



Poster Session Abstracts

Research/Clinical:

1) Dental Findings in Mexican Patients with Cystinosis

Leticia Belmont-Martínez MD, Eduardo De la Teja-Angeles MD, Americo Durán-Gutierrez MD, Marcela Vela-Amieva MD.

**Laboratorio de Errores Innatos del Metabolismo y Tamiz, **Departamento de Estomatología, Instituto Nacional de Pediatría*

Cystinosis is a rare autosomal recessive lysosomal storage disorder with developmental and mineralization anomalies as part of its clinical presentation. Tooth enamel is a calcification process sensitive to general growth, development and mineralization processes.

Ameloblasts are extremely sensitive to stimuli. Those abnormalities in enamel formation are etched permanently on the tooth surface, depending on the dental development stage. Mineralization occurs with the deposit of minerals and in a final stage the enamel gets hardness and translucent

The aim of this report is to present a description of dental findings associated with Mexican patients with cystinosis.

Patients: 10 people well documented as nephropathic cystinosis patients were invited to a dental evaluation, only 4 include in this group, 4 patients live so far Mexico City, and 2 patients lost the evaluation.

Results: We collected dental findings from 2 females with 5 and 14 years old, 2 men 29 and 54 years old. 1) diminished amelodontal tissue quality, severe enamel hypoplasia, opportunistic carious lesions, Stratified condition of lesions determined to be an acquired defect, not congenital. 2) Severe attrition, enamel hypoplasia, opalescent dentin, enamel from the occlusal crown surface shown significant wear of all dental organs. 3) Severe malposition of the second and third molars, enamel hypoplasia is observed as chalk-white spots all over the cusps of teeth that appears as a variations of the translucency of the enamel. 4) decalcification.

Conclusion: Some dental findings (developmental tooth defects, postdevelopmental structure loss and discoloration of teeth), are secondary to systemic disease (Cystinosis) characteristics as: kidney damage, urinary losses, decalcification; other findings are secondary to stress, poor nutrition, and poor hygiene.

2) Hematopoietic stem cell gene therapy with a lentiviral vector for the multi-systemic lysosomal storage disorder Cystinosis

Brian Yeagy¹, Frank Harrison¹, Donald B. Kohn², Daniel R. Salomon¹, and Stephanie Cherqui¹

¹*Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California.*

²*Department of Microbiology, Immunology and Molecular Genetics and Pediatrics, University of California, Los Angeles, Los Angeles, California.*

Cystinosis results from a genetic defect in the gene *CTNS* encoding the lysosomal cystine transporter protein, cystinosin, responsible of the export of cystine out of the lysosome. Cystine accumulates in every tissue compartment and leads to organ damage and dysfunction including renal defects.

Using the murine model for cystinosis, *Ctns*^{-/-} mice, we showed previously that transplantation of hematopoietic stem cell (HSC) expressing a functional *Ctns* gene could improve cystinosis. Cystine content was reduced by 57% to 94% in all tissues tested in the treated mice. Large quantity of transplanted “healthy” cells was observed in all the organs. The natural progression of renal dysfunction was prevented when enough “healthy” stem cell expressing a functional *Ctns* gene were present in the bone marrow. This is a proof of concept for developing HSC transplantation for cystinosis.

The present work represents preclinical studies for autologous HSC transplantation in *Ctns*^{-/-} mice. In patients, this procedure is the use of the patient’s own stem cells that will be genetically modified to express a functional *CTNS* gene using a virus vector and then reintroduced in the patient. Using the latest generation of lentiviral vectors to deliver the *CTNS* gene to autologous HSC in the *Ctns*^{-/-} mice, we showed that genetically modified HSC were capable of decreasing cystine content in all tissues and lead to kidney function improvement. We also showed that genetically modified HSC kept their plasticity capabilities to generate tissue cells and allowed a long-term expression of the transgene. No toxicity has been observed to date.

This work is a proof of concept for autologous lentiviral-modified HSC transplantation as a therapy for cystinosis and should lead to the first gene and cell therapy clinical trial for this disease.

3) Quality of Life in Cystinosis Patients

Ewa Elenberg, MD

Baylor College of Medicine, Texas Children's Hospital, 1102 Bates, Suite 260, Houston, TX 77030, office tel. 832-824-3800. E-mail: elenberg@bcm.edu

Objectives: The objective was to evaluate the quality of life (QOL) in cystinosis patients and compare to their parents' QOL perception. The hypothesis was that the perception of QOL by children would be better than their parents think.

