystinosis. The gene for cystinosis, CTNS, was mapped to chromosome 17p13.

As proteins are degraded within the lysosomes of cells, the individual amino acids that make up the proteins are transported from the lysosome to the cell's cytoplasm via specific transporters. The transporter for cystine is defective in children with cystinosis and this defect causes the cystine to crystallize within tissue. The cystine content of the cell is 50-100 times the normal value.

RESEARCH

In the past, cystinosis research studies were rare due to a lack of funding, but through private funding, research is being advanced. In 2003 Jeff and Nancy Stack founded the Cystinosis Research Foundation, which has raised over \$ 4 million for cystinosis research.

RESEARCH PROPOSAL FUNDING

The Cystinosis Research Foundation is prepared to fund proposals to improve the immediate care of children and young adults with cystinosis and to develop new understanding and treatment of cystinosis to help these children in the future. The Foundation is especially interested in encouraging new investigators to study cystinosis through either fellowships or start-up funds. Awards are given for up to two years.

Proposals are reviewed by the Scientific Review Board comprised of leading experts on Cystinosis who then advise the Cystinosis Research Foundation on the scientific merit of each proposal. The Foundation will balance the funding to support both clinical and bench research.



SCIENTIFIC REVIEW BOARD

The Scientific Review Board is composed of leading Cystinosis scientists and experts from around the world. The members are actively involved in the grant review process and advise the Cystinosis Research Foundation on the merit of each proposal.

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Curriculum Vitae for all SRB members
can be found at www.natalieswish.org.

2006 RESEARCH STUDIES FUNDED AND COMMITTED: \$2,313,962

FEBRUARY 2006

Ranjan Dohil, MD

University of California, San Diego
“A Study to Evaluate Enteric-Coated
Cysteamine Therapy in Patients
with Cystinosis”
\$253,685 – 1-year clinical study

MAY 2006

Corinne Antignac, MD, PhD

Hospital Necker, Paris, France
“Characterization of Cystinosis
Intracellular Trafficking”
\$85,000 – 1-year study

Angela Ballantyne, PhD

and Amy Spilkin, PhD
University of California, San Diego
“Academic Functioning in Cystinosis:
A Comprehensive Study of the Process
of Achievement”
\$213,527 – 2-year study

Bruce Barshop, MD, PhD

and Jerry Schneider, MD
University of California, San Diego
“API-4000 Tandem Mass Spectrometer
for Cystinosis Research”
\$118,400 – 2-year lease and maintenance

Elena Levchenko, MD, PhD

University Medical Centre
St. Radboud Nijmegen, The Netherlands
“Pathogenesis of Interstitial Renal Damage
Leading to Renal Failure in Cystinosis”
\$72,423 – 1-year study

Daniel Salomon, MD

and Stephanie Cherqui, PhD
The Scripps Research Institute,
La Jolla, California
“Treatment of Cystinosis Nephropathy
Using Genetically Modified Adult
Stem Cells in Murine Cystinosis Model”
\$709,170 – 3-year study

DECEMBER 2006

Rita Ceponiene, MD, PhD

University of California, San Diego
“Neural Functioning in Auditory
and Visual Systems in Cystinosis:
Linking Brain to Behavior”
\$287,918 – 2-year study

**Francesco Emma, MD, Anna Taranta, PhD
and Elena Levchenko, MD, PhD**

Bambino Gesù Children’s Hospital and Research
Institute, Rome, Italy and Radboud University
Medical Centre Nijmegen, The Netherlands
“Transcriptional and Post-Transcriptional
Regulation of the *CTNS* Gene”
\$138,824 – 2-year study

Eric Moses, PhD, Mentor

Katy Freed, PhD, Research Fellow
Southwest Foundation for Biomedical Research,
San Antonio, Texas
“Complex Genetic Approaches to Monogenic
Disease: Genomic and Transcriptomic
Dissection of Normal Expression of *CTNS*,
the Gene Involved in Nephropathic Cystinosis”
\$148,535 – 2-year study

Vasiliki Kalatzis, PhD, Mentor

**Claire Hippert, Pre-doctoral
Research Fellow**
Institut Génétique Moléculaire
Montpellier, Montpellier, France
“Gene Transfer Studies for Cystinosis”
\$168,290 – 2-year study

Holger Willenbring, MD, Mentor

Kentaro Okamura, PhD, Research Fellow
University of California, San Francisco
“Targeted Cell Fusion for the Correction
of Tubulopathy Due to Cystinosis”
\$84,530 – 2-year study

Jess G. Thoene, MD

The University of Michigan
“Lysosomal Cystine Enhanced Apoptosis
in Cultured Human Mesenchymal Stem Cells”
\$33,660 – Laboratory supplies

***Jess G. Thoene, MD**

(Reinstated after Hurricane Katrina)
The University of Michigan
“Lysosomal Cystine Enhanced Apoptosis
in Cultured Human Mesenchymal Stem Cells”
\$150,000 – 18-month study

** Dr. Thoene’s study was originally approved
for funding in 2005 but because his lab at
Tulane University was destroyed by Hurricane
Katrina the study was cancelled. In November,
2006 Dr. Thoene’s study was reinstated at
the University of Michigan.*



**NEVER DOUBT THAT A SMALL GROUP OF COMMITTED PEOPLE CAN CHANGE THE WORLD.
INDEED, IT IS THE ONLY THING THAT EVER HAS.** MARGARET MEAD

MESSAGES TO THE CYSTINOSIS RESEARCH FOUNDATION
FROM PARENTS OF CHILDREN WITH CYSTINOSIS

We are so very thankful to you and all of your miraculous work.

We know the research you are funding and inspiring will provide him with the answers he needs to have a better quality of life.

You have been a source of inspiration for us all.

Thank you for your hard work over the years and for building so many bridges linking all of us together.

We are so grateful for people like you and the work that you are doing. May God reward you for it.

We can never thank you enough for all you do! We know our daughter and all children with cystinosis will have greatly improved lives because of the miracles you are making happen.

I am grateful to you and your family and friends for all you are doing to help our girls and every child born with cystinosis.

Thank you for all of your hard work. I am so glad the controlled-release study is progressing. I'm so excited.

I was looking at your website last Thursday and I watched some of the video. The tears were flowing. Thank you! The money you have raised is amazing. It will be so awesome to not have to wake our son up to give him his medicine.

I know that the whole community very much appreciates your efforts and I wanted to let you know personally how important this is.

JULIE R. INGELFINGER, MD

Through the sole support of the Cystinosis Research Foundation we have been able to study and understand how cysteamine is absorbed within the intestinal tract. We have been able to formulate a controlled-release treatment for cystinosis, which we are currently evaluating.

RANJAN DOHIL, MD

Patients with cystinosis are one step away from effective treatment.

WILLIAM A. GAHL, MD, PHD

Support from the Cystinosis Research Foundation has been critical to development of the concept that enhanced apoptosis is responsible for the disease characteristics of nephropathic cystinosis. And it has enabled us to attract a new generation of scientists to the problem.

JESS G. THOENE, MD

I never thought we would have the resources to do a controlled-release study. It has been years since I was so excited about a cystinosis research project.

JERRY A. SCHNEIDER, MD

You save one life, you save the whole world.

TOM JEITNER, PHD