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CYSTINOSIS IRELAND ANNUAL REPORT 2019

2019 was another important year for Cystinosis Ireland and our community.

Our families are the backbone of what we do. They inspire and direct our work as key advocates for their loved ones.

Over the past 16 years we have invested almost €2m in cystinosis research on behalf of all our members. These monies have come from two distinct sources: from fundraising taken on by our friends and families, and from a successful record in attracting co-funding through the HRCI-HRB Joint Funding Scheme. This fundraising reflects the effort from our families and friends who give up days, weeks and even months to train, plan and execute events from church gate collections and school events to iron(wo)man challenges and golf days, with everything in between, as well as the work of our research team in sourcing, reviewing and preparing projects for consideration by the HRCI-HRB Joint Funding Scheme.

Our goal is to work with excellent research teams wherever we find them, to one day – hopefully soon – find the cure for cystinosis.

In 2019 we saw a number of significant research developments including the start of a clinical trial in a gene therapy in the US. This work by Dr Stephanie Cherqui and her team is an incredible leap forward in a potential therapy and offers great promise. It is by no means the only opportunity for the future, but it is a beacon of hope for many. Here in Ireland, after a long campaign, Procysbi was at last approved, enabling people with cystinosis and their families to have a choice of treatments for cystinosis.

At Cystinosis Ireland our yearly program and priorities are set out by our Executive Committee. This work continues to grow and expand across all areas and we are indebted to our Executive for the time and commitment they give to our organisation. On a daily basis our team of Denise Dunne and Ruth Davis provide support for all of our initiatives and research agenda working with Ann Marie O'Dowd and members of our Executive.

One of the highlights of 2019 was the 5th Annual Dublin Cystinosis Workshop which was held in Kilmainham in April. The event was attended by 40 leading researchers and clinicians from the world of cystinosis. This meeting has become a key event in the Cystinosis research year focusing from new ideas and ways of looking at research, to practical demonstrations of the impact of exercise for maintaining muscle mass.

In parallel to the DCW, the family workshop provided an opportunity for people with cystinosis and their families to engage with experts on the topics presented and to review the posters and abstracts presented, as well as building peer to peer and social networks among the adults, parents and children. In a new aspect of the Workshop, we held a session where abstracts were presented in a three-minute lay description. As

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well as the Prof Roz Anderson Memorial Prize, families and attendees voted on the best lay summary presentation. Amer Jamalpoor was the worthy winner of both prizes this year. Part of his prize is to present at the next Dublin Cystinosis Workshop or International Family Conference, and we look forward to seeing his work progress.

Our international work continues to develop and Cystinosis Ireland was honoured to have been selected by Cystinosis Network Europe to host the 2020 International Conference. Cystinosis Ireland is also leading in supporting Cystinosis Network Europe and the Worldwide Cystinosis Community Advisory Board. These projects represent a significant amount of our work and allow us to ensure we are always at the fore of the networks we help to build to ensure our families have access to new information and research as it emerges.

Our work at Cystinosis Ireland is focussed on delivering improvements for people living with cystinosis in Ireland and internationally.

We are delighted that Niamh O'Brien joined the Executive Committee and the Board of Cystinosis Ireland in 2019, with Rory Flynn joining the Executive Committee in a governance capacity. We are always open to new ideas and we encourage you to engage with us where you can.

We are fortunate to have an extremely dedicated team on our Executive Committee who give their time, energy and expertise to ensure the effective running of the organisation. Thank you to Ann Marie O'Dowd, Liam McFadden, Rory Flynn, Sue Maguire, Andy Maguire, Tom McDonald, Niamh O'Brien, Rachael Power and to James Ennis, who represents our members in Northern Ireland, for serving on our Executive Committee and for your continued support.

Thank you for your continued support in 2019 and we look forward to the future with confidence and optimism

Mick Swift

Chairman

Support and Education

At home, we work with our families to build a network of support and information. In 2019 we were able to better reach our Northern Irish families with James Ennis offering his perspective and experience both as an adult with cystinosis and our Northern Ireland representative. James has worked hard through the year to make contacts in various hospital clinics to ensure newly diagnosed families will be made aware of our organisation. He has also advocated for families with cystinosis through the Northern Ireland Rare Disease Partnership and building relationships with elected officials in the Provence. These key relationships are some of the building blocks of the work we do.

We offered grants to families to attend the Cystinosis Research Foundation family and research conference in California, allowing three family representatives to attend. Anne Marie O'Dowd and Denise Dunne represented Cystinosis Ireland at the Cystinosis Research Network meeting in Philadelphia in July.

Fundraising

Our fundraising supporters continued their commitment with varied events this year. Our annual events such as the Grange, Ashbourne and Kilcock Golf Classics were big successes, both in terms of very generous donations and auctions, but also in a great day out for those who attended. In the summer we had a new and incredible challenge. Two of our friends from the UK, Gary and Rob, undertook an epic 800-mile cycle around Ireland for 16 days in May. They raised a phenomenal amount of money and awareness for our cause and we offer them our very heartfelt thanks for their huge undertaking.