Methods: Pediatric Quality of Life (PedsQL™) Survey was delivered via an interview. The collected answers were scored by 2 domains: Physical Health and Psychosocial Health (including: Emotional, Social and School functioning). The Total Score was calculated as the mean of the sum of all the items.

Results: PedsQL™ was answered by 28 respondents: 14 Cystinosis patients (5-18y old) and 14 parents. Total Scores calculated from Cystinosis patients were significantly higher than those of their parents (76 vs. 62, $p=0.019$). Although there was no significant difference in the Physical Health domain, the Psychosocial Health domain analysis revealed a significant difference between Cystinosis patients (higher score) and their parents (75 vs. 60, $p=0.021$). The data was compared to previously published healthy and end-stage-renal disease (ESRD) subjects, using Two-sample t test with unequal variances. Comparison of Total Score to healthy subjects revealed a lower score for Cystinosis patients and their parents. For Cystinosis patients score 76 vs. healthy score 87 ($p=0.004$) and their parents 62 vs. healthy score 87 ($p=0.0001$). There was no statistically significant difference in total score between Cystinosis (patients and parents) versus ESRD sample.

Conclusions: Cystinosis patients perceive their QOL better than their parents think (statistical significance in Total Score and Psychosocial Health domain). Comparing Cystinosis patients to healthy subjects, it is apparent that their QOL is worse, meeting the statistical significance. Comparing Cystinosis patients to ESRD patients their QOL is similar.

4) Localization and regulation of PKA-phosphorylated Cystinosin-LKG

Francesco Bellomo, Serena Corallini, Anna Taranta, Stefania Petrini, Marianna Coccetti, Ezio Giorda, Francesco Emma

Department of Nephrology and Urology, Division of Nephrology, "Bambino Gesù" Children's Hospital and Research Institute, Rome, Italy.

Cystinosin-LKG is a cystinosin isoform that is generated by an alternative splicing of exon 12 and has been shown to be targeted to the plasma membrane and to small cytosolic vesicles (Taranta et al. 2008). In this study we examined the role of PKA and serine 397 (S397) phosphorylation in regulating cystinosin-LKG trafficking and recycling using a transfection model (HK2 cells) with RFP-tagged fusion proteins or mutant cystinosin-LKG proteins. In addition, we performed histochemistry analyses to better identify cells and tissues that express this isoform.

Confocal microscopy analysis was used to evaluate the co-localization of cystinosin-LKG with plasma membrane stained with green WGA (wheat germ agglutinin). Subcellular fractionation was also performed by *iodixanol* density gradient *centrifugation* followed by western blotting analysis with specific antibodies directed against cystinosin-LKG.

The role of serine 397 phosphorylation was assessed by site-directed mutagenesis (S397D mimicking constitutively phosphorylated cystinosin-LKG and S397A mimicking the non-phosphorylated protein). S397A mutation resulted in internalization of cystinosin, whereas the S397D mutation induced a redistribution of cystinosin-LKG to the plasma membrane. Analysis of candidate kinases showed that a 3 hours treatment with 0.5 μ M of KT5720, a specific PKA inhibitor, reduced the presence of cystinosin-LKG at plasma membrane level, while stimulation of PKA with 100 μ M of forskolin re-established basal distribution. 1-Oleoyl-2-acetyl-sn-glycerol (*OAG*) and chelerythrine treatment, an activator and an inhibitor of *protein kinase C* (*PKC*) respectively, did not show significant changes of cystinosin-LKG distribution on plasma membrane.

These results demonstrate that S397 phosphorylation is necessary for cystinosin-LKG plasma membrane expression, and that active PKA is required to maintain S397 in a phosphorylated state, indicating that the expression of this isoform is functionally regulated.

When analysing the distribution of cystinosin-LKG in tissues with a specific antiserum, a strong positivity was observed in secretory cells of the bronchial epithelium, in pancreatic beta cells, in the renal tubular epithelium and in testis. In the testis, one of the tissues where this isoform is more expressed, strong immunostaining was observed in postpubertal Leydig cells and in the spermatogonium; virtually no staining was observed in the prepubertal testis. In renal proximal tubular cells the cytosolic signal was more intense in the basolateral aspects of cells. Altogether, these data support the hypothesis of a specific role of cystinosin-LKG in symptoms related to cystinosis, in particular diabetes mellitus, male infertility and proximal tubular dysfunction.

