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### **A LETTER FROM THE PRESIDENT**

To: All Friends of The Myelin Project

From: Augusto Odone

Date: January 24, 2007

You will note that this report is written in a style different from those distributed in the past. Because I was sick, I could not provide any substantive input. The attached newsletter is a collection of submissions by the various researchers present at the Paris meeting held in October. Nevertheless, it hopefully will give you an idea of the ongoing progress in the field of remyelination. We are grateful to the staff of the European Leukodystrophy Association, in particular to Dr. Marie-Josée Duran, who put the report together.

I would like to inform you of a number of changes recently undergone by our Project. Due to setbacks in my health condition, I decided to retire from the presidency of The Myelin Project (TMP). I recommended to the U.S. Board of TMP that they name Dr. Margaret Weis, an associate professor at Texas Tech University in Amarillo, Texas, as my successor to the helm of our Project. This change will be effective from whenever the transition process is completed and we have taken care of our obligations vis-à-vis the doctors of our Work Group. We will be grateful for any contribution you would send our way in order to facilitate this transition.

On a personal note directed primarily to the ALD families, I would like to disclose that unlike in the past, I now have an interest in the commercial development of Lorenzo's Oil for which I acquired the patent (Patent No. 5,331,009) as its inventor. Recently I entered into an agreement with the oil producer Croda Universal whereby this firm would give me a small percentage (5%) on the gross sales of Lorenzo's Oil. Prior to entering into this agreement with Croda, I had obtained the approval of our U.S. Board. There were two factors that induced me to take this step: (1) I was (and still am) in dire financial straits due to the continuous expenses for the care of Lorenzo; and (2) my decision to retire, which eliminates the possibility of potential conflict of interest.

Lastly, I would like to point out that the Project mission is still intact and that I'll be sticking around for many months to come...

All the best for 2007.

Augusto Odone



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RESEARCH

The 1<sup>st</sup> International Congress of the ELA Research Foundation & The Myelin Project entitled "The vital function of myelin development and maintenance" took place in Paris from October 5-7, 2006. The Scientific Committee in charge of the meeting organization was composed of Drs. Aubourg, Dubois-Dalcq, Boespflug-Tanguy, Lacaze and Baron-Van Evercooren. Over 200 participants (M.D., Ph.D, Postdocs and Ph.D. students) from around the world specialized in leukodystrophies and myelin repair attended the meeting and presented their last results.

The congress was divided into four different scientific sessions:

**Scientific Session I: Myelin development and repair**

Co-chairs: Robin Franklin, Anne Baron-Van Evercooren

Jean-Léon Thomas, Ph.D. (INSERM U711, Paris, France)

A role of vascular growth factor on the development, proliferation and migration of mouse myelin-forming cells has been elucidated.

Vittorio Gallo, Ph.D. (Center for Neuroscience Research, Washington DC, USA)

The kinase cdk2 plays an important role in the control of myelin-forming cells progenitors and Sox 17, a transcription factor, is a key regulator of myelin-forming cells proliferation and differentiation in mouse.

Pascale Durbec, Ph.D. (IBDML, Marseille, France)

Transplantation of adult stem cells from mouse into myelin-deficient adult mice showed that grafted cells perform long distance migration along white matter tracts and are able to differentiate into mature myelin-forming cells. Also, exercise in rodents with multiple sclerosis promoted cell proliferation and increased the number of cells recruited into demyelinated structures.

Hans S. Keirstead, Ph.D. (Reeve-Irvine Research Center, Irvine, CA, USA)

Human embryonic stem cells (hESCs) can be directed in their differentiation into high purity myelin-forming cells progenitors, and that transplantation of hESC-derived cells into adult rat spinal cord injuries enhances remyelination and promotes recovery of motor function. The safety of this cell population in transplant was validated using a retroviral panel. Locomotor recovery in the grafted rats was observed 7 days after transplantation.

Robin J.M. Franklin, Ph.D. (Cambridge Centre for Brain Repair, Cambridge, UK)

Identification of potential targets by investigating the cellular and molecular mechanisms of remyelination. Environmental signalling factors that govern remyelination exhibit a large degree of redundancy. Successful completion of remyelination depends on a matrix of signalling events.



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Anne Baron-Van Evercooren, Ph.D. (INSERM 546, Paris, France)

Even though primate neural stem cells can generate myelin-forming cells, little is known about the factors that govern their differentiation and the cell proportion available for cell therapy remains insufficient for transplantation. Several avenues (regional specificity, immuno-selection and transcription factor over-expression,) were investigated to derive cell populations enriched in myelin progenitors from primate fetal brain.

