

On the Beam

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“Care today... cure tomorrow”

First multistate fundraiser nets \$7,874 for database



New York Walkers: Ron, James and Ed Jerman, Ron and Toby Kasen, Ann Marie Shindel, Irwin, Carolyn and Alec Everitt, Hope Walter, Jones Wong, Tania Rojo, Liz Vasquez, Cori, Vinny and Matthew DeGon, Catherine Rojo, Catherine Rojo-Parra, Jesse Montasino (taking picture), Caroline Barufaldi, Eric, Lisa and Luke Olsen, Abbe and April Weintraub.

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Dr. Brewer Urges Creation of a Clinical Database

To really understand and treat Lowe syndrome we need more comprehensive information about many boys. With this information doctors who treat Lowe syndrome can get a complete picture of how patients are alike, how they are different, how they respond or don't respond to medicines, what groups of symptoms are likely to happen at what ages and what tests might be best for evaluation and follow up.

For these reasons I am very excited about the creation of a computerized clinical database for patients with Lowe syndrome. A clinical database will be invaluable for doctors, research scientists and families to better understand the disease process of Lowe syndrome and how it progresses through childhood and into adulthood. Because

very few patients see the same doctor or go to the same center, information about Lowe syndrome in more than a handful of boys in a single study has never been available.

Getting a more complete clinical picture of the medical history, physical examination, x-rays and laboratory tests over a long period of time from infancy to adulthood in 50-100 patients will help doctors learn to treat Lowe syndrome better and help researchers know what questions to ask to study the disease better. We might also learn to better predict what outcomes to expect or be on the lookout for in boys with certain patterns of symptoms and laboratory values at different ages. Knowing what might happen, we can then try to improve the outcomes

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Cell Biology and Lowe Syndrome

Dr. Nussbaum reports major progress, exciting discoveries

On December 9th 2006, a group of researchers gathered in a satellite meeting at the 46th American Society of Cell Biology (ASCB) meeting in San Diego, to present recent findings on the



Dr. Nussbaum

Oculocerebrorenal Syndrome of Lowe, or Lowe syndrome. This satellite meeting, sponsored by the Lowe syndrome Trust (UK) and given under the auspices of the largest and most prestigious professional scientific society for cell biology in the world, the ASCB, was well attended by 40-50 cell biologists, including a number of young investigators from outside the Lowe syndrome field who were attending the ASCB meeting.

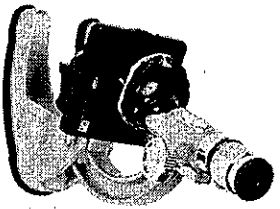
Encouragingly, it appears there is major progress in our understanding of the normal function of the protein (ocrl) encoded by the OCLR gene, with more researchers beginning

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Special Research Section continued

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with new therapies or with prevention of complications. We can also learn more about the carrier state in the same way.

Putting all the information in a computerized database can be done without invading the privacy of each patient's information. Each patient will be assigned a special code used in the computer, instead of using the patient's name, so no one studying the data will know the patient's identity. The persons who send in the information will know the special code in case they need to get a summary of information for an individual patient. Information about carriers can be entered in the computer in the same way.

Having all the information in a computer will make it easier and faster to analyze similarities and differences and follow changes over time in many patients or individual patients. One doctor or a few doctors trying to do the same thing by hand for a few patients with Lowe syndrome cannot come close to doing what can be done with a lot of information in a computerized database by a multidisciplinary team. I hope we will begin to make good progress this year toward our goal of starting a clinical database for patients and families with Lowe syndrome. I look forward to continuing to work with the Lowe Syndrome Association toward this goal. ■

Eileen D. Brewer MD
Professor of Pediatrics & Head, Pediatric Renal Section, Baylor College of Medicine Chief, Renal Service, Texas Children's Hospital, Houston, TX



Dr. Brewer

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to study the problem and making exciting new discoveries. Dr Yuxin Mao, from Dr Pietro De Camilli's group at Yale University, typified this by describing a number of key findings including the determination of the three-dimensional structure of the carboxy-terminal region of ocr1l, which provides a molecular explanation for how it can dock onto membranes and recognise its substrates. Dr Mao also found that ocr1l localised to clathrin-coated pits, which are specialized cellular structures that mediate endocytosis at the cell surface, and interestingly found an enrichment of the protein at the apical side of kidney tubule cells, where absorption of material occurs. Together, these findings suggest that apical endocytosis may be defective in Lowe syndrome, resulting in a failure to properly absorb material in the kidney. Another interesting observation presented by Dr Mao was the binding of ocr1l to a protein called APP1, which is involved in generating intracellular signals at endosomes, suggesting a role for ocr1l in signalling from endocytic intermediates.