5) The 57-KB Deletion in Cystinosis Patients Extends into *TRPV1* Causing Dysregulation of Transcription in Peripheral Blood Mononuclear Cells

Katy A. Freed,¹ John Blangero,¹ Tom Howard,² Matthew P. Johnson,¹ Joanne E. Curran,¹ Yvonne R. Garcia,¹ Hao-Chang Lan¹, Hanna E. Abboud³ and Eric K. Moses¹

¹Department of Genetics, Texas Biomedical Research Institute, San Antonio, TX 78227, USA;

²Department of Pathology and Laboratory Medicine, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA 90073, USA; ³Department of Medicine, University of Texas Health Science Center, San Antonio, TX 78229, USA. Katy Freed PhD, Email:kfreed@txbiomedgenetics.org

Objective

Cystinosis is an autosomal recessive disease that is characterized by the abnormal accumulation of cystine in the lysosome. Mutations in the gene (*CTNS*) that encode a lysosomal cystine transporter represent known causes for the disease. The most common mutation associated with cystinosis is a 57-kb deletion on human chromosome 17p13 that removes the majority of the *CTNS* gene. While the *CTNS* gene was identified by a classical genetic approach, there has been minimal scientific investigation of other genes more directly involved in the pathology that may influence critical parts of the cystinosis pathobiological pathway. Thus, one of the goals in our cystinosis research program was to identify variation in transcript-specific mRNA associated with cystinosis. In this study we used peripheral blood mononuclear cells (PBMC) collected from cystinosis families to identify genes that are differentially expressed in association with cystinosis.

Design and Methods

In 2007, at the Cystinosis Research Network Family Conference, we collected 147 blood samples from individuals with cystinosis and their first degree relatives. PBMC were isolated and DNA and RNA were extracted from these samples. Initially PCR was used to classify the samples according to the status of the 57-kb deletion situated on chromosome 17p13. Whole genome transcriptional profiling was then performed on the extracted RNA using the Illumina Sentrix Human Whole Genome (WG-6) Series 3 Expression BeadChips. The Illumina BeadStudio software was used to view control summary reports, scatter plots and to determine differential gene expression.

Results

In the first instance it was important to validate our gene expression data. The expression profiles for *CTNS*, and the adjacent genes *SHPK*, *TAX1BP3* and *TRPV1*, were determined for cystinotic individuals who were homozygous for the 57-kb deletion (n=15) and for unaffected individuals that did not carry the 57-kb deletion (n=46). Consistent with previous knowledge both *CTNS* and *SHPK* were not expressed in the cystinotic samples. Surprisingly, *TRPV1* showed the same expression profile as *CTNS* and *SHPK*. This result prompted a closer examination of the *Homo sapiens* chromosome 17 genomic contig region (NT_010718) that harbors the 57-kb deletion. It was ascertained that the deletion extends from the end of exon 10 of *CTNS* to within intron 2 of *TRPV1* (NM_080704) thus deleting the first 2 non-coding exons. Therefore, our data is consistent with this deletion taking out likely transcriptional elements of the *TRPV1* gene and for the first time we have shown that expression of the *TRPV1* gene is knocked down in those individuals who are homozygous for the 57-kb deletion. Of immediate relevance to those individuals with cystinosis that are homozygous for the 57-kb deletion is that TRPV1 acts as a capsaicin receptor. We now propose that their craving for salt and spicy foods may have their genesis in the loss of TRPV1 receptors. Furthermore, this data has the potential for far-reaching consequences as TRPV1 (transient receptor

potential vanilloid 1) is a sensory receptor involved in a myriad of functions and may point to new areas of research such as neuronal/cognitive function, thermoregulation and responses to inflammatory mediators.

Conclusion

We now report for the first time that the 57-kb deletion extends into the *TRPV1* gene causing dysregulation of transcription in PBMC isolated from cystinosis patients homozygous for the 57-kb deletion.

6) Cysteamine Prodrugs for the Treatment of Cystinosis

Lisa Frost^a, Paul A. Hambleton^a, Paul W. Groundwater^b, Rosaleen J. Anderson^a

^a *Department of Pharmacy, Health and Well-being, University of Sunderland, Sunderland, SRI 3SD, UK*

^b Faculty of Pharmacy, University of Sydney, NSW 2006, Australia

Cysteamine is a successful treatment for cystinosis; however, its administration remains problematic. The aim of this work was to synthesise and evaluate a number of cysteamine prodrugs as potential therapeutic candidates. These prodrugs target GGT, an enzyme which is found on the surface of most cells and is known to be highly expressed in cystinotic cells. By utilising this transporter, the prodrugs can be transported directly into the cell, where they will be subsequently broken down to release cysteamine *via* enzymes of the glutathione cycle. This is expected to overcome the problem of low bioavailability, reduce the therapeutic dose required and minimise the side effects associated with the high dose. By masking the thiol group with prodrug moieties, oxidation to a disulfide is prevented, and the taste and smell are improved.

