ELA Scientific Day
Book of abstracts

April 4, 2014
Paris, France

Hope is here!
2014 ELA SCIENTIFIC DAY

Morning Program
8:45 - 9 AM  Welcome and introduction
Guy Alba, Chairman of the ELA Foundation, France & Pr. Charles ffrench-Constant, Chairman of the ELA Scientific Committee, France

9 - 10 AM  SCIENTIFIC SESSION 1  DIAGNOSIS OF LEUKODYSTROPHIES
Chair: Pr. Jean-Louis Mandel, Institute of Genetics, Molecular and Cellular Biology, Illkirch, France

New genes identified for undetermined leukodystrophies
Pr. Enrico Bertini, Bambino Gesu Hospital, Roma, Italy
Targeted high-throughput sequencing for improved knowledge and diagnosis of leukodystrophies
Pr. Jean-Louis Mandel, Institute of Genetics, Molecular and Cellular Biology, Illkirch, France

10 - 11 AM  SCIENTIFIC SESSION 2  UNDERSTANDING THE MECHANISMS OF LEUKODYSTROPHIES
Chair: Pr. Raul Estevez, University of Barcelona, Barcelona, Spain

Understanding Aicardi-Goutieres syndrome
Dr. Yanick Crow, Imagine Institute, Paris, France
Mechanisms responsible for polymerase III-related leukodystrophies
Dr. Geneviève Bernard, McGill University Health Centre, Montreal, Canada

11 AM - 12 PM  SCIENTIFIC SESSION 3  NEW EXPERIMENTAL MODELS FOR LEUKODYSTROPHIES
Chair: Pr. Volkmar Gieselmann, Institute of Biochemistry and Molecular Biology, Bonn, Germany

Development of experimental models for megalencephalic leukoencephalopathy with subcortical cysts (MLC)
Pr. Raul Estevez, University of Barcelona, Barcelona, Spain
Establishing an "#Penelope" model of vanishing white matter disease
Dr. Marie Harrisingh & Pr. Charles ffrench-Constant, University of Edinburgh, Edinburgh, United Kingdom

12 - 1 PM  Lunch

Afternoon Program
1 - 4 PM  SCIENTIFIC SESSION 4  THERAPIES FOR LEUKODYSTROPHIES
Chairs: Pr. Patrick Aubourg, Bicêtre Hospital, Le Kremlin-Bicêtre, France & Pr. Alfried Kohlschütter, University Hospital Hamburg-Eppendorf, Hamburg, Germany

PRECLINICAL STUDIES
Brain gene therapy for metachromatic leukodystrophy
Dr. Caroline Sevin, Bicêtre Hospital, Le Kremlin-Bicêtre, France
Efficacious and sustained gene therapy of Canavan’s disease
Dr. Guangping Gao, University of Massachusetts Medical School, Worcester, MA, USA

CLINICAL STUDIES
Phase I/II clinical trial of hematopoietic stem cell gene therapy for the treatment of metachromatic leukodystrophy
Dr. Alessandra Biffi, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy
Understanding mechanisms of lower extremity strengthening in women heterozygous for X-ALD
Dr. Kathleen Zackowski, Kennedy Krieger Institute, Baltimore, MD, USA
Results of the clinical trial testing the effect of a cocktail of antioxidants in patients with ALD
Dr. Aurora Pujol, IDIBELL, Barcelona, Spain
MD1003 in adrenomyeloneuropathy: a randomized double blind placebo-controlled study
Dr. Frédéric Sedel, MedDay Pharmaceuticals, Paris, France

4 PM  Conclusion of the day
Pr. Charles ffrench-Constant, Chairman of the ELA Scientific Committee, France
SESSION 1

DIAGNOSIS of LEUKODYSTROPHIES

Chair: Pr. Jean-Louis MANDEL

Institute of Genetics, Molecular and Cellular Biology,
Illkirch, France
NEW GENES IDENTIFIED FOR UNDETERMINED LEUKODYSTROPHIES

