cystinosis ireland

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MRCG-HRB Co-Funded Projects

Professor Minnie Sarwal, University of California San Francisco, United States of America and

Project Title: Targeting Autophagy in Nephropathic Cystinosis

Duration of Project: 3 years

Total Funding: €300,000 (25% from Cystinosis Ireland, 75% from Health Research Board)

Status: Ongoing

Professor Sarwal's research group at the University of California San Francisco are working to understand the interplay of targeted cell death (autophagy) in nephropathic cystinosis and to evaluate if gene defects in Clusterin could be a pivotal confounder gene for the kidney injury in this disease.

The research group is working on the isolation and generation of primary and immortalized cell lines from various tissues and are validating them as models for improved understanding of the pathophysiology of cystinosis (see also seedcorn project below: Targeting Autophagy in Nephropathic Cystinosis: generation of CTNS mutant cell lines by CRISPr/Cas9 gene editing). The project has made significant progress since it commenced: Major milestones that have been achieved include the following: –

• Renal proximal tubular epithelial (RPTE) cells showed strong induction of self-eating/autophagy in response to glucose, versus amino acid stress, suggesting that this cell type is strongly glycolytic for generation of energy. This is an important finding since damage to mitochondria, which is the powerhouse of energy, is a known hallmark of nephropathic cystinosis.

• RPTE cells have been isolated from the cystinosis patients' urine and showed that these cells are a good model for in vitro cystinosis-related study.

• A lysosomal protein V-ATPase has been identified as another potential trigger/partner that, along with Clusterin, might also play a key role in renal injury associated with nephropathic cystinosis.

• Since Clusterin is up-regulated in cancer, Professor Sarwal's group have used the cervical carcinoma cancer cell line, HeLa, as a model for testing potential compounds that could modulate Clusterin expression. They have showed that the FDA approved drug Telmisartan significantly decreased Clusterin protein expression in the model cell line (HeLa).

• The research group is currently in the process of generating RPTE cell lines with no CTNS protein expression as a model of RPTE cells from Cystinosis patients, which will help to better understand the pathophysiology of the disease cystinosis.

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Project Title: Fertility in male cystinosis patients: Unravelling the mechanisms of azoospermia and potential future treatments in male cystinosis patients

Duration of Project: 2 years

Total Funding: €200,000 (25% from Cystinosis Ireland, 75% from Health Research Board)

Status: Ongoing

Cystinosis is a rare disease that affect mainly the kidneys. However, other organs could be affected; such as the thyroid gland, skeleton, and gonads. Nevertheless, female cystinosis patients show normal fertility, while male cystinosis patients are infertile due to absence of spermatozoa in their semen.

The researchers in this study sought to investigate the possible causes of such infertility problems in male cystinosis patients, along with the possible fertility preservation options.

First, the researchers aimed to investigate the effect of cystinosis treatment (cysteamine) on male fertility. In order to do this, mice were fed cysteamine in their food, and then were checked to see whether this cysteamine had any effect on the fertility of the male mice. Fortunately, cysteamine had no negative impact of male fertility in the mice.

Secondly, the researchers wanted to know if the cysteamine reaches the testicular tissues when taken by the patients. In order to determine, the researchers gave the mice cysteamine and checked whether the mice had cysteamine in their testes or not. The results showed that cysteamine could be detected in the testicular tissues.

Finally, the researchers focused on the effect of the disease itself on the fertility of male patients.

In order to do so, the researchers collected samples and data from cystinosis patients (testicular tissues, epididymal sperm, semen samples, blood samples) under regular care (i.e. for those who are interested to investigate their fertility issues in a clinical voluntary setting).

In addition, they also recruited a number of male cystinosis patients in a clinical study, from whom they collected semen and blood samples.

The preliminary results indicate that infantile cystinosis patients show some kind of obstruction in the male genital tract, despite having intact spermatozoa in the testis and epididymis. This obstruction prevents the spermatozoa from getting out during ejaculation, which interferes with successful fertilization.

This study is the first time to examine the effect of cysteamine treatment on male fertility. It is also the first time that researchers are looking to find the mechanism behind azoospermia in male cystinosis patients.

In so doing, there is the potential to offer patients strategies that may enable them to bank their sperm should they wish to have children in the future.