Welcome

Dear researchers, colleagues and, most of all, those living with cystinosis and their families,

With this compilation of abstracts from the keynote speakers at our 4th Annual Dublin Cystinosis Workshop, 6/7 April 2018, we hope to bring you a flavour of the world class cystinosis research that is ongoing in laboratories across the world. All of the research presented at our workshop aims to advance our understanding of cystinosis and to improve treatments and ultimately find a permanent cure, thereby improving the lives of those living with cystinosis and their families in Ireland and world-wide.

This year, Cystinosis Ireland was delighted to welcome 22 scientists from New Zealand, USA, England, Scotland, Belgium, Netherlands, Germany, Italy and of course from Ireland (North and South) to DCW 2018 which was held on April 7, 2018.

The speakers presented new and cutting-edge research into various aspects of cystinosis including: new drug therapy formulations and delivery strategies including the use of contact lenses for more effective ocular cysteamine delivery; understanding the molecular biology and pathophysiology of the cystinosis disease and various genetic strategies aimed at developing a long-term cure as well as discussions around issues of infertility and treatments of the disease.
that go beyond cystine depletion.

A key objective of this year’s workshop was to highlight important research questions that are relevant to cystinosis patients and their families but that are not well addressed by researchers yet.

The workshop was moderated by Dr James Murray, Trinity College, Dublin and Dr Patrick Harrison, University College, Cork.

2018 is the 15th anniversary of Cystinosis Ireland’s establishment and of its commitment to supporting world-class research into better understanding, treating, and finding a cure for the immensely challenging rare genetic disease that is cystinosis.

Cystinosis Ireland also plays an important role in advocating for and providing support to those living with cystinosis on the island of Ireland.

Cystinosis Ireland continues to seek new research opportunities in our areas of interest that will bring us closer to improving the treatment of cystinosis, enhancing the lives of those living with the disease and taking one step closer to finding a cure. We’ve accomplished a lot in the past fifteen years and we will continue to do so until we find a cure. We value and appreciate everyone who helps us in achieving these goals.

Hosting the 4th Annual Dublin Cystinosis Workshop would not be possible without the very generous support from public donations received by Cystinosis Ireland. We would also like to acknowledge the additional conference support received from the Health Research Board (HRB) and Science Foundation Ireland (SFI).
I would also like to thank the members of the Workshop Organising Committee – Dr James Murray, TCD, Dr Achim Treumann, Newcastle University and Ms Anne Marie O’Dowd, with the able assistance of Ms Sue Maguire, Ms Denise Dunne and Dr Ruth Davis, for all their hard work in organising this event.

I hope you find this publication both stimulating and useful. And even more, I hope that the Dublin Cystinosis Workshop encourages researchers to continue their quest to find the ultimate cure for this disease.

I thank you for your ongoing support and I look forward to seeing you again at our next workshop in 2019.

Mick Swift
Chairman, Cystinosis Ireland
About Cystinosis Ireland

Cystinosis Ireland was founded in 2003 as an Irish registered charity. It was created by volunteers – family members and family friends of those living with cystinosis. Its purpose is dedicated to raising money to fund research into cystinosis in Ireland and all over the world.

As a charity, we aim to reach out to families of those living with cystinosis – children and adults – and to also offer support to newly diagnosed families.

Cystinosis Ireland works closely with Temple Street Children’s Hospital and Beaumont Hospital in Dublin as well as with the Great Ormond Street Hospital in London. Cystinosis Ireland also maintains partnerships with other cystinosis charities abroad including; The Cystinosis Foundation UK, the Cystinosis Research Foundation (CRF) in Irvine, California, USA, the Cystinosis Research Network (CRN) in Lake Forest, Illinois, US and the Canadian foundation - Cystinosis Awareness Research Effort (CARE) and to all the cystinosis patient group representatives and charities in Europe and beyond.

Through these partnerships, we share research findings, discuss drug access programmes, review challenges being faced by the greater community and work towards finding a cure. Cystinosis Ireland is also an active member of the Cystinosis Network Europe and EURORDIS, the European rare disease patient group alliance.

The Executive Committee of Cystinosis Ireland comprises eight members – three of whom are family members of those living with cystinosis and five of whom are industry and other professionals. The Committee has a number of subgroups that manage key activities including; Education and Support, Media and Publicity, Fundraising and Research.