Pr. Enrico BERTINI

Ospedale Bambino Gesu, Rome, Italy

Leukodystrophies (LDs) are inherited rare neurodegenerative diseases affecting the white matter and its main component, the myelin. Most of the disorders have onset in childhood. Classically LDs are classified in 1) disorders that affect myelination and are characterized by a primary defect in myelination (hypomyelinating leukodystrophies-HLDs) and 2) disorders that are characterized by myelin destruction of myelin maintenance (demyelinating leukodystrophies-DLDs). Both of these forms of leukodystrophies are characterized by axonal dysfunction. In the last 15 years MRI has emerged as a precious tool for the differential diagnosis of leukoencephalopathies (Van der Knaap and Valk 2005) and it has been demonstrated that commonly the MRI brain pattern is specific for a corresponding gene defect. In the last 5 years advances in genomic sequencing technology defined as next generation sequencing has allowed to accelerate the definition of new genes responsible for formerly undefined leukodystrophies. The impression is that we now know most of the genes responsible for HLDs and of DLDs limited to the subgroup of megalencephalic leukodystrophies with subcortical cysts and the other subgroup of Vanishing White Matter leukodystrophies. However the prediction is that most of the new genes will be discovered in the DLD subgroup of mitochondrial leukodystrophies. Severe and progressive abnormalities of white matter have been described in patients harboring mutations in NDUFS1 or NDUV1, NUBPL, SDHAF1, COX6B1, in genes encoding aminoacyl-tRNA synthase (DARS2 and EARS2). Proteins participating to the elongation machinery (EFG1 and EFTu) also exhibit characteristic MRI patterns, and finally, patients with MNGIE also display a unique MRI pattern.

Supported by the ELA Research Foundation

TARGETED HIGH-THROUGHPUT SEQUENCING FOR IMPROVED KNOWLEDGE AND DIAGNOSIS OF LEUKODYSTROPHIES

Pr. Jean-Louis MANDEL

Intitute of Genetics, Molecular and Cellular Biology, Illkirch, France

The diagnosis of leukodystrophies (LD) is based initially on careful determination of clinical features and analysis of MRI, complemented, in case a metabolic disorder is suspected, by biochemical testing (very long chain fatty acids or other metabolites, measurement of some enzymatic activities, T3/T4 ratio etc...). When a diagnosis is suspected by such investigations, and if there is one or several genes that can be found mutated in such cases, sequencing of the candidate gene(s) is performed. If a convincing mutation is found, the diagnosis is confirmed. However, clinicians often face with overlapping, incomplete or non-specific forms of leukodystrophies and no clear candidate genes. Other clinical forms show extensive genetic heterogeneity, with 5 implicated genes for Aicardi-
Goutieres or for CACH/VWM diseases. Exhaustive mutation screening in such cases is expensive using classic Sanger sequencing. Thus most patients remain undiagnosed, either by lack of systematic testing of known genes, or by the fact that probably many genes implicated have not been identified yet. Since a precise etiological (molecular) diagnosis appears essential for genetic counseling, improved medical care and in some cases for targeted therapy, including gene therapy, there is a real need for a new method to be developed. We have proposed to test targeted sequencing of known LD genes, using a exon capture strategy (Agilent Sure-select) and high through-put sequencing. For the design of the capture array, we selected 68 genes (790 exons) for a total size 263 kb, including 47 leukodystrophy genes, and 21 leukoencephalopathy genes. Up to now, we have tested 13 samples with a known mutation, for validation purposes (especially for ability to detect gene deletions or duplications) and 122 samples from patients without molecular diagnosis, and who had not yet been extensively tested. The validation phase was very satisfactory. Two mutations were missed, one lying in a promoter not covered in the array, the other one lying in a low complexity sequence, was missed by one bioinformatic pipeline but detected in an improved one. Among the 122 patients without known molecular diagnosis, 17 carried certainly causative mutations and 9 probably or possibly causative mutations for an overall diagnostic yield of 14-21%. The overall diagnostic yield appeared higher among males (19%) than females (9%). Most mutations were identified in autosomal recessive genes (12/17), a few in two of the three X-linked genes included in the design, and only a single one in the autosomal dominant gene GFAP. Among the four mutations in the X-linked genes, 3/4 were detected in males. Two mutations (one hemizygous entire deletion of the gene, and one heterozygous frameshift mutation in a female) were reported in PLP1, and two in SLC16A2 (one hemizygous frameshift mutation, one hemizygous splice mutation). Among the other genes EIF2B2, POLR3A, POLR3B and RNASEH2B were hit twice in the cohort. The results will be discussed.

