

Day of Hope 2016

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We just got back from another amazing Cystinosis Research Foundation family conference. There were 240 people there! With so many people and new families, the CRF actually moved locations to the Island Hotel. We missed the Balboa Bay Resort, but the Island Hotel was beautiful and very accommodating. They even gave us a discounted laundry rate to take care of our bedding every morning!

The conference started with a welcome dinner on Thursday night. We connected with old friends and met a lot of new ones. It didn't take long (about the time it takes to eat two quesadillas) before the boys were running wild with all of their friends. Sam quickly found Henry Sturgis, his favorite pal, and Lars ran along after them. Playtime was only interrupted by a few handfuls of Procysbi, and then they were ready to keep going. We tried to go to bed a little early, knowing that our conference would commence bright and early.

We kicked off the meeting with family introductions. Everyone stood and shared a little of their story. We all wrote down our wishes for our children and loved ones with cystinosis, and we posted them on a giant kaleidoscope heart. There were a lot of tears and laughs and hope shared. It was cool to see some new adults with cystinosis introduce themselves and share a little of their journey with the group. It felt like a big family reunion.

Nancy Stack started the next session with a talk about the Cystinosis Research Foundation, which since 2003 has raised over \$30 million dollars. They have funded 134 multi-year research grants in 12 countries, with 62 publications in prestigious journals. They funded the research that led to the development of delayed release cysteamine, Procysbi. They are the largest funder of cystinosis research in the world.

Dr. Sandra Amaral from Children's Hospital of Philadelphia attended this year, and gave a talk about Fanconi Syndrome. She explained the mechanism of how cystinosis causes damage to the proximal tubule of the kidney, so it is unable to reabsorb important electrolytes, proteins and sugar. She talked about the many medications that people with Fanconi's syndrome must take, including potassium, citrate, phosphorus and others. She made the interesting point that phosphorus and calcium should not be taken at the same time because they bind each other in the gut, which impairs their absorption. Later in the conference she gave a talk about adolescents and adults with cystinosis, and the special challenges that go along with transplant, medication adherence, education, and work. She addressed strategies for coping and improving quality of life and recommended a book called *Building Resilience in Children and Teens: Giving Kids Roots and Wings* by Kenneth Ginsburg.

Dr. Mary Leonard from Stanford gave us an update on her study of muscle and bone health. So far she has obtained data on 23 people with cystinosis, ages 8 to 49. Her preliminary data shows that people with cystinosis have much lower bone mineral density than average. More

than half of study participants had bone mineral density less than the 10th percentile for age. She also found that people with cystinosis have significantly reduced muscle mass. More than half had less than the 5th percentile for age. She found that cystinosis bone is thinner, likely because of lack of muscle forces. She recommended weight-bearing exercise to help build stronger bone. It's also important to have enough phosphorus, calcium and vitamin D to build bone. There may also be a role for growth hormone to improve bone and muscle health. She also noted that two of the participants had unusually good bone mineral density, and this was associated with abnormal dentition. She and Dr. Grimm think this is likely secondary to fluoride toxicity. The increased bone mineral density in fluoride toxicity is actually unhealthy and is more likely to lead to fractures. Since patients with cystinosis drink such high volumes of water they may be at higher risk for excessive fluoride intake, so this is something they will look at in their study.

Dr. Mak provided a summary of many of his studies of muscle wasting in cystinosis. He showed his data on vitamin D. The important thing is that over the counter vitamin D, either cholecalciferol or ergocalciferol, also known as 25-vitamin D, may help improve muscle mass and strength. This vitamin D is different than calcitriol (1,25-vitamin D) that many people with kidney disease require for bone health.

He talked about cachexia, which is a nutritional wasting that is different than malnutrition. Even if you give patients with cystinosis adequate calories they fail to gain weight and build muscle. This process may involve the transformation of white fat to brown fat. Brown fat is something that babies need to stay warm because it burns calories to produce heat. This process is maladaptive in cystinosis because it wastes energy. Dr. Mak has shown that cystinosis mice develop more brown fat, and this is probably driven by increased cellular inflammation. His lab has found increased level of inflammatory cytokines in cystinosis mice, including interleukin-1. They are testing an anti-inflammatory drug that blocks interleukin-1 in cystinosis mice to see whether it reduces inflammation and improves muscle mass.