Recently, Cystinosis Ireland recruited two new part-time members of staff to assist the Executive with the day-to-day operation of the charity.

The members of the Cystinosis Ireland Executive are:

Chairman  Mr Mick Swift
Treasurer  Mr Liam McFadden
Committee Members  Ms Nuala Lawless
                  Mr Andy Maguire
                  Ms Sue Maguire
                  Dr Tom McDonald
                  Ms Anne Marie O’Dowd
                  Ms Rachael Reilly
The operations team of Cystinosis Ireland is:

**MS DENISE DUNNE**

Denise has worked with patient and family carer support and medical research charities for much of her career, including roles with the Irish Lung Fibrosis Association, Fighting Blindness, Care Alliance Ireland and the Medical Research Charities Group.

She has extensive experience in the day-to-day management of organisations and providing one-to-one support to patients and families living with life-long conditions.

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**DR RUTH DAVIS**

Ruth has 20 years’ experience working in both public and private sectors, particularly in the areas of research and academic management in a number of higher education institutions (HEIs) in Ireland as well in the Higher Education Authority (HEA).

Apart from her work with Cystinosis Ireland, Ruth also works as an independent consultant specialising in the areas of higher education and research funding and strategy, management and policy and is currently engaged in projects with the HRB and HEA.
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SPEAKER ABSTRACTS
SESSION 1 - THERAPEUTICS
Work to date has revealed CF10 as a candidate prodrug to improve the treatment of cystinosis.

*In vitro* CF10 showed low cytotoxicity, good uptake into cells, reliable release of cysteamine, and sustained depletion of cystine when compared to cysteamine. *In vivo* studies have shown low/no gastrointestinal damage by CF10, good cystine depletion in the cystinotic mouse model, in the new zebrafish model of Cystinosis, CF10 performed better than cysteamine: 100 µM CF10 added at 48 hpf vs 500 µM cysteamine at 1-2 hpf, it also produced increased hatching, reduced deformities and improved survival; however, CF10 caused no cystine depletion in this model. This strange result may be due to differences in prodrug activation in zebrafish, as cystine depletion was observed in the cystinosis mouse model.

The aims of CF10 are reduced gastric irritation, decreased exposure of blood to cysteamine, decreased metabolism of cysteamine to methane thiol and dimethylsulfide, reliable delivery of cysteamine to cells / tissues, less frequent dosing, effective depletion of cystine and make it easier for patients to comply with their medicine regimen.

Recent evidence of the suitability of CF10 as a prodrug delivery for cystinosis was obtained in pharmacokinetic studies in rats, which demonstrated that administration of CF10 led to a much lower level of cysteamine in the blood than was seen after administration of cysteamine, while greater levels of cysteamine were achieved in the kidney and muscle tissues after CF10 administration, with sustained cysteamine levels. The major plasma species after CF10 administration was a key metabolite of CF10, which was designed to deliver cysteamine to tissues and showed good availability after both IV and
oral administration.

Overall, these results confirm consistent pharmacokinetics and the desired low cysteamine levels in blood, with limited opportunity for metabolism to methane thiol and dimethyl sulfide.

The results also show effective and sustained delivery of cysteamine to tissues, especially the kidney, confirming that CF10 is a suitable prodrug for delivery of cysteamine to tissues and acts as designed. Furthermore, the sustained delivery of cystamine to tissues suggests less doses may be required per day.

Funding is sought for preclinical studies to establish the safety and toxicology of CF10 in mammals. A special purpose vehicle (spin out company) has been set up to progress CF10 through clinical trials to market.
Cystinosis is lysosomal storage disease caused by mutations in the CTNS gene controlling the production of the cystine transporter, cystinosin. The resulting cystine crystals deposition results in damage to many organs including cornea. The corneal disease can be treated with frequent instillation of cysteamine eye drops that is tedious and leads to poor compliance. Additionally, significant drug degradation occurs within one week of opening the bottle, further complicating this approach.

Professor Chauhan presented the design of a contact lens to treat the disease with improved efficacy. The lens is safe and delivers a daily therapeutic dose of cysteamine to the cornea while retaining drug stability.