*Supported by the ELA Research Foundation*
SESSION 2

UNDERSTANDING the MECHANISMS of LEUKODYSTROPHIES

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Chair: Pr. Raúl ESTÉVEZ

University of Barcelona, Spain
UNDERSTANDING AICARDI-GOUTIERES SYNDROME

Dr. Yanick CROW

Imagine Institute, Paris, France

Aicardi-Goutières syndrome (AGS) is a Mendelian inflammatory disorder most typically characterized by brain white matter disease and intracranial calcification leading to microcephaly, spasticity, dystonia and psychomotor retardation. AGS is genetically heterogeneous, occurring due to mutations in any one of the genes encoding: a 3-prime repair exonuclease with preferential activity on single stranded DNA (TREX1), the three non-allelic components of the RNASEH2 endonuclease complex acting on ribonucleotides in RNA:DNA hybrids (RNASEH2A, RNASEH2B, RNASEH2C), a Sam domain and HD domain containing protein which functions as a deoxynucleoside triphosphate triphosphohydrolase (SAMHD1), and an enzyme catalysing the hydrolytic deamination of adenosine to inosine in double-stranded RNA (ADAR1). Although we might not expect to reverse neurological damage already accrued at the time of diagnosis, a fact of particular relevance to children affected in utero and displaying features of illness at birth, the majority of infants with AGS experience the onset of disease in the first 2 - 24 months of life post-natally. Moreover, clinical observation suggests that there is frequently an early period of ‘active regression’, seemingly occurring over several months, after which time the disease apparently stabilises. For these reasons, and also because of the occurrence of later-onset features, most particularly - vasculitic lesions of the skin (chilblains) and an intracranial vasculitis seen in a subset of patients, the development of therapies for AGS is fully warranted. The proteins defective in AGS are all associated with nucleic acid metabolism. We hypothesize that these proteins are involved in clearing cellular nucleic acids, and that a failure of such removal results in immune activation, specifically triggering a type I interferon-mediated innate immune response more normally induced by viral nucleic acid. Evidence exists to suggest that these endogenous nucleic acid species may derive from retroelements embedded in our genome. We have shown that AGS patients of any genotype consistently demonstrate a “type I interferon signature” in blood - indicating a marked induction of the interferon response system in the large majority of patients assayed. With funding from ELA, we propose to assess the safety and efficacy of reverse transcriptase inhibitors, which can act to inhibit retroelement-associated reverse transcription, in reducing a pre-existing interferon signature in patients with AGS. This trial will take place at the Hôpital Necker, Paris beginning in 2014.

Supported by the ELA Research Foundation

MECHANISMS RESPONSIBLE FOR POLYMERASE III-RELATED LEUKODYSTROPHIES

Dr. Geneviève BERNARD

McGill University Heath Centre, Montreal, Canada
Pol III-related leukodystrophies are a group of hypomyelinating leukodystrophies including Tremor-Ataxia with Central Hypomyelination (TACH), Hypomyelination, Hypodontia and Hypogonadotrophic Hypogonadism (4H syndrome), Leukodystrophy with Oligodontia (LO), Ataxia Delayed Dentition and Hypomyelination (ADDH) and Hypomyelination Cerebellar Atrophy and Hypoplasia of the Corpus Callosum (HCAHC). These disorders are now considered along a spectrum of clinical and radiological features with some patients presenting all typical neurological and non-neurological clinical features along with all MRI characteristics, while others present only some of the clinical and radiological features. These disorders are caused by recessive mutations in either POLR3A or POLR3B. These genes encode for the two largest subunits of the RNA polymerase III (Pol III), and, together, form its DNA-binding catalytic core. The RNA polymerase III contains 17 subunits and is responsible for the transcription of more than 200 small RNAs, including all tRNAs, RNA 7SL, RNA 7SK, amongst others. Some mutations in POLR3A or POLR3B are predicted to lead to poor interaction between neighbouring subunits, possibly leading to misassembly of the protein complex, while others are predicted to lead to poor interaction of the RNA polymerase with the DNA, preventing optimal transcription. Our hypothesis is that ultimately, Pol III transcription of specific targets important for myelination is altered, leading to hypomyelination.

