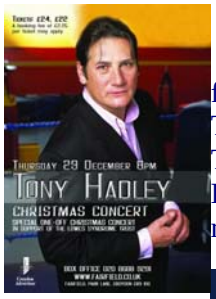
News from the UK Lowe Syndrome Trust
DECEMBER 2006

Lowe Syndrome Trust
"Care today … cure tomorrow"

Since our January 2006 newsletter, the charity has continued raising awareness of the Lowe Syndrome disease and funding to support medical research. which will hopefully lead to better treatments and eventually a cure of Lowe Syndrome, an incurable children's disease. We are delighted to have been able to raise funding to support two new research projects in 2006. The first to Professor Robert Nussbaum(£50,000) and the second a small grant of £10,000 to Imperial College London.

Tony Hadley, Lowe Syndrome Trust Patron, once again supports the cause!



Tony Hadley celebrated 25 years in showbiz by holding a gala Christmas concert for the Lowe Syndrome charity on 29th December 8pm at Fairfields Hall Croydon. Tony was joined by Martin Fry (ABC), Peter Cox and Richard Drummie (GoWest). The concert raised money for two charities - the Lowe Syndrome Trust and the Huntington's Disease Association . The Lowe Syndrome Trust was delighted to receive a donation of almost £5,000 – thanks again Tony!

Tony Hadley also appeared on Who Wants to be a Millionnaire on behalf of the Shooting Star Hospice. Tony kindly asked that £2,500 be donated to the Lowe Syndrome Trust. Thank you Tony for *your continued support!*

Devonshire House School, Hamptead

We were thrilled to be one of the charities that Devonshire House School supported this year. A staggering amount of £9619 was raised for the Lowe Syndrome Trust. Oscar who has Lowe syndrome attended the school just before being diagnosed with the disease.

David Kilbourn – Climbs Mont Blanc !

David Kilbourn raised just under £3000 sponsorship when climbing the highest mountain in Europe! Our thanks go to David whose funds helped support the Lowe research project with Prof Robert Nussbaum.

Skateboarding across the UK and Australia for Lowe Syndrome.

On Friday June 2nd 2006 Dave crossed the finish line at Land's End to end an epic board journey. His 34 day, 896 mile journey from John o'Groats in north-east Scotland to Land's End in south-west England marked the first time anyone successfully skateboarded the length of Britain. Dave's board is called Elsa, and is made by www.boardfree.co.uk . Dave is now on the second leg of the journey from Perth to Brisbane to raise funds for three charities including the Lowe Syndrome Trust.

Saracens Rugby – The Priory Foundation

A huge thank you to Nigel Wray of the Saracens/Priory Foundation for donating £10,000 towards the 2nd year of the Professor Robert Nussbaum research project.

London to Reims Cycle Ride

The Cycle Ride was a huge success raising just over £25,000. Our thanks go to the team:-
Andrew Thomas, Mick Fenning, John Hibberd, Darren Marsh, Lisa Turnbull, Nigel Verdon, Martin Jones, David Mintz, John Kembery, Barry Webster,, James George, Paul Keeling, Anne Ogle, Alf Comparini, Neil Buckingham, Neil Lawson May, Brian Connell

The funds raised on this trip enabled the Trust to fund the next stage of the Lowe research project at Imperial College London

Ladies Who Lunch with Jono Coleman and Jonathan Ross OBE
Friday 12 May 2006 Toast Hampstead

The Lowe Syndrome Trust continued its campaign to raise awareness of Lowe Syndrome and raise funding to support research by holding a 6th year Ladies who Lunch anniversary event at Toast restaurant in Hampstead. Jonathan Ross (Trustee) and Jono Coleman (Patron) hosted the lunch and raffle bringing lots of hilarity to the day! Almost £5,000 was raised via a Silent Bid which included many excellent donated items including a Joss Stone's Skateboard, a signed framed photo donated by George Michael and a pair of Versace shoes signed (and worn?) by actress Elizabeth Hurley.

Sheerwater R&B Lowe Charity Event

We were delighted to be part of the Sheerwater R&B charity gig organized by Martin Paling and John Blackley. The evening was a great success raising over £1000 for the Lowe Syndrome Trust.