As ever, through the year our families and supporters took on individual and incredibly diverse events including tattoo fundraiser with Belfast City Skinworks; a 100km walk by our friends Richard, Gary and Andrew; numerous Facebook fundraisers for birthdays and other events; a cricket challenge day by the Red Lion in Hitchin (UK); a tennis day in Leixlip; the BBQ4Cystinosis weekend; and our very own Liam McFadden taking on the Dublin City Marathon in his €40 for 40 challenge. James Ennis also created Cystinosis pin badges which are available for sale.

These events, along with corporate and family donations, provide the backbone for what we do, and every euro that is raised through our fundraising is invested in the best research we can find, wherever in the world that may be. We thank you all, sincerely, for the effort and commitment you give to make this work possible.

Advocacy

Cystinosis Ireland is registered on the Register of Lobbyists where our advocacy work can be seen (https://www.lobbying.ie/). In 2019 we worked to raise a question in the Dail on the progress of the Human Tissue Bill and "soft opt-out" for organ donation, an issue close to the hearts of our members.

To support our work, Cystinosis Ireland is represented on and engages with a number of national organisations –

Health Research Charities Ireland (formerly Medical Research Charities Group - MRCG), is an umbrella organisation for medical research and patient support charities. It is through the HRCI that

Cystinosis Ireland has been able to access to the Joint Funding Scheme which has been hugely significant in leveraging our research funding work for many years.

Irish Platform for Patient Organisations, Science and Industry (IPPOSI) is a patient-led organisation that works with patients, government, industry, science and academia to put patients at the heart of health policy and innovation.

Rare Disease Taskforce brings together groups working in this area and has been heavily involved in the Rare Disease National Plan development and implementation.

Rare Disease Technology Review Committee incorporates the patient and clinical perspective in the process of medicine reimbursement and approval.

Organ Donor Network is a group of organisations working in the area of organ donor and transplant. The work of the last year has been mainly towards lobbying to implement the 'soft opt-out' system.

International Engagement

In 2019 we continued to work with our partners in Cystinosis Network Europe as well as our colleagues in Cystinosis Research Network to promote the interests of the cystinosis community internationally. The Seedcorn funding scheme, in collaboration with CRN and our UK colleagues, CFUK, continues to promote novel opportunities for developing research opportunities.

Cystinosis Ireland continues to provide the secretariat for CNE with Anne Marie O'Dowd serving as the Network's Chair. In January, the CNE met in Dublin and decided to formalise as an organisation and formally agreed to set up a Community Advisory Board for Cystinosis. This patient advocate lead group will be the main contact point for our network to discuss research, patient engagement, and potential trials and therapies with pharmaceutical companies. The structure of the CAB, with the support of Eurordis, the European Rare Disorders Organisation, will facilitate discussions (in a neutral setting) on the latest developments and challenges related to medical research and procedures with the companies or bodies conducting the research.

For most of history, medical science has evolved with little to no input from the people being studied. CABs change that, and help to design, carry out and communicate on studies that are more rational and inclusive from a patient's point of view. In particular, CABs are a way to communicate on an equal level with the pharmaceutical companies that are running clinical trials and developing new treatments with the ultimate goal of placing patients at the core of these studies.

The CAB met in November 2019 in Dublin with one pharmaceutical company. The meeting was a very useful experience on both sides with strong and valuable input from the CAB members which formed a useful discussion and potential for impact. The CAB members also provided input into the HRCI/HRB Joint Funding Scheme call for Cystinosis Ireland by providing PPI (Public and Patient Involvement) in the process.

As Chair and Co-ordinator respectively, Anne Marie and Denise represent the CAB at meetings and training sessions organised by Eurordis to support the work of the group and ensure we are working to best practice.

Cystinosis Ireland Research 2019

It has been another busy year for Cystinosis Ireland research during which we have continued to develop our reputation as an important funder and driver of cystinosis research worldwide.

Our key research activities this year have been to:

(i) promote and grow our research project portfolio;

(ii) prepare and review projects for submission to the HRCI-HRB (formerly the MRCG-HRB) Joint Funding Scheme 2020;

(iii) develop a Public and Patient Involvement platform for researchers using the worldwide Cystinosis Advisory Board;

(iv) host, and build brand recognition for, the annual Dublin Cystinosis Workshop;

(v) commence preparations for hosting the International Cystinosis Conference 2020.

