Hello to our Lysosomal Community.
We hope that you all had a wonderful summer and Easter break - isn't it starting to get cold in the mornings. We have been a little slow to get started this year due to John Forman, David Palmer and myself attending the WORLD Lysosomal conference in February, so this is our first newsletter of the year in a brand new format.

We have been exploring a new way of communicating with you all using this new program. We are hoping that we will be able to communicate more often and so we thought we would start with sending you some news from around the world and some of the Posters and Abstracts from the WORLD conference. We are keen to know what you think of this.

**Pharmac:** I wish we had news for you on this front. Pharmac are certainly dragging the chain on announcing their decisions on funding of Orphan drugs. However; We are in contact with Pharmac regularly to see how much longer they are going to keep us waiting for a decision. They assure us that they are still negotiating and hope to make their decisions soon with therapies beginning around 1 July 2015.

I am going to be having spinal surgery on 5th May and wont be in the office for a couple of weeks. If you need to speak to someone from LDNZ John will be available at john.forman@xtra.co.nz

Jenny Noble
Field Officer/Administrator.
LDNZ
We warmly welcome the Barnett family to our Lysosomal Family who have a child with Batten disease. They have joined our facebook page please take a moment to say Hello.

Donations can be made to LDNZ by visiting our website www.ldnz.org.nz and clicking the donation button. All donations over $5.00 are tax deductible.

News From around the world...

Ontario to provide 'interim' funding for Soliris
In Canada, the Ontario government will now provide patients with atypical Hemolytic Uremic Syndrome (aHUS) interim funding for the expensive drug treatment – Soliris. aHUS is a progressive disease that causes the formation of blood clots throughout the body, which can lead to stroke, heart attack and kidney failure. The disease can affect both adults and children, and is often linked to genetics. The Ontario government announced Wednesday it would begin "interim" funding for patients who meet the clinical criteria for the disease and require the drug Soliris. Soliris is the only available treatment for these patients but is unaffordable for many patients, as it could cost them an upwards of $500,000 per year. In Canada, Quebec also funds Soliris

Long-Term Correction of Sandhoff Disease Following Intravenous Delivery of rAAV9 to Mouse Neonates.
Abstract
GM2 gangliosidoses are severe neurodegenerative disorders resulting from a
deficiency in β-hexosaminidase A activity and lacking effective therapies. Using a Sandhoff disease (SD) mouse model (Hexb(-/-)) of the GM2 gangliosidosis, we tested the potential of systemically delivered adeno-associated virus 9 (AAV9) expressing Hexb cDNA to correct the neurological phenotype. Neonatal or adult SD and normal mice were intravenously injected with AAV9-HexB or -LacZ and monitored for serum β-hexosaminidase activity, motor function, and survival. Brain GM2 ganglioside, β-hexosaminidase activity, and inflammation were assessed at experimental week 43, or an earlier humane end point. SD mice injected with AAV9-LacZ died by 17 weeks of age, whereas all neonatal AAV9-HexB-treated SD mice survived until 43 weeks (P < 0.0001) with only three exhibiting neurological dysfunction. SD mice treated as adults with AAV9-HexB died between 17 and 35 weeks. Neonatal SD-HexB-treated mice had a significant increase in brain β-hexosaminidase activity, and a reduction in GM2 ganglioside storage and neuroinflammation compared to adult SD-HexB- and SD-LacZ-treated groups. However, at 43 weeks, 8 of 10 neonatal-HexB injected control and SD mice exhibited liver or lung tumors. This study demonstrates the potential for long-term correction of SD and other GM2 gangliosidoses through early rAAV9 based systemic gene therapy.


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**Neurological and cardiac responses after treatment with miglustat and a ketogenic diet in a patient with Sandhoff disease.**

**Abstract:** Sandhoff disease is a progressive neurodegenerative disorder characterized by accumulation of GM2 gangliosides. We describe a 6-year-old male with coarse facial features, developmental delay, refractory seizures, hypertrophic cardiomyopathy, who was later found to have Sandhoff disease. Previous studies have revealed that caloric restriction in combination with miglustat increased survival and motor behavior in mouse model of Sandhoff disease. These findings suggest that combination therapy may result in improved outcomes for patients with Sandhoff. Initiation of treatment with miglustat and a ketogenic diet was followed by improvement of the patient's seizure control and cardiac function. Further clinical investigation is required to better determine the benefit of management in late-onset forms of Sandhoff disease.


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**Long term follow-up to evaluate the efficacy of miglustat treatment in Italian patients with Niemann-Pick disease type C**

**Background** Twenty-five patients with Niemann Pick disease type C (age
range: 7 months to 44 years) were enrolled in an Italian independent multicenter trial and treated with miglustat for periods from 48 to 96 months.