Using therapeutically relevant doses, in an *in vitro* evaluation, has shown the successful internalisation of the prodrugs and subsequent release of cysteamine across a number of cell lines. *In vitro* toxicity testing has shown the low toxicity of several of the prodrugs, leading to the potential for a viable clinical candidate.

We present the method development, its validation and the results of these *in vitro* investigations in this poster presentation.

7) Cysteamine Prodrugs for Treatment of Ocular Cystinosis

Lisa Frost^a, Chloe Auckland^a, Chee Khaw^a, Marina Mankarous^a, Paul A. Hambleton^a, Paul W. Groundwater^b, Rosaleen J. Anderson^a

^a *Department of Pharmacy, Health and Well-being, University of Sunderland, Sunderland, SR1 3SD, UK*

^b *Faculty of Pharmacy, University of Sydney, NSW 2006, Australia*

A range of cysteamine prodrugs has been designed to address the problems associated with cysteamine eye-drops, such as lack of formulation stability and the requirement for frequent administration. Protection of the thiol group with a prodrug moiety may reduce the therapeutic dose required, as enzymatic breakdown of this thioester after topical administration allows the sustained release of cysteamine to the ocular tissue; it also prevents oxidation of cysteamine and may lead to increased stability during storage. Simple cysteamine-thioester prodrugs have been synthesized, along with phenylalanine-cysteamine-thioester prodrugs, to target phenylalanine transporters and promote active transport into the ocular tissues where they can be broken down to release cysteamine. Tests on the toxicity and stability of these prodrugs, along with studies on their physicochemical properties, have highlighted candidates that may be suitable for further *in vitro* evaluation.

8) Proteomic investigation of cystinotic cells and the effects of cysteamine treatment

Jill Jobson¹, Noel Carter¹, Ken McGarry¹, Achim Treumann² and Roz Anderson¹

¹*Sunderland Pharmacy School, Science Complex. University of Sunderland, Sunderland, UK, SR1 3SD.*

²*North East Proteome Analysis Facility, Devonshire Building, University of Newcastle Upon Tyne, Newcastle Upon Tyne, UK, NE1 7RU.*

Abstract

The differences in the proteomes of normal and cystinotic cells have not yet been established; nor has the effect of cysteamine administration on the proteome of cystinotic cells. Such a comparison would provide crucial information on the protein changes at a cellular level caused by cystinosis. Cataloguing the protein expression differences could lead to increased understanding of the beneficial and adverse effects induced by cysteamine treatment.

In this project, we intend to use proteomics to investigate two key aspects of cystinotic cells. Firstly, we will develop a SILAC approach to carry out a whole cell comparison of cystinotic and normal kidney cells. Following collection and evaluation of this data, we will study the effects of cysteamine administration on the proteome of cystinotic cells, refining our analysis by performing subcellular fractionations and investigating changes in the proteome in different subcellular fractions.

We present the findings after the initial 5 months of this project, during which time the incorporation of labelled amino acids into normal cells and validation of the methodology have been investigated in preparation for the SILAC experiments.

9) Synthesis and biological evaluation of pegylated-cysteamine compounds for the treatment of cystinosis

G. Kay¹, Z. Omran, A. Di Salvo, R.C. Mulrooney, M. MacKay, E. Hector, T. Mullen, R.M. Knott, D. Cairns,

¹*School of Pharmacy and Life Sciences, The Robert Gordon University, Aberdeen, AB10 1FR, UK.*

Abstract - Cystinosis is a rare genetic disease, the oral treatment for which currently requires the administration of capsules every six hours. This treatment causes nausea, vomiting and the production of odorous metabolites in the breath and sweat. In an attempt to overcome these problems we have adopted a pegylation strategy. A library of pegylated derivatives of cysteamine has been synthesized and their ability to reduce the cystine burden of cystinotic cells was evaluated. One such compound, PD31, was found to be non-toxic and reduce the cystine levels in cystinotic cells.