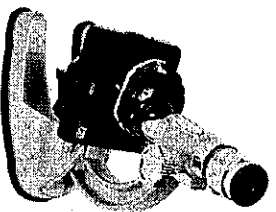
Analysis of ocr1l in other kidney cell based model systems suggested roles for the protein in other membrane traffic pathways in the cell. Dr Chris Guerriero from the lab of Dr Ora Weisz in Pittsburgh reported a role for ocr1l in regulating polarised delivery of certain proteins to the apical side of kidney cells in a mechanism involving changes in actin dynamics. In another interesting presentation, Dr Alex Ungewickell from the lab of Dr Philip Majerus at Washington University of St. Louis described a novel hypothesis in which it was proposed ocr1l regulates the polarised delivery of an ion transporter to the opposite side of kidney cells, where it is required to maintain kidney ion balance and uptake processes. Initial findings suggested that ocr1l might control the polarised distribution of this important protein. Findings presented by Dr Martin Lowe from Manchester University pointed at a role in yet another membrane traffic

step in the cell, namely transport from the endosomes to the Golgi apparatus. At present it is not clear to what extent ocr1l regulates the various membrane flow pathways in a cell or how these pathways contribute to the pathophysiology of Lowe syndrome, but these initial studies lay the groundwork for future advances in this area.

It has emerged in recent years that lipids can be transported between membrane compartments via direct contact sites, and that this is important in the synthesis of different lipid types, including sphingolipids, which have important functions at the cell surface. Dr Antonella De Matteis from the Mario Negri Institute at Santa Maria Imbaro in Italy described a novel role for ocr1l in the production of sphingolipids at the Golgi apparatus, pointing to yet another avenue for future research into Lowe syndrome.

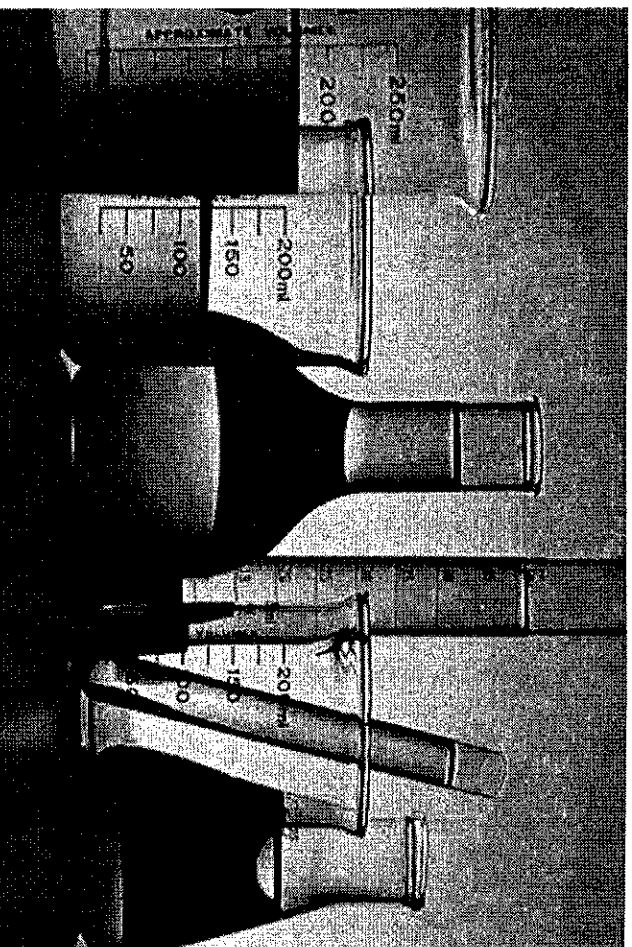
Analysis of yeast proteins related to ocr1l has also proven informative in terms of understanding the basic biology underlying Lowe syndrome, as exemplified by the elegant work presented by Dr Christopher Stefan, from Scott Emr's group in San Diego and Prof. Jeremy Thorner from the University of California in Berkeley. These talks nicely illustrated how a combination of yeast genetics and cell biology can lead the way in studying the mechanisms by which lipid metabolism regulates different aspects of cell behaviour, including endocytosis and cell migration, two processes which are relevant to our understanding of Lowe syndrome.