**Scientific Session II: Pathological mechanism of myelin disorders**

Co-chairs: Francesca Aloisi, Monique Dubois-Dalq

Ian D. Duncan, Ph.D. (University of Wisconsin, Madison, USA)

Most of the characterized leukodystrophies have been found to result from a derangement of development from myelin-forming cells or from abnormalities of the mature cell. In certain leukodystrophies, mature myelinating cells degenerate with resultant demyelination. The knowledge that has been gained by studying early development of myelin progenitor cells and the role of transcription factors will likely lead to the discovery of the origin of uncharacterized childhood leukodystrophies.

Larry S. Sherman, Ph.D. (Oregon National Primate Research Center, Beaverton, OR, USA)

Glycosaminoglycan hyaluronan (HA) accumulates in demyelinated lesions from patients with multiple sclerosis, in spinal cord injuries, in infants with periventricular white matter injury, and during the course of normal aging. HA accumulation in these lesions inhibits the proliferation of myelin-forming cells and blocks remyelination. Degrading HA in myelin progenitor cells promotes cell maturation.

Carlos Matute, Ph.D. (Neurotek, Universidad del País Vasco, Leioa, Spain)

Glutamate can be toxic to myelin-forming cells. The strategy is to study the mechanisms leading to cell death and demyelination as a consequence of alterations in glutamate and their clinical relevance to the disease.

David Attwell, Ph.D. (Department of Physiology, University College, London, UK)

Glutamate-mediated damage to myelin-forming cells contributes to mental or physical impairment in periventricular leukomalacia, spinal cord injury, multiple sclerosis and stroke. Molecular mechanisms involve a new NMDA receptor which can be considered as a novel therapeutic target for preventing white matter damage in a range of diseases. The action of memantine which blocks NMDA receptors in myelin-forming cells is being tested.



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### **Scientific Session III:** *White matter disease of the premature*

Co-chairs: Thierry Lacaze, Patrick Aubourg

Thierry Lacaze, M.D. (Stollery Children's Hospital, Edmonton, Canada)

The risk of developing brain injury is dependent on antenatal factors, with the highest risk in infants born to mothers with intrauterine infection. There is accumulating evidence suggesting that intrauterine infection/perinatal inflammation play a key role in the development of white matter injury (WMI). Little information is available about a possible association between perinatal infection/inflammation and the subsequent occurrence of cognitive limitations without motor deficit in children born prematurely. Magnetic resonance imaging is a sensitive tool in predicting cognitive impairments.

Mary Rutherford, M.D. (MRC Clinical Sciences Centre, Imperial College, London UK)

It is now possible to use magnetic resonance imaging to assess the preterm brain. Recent studies have shown different abnormalities within the white matter that were not detected with routine ultrasound studies. Two appearances have been described: diffuse abnormal signal intensity and punctate white matter lesions. Current research is aimed at establishing the significance of these "new" appearances on the developing brain and their significance for short term and long-term outcome in the child.

Pierre Gressens, Ph.D. (UMR 676 Inserm, Paris, France)

Animal models have permitted to identify some of the potentially key cellular and molecular players involved in the pathophysiology of perinatal white matter damage. These studies have also provided experimental evidence supporting a multiple-hit hypothesis for perinatal white matter damage and have delineated some potential target for neuroprotection and identified good candidate drugs.

### **Scientific Session IV:** *Genetics & Therapeutics of Leukodystrophies*

Co-chairs: Jutta Gärtner, Odile Boespflug-Tanguy

Danielle Pham-Dinh, Ph.D. (INSERM U546, Paris, France)

Alexander disease is a rare neurodegenerative disorder characterized by large cytoplasmic aggregates in myelin-forming cells and caused by mutations in glial fibrillary acid protein and the main intermediate filament protein. Aggregation of proteins was dynamic and reversible in a cell model. A therapeutic approach using geldanamycin has been initiated.

Raphael Schiffmann, Ph.D. (NIH, Bethesda, MD, USA)

The mechanism of CACH/VWM disease, caused by mutations of eIF2B is not well understood. The myelin of the central nervous system is mostly affected but in some cases hypomyelination and axonal loss of the peripheral nerves is also present. Myelin-forming cells become foamy. The enlargement which likely reflects accumulation of



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myelin proteins is followed by cellular death. Secondary axonal damage is associated with white matter rarefaction and progressive neurological deficit. The strategy for therapy is to enhance eIF2B activity.