Using commercial contact lenses is impossible as cysteamine rapidly diffuses out due to its small molecular size. We developed a novel approach of incorporating vitamin E into the lenses to reduce the drug diffusion through barrier effect. The vitamin E loaded contact lenses release cysteamine for about three hours compared to a few minutes for the control lens. The presence of vitamin E has an additional beneficial effect of reduction in the oxidation rates. The therapeutic efficacy of vitamin E and drug loaded lenses is demonstrated in a glaucoma model of Beagle dog and safety of cysteamine and vitamin E loaded lenses is demonstrated in a rabbit model.

Also, preliminary efficacy was demonstrated in an ex vivo model designed by depositing cystine crystals into the cadaver rabbit eye, followed by dissolution through contacts.

Studies that focused on depositing the cystine crystals in the ex vivo model also showed some interesting results...
that could be valuable in understanding and treating ocular cystinosis. For instance, it was observed that the cystine crystals in the \textit{ex vivo} model are needle shaped which is similar to that in the diseased cornea, while the shapes in other organs are polygonal.

Finally, Dr Chauhan showed that the shelf life of the cysteamine formulation could be considerably increased to a few months by optimizing the packaging and formulation.
Dr McKenzie’s presentation focused on reformulation of cysteamine strategies that are being conducted within the laboratories of the Robert Gordon University, Aberdeen, Scotland.

Initially, Dr McKenzie discussed the currently available eye drops (Cystadrops, Cystaran), and their side effects and multiple daily dosage regimes.

Dr McKenzie then spoke about the eye gel which she developed, and the fact that it is bioadhesive, isotonic, non-irritant, non-toxic and naturally hydrating. This eye gel, which contains 0.55% cysteamine has been tested for cell toxicity and stability, and was found to be suitable for potential delivery to the eye. It is hoped that this formulation would have a once or twice-daily dosage, due to the drug having more time to absorb via a gel formulation compared to the eye drop.

Dr McKenzie also discussed the use of the HET-CAM test to analyse eye irritation (as a humane alternative to the Draize rabbit test), and the eye gel was comparable to saline as a non-irritant.

Other drug delivery formulations investigated include suppositories (useful for infants or those with swallowing issues), as well as a dry powder inhaler.

Dr McKenzie also touched upon the alternative uses for cysteamine, such as for Huntington’s disease or Parkinson’s disease.

Dr McKenzie received her PhD in Pharmaceutics from the Robert Gordon University in 2011. During her PhD study, she investigated various alternative formulations of cysteamine, including ophthalmic gels and a dry powder inhaler. In 2013, she joined the faculty of the School of Pharmacy and Life Sciences at the Robert Gordon University as a lecturer.

Dr McKenzie’s current research interests focus on ophthalmic drug delivery, in vitro ophthalmic models, cysteamine treatment for nephropathic cystinosis and problem-based learning approaches.
Cysteamine is the only therapy available for cystinotic patients. It significantly improves life expectancy and allows delaying progression to end-stage renal failure. However, it cannot prevent it. Finding better therapies is, therefore, a priority in the field of cystinosis research.

Dr Rega previously observed that genistein, an isoflavone particularly enriched in soy, is able to revert in vitro part of the cystinotic cellular phenotype that is not sensitive to cysteamine (Rega et al.; 2016).

To test the benefits of genistein in vivo, wild type and Ctns -/- mice are being fed with a control diet or with a genistein-supplemented diet.

Preliminary evidence suggests that genistein delays the onset of kidney dysfunction in cystinosis and has a good safety profile.

Genistein therapy represents a potential treatment to improve outcome of patients with cystinosis.
SPEAKER ABSTRACTS
SESSION 2 - MOLECULAR BIOLOGY OF DISEASE
A single gene defect (monogenetic disease) can result in a life-threatening disease and be responsible for a large number of clinical problems. Gene therapy is aimed at restoring the function of this gene, thereby providing a complete and lasting cure.

Currently, many clinical trials are being conducted using gene therapy and some already made it to the market, like the one for severe combined immune deficiency (Glyberia) or for lipoprotein lipase deficiency (Strimvelis). Here, a copy of the affected gene (cDNA) is stably introduced into cells to restore cell function and halt disease progression. The greater our knowledge on disease mechanisms, the more pathologies will become realistic targets for gene therapy.

