First International Congress of the ELA Research Foundation

October 5-7, 2006

Paris, France

The 1st 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 to 7, 2006. The Scientific Committee in charge of the meeting organization was composed of Prs. 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 in 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 as 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.

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-Dalcq

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.

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 physiopathology 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, Besthesda, 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 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 Sanita, 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 physiopathogical 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 defiency 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.