Supported by the ELA Research Foundation
SESSION 3

NEW EXPERIMENTAL MODELS for LEUKODYSTROPHIES

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Chair: Pr. Volkmar GIESELMANN
Institute of Biochemistry and Molecular Biology,
Bonn, Germany
DEVELOPMENT OF EXPERIMENTAL MODELS FOR MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS (MLC)

Pr. Raúl ESTÉVEZ

University of Barcelona, Barcelona, Spain

Defects in the astrocytic membrane protein MLC1 or the adhesion molecule GlialCAM underlie MLC. GlialCAM binds MLC1, and this binding is required for MLC1 endoplasmatic reticulum exit and its targeting to cell junctions. Furthermore, GlialCAM also binds and targets the chloride channel CIC-2 to cell junctions, and modify CIC-2 currents. Recently, mutations in CLCN2 have been identified in a different type of leukodystrophy. Taking into account these biochemical relationships, it remains unclear why patients with recessive mutations in MLC1 (MLC1 patients) or GLIALCAM (MLC2A patients) show the same clinical phenotype. In this talk, I will present new results obtained from zebrafish and mice models of MLC disease and a brain biopsy from a human MLC patient. Our data points to a functional relationship between astrocytic MLC1 and oligodendrocytic CIC-2 mediated by GlialCAM trans-homophilic interactions. The work suggests that CIC-2 dysfunction in glial cells may contribute to the pathogenesis of MLC. Finally, we demonstrate an evolutionary activity-dependent conserved role of MLC1 in regulating glial surface levels of GlialCAM, and this relationship rationalize the undistinguishable symptomatology of MLC1 and MLC2A patients.

Supported by the ELA Research Foundation

ESTABLISHING AN IN VITRO MODEL OF VANISHING WHITE MATTER DISEASE

Dr. Marie C. HARRISINGH and Pr. Charles ffrench-CONSTANT

MRC Centre for Regenerative Medicine, The University of Edinburgh, United Kingdom

Vanishing white matter disease (VWM) is one of the most common forms of childhood leukodystrophy. This autosomally inherited disorder characteristically affects patients in early childhood, leading to progressive neurological deterioration and death. VWM disease is caused by mutations in eukaryotic initiation factor 2B (EiF2B), which consists of a complex of proteins that act as a guanine exchange factor for eIF2. Although EiF2B plays a key role in global translation initiation in all cell types, these mutations appear to be especially harmful to oligodendrocytes and astrocytes. However, it is unclear what the effects of these mutations are on the biology of these cells. The mechanism by which these changes result in the observed pathology is likely to be complex, with abnormal interactions between oligodendrocytes and astrocytes leading to the development of the disease. In order to understand the effects of these mutations it is essential to study the relevant cell types but, since patient-derived oligodendrocytes and astrocytes are not readily available, most previous work has focused on the effects of these mutations on easily accessible cells types such as fibroblasts. To overcome this problem, we decided to generate oligodendrocytes and astrocytes carrying VWM mutations from ES cells. We chose to model two point mutations: T91A, which is a
relatively common mutation associated with a ‘classical’ disease course; and R269G, which is associated with early onset and rapid disease progression. We have used BAC recombineering to generate targeting constructs containing these point mutations and have successfully introduced them into mouse ES cell lines. These VWM mutation carrying ES cells can now be differentiated into astrocytes and oligodendrocytes and the effects of the mutations on these cells can be examined in detail.

*Supported by the ELA Research Foundation*
SESSION 4

THERAPIES for LEUKODYSTROPHIES

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Chairs: Pr. Patrick AUBOURG
Bicêtre Hospital, Le Kremlin-Bicêtre, France
& Pr. Alfried KOHLSCHÜTTER
University Medical Center Eppendorf,
Hamburg, Germany
PRECLINICAL STUDIES