Another pathway involved in cachexia is leptin signaling. Leptin is a hormone that regulates appetite and is very important in regulating energy and metabolism. Dr. Mak and his lab have treated cystinosis mice with a leptin blocker, and they found that it reversed muscle wasting and improved muscle function. This is another exciting potential target to treat muscle wasting in cystinosis.

After Dr. Mak we heard from Dr. Kate Dahl, a clinical psychologist from Stanford who specializes in child and adolescent psychiatry. She talked about the ways a medical diagnosis affects every member of the family and how it can trigger distress emotions. She talked about the different ways people cope with challenges and reviewed strategies to enhance coping and communication for caregivers and people with cystinosis. She walked us through a practice run in mindfulness training, and recommended a couple apps, including "Headspace" and "Calm." After her talk she conducted special sessions for adults with cystinosis and for caregivers of adults with cystinosis.

While Dr. Dahl did her more private sessions, the rest of us had a forum on troubleshooting many of the daily challenges of cystinosis. We talked about ways to organize medications. Some people use color coding, others lettering systems. Many families draw up enough medications for a month so syringes are ready to go anytime. Denice Flerchinger recommended monoject slip tip syringes because the numbers never wear off. Nicole Manz talked about how to do a blended diet. We talked about getting a 504 plan for school in order to accommodate things like free access to the bathroom. We also talked about bedwetting, something we have continued to struggle with. I think the takeaway there was that the child will night train when they are ready, and in the mean time we should try to keep up with the laundry.

Next we heard from Dr. Bruce Barshop of UCSD about the new cystine measurement assay. He explained how 1.9 became our new target for cystine levels. Apparently 99.9% of carriers (people with one cystinosis gene) have levels less than 1.9. This number also seems to correlate very well with 1.0 and the old test. He says that his lab will still run the old white blood cell cystine test if local labs are having difficulty, but the new test should be much easier. All you need is a yellow top tube, shipped overnight to UCSD on ice. He also clarified a very important thing that was a little confusing from the original trial. Blood should be drawn 12 hours after the last dose of Procysbi and 6 hours after the last dose of Cystagon, AND THEN the medication should be taken. Some patients would take the medicine and then get the blood drawn, but if there were delays in blood collection, then cystine levels could be falsely low. He also recommended that you get cystine checks at least 2-3 times a year, and much more frequently when converting from Cystagon to Procysbi.

Betty Cabrera from UCSD talked about the importance of registering and updating our profiles on CCIR. The survey has been updated with new questions that are relevant to upcoming clinical trials. It is a very important source of information for our researchers. She recommended that everyone try to update their profiles by May 1, or May Day.

We capped off Friday's sessions with the Adult and Teen Panel where we got to hear from some of the giants in the cystinosis community. We heard enlightening insights about medication compliance, moving out, working and the hope they have for a cure.

While we were at talks, the kids were having a blast with the babysitters. They had a great itinerary, including yoga training, a magician, and a visit from some wild animals. The kids got to pet a porcupine, a hedgehog, an armadillo, an alligator, a boa constrictor, and a kinkajou! Sam loved the endless potato chips and Lars was in juice heaven.

Friday night we had another wonderful dinner, and yes, there was cotton candy with light-up wands. I think Sam looks forward to that more than anything else. He and Henry immediately set to work gathering an army of boys and declared war on the girls. There was a little bit of chaos in the hotel lobby. The whole lightsaber battle worked better on the beach at Balboa Bay

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Saturday morning was packed with translational research updates. We heard from Dr. Sergio Catz about a protein called LAMP2A that acts as a port of entry to the lysosome. It's an important receptor in chaperone-mediated autophagy. It's built somewhere else in the cell and has to be transported on the cellular highway to the lysosome. When the protein cystinosis is absent, LAMP2A has difficulty getting to the lysosome, and this leads to a build-up of junk outside the lysosome. This can be just as disruptive as stuff building up inside the lysosome (i.e. cystine) and leads to increased cellular stress. He is collaborating with another researcher, Ana Maria Cuervo, at Albert Einstein College of Medicine. She has already found some molecules that stabilize LAMP2A, improve its trafficking to the lysosome and reduce cellular stress. They are testing these molecules in cystinosis mice.