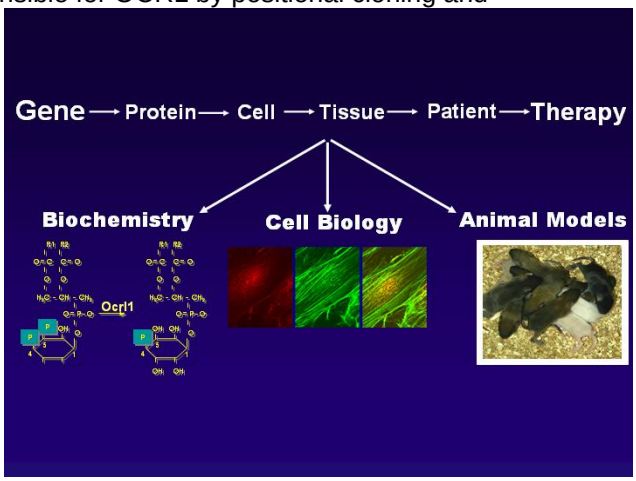
Lowe Syndrome Trust announces Grant Award to UCSF

The Lowe Syndrome Trust (a small voluntary charity), is delighted to announce an award of £50,000 to Professor Robert L Nussbaum, MD Institute for Human Genetics and Department of Medicine, University of California San Francisco.

Lowe Syndrome charity chair Lorraine Thomas stated "Building on the current research projects funded by the Lowe Syndrome Trust, this project presents the next small but significant step in a very long journey- hopefully leading to an understanding of the basic underlying defect. If it results in a deeper understanding of how the diseases comes about, it may make the medical profession much better in developing therapies".

Professor Nussbaum has been been an outstanding leader in efforts to understand the rare X-linked disease known as the oculocerebrorenal syndrome of Lowe (OCRL), characterized by congenital cataracts, Fanconi syndrome of the renal proximal tubules, neurological dysfunction, and developmental delay.

Professor Nussbaum discovered the gene responsible for OCRL by positional cloning and demonstrated that the gene encodes a phosphatidylinositol (4,5) bisphosphate 5-phosphatase that was shown to be enriched in the trans-Golgi network and early endosomal compartments. Current treatment is purely symptomatic and palliative.



The relationship between the enzyme deficiency and the pathophysiological abnormalities in OCRL remain obscure. In previous experiments, Mice lacking the OCRL gene had no signs of the disease. Professor Nussbaum will investigate why these mice are protected from a deficiency in this enzyme and how this information might be exploited to expand our understanding of this enigmatic disorder and develop new, specific therapies.

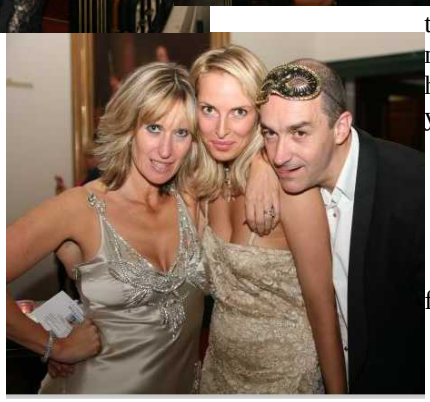
On 20th March 2006 a meeting organised by the Charity was held at the UK Institute of Child Health attached to Great Ormond Street Children's hospital. Professor Nussbaum presented and discussed the project with the Lowe Syndrome Trust scientific advisors and researchers who hope to be able to Dr Naussbaum's results in their research projects. The meeting also discussed the possibility of joint collaborative research projects and the establishment of a clinical and cell tissue database.

Studies indicate that the clinical, physiological manifestations of an OCRL-1 mutation do not singularly account for just the clinical manifestations used to describe Lowe Syndrome; rather they can be presented as another phenotype describing a different disease (Dent's Disease) which has similar renal problems but very distinct clinical characteristics.

THE LOWE SYNDROME TRUST MASQUERADE BALL

The Lowe Syndrome Trust held a Masquerade Ball on the 5th October at the fabulous Renaissance Chancery Court Hotel in central London.

Dame Edna look a like welcomed guests to much hilarity with his continuous Dame Edna impressions and quick witted one liners!!



Guests enjoyed a wonderful evening of entertainment including a short speech from Lowe Trust patron **Jono Coleman** who introduced a special video clip from another Lowe Patron **Penny Lancaster. Penny and Rod Stewart with baby Alastair** conveyed their best wishes for the evening as they could not attend as in the USA at that time. Rod asked people to bid generously for his gold disc which he had donated!

The evening progressed with a full programme including a host of songs from **Tom Jones l**ook a like Martin Jarvis who gave a fantastic rendition of "Its not Unusual" getting the evening off to a cracking start!. The Auction was well received which included items from **Dame Shirley Bassey, George Michael, Pink Floyd, Jonathan Ross** and signed items from both Arsenal and Tottenham Hotspur football clubs!

The guest star of the evening, Lowe Trust Patron **Tony Hadley,** had all of the guests on their feet when he performed a medley of songs.

The evening was a great success raising £30,000.