S4-01

BRAND ENRY THERAPY FOR METACHROMATIC LEUKODYSTROPHY

Dr. Caroline SEVIN

Bicêtre Hospital, Le Kremlin-Bicêtre, France

Metachromatic Leukodystrophy (MLD) is a lethal neurodegenerative disease caused by deficiency of Arylsulfatase A (ARSA). Lack of functional ARSA enzyme results in accumulation of sulfatides in brain cells, especially oligodendrocytes, leading to leukodystrophy and neuronal degeneration. Sulfatides also accumulate in peripheral nerves, leading to severe peripheral neuropathy. The most severe late-infantile form starts around 1-2 years, leading to rapid and severe motor and cognitive degradation and death within few years. There is no treatment for this early onset form of the disease when patients are asymptomatic. Among potential therapeutic interventions, brain gene therapy could ensure rapid and sustained delivery of ARSA enzyme in the brain, a prerequisite to arrest the neurodegenerative process in due time. We have demonstrated efficiency and safety of intracerebral delivery of adeno-associated-vector serotype rh.10 encoding human ARSA (AAVrh.10/ARSA) in the mouse model of the disease (MLD mice). Particularly, sulfatide isoforms that accumulate specifically in oligodendrocytes of MLD mice were normalized after treatment. We have optimized and validated, in non-human primates, the neurosurgical procedure to allow simultaneous infusion of vector at 12 different brain sites, and demonstrated that the injection of AAVrh.10/ARSA results in significant ARSA overexpression in normal monkey, without any side effect. Toxicological studies have been achieved and we have obtained authorizations from regulatory agencies to move towards phase I/II tolerance and efficacy clinical trial that is opened for recruitment. This phase I-II clinical trial will enroll five children (age between 6 months and 5 years) with early-onset forms of MLD, following specific motor and cognitive inclusion criteria. AAVrh.10/ARSA vector will be administrated to 12 locations in the CNS, guided by brain imaging. Safety and efficiency parameters will be evaluated up to 2 years, a period that will be sufficient enough to assess the potential therapeutic efficiency of brain gene therapy in rapidly progressing forms of MLD.

Supported by the ELA Research Foundation

S4-02

EFFICACIOUS AND SUSTAINED GENE THERAPY OF CANAVAN’S DISEASE BY SYSTEMICALLY OR INTRACEREBROVENTRICULARLY (ICV) DELIVERED rAAV-THERAPEUTICS

Dr. Guanping GAO

University of Massachusetts Medical School, Worcester, MA, USA

The CNS is an important target for gene therapy of neurological disorders. Recombinant adeno-associated virus (rAAVs) holds the promise for therapeutic gene transfer to treat a variety of diseases including the CNS diseases. Recent discovery of some novel primate rAAVs that can cross the blood-
brain-barrier and achieve wide spread CNS gene transfer, after intravascular delivery, remarkably expanded potentials of rAAV-based gen therapeutics in treating neurodegenerative disorders such as leukodystrophies. Canavan’s disease (CD) is a lethal pediatric leukodystrophy caused by genetic loss of functional aspartoacylase. CD is characterized by dysmyelination, hydrocephalus, progressive central nervous system vacuolation and psychomotor retardation. Patient survival is based on general medical care due to lack of efficacious therapy. Gene replacement therapy using rAAV holds promise for the treatment of CD. A recent follow-up study on rAAV-mediated gene therapy using first generation rAAVs emphasized the long-term safety of rAAV and showed encouraging though marginal clinical improvements in patients. This study also suggested possible improvement of therapeutic efficacy using the second generation of rAAVs with wider spread transduction at higher efficiency and an ability to cross the blood-brain-barrier for global CNS transduction. To this end, we investigated two different routes of vector administration for the efficacy and sustainability of rAAV gene therapeutics in an aspartoacylase gene knockout mouse model which authentically recapitulates the severest clinical phenotypes of CD including uniform lethality at 4 weeks. We first evaluated the feasibility of gene therapy treatment for CD mice by systemic gene delivery. To define the therapeutic window for effective rescuing the early lethality in CD mice by IV delivered rAAVs, we assessed the effectiveness of such a treatment at postnatal day (PD) 0, 6, 13 and 20. We found a complete rescue of lethality, extending the lifespan from <4 weeks to >7 months and restoration of growth even when treated as late as PD 20, 5 days before their death. In addition, improvement of motor functions and reduction of hydrocephaly in the treated animals were positively correlated with the ages of treatment, highlighting the benefits of earlier therapeutic intervention. Importantly, improvement in disease phenotypes was well correlated with reduced CNS histopathology in the injected groups. To minimize potential systemic vector toxicity and reduce vector manufacturing burdens, we tested if single intracerebroventricular (ICV) injection of different serotypes of rAAVhAspa at an 100-fold lower dose can efficiently rescue disease phenotypes. All ICV injections of rAAVs resulted in extended survival up to 2 years, normalized growth, improved motor function and clinical symptoms; which again correlated well with amelioration of neuro-histopathology and reduction of hydrocephaly in the injected groups. However ICV injections were less effective than IV in improving motor functions which suggests the importance of peripheral AspA gene transfer. In addition, at later ages, ICV injected animals developed paralysis earlier than the IV injected animals. Collectively, we achieved complete rescue of lethality and effective alleviation of hydrocephalus and motor dysfunction by novel rAAV gene therapy irrespective of administration route or time of intervention. Our study is the first to demonstrate efficacious and sustained CNS gene therapy not only by a single IV dose of rAAVs as late as PD21 but also by ICV at a 100 fold lower dose. Our study emphasizes the potential to further refine approaches for CD gene therapy using the second generation of rAAVs and opens up newer vistas for the effective treatment of other currently untreatable monogenic leukodystrophies.