In case of cystinosis, mutations in the lysosomal cystine transporter cystinosin (CTNS) are known to be responsible for this disease. Studies in mice have already shown that a bone marrow transplantation from healthy mice can prevent kidney failure in cystinosic mice. Also, overexpression (gene addition) of the gene product of cystinosin in haematopoetic stem cells was able to prevent disease progression. This indicates that only a subset of cells needs to produce the functional gene product (in this case the blood cells) to support other tissues as well, which is promising for developing a new gene therapy.

The disadvantage of overexpression is that cells lose the ability to regulate the gene levels and that only one (iso) form of the gene can be expressed. CTNS gene has two isoforms with distinct expression patterns, which are thought to play different roles in the cell. In the case of gene repair the affected DNA sequence is replaced with the functional sequence and also gene regulation...
and isoforms are restored. Gene repair has become possible with the discovery of CRISPR/Cas9 nuclease.

Dr Janssen is now testing if this can be done for the CTNS gene as well, by introducing DNA fragments in the cell with high homology to the genomic sequence, together with the induction of a double strand break, the cell can repair the genetic mutation. Only a few base pairs can make the difference between health and disease, and she hopes that this will be a hurdle that can overcome in the future.
The generation of induced pluripotent stem (iPS) cells from patients with hereditary diseases and the differentiation of these cells into mini organs (organoids) provides a new way to study and find treatments for illnesses *in vitro*. The lysosomal storage disease nephropathic cystinosis results from mutations in the CTNS gene, encoding a cystine transporter, and initially causes kidney proximal tubule dysfunction followed by kidney failure. Patients receive the drug-based therapy cysteamine from diagnosis, however, despite long-term treatment with this drug, patients still progress to kidney failure with the need for transplant inevitable. There is an urgent need for alternative treatments as there is increasing evidence that secondary complications are associated with loss of CTNS that are unrelated to the accumulation of cystine.

Dr Hollywood’s presentation describes the characterization of iPS cells from a patient with nephropathic cystinosis as well as a CRISPR/Cas9-induced line and the development of a simple protocol for generating human kidney organoids. As expected, cystine (and cysteine) levels are elevated and basal autophagy flux is reduced in CTNS-iPS cells and CTNS-kidney organoids. Some CTNS-iPS cells displayed large degradative vacuoles with multivesicular inclusions. RNA-Seq analysis of CTNS-iPS cells identified new biomarkers for cystinosis, including the DDIT3 gene (aka CHOP), which encodes a C/EBP-homologous protein which functions as a cellular stress sensor.

Dr Hollywood has found that cysteamine treatment of CTNS-iPS cells and organoids lowered cystine and cysteine levels, reduced the number of large degradative vacuoles and restored the expression of DDIT3 and other biomarkers to normal levels. However, the basal...
autophagy flux defect was not corrected. Similar results were found, with the addition of correction of autophagy flux, using the FDA-approved drug Everolimus, which inhibits the mTOR pathway and has recently been implicated in cystinosis.

Together, the results indicate that the iPS cell/organoid platform can be used to model aspects of cystinosis and suggest that mTOR-inhibiting drugs may have therapeutic value in the treatment of this disease.
CRISPR-MEDIATED CTNS KNOCKOUT PROXIMAL TUBULE EPITHELIAL CELLS OFFER A VERSATILE TOOL FOR STUDYING NEPHROPATHIC CYSTINOSIS

A. Jamalpoor, R. Masereeuw, M. Janssen

To study the link between the CTNS gene and the cystinosis, and investigate novel therapeutic strategies we have generated a cystinosis phenotype in human kidney cells, ciPTEC using CRISPR/Cas9 system and study cystinosis pathology.

Using CRISPR/Cas9 technology, heterozygous (CTNS\textsuperscript{+/-}) and homozygous (CTNS\textsuperscript{-/-}) isogenic cell lines of ciPTEC were generated. Consistent with a cystinotic phenotype, CTNS\textsuperscript{-/-} but not CTNS\textsuperscript{+/-} cells displayed a significantly high level of cystine as compared to control cells (6.32 ± 0.9 vs. 0.05 ± 0.02 nmol/mg protein; p<0.001). Upon treatment with cysteamine (100 μM), a cystine depleting agent, CTNS\textsuperscript{-/-} cells showed a significant reduction in cystine levels (0.74 ± 0.05 nmol/mg protein; p<0.01). Immunostaining revealed that mTORC1 was dislocated from lysosomes and inactivated in cystinotic cells, resulting in 2 and 2.5-fold increase (p<0.001) in TFEB nuclear translocation in CTNS\textsuperscript{+/-} and CTNS\textsuperscript{-/-} cells, respectively, when compared to control cells. This suggests an abnormal induction of autophagy in cystinosis, which was confirmed by the increased production of LC3-II, an autophagy marker, in both CTNS\textsuperscript{+/-} and CTNS\textsuperscript{-/-} cystinotic cells (p<0.001).

