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Joint Funding Scheme with Health Research Board 2015 - Lay Abstracts

Prof Anuj Chauhan, University of Florida, Gainesville

Project Title: **Drug Eluting Contact Lenses for Cystinosis Therapy**
Duration of project: **2 years**
Total Funding: **€72,000 (25% from Cystinosis Ireland, 75% from Health Research Board)**

Cystinosis is a metabolic disease characterized by accumulation of cysteine crystals in various tissues including cornea. Cystinosis patients begin showing ocular symptoms at the age of 16 months and without appropriate treatment, the entire peripheral stroma and endothelium can be packed with crystals. Eventually complications such as corneal scars and band keratopathy can occur resulting in irreversible damage to the eye.

Cystinosis is treated with an anti-oxidant drug cysteamine (β-mercaptoethylamine), which reacts with cystine to convert it to a more soluble form. The oral dose of cysteamine achieves therapeutic effects in several organs but its concentration in corneal tissue is inadequate to reduce crystal accumulation. Cysteamine eye drops, delivered hourly, are utilized for treating the ocular complications of cystinosis. While the eye-drop based therapy is effective, the high frequency of drop instillation often leads to poor compliance and a significant impact on the quality of life of patients.

The high frequently of eye drop instillation is required because a very large fraction of the drug administered as eye drops is lost to the systemic circulation and because with every blink a large fraction of the drug drains into the nose. A more compliant drug delivery approach can be developed by using a slow releasing device that can preferentially release the drug to the cornea. A contact lens is the ideal choice for the delivery of cysteamine from the contact lenses because of the placement of the contact in proximity to the cornea. Our research suggests that 50% of the drug loaded in the lenses reaches the cornea compared to 1% with eye drops. Our research aims to replace the hourly instillation of eye drops with a daily disposable contact lens that needs to be worn for only a few hours each day.

About Cystinosis & Cystinosis Ireland

Cystinosis is a rare, degenerative, inherited disease in which the amino acid, cystine, accumulates abnormally in all cells of the body due to a defective mechanism to transport it out of the cells. This in turn leads to early cell death. Cystinosis therefore slowly destroys all the organs of the body; the kidneys, liver, eyes, muscles, pancreas, thyroid and the brain.

Cystinosis Ireland is an Irish registered charity. We are an all-volunteer, non-profit organisation dedicated to providing services for those affected by Cystinosis. Cystinosis Ireland was founded in 2003 by those people and their families primarily affected by Cystinosis.Please visit our website cystinosis.ie, Facebook or Twitter pages for more details.

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Professor Alan Davidson, University of Auckland, New Zealand (collaborating with UCC)

Project Title: **Modelling cystinosis with human stem cells and the therapeutic potential of aspartate**
Duration of project: 3 years
Total Funding: **€288,000 (25% from Cystinosis Ireland, 75% from Health Research Board)**

Cystinosis is a rare genetic disease that causes the amino acid cystine to accumulate in the body due to mutations in the *CTNS* gene. In its severest form, cystinosis causes kidney failure before the age of 10. Treatment is limited to cysteamine, a cystine-depleting drug, but this only slows the progression of the disease.

The toxic effects of cystine on the kidney are not well understood, yet likely hold the key to developing new treatments.

We have generated stem cells from a patient with cystinosis and used these as a limitless source of tissue to study cystinosis in the laboratory. We have discovered that cystinotic stem cells are deficient in aspartate, an amino acid vital for metabolic processes including energy (ATP) production. We hypothesise that a reduced ability to generate ATP in highly metabolic kidney cells is responsible for the progressive renal failure in cystinosis.

To confirm this, we propose to use state-of-the-art gene editing technology to correct the genetic defect in cystinotic stem cells. We will then coax the diseased and 'rescued' stem cells to mature into kidney cells and measure their aspartate and ATP levels. In addition, we will test the therapeutic potential of aspartate by assessing its effects on the metabolism of cystinotic cells.

This work will greatly advance our understanding of how cystinosis causes kidney damage and may lead to an aspartate based therapy to treat the disease.

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