"Care today … cure tomorrow"

LOWE SYNDROME TRUST

5 February 2014

Thank you for your ongoing support of the *Lowe Syndrome Trust* - your help is truly invaluable to us as we seek to support children and families affected by Lowe Syndrome as well as increasing awareness of the disease among healthcare and educational workers.

As you know, we are also committed to funding important scientific research into Lowe syndrome to help find a cure. I'm writing to keep you up to date with some exciting recent discoveries, all made possible with your support. . Of course, the scientific information below has been written by one of the Lowe scientific board members and Lorraine (Founder and Chair), as not sure my version would be the same! Never the less, as I have been involved since the beginning of the charity 14 years ago, I am proud to be part of such a worthy cause and hope this letter helps better understand how funds raised have supported vital research into Lowe Syndrome, an incurable disease.

One of the difficulties we face in research into Lowe Syndrome is the diverse array of symptoms that arise in different parts of the body – especially the eyes, brain, muscles and kidneys - and how these are linked. We know what the underlying cause is: a genetic mutation resulting in a defective version of an enzyme called *OCRL*, which leads to a subtle metabolic imbalance. However, we still do not fully understand how and why this imbalance causes the symptoms seen in Lowe Syndrome, and this is one of the key aims of the research we are funding. Under the guidance of our Scientific Advisory Board, the research you help us fund is designed to investigate Lowe Syndrome and answer a number of key questions:

- What is going on at the genetic/biochemical level?
- How does the metabolic imbalance affect the function of individual cells?
- What is the effect upon whole organs – esp. eyes, brain, kidneys?
- Can Lowe Syndrome be modelled in other organisms to help develop possible drugs?

Recently there have been some exciting steps forward in answering these questions, which have advanced our understanding of Lowe Syndrome and encouraged us in our search for a cure. There are reports from each of the projects we are funding in the following pages, but here are the main points:

One of the most exciting findings was made by **Dr Claudio Aguilar (Purdue University**, USA) and **Prof Philip Beales** (**UCL**) who received an LST grant of **£180,000**, and discovered that cells from Lowe Syndrome patients share similar abnormalities with a group of other developmental diseases known as *ciliopathies*. This is a major breakthrough as it means Lowe Syndrome is not just an isolated disease but is linked to other conditions so we can also benefit from research into them, especially in the area of drug development.

Another exciting breakthrough has been made by **Dr Rudiger Woscholski (Imperial College London - £330,000**) who has been working on developing a chemical compound that will reduce the metabolic imbalance caused by the defective OCRL enzyme. So far the research has produced a promising candidate compound which can be used as a tool to more

easily diagnose Lowe Syndrome and ultimately may provide a first step towards potential drugs to treat Lowe Syndrome.

In order to test any potential drugs and treatments, as well as to further study what is happening in Lowe Syndrome at a cellular level, it is vitally important to develop models of Lowe Syndrome in other organisms. Through research funded by the LST there have been two major breakthroughs. **Professor Martin Lowe** at **Manchester University** (3 grants totalling **£253,000**) has generated a model in zebrafish, which recapitulates Lowe Syndrome symptoms in kidneys and the nervous system. They are now starting a drug screen to identify compounds to restore kidney function, as well as distributing these fish to other labs investigating other aspects of Lowe Syndrome. In the USA at **University of California, Professor Robert Nussbaum** (UCSF, £**163,000**) has created a mouse strain which models the abnormal kidney function seen in Lowe Syndrome patients.

At a cellular level, **Dr Tim Levine** at the **UCL Institute of Opthalmology** (£**130,000**) is looking at how Lowe Syndrome cells behave in the lab and has shown that unlike normal cells they do not grow together properly in sheets. This is important as it helps us understand why there are specific problems in eyes and kidneys in Lowe Syndrome. They are now looking at how to restore normal growth.

At a molecular level, a number of our projects are investigating the function of the OCRL enzyme by looking at what other molecules it interacts with inside cells, and what interactions are disrupted by the mutations in Lowe Syndrome. **Dr Pietro De Camilli** and **Dr Laura Swan** (Yale - £**80,000**), have shown defective OCRL cannot bind two other proteins called APPL1 and Ses1/2, thought to be involved in targeting OCRL to the correct part of the cell. **Prof Shamshad Cockroft** (**UCL - £50,000**) has shown that OCRL is switched on and off by a protein Rab6, and is now looking at how Rab6 itself is regulated. **Dr Anthony Norden** (Cambridge University - **£20,000**) is researching the interaction between OCRL and megalin and cubulin, which are two proteins involved in cell budding. **John Lucocq** (Dundee **University** - £60,000) is researching the role of OCRL in protein transport around cells.

In January 2014, results of a project funded by the LST were published in the world's leading medical journal - the New England Journal of Medicine. In it **Prof Robert Kleta, Dr Detlef Bockenhauer and Prof Robert Unwin (Great Ormond Street Hospital / Royal Free Hospital / UCL – grant of £84,000)** and collaborators describe a new disease mechanism in kidneys, shedding light onto how the kidney works and providing ideas about how to better diagnose and treat the kidney problems seen in Lowe syndrome.

This latest publication adds to a previous project at **Great Ormond Street funded by the LST (£9,000) headed by Dr William Van't Hoff, Robert Unwin and Guido Laube**, who cultured OCRL kidney cells from Lowe Syndrome patients in the lab. This allowed them to investigate exactly what effects of Lowe Syndrome are on the function of kidney cells – a selective proximal tubulopathy, where small proteins and calcium are lost in the urine.

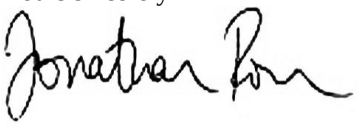
The LST has also co-operated with the US-based **Lowe Syndrome Association** in funding a couple of research projects to a total of **£30,000** and also funded small research projects such as a behavioural

study at **Birmingham University.** The Trust has just announced another new research grant award to **Birmingham University** where they will look at the neurological aspects of the disease. This award is just under £**68,000**.

Every two years the LST also funds an international Lowe Syndrome Research Symposium at the Royal Academy in London, bringing together medical and scientific research experts as well as members of other Lowe Syndrome charities from around the world, to share research, experiences and ideas. A number of key collaborations between different projects have come about through these meetings, and the next symposium in December 2014 promises to be even more fruitful. The charity has also funded meetings to raise awareness and scientific interest of the disease at The American Cell Biology conference in the USA.

So overall, thanks to your support we are funding high quality and cutting-edge scientific research which is resulting in major breakthroughs in our search for a cure.

Yours sincerely



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