**Methods** Based on the age at onset of neurological manifestations patients' phenotypes were classified as: adult (n = 6), juvenile (n = 9), late infantile (n = 6), early infantile (n = 2). Two patients had an exclusively visceral phenotype. We clinically evaluated patients' neurological involvement, giving a score of severity ranging from 0 (best) to 3 (worst) for gait abnormalities, dystonia, dysmetria, dysarthria, and developmental delay/cognitive impairment, and from 0 to 4 for dysphagia. We calculated a mean composite severity score transforming the original scores proportionally to range from 0 to 1 to summarize the clinical picture of patients and monitor their clinical course.

**Results** We compared the results after 24 months of treatment in 23 patients showing neurological manifestations. Stabilization or improvement of all parameters was observed in the majority of patients. With the exception of developmental delay/cognitive impairment, these results persisted after 48–96 months in 41 – 55% of the patients (dystonia: 55%, dysarthria: 50%, gait abnormalities: 43%, dysmetria: 41%, respectively). After 24 months of therapy the majority of the evaluable patients (n = 20), demonstrated a stabilization or improvement in the ability to swallow four substances of different consistency (water: 65%, purée: 58%, little pasta: 60%, biscuit: 55%). These results persisted after 48–96 months in 40-50% of patients, with the exception of water swallowing. Stabilization or improvement of the composite severity score was detected in the majority (57%) of 7 patients who were treated early (within 3.5 years from onset) and rarely in patients who received treatment later.

**Conclusions** The results of this study suggest that miglustat treatment can improve or stabilize neurological manifestations, at least for a period of time; the severity of clinical conditions at the beginning of treatment can influence the rate of disease progression. This conclusion applies particularly to patients with juvenile or adult onset of the disease.

http://www.ojrd.com/content/10/1/22/abstract

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**Posters and Abstracts from WORLD conference**

*There were some amazing posters at the WORLD symposium. Over the next few weeks we will be sending these to you. Here is just a few that caught our attention.*

**Effective Gene Therapy in Ovine CLN5 Batten Disease**

David N Palmer, Lincoln University, Lincoln New Zealand,
Lambs homozygous for a mutation causing CLN5 Batten disease (neuronal ceroid lipofuscinosis, NCL) injected with viral vectors containing the corrective gene showed no signs of disease development a year later, whereas un-injected affected animals declined considerably. AAV9 and lentiviral derived vectors expressing green fluorescent protein showed widespread expression 30 days after direct injection into the lateral ventricles or cerebral parenchyma of sheep with no ill effects. Injection of AAV9 or Lentiviral vectors loaded with the corrective ovine CLN5 sequence into preclinical affected lambs at 2-4 months was followed by monitoring over the next 12 months. In all three tests performed monthly, neurological and eyesight tests, monitoring of their ability to join cohorts by navigating through a maze and estimates of cranial cavity volumes in vivo from CT scans, the injected sheep were indistinguishable from the unaffected controls. Over this time the non-injected affected controls declined markedly and developed obvious clinical symptoms, to the point of being unable to navigate the maze. Both vectors were equally effective. Monitoring of the injected sheep continues. Similar injections into CLN6 affected sheep were not as effective, only 1/6 showing a difference from non-injected affected controls. This research was funded by grants for Cure Kids New Zealand the Batten Disease Support group and Research Association (BDSRA) Batten Diseases New Zealand and the American New Zealand Association.

Pharmacological chaperoning in Fabry and Schindler diseases
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Two homologous lysosomal enzymes include α-galactosidase(α-GAL) and α-N-acetylgalactosaminidase (α-NAGAL), which are deficient in the lysosomal diseases known as Fabry and Schindler diseases, respectively. One approach for the treatment of the diseases uses pharmacological chaperones, or small molecules that bind to the enzymes and confer stability to the folded form of the proteins. We have determined the three-dimensional structures of the α-GAL and α-NAGAL enzymes, both alone and in complex with a range of pharmacological chaperones. In this work, we will present the molecular basis for pharmacological chaperoning in the family of enzymes that include α-GAL and α-NAGAL. Using rational design approaches, we were able to engineer affinity improvements of more than 1 million fold for small molecules that bind and stabilize the enzymes. We will present guidelines for improving the specificity and affinity of compounds for these and other lysosomal enzymes.

Is melanogenesis disturbed in mucolipidosis II/III? A multicenter study based on clinical and genetic findings

Mucolipidosis (ML) II and III are inborn errors of metabolism caused by deficient activity of GlcNAc-1-phosphotransferase, an enzyme responsible for targeting of lysosomal hydrolases to the lysosomes. We hypothesized that melanogenesis would be altered in patients with ML II and III.

Objectives: 1) To characterize the skin, hair, and eye color of patients with ML II and III and compare these features to healthy controls; and 2) to establish a genotype–phenotype association involving SNPs known to be associated with skin, hair, and eye color in normal populations.

Methods: This multicentre, prospective, controlled, cross-sectional study employed a convenience sampling strategy. Brazilian patients with ML II and III aged N1 year and their parents. As well as healthy controls based in samples of the CANDELA project, were examined for skin, hair, and eye characteristics using standard (such as the Fitzpatrick scale) and/or visual classifications. Patients were screened for SNPs rs1126809 (TYR gene), rs16891982 (SLC45A2 gene), rs1426654 (SLC24A5 gene) and rs1129038 (HERC2 gene) through KASP genotyping assay.