10) Cystine levels in various tissues of a patient with nephropathic cystinosis

Galina Nesterova¹, Isa Bernardini¹, Ross Miller², Geoffrey Talmon², Stephanie Schutte²,
Jon A. Gangoti³, Bruce A. Barshop³, Jerry Schneider³, William A. Gahl¹

¹*National Institutes of Health, NHGRI, Bethesda, MD – Cystinosis Research Network*

²*Medical Center, University of Nebraska, Omaha, NE,*

³*Cystine Determination Lab, University of California, San Diego, CA*

Introduction: Cystinosis is a lysosomal transport disorder characterized by intra-lysosomal accumulation of cystine, the disulfide of the amino acid cysteine, which leads to dysfunction of the organelle, the cell, and eventually the entire organ. Cystine is poorly soluble and forms crystalline deposits in virtually all tissues. Cystine is normally present in small quantities in tissues because the large quantities of GSH present reduce cystine to cysteine; it may be that GSH also serves as a cyst(e)ine reservoir during cystine depletion. It is not known whether the cystine content of white blood cells (WBC) is representative of storage in other tissues. WBC cystine levels are directly proportional to disease severity, but normal WBC cystine levels do not exclude the possibility of higher levels in tissues, where metabolic damage can occur. Cysteamine significantly diminishes damage to many organs by lowering the intracellular cystine level, so the measurement of cystine levels in tissues is particularly valuable in determining how well cysteamine treatment is working. To our knowledge, few human tissues have been analyzed for cystine content; those studied include kidneys, skeletal muscles, rectal mucosa, cornea, cerebral tissue, aorta and myocardium.

Methods: We had an unusual opportunity to analyze tissues postmortem in one post-transplant patient. The natural history of cystinosis in this patient reflected variable compliance with cysteamine therapy for a few months prior to death. The last time the patient was seen at the National Institutes of Health was a year prior, and the cysteamine dose was indicated as 600 mg every 6 hours. At that time, the WBC cystine measurements were 2.26 and 2.64 nmol half cystine/mg protein 5 hours post dose. All laboratory data were unremarkable with normal thyroid function tests, normal liver function panel, some elevation of triglycerides levels, normal renal function with corrected creatinine clearance of 70.6 mL/min, normal tomography of the brain and normal echocardiogram. Postmortem investigation of alcohol fixed tissues was performed using polarized light within 24 hours of death. Dissected tissues initially were fresh frozen in liquid nitrogen. Cerebral, muscle, hepatic, pancreatic and thyroid tissues were thawed and immediately homogenized in 12% SSA (Sigma, St. Louis, Mo.). A protein assay was performed using BCA reagent Kit (Pierce, Rockford, IL) and cell pellets were shipped to the UCSD Cystine Determination Laboratory. Cystine levels were measured using an API 4000 triple quadrupole mass spectrometer and calculated as ½ cystine nmol/mg of protein.

Results: The gross autopsy findings included pericarditis and bilateral atrial and ventricular dilatation. The cause of death was viral acute myopericarditis; contributing factors were acute and chronic rejection of the renal allograft. Left ventricular interstitial fibrosis could be associated with cystine buildup in myocardial and interstitial cells. Alcohol fixed sections failed to demonstrate significant deposition of cystine crystals. Biochemical results are shown in Table 1 and indicate variably elevated cystine levels with the highest content in thyroid.

Table 1: Tissues cystine levels:

Tissue	Sample weight (mg)	Supernatant volume (μ L)	Protein (mg)	$\frac{1}{2}$ Cystine (nmol/mg protein)
Brain	9.6	440	0.835	0.41
Distal muscle	43.3	440	5.71	3.24
Proximal muscle	41.1	440	6.45	2.19
Liver	56.6	440	8.72	7.02
Pancreas	44.5	440	4.26	16.17
Thyroid	30.2	440	3.57	71.22

Conclusions: Considering the fact that the cystine loads of different tissues are associated with tissue damage, we can conclude that relatively low levels in some tissues do not exclude high levels in others. It is possible that the cysteamine effect is variable in different tissues, and available data are not sufficient to determine the threshold for crystal formation. Determination of cystine in other organs is in progress, including heart and native kidney. Due to limitations to studying human tissues in well-treated patients it remains a challenge to correlate disease severity, clinical symptoms, cysteamine therapy and level of organ cystine content.

