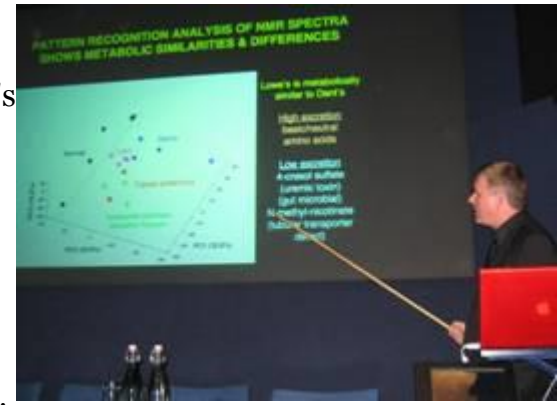
2007 International Lowe Syndrome Medical Symposium at the Royal Society London

Funded and organised by the charity, the second international conference on Lowe Syndrome was held on 7th December 2007 at The Royal Society in London, followed by a dinner at the RAC club. This historical event brought together over 50 international researchers, medical professionals and parents to present and discuss the disease, current research underway and ideas for future projects.

Nationalities and Lowe organisations represented at the meeting included Debbie Jacobs, president of the Lowe Syndrome Association (**LSA)** USA, Ana Suárez Gisbert from Spain (**asle**), France (**ASL**), Germany, Holland and Italy (**AISLO**). The outcome of the research on the mutations of Dents disease and Lowe syndrome confirmed that the clinical syndromes as they are described in the medical literature are not simply accounted by a single or multiple gene defects, the need for a focus on the enyzme deficiency for detection and potental therapies, the need for animal/fish models and clinical databases, and sharing of discoveries (and cells samples) and collaboration between researchers.



The meeting was chaired by Prof. Robert Unwin UCL , followed by the plenary lecture by Prof. Nussbaum who discovered the Lowe's syndrome gene on the X-chromosome and has been instrumental in Lowe Syndrome research.

Presenters included Dr Martin Lowe, University of Manchester, Dr Andrew Wallace, National Genetics Reference Laboratory, Manchester; Prof Pietro De Camilli, Yale University USA; Prof. J Lunardi, Laboratoire de Biochimie de l'ADN, Grenoble, France, Prof. Michael Ludwig, Clinical Biochemistry, University of Bonn, Germany, Prof. Arend Bokenkamp, Department of Paediatrics, Amsterdam; Rudiger Woscholski, Division Cell & Molecular Biology, Imperial College, Dr Helen Cross, Institute of Child Health (UCL), Dr Tim Levine, Department of Cell Biology, Institute of Opthalmology (UCL) and Prof. Steve Scheinman, Upstate Medical University, USA .

The meeting concluded with a stimulating presentation on the emerging science of Metabonomics by Guest lecture – Prof. Jeremy Nicholson of Imperial College, London. The meeting was followed by a dinner at the nearby RAC club in the Terrace Room.

The charity would like to thank all the participants and was greatly encouraged by the professionalism, enthusiasm, dedication and camaraderie of this global scientific movement tackling this devastating desease!

The Second International Symposium of the Lowe Syndrome Trust 'Molecular and Clinical Advances in Lowe Syndrome' Royal Society, London, 7 th December, 2007

Martin Lowe -

Summary of presentations:
The presentations started with a plenary lecture from Professor Robert Nussbaum, University of California, the discoverer of the OCRL1 gene. Professor Nussbaum described a novel strategy for developing a mouse model for the study of Lowe syndrome based upon 'humanizing' a protein closely related to OCRL1, called INPP5B. It has been known for several years that mice lacking OCRL1 fail to develop Lowe syndrome. This is likely due to compensation by INPP5B, which is spliced differently in mice compared to humans. Professor Nussbaum suggested that it is this differential splicing that explains why mice fail to develop Lowe syndrome. He described the generation of a mouse containing the human INPP5B gene, and could show that it splices in the same way as it does it humans. These mice must now be bred with mice lacking OCRL1 to hopefully generate a mouse that recapitulates the Lowe syndrome pathology. If successful, this will provide an invaluable resource for the research community, and allow significant progress in our understanding of Lowe syndrome. Dr Martin Lowe, University of Manchester, followed on from Professor Nussbaum to describe studies on the cell biology of OCRL1 and INPP5B, including their localisation to different subcellular compartments and their interactions at these locations. Professor Pietro De Camilli of Yale University presented a number of key findings including the structural determination of several OCRL1 domains, its interaction with other proteins including the vesicle coat protein clathrin and the signalling adaptor APPL1. Professor De Camilli went on to describe a compelling model for how OCRL1 might participate in endocytic trafficking that could explain how its loss leads to defects in the brain and kidney. Dr Tim Levine, Institute of Opthalmology, London, also described a cell biological characterisation of OCRL1, focussing on its potential role in maintaining the

integrity of junctions between epithelial cells, which are of critical importance in the development and maintenance of several tissues including the kidney.

There were several talks on the genetics of Lowe syndrome. Dr Andrew Wallace from the National Genetics Reference Library, Manchester, described the genetic screening process for Lowe syndrome detection. Professor Joel Lunardi from Grenoble, Professor Arend Bokenkamp from Amsterdam, and Professor Steve Scheinman from Syracuse described the spectrum of OCRL1 mutations giving rise to Lowe syndrome and another condition called Dent's disease, which has the same renal symptoms associated with Lowe syndrome but not the eye or brain defects. Among the important findings presented were the identification of identical mutations that give rise to vastly different severity in clinical symptoms, indicative of additional modifying factors, and the striking correlation between the location of mutations in the OCRL1 gene and the prevalence of a Lowe syndrome or Dent's phenotype. Mutations in the first 7 exons give a kidney-restricted Dent's phenotype, whereas mutations downstream from this position give the full range of renal, brain and eye defects associated with Lowe syndrome. Professor Scheinman suggested these findings could be explained by differential splicing of OCRL1 in different tissues, although this remains to be tested.

Dr John Land from UCL described a number of previously published observations suggestive of mitochondrial abnormalities in Lowe syndrome and proposed a model where defects in mitochondria may contribute to the syndrome pathology. Dr Helen Cross, also of UCL, described the complex neurological symptoms of Lowe syndrome. Dr Rudiger Woscholski, of Imperial College described a synthesised chemical molecule designed to bind the substrate of OCRL1, a lipid called PIP2. The compound appeared to bind PIP2 with high specificity, and was able to affect certain PIP2-dependent processes in intact cells. The hope is that this chemical may be suitable as a future treatment of Lowe syndrome by reversing the increase in PIP2 levels seen in patients. Further studies will be required to determine whether this is a realistic proposition. The meeting was concluded by Professor Jeremy Nicholson from Imperial College who gave an overview of metabonomics, a systems approach to studying metabolism, and its application to disease.

It is clear that significant progress in our understanding of OCRL1 and Lowe syndrome is being made on several fronts. Although our understanding has increased enormously since the last Lowe Syndrome Trust meeting 3 years ago, there are still much we do not know. It is likely that only through the combined efforts of biochemists, cell biologists, geneticists, and clinicians that we will get to a point where we know the mechanisms responsible for Lowe syndrome, and how to combat these to bring benefit to the patient.