Cystinosis Ireland Research Portfolio in 2019

In 2019 Cystinosis Ireland had six research projects in its portfolio as follows:

- *Azoospermia and potential future treatments in male cystinosis patients* by Professor Elena Levtchenko and her team in KU Leuven. The value of this award was €200,000 of which Cystinosis Ireland contributed 25% and the Irish Health Research Board contributed 75%.
- *Targeting Autophagy in Nephropathic Cystinosis* by Professor Minnie Sarwal and her team at University of California San Francisco, USA. The value of this award was €300,000 of which Cystinosis Ireland contributed 25% and the Irish Health Research Board contributed 75%.
- *Characterisation of a novel cystinosin transporter knockout rat model* by Dr Jennifer Hollywood at the University of Auckland, New Zealand. The value of this award was €10,000 and was 100% funded by Cystinosis Ireland.
- *Repair of the 57kb CTNS deletion in kidney cells* by Dr Manoe Janssen, Utrecht University and Dr Paddy Harrison, University College Cork. The value of this award was €10,000 and was 100% funded by Cystinosis Ireland.
- *A pilot study to holistically target dysfunctional pathways in cystinosis: Drug repurposing with gene expression connectivity mapping* by Dr Shu-Dong Zhang, Ulster University and Dr James Murray Trinity College Dublin. The value of this award was €9,908 and was 100% funded by Cystinosis Ireland.
- *Endogenous tagging of CTNS using CRISPR/Cas9* by Professor Elena Levtchenko and Dries David in UZ Leuven in Belgium. The value of this award was €10,000 and was 100% funded by Cystinosis Ireland.

Summary reports on each of these projects are provided in Appendix 1.

HRCI-HRB Joint Funding Scheme 2020

In August 2019, Cystinosis Ireland issued a call for expressions of interest to the cystinosis research community to submit proposals to the HRCI-HRB Joint Funding Scheme 2020.

We received eight expressions of interest from cystinosis researchers worldwide from which five full proposals were subsequently submitted to the charity for consideration and peer review.

The final quarter of 2019 was focused on progressing the scientific peer review process for each of these five research proposals. The final submission date to the HRCI-HRB Joint Funding Scheme 2020 was 22 April 2020.

Developing a Public and Patient Involvement Platform for Researchers using the Worldwide Cystinosis Advisory Board

A core tenet of Cystinosis Ireland is to ensure that the patient's voice is heard at all stages of the research process. In that regard, Cystinosis Ireland aims to be the driver of the Public and Patient Involvement (PPI) process in respect of all of its funded research activities.

To achieve this, Cystinosis Ireland sought the assistance of the Worldwide Cystinosis Community Advisory Board (Cystinosis CAB) in order to get a broad perspective from an educated and informed panel of patient experts from cystinosis patient organisations worldwide.

Cystinosis Ireland introduced its PPI process for the first time in its call for proposals to the HRCI-HRB Joint Funding Scheme 2020. With the support of EURORDIS, the Cystinosis CAB met at the end of October 2019 to consider the expressions of interest received by Cystinosis Ireland from prospective researcher applicants to the HCRI-HRB Joint Funding Scheme 2020. The Cystinosis CAB reviewed each of the expressions of interest received by Cystinosis Ireland and provided feedback and recommendations from the patient stakeholders' perspective to the applicants to assist them in the planning their final research proposals.

In addition to the pre-application public and patient input described above, each of the five full proposals submitted to Cystinosis Ireland was also reviewed and scored from a patient perspective by a member of the Cystinosis CAB.

This PPI feedback and score was considered by the Cystinosis Ireland Executive Committee and Research Group when prioritising the proposals to be submitted by Cystinosis Ireland to the HRB's final assessment for research funding.

In wider PPI engagement, Anne Marie made a presentation to health economists in NUI Galway's PPI Ignite Department in August.

5th Annual Dublin Cystinosis Workshop 2019 - Positioning Cystinosis Ireland as a driver of cystinosis research in Ireland and internationally

2019 continued to establish the Annual Dublin Cystinosis Workshop as an important event in the cystinosis scientific calendar at which world-class international scientists from various disciplines

network, share ideas, discuss scientific breakthroughs and work together with the common aim of conquering this rare disease.

This year the one and a half day scientific workshop, which ran over two consecutive days on 26 and 27 April, 2019, was combined with a half-day family-focused event to allow greater interaction between the scientist/clinicians with patients and families living with cystinosis.

This was our fifth year hosting the scientific workshop and we were delighted to welcome 35 participants including 29 scientists and healthcare practitioners from the US, Canada, England, Scotland, Belgium, Netherlands, Germany, Italy and of course from Ireland (North and South) to Dublin. The workshop comprised 17 excellent speakers and spanned research topics in areas such as: bone disease and muscle wasting in cystinosis patients, genetic indicators in transplant patients, updates on new therapeutic approaches for cystinosis, a better understanding of the molecular and physiological basis of cystinosis, fertility and pregnancy for those living with cystinosis and understanding the significant social impacts of living with cystinosis.

Building research capacity in the area of cystinosis research and supporting new initiatives and collaborations in the area of cystinosis research

A key objective of DCW 2019 was to extend our workshop to include a number of new scientists from research areas that are not directly linked with cystinosis but which intersect with it. In this regard, we were delighted to welcome Dr Olivier Govaere from Newcastle University who presented on the drug cysteamine in the context of non-alcohol related liver disease and Dr Brendan Keating from the University of Pennsylvania who presented on the use of genome-wide genotyping and exome sequencing to uncover genetic markers which may provide insight into the causes of chronic kidney disease and which may assist in the clinical management of post-transplant patients.