11) Feasibility of protein replacement therapy in disorders of lysosomal transport

Jess Thoene, Marc J Witcher, Jodi Mullet

Division of Pediatric Genetics, University of Michigan, Ann Arbor, MI

Cystinosis and infantile sialic acid storage disease (ISSD) are both disorders of lysosomal transport due to defective cystinosin and sialin, respectively. Both have severe phenotypes. Cystinosis results in renal death by age 10 years, and ISSD causes a neuropathic death in the first few years of life. Baculovirus efficiently infects insect cells causing a lytic infection. It can be modified to over-express heterologous genes in cultured insect cells, particularly *Spodoptera frugiperda* (Sf9), and not to replicate or express in mammalian cells (BEVS, Invitrogen). The dialyzed fraction of 4 day conditioned medium from cultured Sf9 cells infected with baculovirus containing the human cystinosin gene produces 61 % cystine depletion in cultured cystinotic fibroblasts in 96 h compared to 21% for controls ($p < 0.01$). Dialyzed conditioned medium from non-infected Sf9 cells does not produce cystine depletion. Ultracentrifugation of conditioned medium from Sf9 cells infected with baculovirus containing the human cystinosin gene, at 140,000x g for 3 h, yields a pellet that on TEM shows a dense collection of vesicles, many between 40 and 140 nm. Re-suspension of vesicles in Ham's F12, passing through a 0.22 μ filter, and placing on cystinotic fibroblasts causes 57 \pm 21% cystine depletion in 96h, compared to 27 \pm 10% depletion from vesicle-free controls, ($p=0.03$, $n=5$). Vesicles from Sf9 cells infected with baculovirus containing the human sialin gene produces 40 \pm 6% depletion in sialic acid content of ISSD fibroblasts at 96h compared to an increase of 4 \pm 8% in vesicle-free controls ($p=0.04$, $n=9$). Placement of cystinosin medium vesicle fraction on ISSD fibroblasts produced no sialic acid depletion, but a non-significant increase in sialic acid content (+19 \pm 9% over T_0 , vesicle free control +4 \pm 0.08% over T_0 . $p=0.17$, $n=3$.) Depletion of cystinotic fibroblast cystine persists to at least 192 h after media change to vesicle-free Ham's F12 at 96 h. This duration is consistent with the long half-life of transmembrane proteins. The vesicles do not produce increased clearance of 3[H]-mannitol, hence increased exocytosis is not the mechanism. Toxic effects of the empty baculovirus vesicles on cells were evaluated via MTT dye reduction, a test of metabolic viability: Cells were exposed to vesicles for 96h and then dye reduction was performed as per protocol (Invitrogen/Molecular Probes, cat# V13154, Vybrant MTT Cell Proliferation Assay Kit). The absorbances were read at 570nm. Results: Empty Bac fraction = .192AU, Control = .220AU. Thus there is no apparent toxicity to cells from this vesicle preparation. We conclude there is a bioactive sedimentable factor present in the baculovirus-infected Sf9 conditioned medium associated with the vesicles. The vesicle and bioactive macromolecule formation and /or release may be stimulated by infection with baculovirus, and may represent either the human gene product, or endogenous *Spodoptera* proteins present in the vesicles. They may represent ectosomes, which fit the parameters better than exosomes and also have been demonstrated to convey functional transmembrane proteins between cells. We speculate that fusion of the vesicles with the target cell plasma membrane enables delivery of functional transport molecules to the endovacuolar system and hence to lysosomes where they function to remove the accumulated material. Depletion of sialic acid storage in ISSD fibroblasts has not been previously reported.

Industry/Advocacy:

1) AIRG France

Francois and Beatrice Couppey

The Association for Information and Research on Genetic Kidney Disease (AIRG-France) was created in 1988 under the leadership of Professor Jean-Pierre Grünfeld, a few patients, their families and doctors eager to create between their exchange networks in which knowledge of some enriched by the experience of others.

The AIRG-France is an association governed by the 1901 Act recognized a public utility by decree of 3 March 2007. It is assisted by a Scientific Council made up of nephrologists, chaired by Professor Dominique Chauveau.

2) Cystinosis Foundation, Inc.

Valerie Hotz

Since 1983 raising global awareness about cystinosis in more than 36 countries

Empowering families and patients by helping to establish 11 patient support groups internationally

Hosts bi-annual International Cystinosis Congress **Beyond Borders** since 2000

Partnering with Cystinosis Research Foundation to encourage patients to expand researchers' knowledge by registering with CCIR -www.cystinosisregistry.org

Collaborated to publish, "NephropathicCystinosis Explained to Children" - 2011

Funded research beginning in 1987, and recognized by cystinosis expert as "having kept cystinosis research alive during the 1980's and 1990's, when other funding was severely cut"

Annually Administers the Deanna Lynn Potts Scholarship benefitting an individual with cystinosis

3) The Cystinosis Research Foundation

Tricia Sturgis

The CRF's mission is to find better treatments and a cure for cystinosis. The CRF supports bench, clinical and translational research focused on its mission statement.

