cystinosis ireland

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Seedcorn Funding Projects

Dr Jennifer Hollywood, Department of Molecular Medicine and Pathology, The University of Auckland, New Zealand

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

Duration of Project: 6 months

Total Funding: €10,000 (100% from Cystinosis Ireland)

Status: Completed

Animal models of human diseases are an essential tool used by researchers to help them understand the underlying mechanisms of the disease they are studying as well as to assist them discover new drugs or therapies that have potential to treat, and perhaps cure, the disease in humans.

Dr Hollywood is a Postdoctoral researcher in the laboratory of Professor Alan Davidson lab at the University of Auckland. Professor Davidson's research group has discovered that a new drug either alone or in combination with cysteamine, has a superior effect compared to cysteamine alone on the endpoint metrics in our cystinosis cell line model. This novel drug combination may be of potential therapeutic benefit to patients but needs further testing in an appropriate cystinosis disease animal model.

Although a mouse model of cystinosis already exists, it does not display all the characteristics of the cystinosis disease and, as a result, it is of limited use when testing the potential therapeutic effect of drugs.

It is hoped that a rat model may prove to be a better animal model if it develops a cystinosis disease more similar to human patients in a reasonable time-frame. The purpose of this research is to characterise a novel cystinotic rat model to determine how closely it resembles the human disease.

To date, the researchers in Professor Davidson's laboratory in Auckland have generated three founder cystinotic rat lines by creating a mutation in the cystinosin gene. These rats were bred to generate litters of pups that are either; wild-type (i.e. no disease), heterozygote (i.e. one gene is normal, one gene has cystinosis causing mutation) and homozygote (i.e. both genes contain mutations that cause cystinosis). These rats are now being closely monitored for disease onset by measuring their growth and water intake, assessing the loss of important substances in the urine, measuring kidney function and by observing the development of cystine crystals in certain organs.

If the rat model develops cystinosis disease in a reasonable time-frame then the researchers will test their novel drug treatment combination with cysteamine on this rat model to determine if it might have potential therapeutic benefits for patients living with cystinosis.

A cystinotic rat model will be a highly valuable tool for preclinical studies into new therapeutic approaches toward tackling this disease.

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Dr Shu-Dong Zhang, School of Biomedical Sciences, Ulster University, Northern Ireland

Project Title: A pilot study to holistically target dysfunctional pathways in cystinosis: Drug repurposing with gene expression connectivity mapping

Duration of Project: 6 months

Total Funding: €9,908 (100% from Cystinosis Ireland)

Status: Ongoing

This research project aims to use the technique of gene expression connectivity mapping to screen approved drugs or drug combinations for potential new uses to treat cystinosis. The novelty of the proposed project is that for the first time, the connectivity mapping analysis will be used to target several key pathways involved in the cystinosis disease simultaneously.

As an initial step, the aim is to conduct a systematic and critical review of the cystinosis literature, and a meta-analysis of public gene expression datasets, in order identify a core set of genes/proteins which form a coherent molecular network playing important roles in the pathogenesis of cystinosis.

The second aim of the project is to create a short list of candidate approved drugs able to supress the expression pattern of the core gene network in the cystinosis disease state will be identified.

This research is expected to identify novel candidate drugs or combinations (which are already FDA approved) that will benefit people with cystinosis and their families and that can reach the market rapidly. The researcher hopes to identify drugs that can target a number of interacting pathways at the same time, and to provide drug combinations for further experimental validation.

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Dr Manoe Janssen, Department of Pharmaceutical Sciences, Utrecht University, the Netherlands

Collaborator: Dr Patrick Harrison, Department of Physiology, University College Cork.

Title of Project: Repair of the 57kb *CTNS* deletion in kidney cells

Amount of Funding Requested: €10,000

Status: Ongoing

The aim of the project to insert the missing part of the CTNS gene in cells with the 57kb deletion in such that the repaired cells are essentially normal. 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.

This strategy can also be used to introduce patient specific variations of the CTNS gene, that could tell us why some mutations have near normal levels of cystine transport yet very severe disease, whereas other mutations have essentially no cystine transport yet only mild disease. This knowledge may help develop screens to identify novel lead compounds that could be used in combination with cysteamine to better treat cystinosis.

The research aims to establish proof-of-principle for a simple and rapid generation of isogenic cystinotic and healthy ciPTEC cells which will benefit patients in three ways: a) isogenic healthy and cystinotic cells are a necessary pre-requisite for drug screening protocols; b) isogenic cells will be ideal resource to analyse previously characterised mutations to dissect the relative contribution of the role of cystine transport from other functions such as autophagy; c) the technique could yield better understanding of CTNS promoter, role of CARKL and TRPV1 genes in disease and generate valuable data for future gene and/or cell-based therapies.

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Research - Awareness - Support

Cystinosis is a rare, degenerative, incurable disease that primarily affects children. It slowly destroys all the body's organs and muscles.
Cystinosis Ireland is a volunteer-led, non-profit organisation dedicated to funding cystinosis research and providing support to those living with the condition.

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