Despite not being the focus of this meeting, there have been a number of studies into the genetic basis of Lowe syndrome. It has been known for years that the severity of the disease can vary dramatically, even in patients with identical mutations in the gene encoding ocr1l. Furthermore, recent studies on Dent disease have revealed that patients with this disorder, which shares only some of the renal findings in Lowe syndrome, have mutations in ocr1l. These findings suggest there are other genes that influence



Special Research Section

continued



the range and severity of Lowe syndrome symptoms, so-called "genetic modifiers". Dr Sharon Stucky of the NHGRI at Bethesda has undertaken a "gene expression chip" based approach to identify other genes that are more or less highly expressed in Lowe syndrome and Dent disease patients and to try and correlate these with differing physical symptoms. Initial studies suggest a link with the Wnt signalling pathway which is important for establishing cell polarity during early development. Considering the tissues affected in Lowe syndrome are polarised, this is an exciting finding, and one that merits further investigation.

It is worth emphasizing the role played by the voluntary parent organizations in promoting research in Lowe syndrome. Research into this disorder is gathering momentum, which has a lot to do with the interest and curiosity of the researchers involved, but also the dedication, encouragement and financial support offered by organisations such as the UK Lowe Syndrome Trust and the US Lowe Syndrome Association. For example, The Lowe Syndrome Trust, under the leadership of Lorraine Thomas, helped organise this

meeting together with Dr. Robert Nussbaum, the original discoverer of the *ocrl1* protein, and has supported a number of research projects in Lowe syndrome, including work in Dr. Nussbaum's laboratory. As another example, two of the other eminent speakers at the meeting, Dr. Thorner and Dr. De Matteis, have received funding for research from the Lowe Syndrome Association.

The meeting in San Diego was stimulating from a cell biological perspective, but also importantly, encouraging from the broader view of trying to understand and treat Lowe syndrome. Let us hope the findings presented at the meeting pave the way for further breakthroughs in Lowe syndrome research that ultimately transmit to the clinic. ■

Dr Martin Lowe
University of Manchester, UK.

Dr. Robert Nussbaum
University of California, San Francisco

January 29th, 2007

Other Research Highlights

In addition to the grants awarded by the USA, there have been many other research projects supported, sponsored or conducted by the USA. Many of these grew out of the commitment of the doctors and scientists who came to know the USA family and to the families whose participation showed their commitment to making a better future for individuals with Lowe syndrome. Following is a list of some of the most notable:

- Discovery of the *OCRL* gene at NIH by Dr. Nussbaum and his team
- NIH Clinical Study conducted by Dr. Charnas
- NIH Behavioral Study, which grew out of the Clinical Study and the Behavior Conference in Wilkes Barre
- Scientific symposium on the Lowe syndrome enzyme in 2000, by Dr. Nussbaum
- Clinical research symposium on Lowe syndrome at NIH in 2002, by Dr. Nussbaum
- Genetic and Carrier Testing, conducted by Dr. Lewis at ISA conferences and on an ongoing basis at the Baylor University Labs
- USA Comprehensive Survey and published report, 1991
- Partnership between the USA and the University of Maryland Brain and Tissue Bank

The creation and maintenance of the Website by Jeff Smith has been an invaluable research tool for doctors in diagnosing and treating Lowe syndrome and for families and professionals in staying informed of the latest discoveries and advances. The booklet *Living With Lowe Syndrome*, which many of us provide to all the professionals and caregivers who treat our sons, is a vital tool for doctors, specialists, therapists and educators who work with us. ISA Conferences provide a public forum for researchers to share information about their discoveries and ongoing projects. ■