Results/discussion: Seventeen patients (ML II= 7, ML III alpha/ beta=7, ML III gamma=3; 13 male, 4 female; mean age, 13 ± 12.5 years) and 29 parents were included in the study, as well as 185 healthy subjects from CANDELA project. Most patients had Fitzpatrick skin types I–III (n =14/17, 82%) a rate discrepant with the skin type of their parents (n =19/29, 66%). One of our patients (Fig. 1) had Fitzpatrick skin type II (blond hair, blue eyes, fair skin) at the age of 2 years, while both parents were skin type IV, corroborating the biological plausibility of skin pigmentation changes as manifestations of ML II and III (Figure). Regarding genotype–phenotype association, for rs1126809 2/17 had lighter hair than expected; for rs16891982 4/17, 6/17 and 10/17 patients had, respectively, lighter eyes, hair and skin color; and 3/17, 4/17 and 2/17 patients had, respectively, darker eyes, hair, and skin color than expected; and for rs1426654, 2/17, 1/17 and 1/17 had lighter hair, eyes and skin and 9/17 and 3/17 had darker hair and skin than expected; and for rs1129038 6/16 patients had darker eyes than expected. Any significant discrepancy was not found between the eye and hair color predicted by genotype and those found in healthy controls.

Conclusion: Patients with ML II/III appear to exhibit changes in melanogenesis (most commonly hypomelanosis). Further studies are required to corroborate these findings.

Long-term neuropsychological follow-up in a patient with α-mannosidase

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α-Mannosidosis is a very rare lysosomal disorder resulting from deficiency of α-mannosidase. No therapy was available until now; a phase III study on the effect of enzyme replacement therapy is currently underway. The limited studies on the natural course of cognition show intelligence in the range from mild mental development to profound mental retardation. Studies on long term intellectual development present inconsistent data and there are no studies on neuropsychological development. With this case report, we present a 16 year neuropsychological follow-up of an untreated Caucasian patient. The patient had a mild developmental delay which remained stable in time (range IQ 71–81; 8 measurements between age 1 and 17 years). At last assessment his mental age was 8.0 years (chronologic age 17.9 years). Three additional neuropsychological tests showed difficulties in attention, memory and fine motor skills (age 9, 14 and 17 years; data was corrected for intelligence). His fine motor skills and memory deteriorated in time. School performances were in accordance to his intelligence. Behavioral questionnaires filled out by the parents and an interview according to DSM IV criteria showed symptoms of pervasive development disorder (PDD, not otherwise specified). Brain MRI at age 16 showed mild atrophy in the cerebrum and cerebellum. He had diminished myelination of the periventricular white matter. Here we report a patient with alpha-mannosidosis having a subnormal intelligence, which remained stable in time. The patient performed relatively well on his intelligence tests, when compared to literature on cognition. So far, our case report adds to the existing literature that alphananosidosis is not a progressive mental disorder. The patient had difficulties in his attention, fine motor skills and memory. His fine motor skills and memory deteriorated in time. The impairment in memory and attention was not reported before. With the phase III trial underway, solid knowledge of the natural course and the specific neuropsychological deficits of the disease is important, especially of mental development which is the main characteristic of the disease.

Further expanding the phenotype of treated infantile onset Pompe disease
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Although more than a decade has passed since the first clinical trials with children with infantile onset Pompe disease (IOPD), there is still a paucity of data on long-term outcomes, with follow-up data from the original clinical trials only up to age 41.5 months. To further contribute to the understanding of the clinical history of this group, we previously reported on the success and management challenges in a group of children with a median age at that time of 8.0 years (5.4–12.0 years; n = 11). This older cohort had sustained improvements in cardiac parameters and gross motor function, however, residual muscle weakness, hearing loss, risk for arrhythmias, hypernasal speech, dysphagia with risk for aspiration, and osteopenia were also reported. Further information is now available regarding this group of children with IOPD; the first children treated with enzyme replacement therapy (alglucoamylase alfa) are now as old as 15 years. Since the description of the long-term survivors up to age 12 years, further challenges have been identified. We continue to describe an expanding phenotype with a retrospective review of children with IOPD. The clinical phenotype includes ocular manifestations, premature pubarche, sleep disturbances, lower urinary tract symptoms and incontinence, poor anal tone, and cardiac rhythm disturbances with 2 cases of sudden death in patients aged almost 11 years and 13 years. Muscle histology from infantile patients will be presented as it continues to contribute to the understanding of the current treatment regimen and provides knowledge for new approaches. Clinical outcomes will be presented with recommendations for management. Advancements in the management and treatment of IOPD will be seen in the coming years; meanwhile, more effective and consistent implementation of current knowledge and approaches is essential as we face these remaining challenges.