UP AND COMING

We have places in the **London Marathon,** new **London 10K 2008 Marathon**, **New York Marathon** and various others. The Trust can organize a private event on the **London Eye capsule and in doing so raise funding for the LST! W**e are about to publish a 2007 calendar of events which will include Ladies who Lunch and Wine tasting evening amongst other fun things!

AMERICAN SOCIETY CELL BIOLOGY CONFERENCE SAN DIEGO, CALIFORNIA 8th DECEMBER 2006

During the Lowe Scientific Board meeting when Professor Robert Nussbaum attended from the USA. The issue of raising the profile of Lowe syndrome disease and the need for more research was raised by Lowe Syndrome Trust Chair Lorraine Thomas. It was decided that the Trust should apply to participate in the American Cell Biology Conference as well attended by worldwide scientists. Professor Robert Nussbaum kindly offered to put together the necessary proposal and we are delighted that we have been accepted to present on Lowe Syndrome disease on the 9th December. A full report will be issued following the event.

LOWE SYNDROME TRUST FLYER

The first UK Lowe Syndrome Trust Flyer was produced by the Trust during 2006. The funds for this flyer were donated by the Lloyds TSB Foundation. This flyer will be distributed to all UK and Ireland Paediatric Hospitals.

LOWE SYNDROME TRUST MEDICAL BOOKLET FOR PROFESSIONALS AND FAMILIES

The Lottery donated funds to allow the Trust to produce a Lowe Syndrome Trust medical booklet for both families and professionals. The booklet has just been completed (50 pages) which includes information on all aspects of the disease. This booklet will shortly be added to the Lowe Trust website www.lowetrust.com

LOWE SYNDROME TRUST CLINICAL DATABASE

Dr Anthony Norden of the Lowe Syndrome Trust Scientific Advisory Board and Lorraine Thomas, Chair of the Lowe Syndrome Trust recently met with Dr Andrew Wallace at Manchester Hospital to discuss a UK Lowe Syndrome Trust clinical database. Dr Andrew Wallace has been responsible for DNA testing of Lowe children since the test became available. Due to UK government data protection act, the Lowe Syndrome Trust is unable to access this information direct. Therefore, the Trust will work with Dr Andrew Wallace setting up a database of all Lowe Syndrome patients in the U.K. based on the genotype information which is held at Manchester.

To use the gentotype data, in conjunction with enzyme data (where available) and clinical data on both multi-organ phenotype and behaviour to test the hypothesis that there are genotype-phenotype correlations in Lowe Syndrome.

LOWE SYNDROME TRUST LOWE ENZYME DIAGNOSTIC SERVICE

The LST Trust and Dr Anthony Norden (LST Scientific Advisory Board member) are in discussion about the setting up of a UK Lowe enzyme diagnostic service – which at present is only offered in either the USA or France. This service will enable accurate confirmation of the Lowe disease and aid future research.

The Lowe Syndrome Trust – where are we now and what have we achieved.

The charity has achieved an enormous amount of work since it was founded in June 2000. Prior to the Trust there was no charity in the UK for either research or support.
The Trust was set up and a group of top scientists enlisted to advise the Trust on various aspects of research and any future research proposals received.

A standard Lowe Syndrome Trust grant proposal was produced and when the first £50,000 was raised, an advert was put into medical journals advertising the grant for research into the disease. We are now hopeful that the research funded will lead on to new exciting projects. The Trust organized the first UK Lowe symposium to raise awareness of the disease within the medical arena and from that meeting new projects were submitted.

Continuous campaigns and events have resulted in the Trust awarding seven research grants. Here is where we are to date

1. **Great Ormond Street – Dr William van't Hoff**
   The projects aim of culturing Lowe kidney cells was successfully completed and now available to enable future research projects.

2. **Dundee University – Dr John Lucocq**
   One main feature of Lowe syndrome is mental retardation. The syndrome is due to a lack of an enzyme called OCRL1 and we are testing the idea that this enzyme may control the formation of connections between nerve cells. Nerve cell connections allow proper nerve cell communication in brain functions. We aim to find out whether OCRL1 controls nerve cell connections by a direct action on membranes or by controlling the cellular filaments within the nerve cell connections. With knowledge of these mechanisms we hope to explain the problems in brain function found in boys with Lowe syndrome and develop better treatments.