Dr. Stephanie Cherqui gave an inspiring talk about the potential for stem cell transplantation to cure cystinosis. She is almost done with the safety and toxicology studies. They have been working out the best way to transduce human stem cells with the lentivirus that holds the corrected cystinosis gene. Their protocol worked great in healthy human stem cells, but in cystinosis stem cells the lentivirus is not taken up as avidly. She is hoping to submit the IND (investigational new drug) paperwork and IRB this fall, and then we will anxiously wait for FDA approval to start the clinical trial. They will start with 2 adults, followed by another 2 adults. Then they will re-evaluate the safety of the treatment and consider 2 adolescents. The treatment will require a full month in the hospital, followed by weekly visits at UCSD for 2-3 months. The cure is coming!

Dr. Cherqui was followed by her PhD student Spencer Goodman. He did a fantastic job explaining the mechanism by which hematopoietic stem cells can rescue organ function in cystinosis. Stem cells turn into macrophages, which transfer healthy lysosomes to cystinosis cells through tunneling nanotubules. This mechanism holds great potential for other organelle based diseases.

Next up we heard from Dr. Jennifer Simpson of UC-Irvine. She talked about how there is more to ocular cystinosis than corneal crystals. Every compartment of the eye is affected, including the retina, conjunctiva, iris and ciliary bodies. Patients with cystinosis are at high risk of dry eye because the goblet cells that secrete mucus, an important part of your tear film, are lost over time. She also noted that corneal crystals should not affect vision, so if your vision is worse than 20/30, then your ophthalmologist should look for another cause. She also talked about the risk of glaucoma, which is caused by increased pressure in the eye. This manifests as pain in the eye, redness, tearing, seeing halos, nausea and vomiting, and is an eye emergency. She also spent some time on pseudotumor cerebri, aka idiopathic intracranial hypertension, which has been seen in some patients with cystinosis. Increased intracranial pressure can damage the optic nerve, which carries visual signals from the eye to the brain. This damage can cause blindness. Any vision loss should involve evaluation of the optic nerve. She also talked about how optical coherence tomography (OCT) is superior to slit lamp exams for monitoring crystals

in the cornea. She is working on cystinosis guidelines to share with our ophthalmologists.

Ghanashyam Acharya updated us on the nanowafer for corneal cystinosis, which is gearing up for a clinical trial. The nanowafer is like a very thin contact lens made of polyvinyl alcohol. It is 80 microns thick, compared to a contact lens which is 200 microns thick. The nanowafer is more effective than cysteamine drops and does not need to be refrigerated because the drug is more stable. It will also improve compliance significantly. He also gave us an update on the transdermal patch, which will pump cysteamine in through the skin. It would hopefully produce more steady drug concentration in the blood and have less side effects. He is currently testing it on cadaver skin and pigs!

The final speaker was Doris Trauner, who summarized her findings of her study on quality of life and psychosocial functioning in teens and adults with cystinosis. She found that adults and teens with cystinosis have problems with sleep, anxiety, depression, fatigue and independence. They also reported strong emotional and family support.

We concluded the session with a Q&A panel with the physicians and researchers. As in previous years people expressed interest in doing research on male fertility. There were several questions about medication compatibility. Procysbi should be taken with acids, like orange juice, and should not be taken with bicarbonate.

Saturday night was the big Natalie's Wish event. Twenty-one families presented checks to the CRF this year! The CRF brought in a record 3.3 million dollars that night, and the money keeps coming in!

This year Rachel Platten, popular singer of "Fight Song" provided the entertainment. She met the kids before the event and took pictures. At the end of the gala she had all the kids come up to the stage to sing "Fight Song." There were a lot of tears. It was the perfect end to the perfect conference. We all left energized to keep fighting cystinosis every day.