Of note, cysteamine had no effect on the restoration of autophagy, which might explain its limited effect on treating renal Fanconi syndrome.

Mr Amer Jamalpoor is a PhD candidate at Utrecht University working on the project entitled “Gene therapy as a new strategy for the treatment of cystinosis”. His academic and research interests lie in the development of a novel therapeutic intervention that can be used to treat patients suffering from nephropathic cystinosis.

He believes that gene therapy using designer nucleases like CRISPR/Cas9 can be utilized to repair a site-specific gene mutation and thereby used as a potential therapy for cystinosis.
SPEAKER ABSTRACTS
SESSION 3 - FUNDING STRATEGIES
Ms O’Dowd described the main research questions that are important for all the families, including those with small children. In particular, Ms O’Dowd highlighted the concerns of parents that health issues arise for children transitioning into adulthood even where the patients’ have demonstrated excellent adherence to cysteamine treatment.

Ms O’Dowd identified four key research questions that remain as yet, insufficiently addressed by the research community and that are key challenges for patients and families. These are:

1. Side effects of cysteamine - halitosis and body odour become major issues as children age and this interferes with the level of adherence to cysteamine. It also causes major psychological issues. Work had been done on developing new compounds but something that would work with cysteamine would be very welcome. Concern about other side effects of cysteamine – for example, Ehler Danlos-type symptoms, collagen issues and subsequent death in one patient. What other effects is it having that we don't know about?

2. Muscle weakness - swallowing problems have led to aspiration and death in some patients plus weakness in other muscles such as hands, legs, arms. Even patients who adhere well to their drug therapy have these issues. Is it caused by cysteamine and/or the cystinosis disease?

3. Bone issues, including knock knees, which occur in most children whatever level of drug therapy adherence; spontaneous fractures and weak bones. Nearly all children have flat feet/fallen arches. These are in children who are well maintained on vitamin D, calcium
etc and who have had diagnosis at birth.

4. In early childhood, not eating is a major issue. Most children need a g-tube for feeding after diagnosis. There's a question about if it's cysteamine treatment or cystinosis that is the main reason for lack of appetite/not eating, or kidney damage - although siblings without kidney damage can also have these problems. Of course, vomiting in early childhood is so common that it is difficult to know where one issues starts/ends. Lack of eating has knock-on effects for life.
SPEAKER ABSTRACTS
SESSION 4 - MECHANISTIC UNDERSTANDING OF DISEASE
GENE EXPRESSION CONNECTIVITY MAPPING AND ITS APPLICATION TO TARGETING KEY GENES IN CYSTINOSIS

Dr Shu-Dong Zhang
Senior Lecturer in Stratified Medicine (Bioinformatics/Statistics)
Northern Ireland Centre for Stratified Medicine, University of Ulster, C-TRIC, Derry/Londonderry

Gene expression connectivity mapping is an advanced bioinformatics technique that establishes connections among different biological states via their gene expression profiles/signatures. An important application of connectivity mapping is the identification of small molecule compounds capable of inhibiting a disease state, or more generally, altering a disease state towards a more favourable condition.

In this talk, Dr Zhang introduced the concept of Connectivity Map and the Principle of Phenotypic Targeting as the theoretical foundations, and then presented examples of successful application to a number of human diseases including cancers [1] and cystic fibrosis [2]. Recently, this connectivity mapping approach has been applied to targeting clusterin in cystinosis research, following the discovery by Minnie Sarwal and colleagues (UCSF) that intracellular clusterin is implicated in nephropathic cystinosis, and the inhibition of intracellular clusterin attenuates cell death in nephropathic cystinosis [3].

From the connectivity mapping analyses, a number of FDA-approved small molecules were identified as candidate drugs to inhibit clusterin, which were subsequently validated in James Murray’s lab in TCD using human cellular models. In summary, the application of connectivity mapping to cystinosis as a target disease is promising with some initial success.