INFORMAL COMMENTS FROM DCW 2019 RESEARCHER PARTICIPANTS

"*Dear friends,*

Thanks again for inviting me to your meeting, and I think it was one of the best I have attended for Cystinosis in a long time. I learned a lot and made some great connections"

Professor Craig Langman

The Isaac A Abt MD Professor of Kidney Diseases

Feinberg School of Medicine, Northwestern University

USA

"*Thank you all very much for the opportunity of joining in your outstanding workshop.*

To say I learnt a lot would be a massive understatement! Not least, I learnt what a wonderful community Cystinosis Ireland is and I could not have felt more welcome."

Emeritus Professor Herbie Newell

Newcastle University, UK

"*Thank you so much for your excellent meeting and hospitality!*"

Dr Koenraad Veys

UZ Leuven, Belgium

"*Thanks again for the invite to the meeting – I really enjoyed meeting everyone and I think there is some great science going on here*."

Dr Brendan Keating

Assistant Professor Pediatrics and Surgery (Transplantation)

School of Medicine,

University of Pennsylvania, USA

In addition, we were also delighted to welcome Emeritus Professor Herbie Newell (Newcastle University) to the cystinosis research family. Professor Newell is a distinguished researcher in the development of cancer therapeutics and he recently taken over as Principal Investigator on the UK Medical Council research project of the late Professor Roz Anderson, University of Sunderland. Professor Newell brings his immense experience to Professor Anderson's

legacy project which is focused on the development of a cysteamine pro-drug that should provide a more effective, easier to administer treatment than cysteamine itself and with less side effects.

Although it is too early to identify a concrete joint research initiative arising from the workshop, feedback from the participants (both formal and informal) indicates that a number of new collaborations have been initiated.

Supporting early stage researchers

This year, as part of the scientific programme, we invited researchers, particularly early-stage researchers, to submit posters to the workshop and also to make a short oral presentation during the workshop aimed at explaining their research to the families. We accepted 10 posters at the workshop.

We had two guided poster sessions during the workshop at which the scientific researchers and clinicians as well as the families were encouraged to mingle, view the posters and ask questions. In addition, Session 4 of the Workshop was a dedicated public/patient engagement session at which the scientists were tasked with explaining the research presented in their poster clearly and succinctly to a non-research audience which will include people who live with cystinosis as well as their families.

We awarded two prizes: the Professor Roz Anderson Memorial Prize for Best Scientific Poster and the Cystinosis Ireland Prize for Best Oral Presentation to a Lay Audience.

The inaugural Professor Roz Anderson Memorial Prize for Best Scientific Poster went to Amer Jamalpoor, a young and passionate researcher from Utrecht University, for his poster "*Investigating the pathophysiology and a potential therapeutic approach for Nephropathic Cystinosis*". Amer also won the Cystinosis Ireland Prize for Best Oral Presentation to a Lay Audience, which was decided exclusively by the votes of the families who attended this session.

Promoting the impact of health research, information and evidence for patient care and health service delivery

Eleven families took part during the associated DCW 2019 family event and the public/patient engagement Session 4 of the DCW 2019 itself.

The family event included a number of practical talks and a question and answer session between the families and a panel of eight clinicians and healthcare specialists. This year there was a particular focus on the positive impacts of physiotherapy and exercise regimes on the muscle and bone development of children and adults of all ages living with cystinosis as well as on speech and language therapy and exercises in developing speech and good throat and larynx muscles.

At Session 4 (the public and patient engagement session) of the DCW 2019, the families listened to lay oriented updates and new developments in the field of cystinosis research.

At both the family event and at session 4, all of the families, scientists and healthcare professionals took part in lively, two-way question and answer sessions which proved to be highly informative not just for the families but also for the scientists and healthcare professionals involved.

Feedback from the researchers highlighted the interaction with families as a major positive feature of the workshop with one researcher stating "*The feeling that my work is valued, gives my work purpose*."

Feedback from participants regarding the DCW 2019

Overall the free comments from participants who provided feedback on the DCW 2019 were very positive and were summed up in the following comment:

- *"Nice speakers, poster session helped networking, great meeting, very inspiring, thank you!"*

Hosting the 5th Annual Dublin Cystinosis Workshop 2019 would not have been possible without the very generous support from public donations received by Cystinosis Ireland. We would also like to thank the HRB for providing us with crucial additional conference support.

Cystinosis Ireland also thanks the members of the Dublin Cystinosis Workshop Organising Committee – Professor Elena Levtchenko (Scientific Chairperson), Dr Atif Awan (Irish Medical Organiser), Dr Achim Treumann and Ms Anne Marie O'Dowd, with the able assistance of Dr Tom McDonald, Ms Sue Maguire, Ms Denise Dunne and Dr Ruth Davis, for all their hard work in organising this event.