3. **University College London under Professor Shamshad Cockcroft.**
   The X-linked disorder oculocerebrorenal syndrome of Lowe is caused by mutation of the OCRL1 protein, whose enzymatic function is to hydrolyse a unique lipid, phosphatidylinositol(4,5)bis phosphate. Removal of the terminal phosphate by OCRL1 results in the production of another lipid, phosphatidylinositol 4-phosphate (PtdIns4P). OCRL1 is localized to the Golgi apparatus and the early endosomes and we have identified that the Golgi and able to switch from an inactive form when loaded with GDP to an active form when loaded with GTP. This molecular switch can regulate the activity of many different proteins and so co-ordinate membrane traffic.We therefore examined whether the Rab proteins in the active form could regulate the activity of OCRL1. We first established an assay in vitro to analyse the catalytic activity of OCRL1. When Rab5 or Rab6 (but not Rab1 or other GTPases such as Rac1 or ARF1) were added with OCRL1, a marked increase in activity was observed. **These data provide the first suggestion that at the Golgi a cycle of lipid hydrolysis may regulate the membrane traffic through this compartment.**

4. **Institute of Ophthalmology Moorfields – Dr Tim Levine**
   Previous studies have shown that cells lacking the Lowe Syndrome protein OCRL1 are altered, but the differences have been hard to trace in detail. One thing that has been known for some time is that the levels of a highly active molecule called PIP2 rise, however it has not been shown previously where the PIP2 is. Normally PIP2 is on the external (plasma) membrane of cells, and this might be where the extra molecules also build-up. Alternatively, the extra PIP2 might be on internal membranes inside cells. As part of an ongoing project to look at how lack of OCRL1 affects the development of lens cells, we have developed a technique that detects some of this PIP2 for the first time in the internal parts of living cells. Our next goal is to apply this to lens cells.

5. Imperial College London – Dr Rudiger Wolchoski & Dr Ramon Vilar Compte

The Lowe Trust funded a PhD project on the development of a chemical receptor for the lipid substrate (PIP2) of the OCRL enzyme, deletion of which is causing the Lowe syndrome. Chemical receptors are small molecules that can bind to other molecules in a specific fashion. The receptor designed and tested in the Lowe trust funded PHD project aimed to recognise the vicinal phosphate and alcohol groups on the inositol headgroup of the lipid substrate. In order to develop such a chemical receptor, it is necessary to first prepare a series of building blocks that can selectively interact with specific parts of the targeted molecule (i.e. the phosphates or the head group). These building blocks can then be assembled together (using a modular approach - like a chemical ³Lego²) into a series of potential receptors, generating a small library of compound that can be evaluated and screened for their ability to interact with the targeted molecule. In parallel, a way of visualising this interaction needs to be devised. This can be based in optical changes such as a change of colour or luminescence of the receptor when it binds to IP3 or PIP2.

Over the past three years, we have managed to tackle most of these challenges establishing the proof-of-concept. More specifically, we have:

- Developed a library of molecular building blocks with good binding capabilities to different parts of the targeted IP3/PIP2
- Assembled these building blocks in different combinations to achieve a small library of receptors
- Evaluated the binding abilities of these receptors towards IP3 in aqueous solutions
- Demonstrated that some of these receptors can indeed bind IP3 selectively, in aqueous solution and this molecular event can be detected by a colour change

It is worth noting two key achievements of the research carried out over the past three years: the receptors are able to bind with good affinity the targeted molecule in **aqueous solutions** and they do this with a good degree of **selectivity** (i.e. they bind IP3 better than other competing analytes in the medium).

Where are the challenges for the future? Although the past three years have been successful, we recognise that there are still several important challenges that need to be tackled. Some of them are:

- Increase the binding affinity of the receptors - for these receptors to be successfully used as part of a diagnostic tool (and eventually as a component of an ³artificial enzyme²) their binding affinities need to increase a couple of orders of magnitude. We propose to do this by including metal complexes as modules for the synthesis of a second generation of receptors.
- Improve selectivity - although the receptors can discriminate well between different competing species, we need even better selectivity (this will be directly linked to the above)
- Better means of detecting the ³binding² event - so far, the change in colour observed when the receptor interacts with IP3 has been based in the so-called displacement assay of a dye from the receptor. Now we want to take one step forward an incorporate the optical reporter as one of the building blocks of the receptor.

All these improvements will strengthen the current lead compound towards a real chemical alternative to investigate OCRL dependent signalling and may even be the foundations of a future drug development programme to tackle the symptoms of Lowe Syndrome.

6. **Addenbrooke's Cambridge – Dr Anthony Norden**

'Work is on-going to understand the role of two very large proteins, named megalin and cubilin, in the normal human kidney. These proteins are themselves involved in making sure that, unlike Lowe patients, protein is normally not lost in the urine. Understanding the role of these proteins in the normal kidney will be essential to working out how to help reduce the chance of kidney damage in patients with Lowe Syndrome.'

7. **Institute of California – Professor Robert Nussbaum**

This grant was awarded mid 2006 and a report will be issued shortly.