

**American Society Cell Biology Conference
San Diego, California**

**Summary of Lowe syndrome session at the 2009 ASCB meeting
Funded by the Lowe Syndrome Trust and Lowe Syndrome Association**

On December 5th 2009 a group of researchers gathered in San Diego at a special interest meeting entitled “Cell biology of Oculocerebrorenal syndrome of Lowe” as part of the annual American Society for Cell Biology conference.

Oculocerebrorenal syndrome of Lowe (OCRL) is a rare X-linked genetic disorder that affects the brain, eyes and kidneys, with characteristic symptoms of mental retardation, congenital cataracts, and defective proximal kidney tubules. It is known that mutation of a single gene, OCRL1, is responsible for the condition. However, how mutation of OCRL1 leads to the symptoms of Lowe syndrome remains poorly understood. The presentations given at this meeting highlighted the rapid rate of progress that is being made in our understanding of OCRL1 biology. The hope is that the continued progress in this area will open the way for better treatment of this devastating condition in the future.

The session started with a general introduction by Robert Nussbaum (UCSF), the discoverer of the OCRL1 gene, who described the history and current status of OCRL1 research. This was followed by a talk from Pietro de Camilli (Yale University), who described the dynamics of OCRL1 within the endocytic pathway, which is the major pathway for the uptake of material into our cells. Professor de Camilli also introduced two new binding partners for OCRL1, which he has called Ses1 and Ses2. These bind OCRL1 with high affinity and reside on sorting endosomes, a major trafficking hub inside cells, but their function remains unclear at present. Yuxin Mao (Cornell University) discussed the outstanding progress that has been made in determining the 3-dimensional structure of the protein. Much of this work was performed by Dr Mao while he was in the de Camilli lab. He discussed the structure of the major domains of the protein, and using this information how mutations that cause Lowe syndrome could lead to loss of function of the OCRL1 protein.

Antonella de Matteis gave a very interesting talk on the cellular function of OCRL1. Using both cells derived from the kidneys of Lowe syndrome patients and more generic cell lines, Dr de Matteis was able to show that OCRL1 functions in the trafficking of proteins out of the sorting endosome. This included receptor proteins that normally recycle from the sorting endosome to the cell surface, or receptors that are normally trafficked to another intracellular compartment, the Golgi apparatus. Dr de Matteis could also show that the enzymatic activity of OCRL1 (it is an enzyme that ‘degrades’ a specific type of lipid found in cell membranes) is important for its role in these processes, and went on to show that by altering the lipid composition of cells the defects caused by loss of OCRL1 could be corrected. This exciting finding suggests that drugs that alter cellular lipid metabolism may be worthwhile for the treatment of Lowe syndrome. The next talk was by Maria Paz Marzolo (Pontificia Universidad Católica de Chile, Chile), who described her studies on megalin, a large cell surface receptor for the uptake of many types of molecules into cells of the kidney proximal

tubule, regions of the developing brain, and several other tissues in the body. Dr Marzolo showed that trafficking of megalin is perturbed when OCRL1 is lost from cells, most likely due to a defect in recycling from endosomes to the cell surface, and described a possible mechanism by which this recycling may be regulated in an OCRL1-dependent manner. These findings may help explain the renal symptoms of Lowe syndrome, which have previously been suggested to arise from defective megalin trafficking.

The first part of the session was concluded by Martin Lowe (Manchester University, UK), who described recent work on the development of a zebrafish model for Lowe syndrome. Encouragingly, zebrafish lacking OCRL1 display eye and brain defects, similar to humans, suggesting this model may be valid for the investigation of the disease mechanisms of Lowe syndrome.

Claudio Aguilar started after the break with a presentation of his group's recent findings on a role for OCRL in cell migration. This fundamental process is highly important during embryonic development, for example in development of the nervous system and in organ formation, as well as having a vital role in later stages of development and in adults in processes such as wound healing. Dr Aguilar found that cells lacking OCRL1 had a reduced ability to migrate. He also showed that the catalytic activity of OCRL1 was important for cell migration, and that migration defects in OCRL1-deficient cells could not be 'rescued' by expressing the closely related protein INPP5B, indicating that this function for OCRL1 is not overlapping with INPP5B, at least in the assay that was used. These findings suggest the developmental defects of Lowe syndrome may arise, at least in part, through defects in cell migration. Current studies are focusing on the mechanisms by which OCRL1 may influence this process.

Steve Scheinman (State University of New York, Upstate Medical University) described the relationship of Lowe syndrome to Dent's disease, which displays renal defects very similar to Lowe syndrome without the associated neurological and eye problems. Interestingly, 15% of Dent's patients have mutations in OCRL1. These mutations tend to cluster near the beginning of the gene, while those associated with Lowe syndrome are further downstream. Professor Scheinman suggested that differences in gene splicing in the kidney compared to eye and brain may account for the different outcomes of OCRL mutation, giving rise to either a Dent's or Lowe syndrome condition. An intriguing possibility is that differential splicing may result in a truncated but functional version of OCRL1 in the eyes and brain but not kidney, explaining why mutation at the start of the gene only affects the latter tissue. Further studies will be required to test this interesting hypothesis.

Sandra Guggino presented findings relating to the trafficking of ion transporters in the kidney proximal tubule, focusing on the NHE3 transporter found at the lining of the tubule, where it transports sodium ions into cells in exchange for protons. Dr Guggino found that in a mouse model for Dent's disease the NHE3 transporter was less abundant at the cell surface suggesting a recycling defect. It will be interesting to investigate whether NHE3 trafficking is also impaired in Lowe syndrome, which may contribute to the renal problems associated with this condition.

The final talk was by Robert Nussbaum, who described a new mouse model for investigating Lowe syndrome. Previous attempts to generate a mouse model for Lowe syndrome were unsuccessful, most likely due to compensation of OCRL1 loss by the related INPP5B. Professor Nussbaum has now generated a 'humanized' mouse expressing the human version of INPP5B instead of the mouse version, the rationale being that human INPP5B should not fully compensate for loss of OCRL1, as is the case in human Lowe syndrome. Indeed, this approach has worked, resulting in mice that have a similar renal defect to that seen in Lowe syndrome. Interestingly, this is seen in mice containing only one copy of human INPP5B, rather than the usual two copies, indicating that the expression level of INPP5B is important in determining the severity of the defects observed. Interestingly, the mice have normal eyes, and no obvious neurological changes, although this has yet to be fully investigated. Professor Nussbaum has kindly offered to distribute his transgenic mice to investigators interested in studying OCRL1 function and the disease mechanisms of Lowe syndrome. Hopefully these mice, together with the OCRL1-deficient zebrafish described above will allow rapid progress to be made in these areas.

The meeting concluded with a general discussion of where to go next, what key aspects remain to be understood, and what barriers exist to future progress. With regard to the latter point, it was agreed that obtaining good antibodies to OCRL1 and INPP5B that work in microscopy and histology would be of great benefit. Generating panels of monoclonal antibodies to these proteins likely offers the best hope, since numerous previous attempts to generate good polyclonal antibodies have so far failed.

I would like to acknowledge the UK Lowe Syndrome Trust and the Lowe Syndrome Association for generously supporting this meeting, as well as Robert Nussbaum and the ASCB for organizing it.

Martin Lowe
31/12/09