Commencement of Preparations for the International Cystinosis Conference 2020

Cystinosis Ireland was proud to accept the honour of hosting the 11th biennial International Cystinosis Conference 2020 on behalf of Cystinosis Network Europe on 10-11 July 2020 at the Royal Marine Hotel, Dun Laoghaire, Co Dublin. Planning for this major conference commenced during the summer of 2019 with the identification of, and invitations to, speakers; sourcing of industry and state sponsorship funding and general organisational planning.

The purpose of the ICC 2020 is two-fold:

(i) to present advances in the clinical care of cystinosis patients, the development of new therapeutic treatments and our understanding of the cellular and molecular basis of this disease;

(ii) to host a series of targeted clinician-led family-focused panels aimed at sharing knowledge between professionals and those living with cystinosis and their families with a view to improving healthcare outcomes for individuals and families living with this challenging rare disease; and

Although all of Cystinosis Ireland's planning efforts in 2019 were focused on preparing for an in-person event in July 2020, the emergence of the Covid 19 pandemic in February 2020 necessitated the difficult decision to cancel the in-person conference. Instead, Cystinosis Ireland converted the disappointment of cancelling the in-person event into a highly successful virtual conference. The first ever completely virtual International Cystinosis Conference was hosted by Cystinosis Ireland on behalf of the Cystinosis Network Europe, on Saturday 25 April 2020. It attracted an audience of more than 470 participants from 49 different countries in 20 time zones across the world. The conference was simultaneously translated into 7 different languages and featured presentations on a wide variety of clinical and research aspects of cystinosis from 16 world renowned clinicians, researchers and other healthcare professionals from USA, Canada, Ireland, Belgium, Germany, France, England and Scotland.

Acknowledgments

A sincere note of thanks goes to the volunteer members of the Cystinosis Ireland Research Group – Anne Marie O'Dowd, Dr Thomas McDonald and Dr Achim Treumann who give so much of their time and expertise to supporting and advising the research activities of the charity. Thank you.

Appendix 1

Project Title	**Unravelling the mechanisms of azoospermia and potential future treatments in male cystinosis patients**
Principal Investigators	Professor Elena Levtchenko and Dr Ahmed Reda, University Hospitals Leuven, KU Leuven, Belgium
Duration of Project	Start date of grant: Jan 1, 2017 End date of grant: December 31, 2019
Total Funding	€200,000 (25% from Cystinosis Ireland, 75% from Health Research Board)
Project Objectives	Cystinosis male patients suffer from infertility. The cause for this infertility is not fully understood yet. Patients are highly dependent on taking oral cysteamine in order to treat the cystinosis disease, yet the impact of this cysteamine treatment on male fertility is unknown. Some animal studies suggest that cysteamine can have a negative effect on male reproduction. In this study, the researchers explore the effect of cysteamine on male fertility using an animal model for cystinosis. In addition, the researchers investigate the mechanisms by which the cystinosis disease affect fertility in the male patients.
Project outcomes	The results of the study show that there is no negative effect for oral cysteamine on male fertility. This finding is of great importance as cysteamine which must be taken by cystinosis patients throughout their lives appears to be a safe drug for the male reproductive system. In addition, the results of a clinical trial conducted as part of the study revealed that the cause of the infertility in male patients is not at the level of the testes where normal spermatogenesis can be observed, but at the level of epididymis (a part of the reproductive male tract where sperm undergoes maturation). The results of the same clinical trial also suggest that the cause of the infertility in male patients is most probably an obstruction in the male reproductive tract. This means that the male patients can produce sperm and while sperm cannot get out through the male reproductive tract, men with cystinosis may be able to have their own biological children using assisted reproductive techniques. However, the researchers also observed the deterioration of testicular function with age. The overall results of the project are:

	Cysteamine has no negative effect on male fertility and can be safely administered in cystinosis males throughout their lifetime. Male cystinosis patients produce sperm normally, but cannot release it because of a probable epididymal obstruction. Thus, sperm preservation is recommended for men living with cystinosis who wish to have their own biological children via assisted reproduction.
Future research objectives	A future objective of this research will be to conduct a study on mice to check if the cysteamine treatment reaches the testicles or not. The results of such a study will show whether or not the infertility in male patients is related to how the cysteamine treatment is distributed to the testicles. In addition, the researchers will perform studies on cells isolated from the epididymis (a part of the reproductive male tract) to see whether the cystinosis has a harmful effect on these cells and hence causing the infertility in men with cystinosis. Furthermore, the researchers will check semen samples from male cystinosis patients for obstruction markers, which are markers known to be absent or at low levels in case of male reproductive tract obstruction. In addition, the researchers are currently finalizing an experiment on cells isolated from the epididymis to see how cystinosis causes a harmful effect on these cells and hence causing the infertility in men with cystinosis.