References:


Mainly, kidney is the organ that suffers most with cystinosis. However, hypogonadism and delayed puberty has been also reported in male patients. In addition, male cystinosis patients show azoospermia, regardless to their kidney functions.

In order to understand the mechanism of azoospermia in such patients, Dr Reda’s study aimed to assess the gonadotoxicity of cysteamine, which is used as a first line treatment for cystinosis patients.

In an animal study, cysteamine was given orally to wild type mice. The results have shown that cysteamine had no effect on fertility or sperm parameters of the mice taking cysteamine orally.

Next, he aimed to analyse testicular samples from male cystinosis patients histologically. It was observed that testicular tissues from three different patients have revealed full spermatogenesis, which showed normal hormonal and testicular function in those patients. Moreover, two male cystinosis patients underwent percutaneous epididymal sperm aspiration (PESA) in which it was successful to retrieve sperm and achieving pregnancies. These observations indicate that the only possibility to lose the sperm is via post-epididymal obstruction.

In conclusion, Dr Reda suggests that cysteamine has no negative impact on male fertility, male cystinosis patients have the opportunity to achieve pregnancies through PESA technique, and the mechanism of azoospermia in such patients is most probably due to post-epididymal obstruction.

Further studies are following to reveal the definite mechanism of that obstruction.
A subtype of cystinosis is nephropathic cystinosis, which causes kidney failure in children and young adults.

The gene (cystinosin or CTNS) defect does not explain the diverse symptoms of nephropathic cystinosis. Despite substantial improvement in prognosis with drug cysteamine, no cure of the disease is currently available.

The Sarwal Lab, previously at Stanford University for 16 yrs and now at the University of California San Francisco, has been jointly funded by Cystinosis Ireland and the Health Research Board, Ireland, together with the Murray Lab at Trinity College, Dublin to investigate the transcriptional, cellular and molecular mechanisms causing kidney injury, and identify novel drugs that may prevent kidney cell death (autophagy), mitochondrial dysfunction (injury to the powerhouse of the cell) - previously identified as key pathways by these researchers.

Dr Sur presented the experimental data that induction of autophagy in the kidney requires glucose for energy and that a novel molecule, clusterin (CLU) is a factor that drives the kidney cell injury. Transcriptional studies in cystinotic kidneys have offered novel insights into other cellular processes that may further explain why the kidney is uniquely susceptible to injury in cystinosis.

New drugs are being tested to reverse kidney injury in cystinotic cells, so as to allow them to be used to prevent and treat kidney damage in this condition.

Dr Swastika Sur is a Postdoctoral Researcher at the Sarwal Lab in the Department of Surgery, University of California San Francisco, California, USA, where she is carrying out cutting-edge research in renal diseases under the mentorship of Dr Minnie Sarwal, who leads the translational program in solid organ transplantation and kidney diseases at the UCSF.

Dr Sur’s research interests include designing and identifying therapeutic targets and validating their function in vitro and in vivo.

Dr Sur received the BSc and MSc degrees in Biotechnology from Bangalore University, Bangalore, Karnataka, India in 2004 and 2006, respectively. In 2016, she received her PhD in Biomedical Sciences from Creighton University, Omaha, Nebraska, USA. She is a member of the American Society of Nephrology.
Cystinosis is an autosomal recessive lysosomal storage disorder characterized by the gradual accumulation of the amino acid cystine in the lysosomes of different body cells. This is due to pathogenic mutations in the CTNS gene coding for the specific cystine lysosomal transporter cystinosin. The earliest manifestation of the disease usually involves renal proximal tubular cells, leading to the loss of different solutes in urine known as the renal Fanconi syndrome. Glomerular disease is also an early finding in many patients. If not treated, cystinosis will result in renal failure by the end of the first decade of life.

However, the disease is not restricted only to the kidney. It is a multi-systemic disorder affecting most tissues and organs.

Cysteamine is an aminothiol compound that can facilitate the depletion of lysosomal cystine through its biochemical reaction with the cystine molecule. Although cysteamine is the standard current therapy for cystinosis patients, it cannot prevent the development of the renal Fanconi syndrome and cannot restore the lost renal function. Moreover, cysteamine treated cystinosis patients still develop the multi-systemic disease complications at a later stage in life.

Finding new therapies for cystinosis, which can replace or compliment cysteamine therapy and new biomarkers that can monitor therapy in a more efficient way are of utmost importance.