Elena Ambrosini, Ph.D. (Istituto Superiore di Sanità, Rome, Italy)

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a childhood-onset spongiform leukodystrophy characterized by white matter abnormalities with vacuolation of the outer myelin sheaths. Mutations of the MLC1 gene has been identified and linked to the disease. An abundant expression of MLC1 has been identified in myelin-forming cells. Its pathophysiological role is still unknown. An interaction between MLC1 and dystroglycan has been observed.

David Wenger, Ph.D. (Jefferson Medical College, Philadelphia, PA, USA)

Krabbe disease is due to a deficiency in galactocerebrosidase (GALC). An accumulation of psychosine is also observed and results in myelin-forming cells death. The current treatment is bone marrow transplantation. The GALC DNA delivered by viral vectors into sick mouse brains lead to an improved myelination and a reduction in the amount of psychosine.

Francesca Cambi, Ph.D. (University of Kentucky, Lexington, KY, USA)

The therapeutic strategy for Pelizaeus-Merzbacher disease, characterized by overexpression in the PLP gene and accumulation in cholesterol, lies in the inhibition of the PLP gene expression. Reduction of PLP in cells was achieved successfully and abnormalities in cholesterol metabolism were reversed.

Scientists, physicians and students contributed to the success of the First Congress of the ELA Research Foundation & The Myelin Project. Outstanding scientific presentations were given and demonstrated the progress made in the past years. The congress was a good opportunity for investigators to initiate collaborations with other laboratories and gain new knowledge.

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### IN MEMORIAM

I regret having to inform you that Dr. Hugo Moser passed away in Baltimore, Maryland on January 20, 2007. The news of his passing has made me very sad, not only because of the loss of the prominent doctor researching adrenoleukodystrophy (ALD), my son Lorenzo's disease, but also because of the intertwining of our lives. So much so, that his death has struck me as the loss of an older brother.

The indisputable world authority on ALD, Hugo diagnosed Lorenzo back in 1984. At my late wife Michaela's request, he was instrumental in the organization of the first international symposium on ALD. He came several times to my home to visit Lorenzo. Over the last decade, he offered me co-authorship of various articles, which were then published in prestigious scientific journals such as the *Annals of Neurology* (1987). In the face of the skepticism of his neurologist colleagues about Lorenzo's Oil, Hugo kept an open mind and in the early 90s, commissioned an international, multicenter study investigating whether or not Lorenzo's Oil worked as a therapy for ALD. He subsequently agreed to become a member of The Myelin Project Work Group. True, there were times we had heated discussions about the efficacy of the Oil, but they always concluded with cordial handshakes.

We also had some common interests: one of them was that we like good food. Famous was the lunch we had in Belgium, attended by Ann Moser and my daughter Cristina. We both shared some nostalgia for Europe, as we walked the cobbled stones of Ghent facing its gothic cathedral.

In later days, Hugo was instrumental in ensuring that I got the best available medical attention by referring me to the top specialists at Johns Hopkins University Hospital. If not for him, I am not sure I would be here today.

Good-bye, Hugo.

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### *Acknowledgments*

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We are grateful to all who helped us throughout 2006. However, we would like to acknowledge several whose generosity and efforts were especially helpful during the latter part of the year:

The European Leukodystrophy Association; Peregrine Charities; The Jean-Pierre and Nancy Boespflug Foundation for Myopathic Research; Mr. Eric Hovde & the Hovde Foundation; Mrs. Jean Kelley & the 9<sup>th</sup> Annual Hammerfest Triathlon; Mr. Ron Meneo, Mr. Scott Roth & Race Productions; The Penates Foundation; The Armin & Esther Hirsch Foundation; The Daniell Family Foundation Inc.; The Modestus Bauer Foundation; The Porter E. & Helenmae Thompson Foundation; Mr. & Mrs. A. Larry Chapman; John & Hoby Brenner of Cutting Edge Supply; Mr. J. Michael Johnson; Mr. James Stark; Ms. Betty Jo Tucker & ReelTalk Movie Reviews; and Dr. Marie-Josée Duran.

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*You may be able to contribute to The Myelin Project at your workplace. Federal employees can donate through the Combined Federal Campaign (CFC number 2572). To donate through the United Way, please obtain a donor option card from your local United Way campaign and enter The Myelin Project's name and complete address as shown below.*

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