Project Title	**Targeting Autophagy in Nephropathic Cystinosis**
Principal Investigators	Professor Minnie Sarwal and Dr Swastika Sur, University of California San Francisco, USA
Duration of Project	Start date of grant: Jan 1, 2017 End date of grant: December 31, 2019
Total Funding	€300,000 (25% from Cystinosis Ireland, 75% from Health Research Board)
Project Objectives	This is a basic research project which focuses on some cellular and molecular processes in kidney cells that are involved in cystinosis and in particular on molecular processes associated with the mitochondria within these kidney cells. Mitochondria are vital structures that are present in all cells of the body and they are means by which all cells generate energy to survive. Previous studies by these researchers showed that kidney cells have altered cellular processes of autophagy (the means by which a body clears out damaged cells to allow new, healthy cells to grow) and mitophagy (a similar mechanism to autophagy by which the mitochondria in cells are refreshed). Theses researchers have also previously shown that a disturbance in the regulation of a protein called clusterin (CLU) which is involved in the cellular processes of

	autophagy and mitophagy, may be a cause of the renal injury seen in nephropathic cystinosis. This research project aims to better understand how these molecular disturbances in kidneys give rise to kidney damage in patients with nephropathic cystinosis, with the aim of eventually identifying novel drug therapies that may potentially reduce, prevent or even reverse some of the kidney damage caused by cystinosis. The research project also aims to better understand some of the cellular processes in kidney cells that cause renal Fanconi Syndrome in cystinosis patients and to examine relationship between renal Fanconi Syndrome and the eventual renal failure experienced by some cystinosis patients.
Project outcomes	In this research project, the Sarwal research group have studied disturbances in the cellular functions of autophagy and mitophagy in kidney cells with nephropathic cystinosis. To this end the researchers have uncovered the following key findings: 1. Molecular and cellular pathways have been identified in the kidney in cystinosis, that are unique to the kidney and are not seen in other cystinotic tissues. 2. A new family of genes (V-ATPase genes) has been identified that explains some changes seen in the proximal renal tubular acidosis in Fanconi Syndrome, and it appears that these genes are also involved in renal damage. These genes are independent of the levels of cysteine found the cell. Cellular studies are underway to investigate potential new drug therapies aimed at these pathways to see if the rate of kidney cell damage can be reduced. 3. CRISPR cell lines have been generated to provide an *in vitro* model to study kidney cell damage and treatment effects in cystinosis. 4. The same gene family of V-ATPases has been found to be similarly affected in a testicular sample from a cystinotic patient providing preliminary data that may link these genes with male infertility in cystinosis. 5. A research paper is in preparation for submission on the new gene family discovery for kidney damage in cystinosis.
Future research objectives	This research project identified a new family of genes - V-ATPases - that appear to be highly expressed both in kidney and in testis cells. Given that male cystinotic patients experience infertility, a similar dysregulation in these renal and testis specific V-ATPases may drive the cellular injury seen in both the kidney and the testis. Further analysis of both renal and testis specific injury pathways will be the focus of future research efforts by this group.

Project Title **Characterisation of a novel cystinosin transporter knockout rat model**

Principal Investigator	Dr Jennifer Hollywood, Department of Molecular Medicine and Pathology, The University of Auckland, New Zealand
Duration of Project	6 months
Total Funding	€10,000 (100% from Cystinosis Ireland)
Project Objectives	The purpose of this study was to develop and characterise the phenotype of a novel cystinosin transporter knockout rat model to determine how closely it resembles the human disease. If a disease phenotype occurs, then a 2-year study will follow to investigate whether treatment with a combination drug therapy (comprising Everolimus [an FDA-approved drug] and cysteamine) can rescue the cystinosis phenotype as the group has previously observed in its cell line model.
Project outcomes	Within the 6 months we have achieved the desired objectives outlined in the grant. The research group has generated 3 independent cystinotic rat models by creating a mutation in the cystinosin gene. These rats were bred to generate litters of pups that are either; wild-type (no disease), heterozygote (one gene is normal, one gene has cystinosis causing mutation) and homozygote (both genes contain mutations that cause cystinosis). From birth these cystinotic rats have been monitored for signs and symptoms of the disease such as failure to thrive and kidney dysfunction. At 2 ½ - 3 months of age, the experimental animals started to exhibit a failure to thrive phenotype as seen by a decrease in body weight in the homozygote rats compared to littermate controls. Urine output is also increased in these animals. Blood and urine samples have been collected at monthly timepoints and once a large enough sample size is achieved, the research group will begin analysis to determine kidney function which will be assessed by examining serum chemistry markers (e.g. creatinine, blood urea nitrogen) and urine parameters (water content, glucose, phosphate and proteins). The levels of cystine loading in these animals will also be determined using a mass spectrometry method which is currently being optimised. The research group is currently generating new animals and once born these animals will be sacrificed at 1, 2 and 3-month timepoints to examine the organs for cystine crystal formation.
Future research objectives	This rat model appears to be developing a cystinotic disease in a reasonable time-frame and the researchers plan to continue to collect data for the next 6 months. Following this, the researchers plan to use this model to test our novel drug treatment to determine if this would be a good treatment for patients. A cystinotic rat model will be a highly valuable tool for preclinical studies into new therapeutic approaches toward tackling this disease.