The CRF is funding research in eight countries, and since our formation in 2003, we have raised in partnership with other cystinosis families, more than \$16.5 million for cystinosis research. The CRF remains the largest private funding source of cystinosis research in the world.

Aggressive research efforts funded by the CRF have produced the discovery of a delayed-release form of cysteamine which is the first significant advancement in treatment in nearly 35 years.

CRF funding of stem cell and gene therapy has resulted in recent scientific breakthroughs that puts a cure for cystinosis within reach. The CRF established the CRF Cystinosis Gene Therapy Stem Cell Consortium, comprised of a group of world renowned cystinosis and gene therapy experts, to advance potential stem cell therapies.

To date, the CRF has funded 78 research studies and fellowships, totaling more than \$11.8 million.

As donations are received, they are quickly and judiciously invested in research. The CRF has two calls for research proposals every year resulting in a dynamic and synergistic research cycle. Currently, the CRF is funding 34 bench and clinical studies in eight countries. Every research grant awarded by CRF has been rigorously evaluated by the Foundation's Scientific Review Board, which is comprised of world-renown cystinosis researchers and scientists from around the world.

CRF hosts the Day of Hope Family Conference every year in Newport Beach, California. The next conference is scheduled for April 19-21, 2012.

In 2010 the CRF established, in partnership with twelve other family foundations from around the world, the first international cystinosis patient registry – Cure Cystinosis International Registry - CCIR.

The CRF supports cystinosis families through social networking sites, the CRF Resource Center, and family to family network connections.

Contact: Nancy Stack, President, Cystinosis Research Foundation,

Email : nstack@cystinosisresearch.org (949)760-5375

4) Cystinosis Research Network Education and Awareness Program

Karen Gledhill

The Cystinosis Research Network (CRN) is a volunteer, non-profit organization dedicated to advocating and providing financial support for research, providing family assistance and educating the public and medical communities about cystinosis.

The vision of CRN is the discovery of improved treatments and ultimately a cure for cystinosis. The CRN funds research and programs primarily through donations from the public, grassroots fundraising events and grants.

As our mission states, we work on educating the public and medical communities about cystinosis. This table top display, stand up display, brochures, pens and key rings are some of the items that we bring with us to medical meetings that have been targeted by CRN. These include ASN (American Society of Nephrologists), Genetic Research Alliance of Children, NORD (National Organization of Rare Diseases), ASPN (American Society of Pediatric Nephrologists), and Genetic Alliance. In October 2011 CRN will be a sponsor of the Latin American Pediatric Nephrology Association meeting in Sao Paulo, Brazil. Our members volunteer their time to attend these conferences and speak and hand out information to interested professionals.

5) CRN Scholarship Program

Pam Woodward

CRN Academic Scholarship for Individuals with Cystinosis

The Cystinosis Research Network has established a scholarship fund to provide supplemental financial assistance to a student diagnosed with Cystinosis who is enrolling in a regionally accredited collegiate or vocational program, or who is currently attending a post – secondary school. The scholarship award, \$1000, is awarded contingent upon the winner's acceptance to an accredited college, university, or vocational program, or documentation of continued enrollment, and will be payable to the educational institution to be applied toward tuition. An application form is available on the CRN website at www.cystinosis.org/scholarships. For more information or to have an application mailed to you, please contact CRN at 1-866-276-3669 or info@cystinosis.org.

CRN Sierra Woodward Sibling Scholarship

The Cystinosis Research Network has established a scholarship fund to provide supplemental financial assistance to a student who has a sibling diagnosed with Cystinosis who is enrolling in a regionally accredited collegiate or vocational program, or who is currently attending a post – secondary school. The scholarship award, \$1000, is awarded contingent upon the winner's acceptance to an accredited college, university, or vocational program, or documentation of continued enrollment, and will be payable to the educational institution to be applied toward tuition. An application form is available on the CRN website at www.cystinosis.org/scholarships. For more information or to have an application mailed to you, please contact CRN at 1-866-276-3669 or info@cystinosis.org.