For this reason we developed and validated a new zebrafish mutant model for cystinosis with a nonsense mutation in exon 8 of the zebrafish ctns gene. The new zebrafish mutant shows early phenotypic characteristics...
of the human disease including cystine accumulation, delayed development, enhanced apoptosis, increased pronephric glomerular permeability, decreased GFR and defective proximal tubular reabsorption. Similar to the human disease, cysteamine treatment decreased cystine accumulation and improved apoptosis.

The described zebrafish model is useful for the study of the pathophysiological aspects of cystinosis and for the \textit{in vivo} screening of novel therapeutic agents, which is currently ongoing.

During the symposium some examples of drug screening in the cystinotic zebrafish model have been provided. Special focus has been put on restoration of endocytosis in the cystinotic zebrafish.

Professor van den Heuvel has been studying the pathophysiology of cystinosis since 2001. At present the cystinosis research line is studying the involvement of podocytes in the pathophysiology of cystinosis, testing novel compounds for treatment of cystinosis in a zebrafish model, investigating the molecular base for infertility in male cystinosis patients and looking for new biomarkers for treatment compliance in cystinosis patients. The research part is of the department of Development and Regeneration of the research institute Biomedical Sciences at KU Leuven (Belgium).
CYSTINOSIS RESEARCH FUNDING OPPORTUNITIES
2018/2019
The Cystinosis Seedcorn Funding Programme aims to provide researchers with the opportunity to generate solid preliminary data which would contribute to a sustainable, longer-term application for funding.

Funding is available to research institutions worldwide.

Researchers new to the field are welcomed.

Research can be in any area of cystinosis. But, areas of interest currently for families of those with cystinosis are bone issues; muscle problems; vomiting in young children; use of ‘blended’ diet; combatting halitosis and the smell of cysteamine treatment and healthcare transition models.

We are open to high-risk, ‘blue sky’ applications and will consider these favourable as long as applicants highlight this in their application.

We operate a rigorous peer review process.

Cystinosis is a very rare autosomal recessive disease, a lysosomal storage disorder. It is characterised by raised intracellular levels of cystine which has major systemic effects.

This Seedcorn Fund is supported by Cystinosis Ireland, Cystinosis Research Network USA (CRN) and Cystinosis Foundation UK (CF UK), all of whom are voluntary organisations that support those living with cystinosis and their families.

MAXIMUM FUNDING AVAILABLE: €10,000 per project (more in exceptional circumstances)
DURATION OF PROJECTS: 2-6 months
CLOSING DATE FOR APPLICATIONS: 31st May, 31st August, 30th November 2018

CONTACT US NOW FOR FURTHER INFORMATION: RESEARCH@CYSTINOSIS.IE
MRCG/HRB Joint Funding Scheme
CALL FOR PROPOSALS 2019
Partnering with Cystinosis Ireland

Cystinosis Ireland participates in the MRCG/HRB Joint Research Funding Scheme in which patient organisations, such as Cystinosis Ireland, and the Health Research Board (HRB) share the cost of funding high quality research activities of particular relevance to the patient organisation.

Funding is available to research institutions worldwide.

Cystinosis Ireland is interested in all areas of cystinosis research including fundamental research as well as translational research. Some of the research areas of particular interest for the families of those with cystinosis include bone issues; muscle problems; vomiting in young children; use of ‘blended’ diet; combating halitosis and the smell of cysteamine treatment and healthcare transition models. However, all areas of research relevant to cystinosis are encouraged.

Researchers interested this funding are encouraged to send an expression of interest in the first instance to Cystinosis Ireland.

This scheme is subject to a rigorous peer review process.

MAXIMUM FUNDING AVAILABLE: €300,000 per project
DURATION OF PROJECTS: 12-36 months
CLOSING DATE FOR APPLICATIONS: The MRCG-HRB Joint Funding Scheme opens for applications in Autumn 2019 with a view to a project start date in 2020

CONTACT US NOW FOR FURTHER INFORMATION: RESEARCH@CYSTINOSIS.IE

Cystinosis is a very rare autosomal recessive disease, a lysosomal storage disorder. It is characterised by raised intracellular levels of cystine which has major systemic effects.

The MRCG/HRB Joint Funding Scheme enables MRCG-registered research charities like Cystinosis Ireland to support research of particular interest to specific patient populations.