Project Title	Repair of the 57kb CTNS deletion in kidney cells
Principal Investigators	Dr Manoe Janssen, Utrecht University and Dr Paddy Harrison, University College Cork.
Duration of Project	**Start date of grant: May 1, 2019** **End date of grant: 30 April 2020**
Total Funding	€10,000 (100% from Cystinosis Ireland)
Project Objectives	Restoring the *CTNS* gene function in kidney cells could provide a long-lasting cure for patients with cystinosis and prevent kidney function decline in the future. However, many gene editing strategies are mostly suitable for small genetic alterations, whereas the most common mutation in cystinosis patients is a large genomic deletion (57kb) resulting in loss of exons 1-10 of the CTNS gene. The large genomic 57kb deletion results in loss of the gene's promotor (gene regulator) as well as the first 10 exons (an exon is the part of the gene that codes for amino acids in the final protein) of the CTNS gene. Fortunately, a new technique called CRISPR HITI was recently developed, which is ideally suited for the precise insertion of large DNA fragments in both dividing and non-dividing cells. The objective of this project is to restore the *CTNS* gene function in cystinotic kidney cells containing the large 57kb deletion using CRISPR HITI *in vitro*.
Project progress	1. The researchers have amplified and sequenced the genomic region between exon 10 and 11 (the superexon) in patient kidney cells to identify suitable sequences for designing the CRISPR/Cas9 gRNA (the precise molecular scissors). 2. This superexon is designed in such way that it completely restores both the regulatory sequences and coding sequence of the CTNS gene. By precisely inserting the superexon in the genome between CTNS exon 10 and 11, the cell gains full control in regulating the cystinosin levels and isoforms required for normal cell function. 3. Based on (outcome 1), the researchers have selected four guide RNA (gRNA) sequences and created the relevant gRNA plasmids for use in cells. 4. The researchers then transferred the gRNA plasmids into kidney cells to determine which of the molecular scissors was most efficient to include in the superexon. 5. The researchers then ordered the complete sequence of the superexon as a gBlock flanked with restriction sites for cloning. However, due to a high CG content and repetitive sequences in the superexon the researchers ran into technical problems as they could not clone the gBlock into our plasmid. They, therefore, ordered the superexon again, but already placed into a suitable plasmid to allow easy amplification (ready for use).

Future research objectives

1. Having obtained a suitable superexon, the researchers now plan to transfect the genetically engineered plasmid containing the superexon into the patient kidney cells together with the gRNA plasmids to facilitate the insertion of the superexon into the genome.
2. To evaluate efficiency, they will amplify part of the genomic region to check for presence of the superexon and will enrich for repaired cells.
3. Next, the researchers will check whether the cystine levels have dropped and whether other cell functions associated with nephropathic cystinosis are restored.

Project Title	**Repair of the 57kb CTNS deletion in kidney cells**
Principal Investigators	Dr Manoe Janssen, Utrecht University and Dr Paddy Harrison, University College Cork.
Duration of Project	**Start date of grant: May 1, 2019** **End date of grant: 30 April 2020**
Total Funding	€10,000 (100% from Cystinosis Ireland)
Project Objectives	Restoring the *CTNS* gene function in kidney cells could provide a long-lasting cure for patients with cystinosis and prevent kidney function decline in the future. However, many gene editing strategies are mostly suitable for small genetic alterations, whereas the most common mutation in cystinosis patients is a large genomic deletion (57kb) resulting in loss of exons 1-10 of the CTNS gene. The large genomic 57kb deletion results in loss of the gene's promotor (gene regulator) as well as the first 10 exons (an exon is the part of the gene that codes for amino acids in the final protein) of the CTNS gene. Fortunately, a new technique called CRISPR HITI was recently developed, which is ideally suited for the precise insertion of large DNA fragments in both dividing and non-dividing cells. The objective of this project is to restore the *CTNS* gene function in cystinotic kidney cells containing the large 57kb deletion using CRISPR HITI *in vitro*.
Project progress	1. The researchers have amplified and sequenced the genomic region between exon 10 and 11 (the superexon) in patient kidney cells to identify suitable sequences for designing the CRISPR/Cas9 gRNA (the precise molecular scissors). 2. This superexon is designed in such way that it completely restores both the regulatory sequences and coding sequence of the CTNS gene. By precisely inserting the superexon in the genome between CTNS exon 10 and 11, the cell gains full control in regulating the cystinosin levels and isoforms required for normal cell function. 3. Based on (outcome 1), the researchers have selected four guide RNA (gRNA) sequences and created the relevant gRNA plasmids for use in cells. 4. The researchers then transferred the gRNA plasmids into kidney cells to determine which of the molecular scissors was most efficient to include in the superexon. 5. The researchers then ordered the complete sequence of the superexon as a gBlock flanked with restriction sites for cloning. However, due to a high CG content and repetitive sequences in the superexon the researchers ran into technical problems as they could not clone the gBlock into our plasmid. They, therefore, ordered the superexon again, but already placed into a suitable plasmid to allow easy amplification (ready for use).