6) Mexican Association of Cystinosis

Victor Gomez

The Mexican Association of Cystinosis is a volunteer, non-profit organization dedicated to support and assistance of patients with cystinosis in Mexico and Central America; and to promoting awareness for medical personnel and interested public for this rare disease. www.cystinosismexico.com, www@cystinosismexico.com

7) Advocacy Through Collaboration to Achieve Patient-Centered Goals

Mary E. Cobb, Senior Vice President, National Organization for Rare Disorders (NORD), mcobb@rarediseases.org, 202-821-3699 (business cell)

The National Organization for Rare Disorders (NORD) is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the patient organizations that serve them. As an umbrella organization, NORD is committed to being the voice of the rare disease community and works tirelessly to further the identification, treatment, and cure of rare disorders through advocacy, education and awareness-building, supporting innovation, promoting access and providing patient assistance. NORD believes in the *power of collaboration and the value of diverse perspectives – all in the interest of achieving patient-centered healthcare*. It is the foundation of NORD's overall approach. NORD works with partners in the patient community, government, academia, healthcare community and industry who share the ultimate goal of identifying, treating, and curing rare diseases and, above all, representing the interests of patients. This poster presentation will highlight key patient-oriented initiatives in each area of focus at NORD that have been successful due to collaborative efforts with different and valued stakeholders.

Patient/Family:

1) The Living with Cystinosis Survey – Identifying Concerns of Emerging Adults with Rare Disease

Cystinosis Research Network; Maya Doyle, LCSW, ABD, Children's Hospital at Montefiore; Colleen Hammond, RN

Introduction: Medical innovations have transmuted cystinosis from progressive/fatal in early adolescence, to chronic/manageable into adulthood (Feudtner, 2003; Gahl, 2009; Nesterova & Gahl, 2008; Rolland & Werner-Lin, 2006). Children diagnosed in the 1990's comprise the first generation to survive into late adolescence and emerging adulthood. They must incorporate a demanding treatment regimen (Kleta & Gahl, 2004; Schneider, 2004) into an increasingly independent lifestyle, and renegotiate relationships with family, partners, and providers. The cystinosis community has identified transitioning to adulthood and adult-oriented healthcare as a research and programmatic priority.

Methods: The Living with Cystinosis (LWC) survey (Cystinosis Research Network & Doyle, 2011), a pilot exploratory needs-assessment, is part of a participatory action project designed and implemented by patients and families affiliated with the Cystinosis Research Network (CRN), assisted by scientific and professional advisors. Ten questions elicited demographic information; 8 multiple-choice items addressed financial, educational, employment, social, medical, and emotional/mental health domains; 5 Likert scales addressed impact of illness, fatigue, satisfaction with medical care, transitioning concerns, and research priorities. Each question included space for open-ended responses. LWC demonstrated content validity when reviewed by patients, families, and providers before distribution. Participants were recruited over a 2-month period by online postings and email blasts. Results were cross-tabbed by age of affected family member; open-ended responses were coded by domain of concern. Results were disseminated through CRN's website to families, providers, and researchers.

Findings: 148 responses were received from self-identified patients and parents (approximately 250 individuals with cystinosis live in the US), 29 from participants aged 19-25 (of an estimated 60). The most common medical concern for 19-25 year olds was kidney transplant rejection (41%); participants indicated concerns about muscle wasting, a long-term outcome of carnitine deficiency that affects swallowing, speech, and breathing. The intrusive treatment regimen, which requires unpalatable medication ever 6 hours and eyedrops every waking hour, was the strongest concern across age groups. Treatment adherence was of greater concern for 19-25 year olds than for other age groups. 40% of participants aged 19-25 expressed concerns about finding knowledgeable specialists. Of 9 participating families with children aged 12-18, none reported their medical team was developing a transition plan. Participants aged 19-25 indicated fear of aging out of parents insurance (53%) or falling into medical debt (47%). Among all groups, males aged 19-25 expressed the greatest concern about relationships/ marriage, and having children.

Implications: Transitioning to adulthood and adult-oriented care raises practical, medical, and reproductive concerns for emerging adults with cystinosis. Patients and families need resources and responsiveness from healthcare providers to navigate these transitions successfully. Social workers can play a vital brokering and coaching role in this process. Survey results are being used to design educational materials for cystinosis patients and families and to facilitate education of pediatric and adult-care providers. The National Organization for Rare Disorders (NORD) recognized the survey as a model for other advocacy groups whose members are transitioning to adult-oriented care.

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