Future research objectives	1. Having obtained a suitable superexon, the researchers now plan to transfect the genetically engineered plasmid containing the superexon into the patient kidney cells together with the gRNA plasmids to facilitate the insertion of the superexon into the genome. 2. To evaluate efficiency, they will amplify part of the genomic region to check for presence of the superexon and will enrich for repaired cells. 3. Next, the researchers will check whether the cystine levels have dropped and whether other cell functions associated with nephropathic cystinosis are restored.

Project Title	**A pilot study to holistically target dysfunctional pathways in cystinosis: Drug repurposing with gene expression connectivity mapping**
Principal Investigators	Dr Shu-Dong Zhang, Northern Ireland Centre for Stratified Medicine, Ulster University
Duration of Project	Start date of grant: July 1, 2019 End date of grant: March 31, 2020
Total Funding	€9,908 (100% from Cystinosis Ireland)
Project Objectives	This pilot research aims to demonstrate an innovative application of the Principal Investigator's established and tested techniques to a rare disease area with urgent unmet need. Before this project, the Principal Investigator had always been interested in applying the connectivity mapping to drug repurposing in a rare disease. This seedcorn funding enabled the implementation of such research efforts and the outputs clearly demonstrated the feasibility of this approach. The objectives of this pilot study, were: 1. To conduct a systematic review on the mechanistic understanding of cystinosis beyond cystine transport and the accumulation of lysosomal cystine. The known dysfunctional pathways and key interactions in cystinosis will be complied. Integrating the information/knowledge stored in public domain databases, such as curated human biological pathways and protein-protein interaction networks, the researchers aim to perform a meta-analysis to construct a core gene network for cystinosis. This will define a set of key genes, proteins and molecules that are shown to be involved in cystinosis, and determine their altered state in this disease. 2. Using an advanced and tested bioinformatics technique of gene expression connectivity mapping, the researchers plan to identify potential drugs that are able to reverse the expression pattern of the key molecules defined in objective 1.
Project progress	The Principal Investigator and his research team have been particularly encouraged by the significant amount valuable data generated from this project, and also the new knowledge and insights we have obtained into cystinosis. In turn, the connectivity mapping approach has become better known by traditional cystinosis researchers. Key outputs of this research are as follows: 1. A core network of genes/proteins involved in cystinosis has been complied which consists of 67 genes/proteins. The roles and directions of change of these genes/proteins in the disease have been ascertained with supporting evidence from our systematic literature review and meta-analysis.

	2. Extensive connectivity mapping analyses have been conducted using the core set of genes/proteins as input with three strategies to target (a) all 67 genes holistically (b) a subset of prioritised genes based on weighting of literature support (c) individual genes featured in prominent publications or drug repurposing research elsewhere. 3. Candidate drugs to target all those three scenarios have been identified.
Future research objectives	This pilot research has facilitated the Principal Investigator's collaborations with experimental scientists and clinicians in this field. He is now in a stronger position now to forge further collaborations with international partners in cystinosis, and plans to develop collaborative research proposal(s) to advance his research endeavours in this field. In a longer term, the researcher group's collective research activities will eventually bring benefits to the lives of people living with cystinosis, and this remains the ultimate goal of our research activities in cystinosis.

Project Title	**Endogenous tagging of CTNS using CRISPR/Cas9**
Principal Investigators	**Professor Elena Levtchenko and Dries David, KU Leuven Belgium**
Duration of Project	Start date of grant: September 1, 2019 End date of grant: December 31, 2020
Total Funding	€10,00 (100% from Cystinosis Ireland)
Project Objectives	This research project aims to tag the cystinosin gene endogenously with eGFP (Enhanced Green Fluorescence Protein) using CRISPR/Cas9 technology. If successful, this will be the first time that cystinosin would be visualized within cells and it has the potential to open up new experimental avenues to better understand the molecular mechanisms of the cystinosis disease. This is especially significant as at present an antibody specifically recognizing cystinosis is not currently available and efforts to produce such an antibody have been unsuccessful. This project aims to circumvent the requirement for a cystinosin antibody by fluorescently tagging the cystinosin gene instead so that cystinosin can be detected endogenously using live cell imaging. This will help to unravel the molecular localization of cystinosin in mutant and wild type cells and will also help to elucidate the various molecular interactions and expression levels of endogenous cystinosin.
Project progress	This research project has proved difficult to progress. Initial attempts to develop an effective fluorescent-tagged cystinosin gene have not been successful. This may be because the cystinosin gene is expressed at very low levels and the microscope is not sensitive enough to pick this up. Currently the researchers to use an alternative strategy for tagging CTNS using single stranded oligodinucleotides (ssODNs). The researchers will continue with this approach by transfecting the ssODNs together with the Cas9 protein and will check whether this approach proves successful to tag CTNS endogenously.