**CLINICAL STUDIES**

S4-03

**PHASE I/II CLINICAL TRIAL OF HEMATOPOIETIC STEM CELL GENE THERAPY FOR THE TREATMENT OF METACHROMATIC LEUKODYSTROPHY**

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Metachromatic Leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by Arylsulfatase A (ARSA) deficiency leading to severe demyelination, neurodegeneration and premature death of affected patients. Currently, there is a need for new treatment options for this devastating disease. According to preclinical data demonstrating the safety and efficacy of hematopoietic stem cell gene therapy in the animal model of the disease, and based on the experience we acquired on the natural clinical course of the disease, on March 2010 a clinical trial based on transplantation of autologous hematopoietic stem cells transduced with a lentiviral vector (LV) encoding ARSA was approved by the Italian Regulatory Authorities. The clinical protocol enrolls late infantile (LI) and early juvenile (EJ) patients, in pre- and, in the case of EJ patients, early-symptomatic stage, in order to provide them a reasonable expectation of clinical benefit. The study objectives are the evaluation of i) the safety of the treatment, related to the myeloablative conditioning regimen employed and to the use of LVs, and ii) its efficacy by measuring patients’ motor and cognitive abilities and demyelination occurring in the nervous system through the use of validated instrumental readouts. Preliminary data will be presented for the first 9 patients enrolled in the study, three of whom have completed at least 30 months of follow up. Seven subjects had a biochemical, molecular and family history compatible with a diagnosis of LI MLD and have been treated in a pre-symptomatic stage of their disease. Two EJ MLD patients were treated in an early symptomatic stage. Thus far, the transplant procedure has resulted in good bone marrow recovery and evidence of short/medium term safety of both the conditioning regimen and of the use of LVs in all the patients. Moreover, we report stable ARSA activity reconstitution often above normal levels both in the hematopoietic lineages and in the cerebrospinal fluid. These findings are associated with protection from marked disease progression in LI patients. Follow-up of these patients, performed up to 3.5 years after the expected symptoms onset (as defined according to disease onset in the affected older siblings), shows that disease had not significantly progressed. Most patients exhibit continuous motor and cognitive development, which is at odds with the natural disease course and the disease course of their siblings. The observation of the only two EJ patients treated thus far does not allow drawing conclusions in terms of therapeutic benefit due to their different disease stage at treatment and post-treatment course. Overall, these data are encouraging, but need validation with further long-term follow up.

Supported by the ELA Research Foundation

S4-04

UNDERSTANDING MECHANISMS OF LOWER EXTREMITY STRENGTHENING IN WOMEN HETEROZYGOUS FOR X-ALD

Dr. Kathleen ZACKOWSKI

Kennedy Krieger Institute, Baltimore, MD, USA
The objectives of this study is to determine 1) if ALD heterozygote participants are responsive to progressive resistance training (PRT) and, 2) if tract specific imaging in combination with clinical measures will predict who is likely to respond best to this training. To address this we evaluate the CST and DC across the brain and cervical spinal cord using tract-specific magnetization transfer imaging and diffusion tensor imaging. Quantitative clinical assessments include measures of walking as well as measures of lower extremity impairments of vibration sensation, strength and spasticity. The PRT consisted of guided resistance training three times weekly for 12 weeks. We show results for 13 ALD heterozygote carriers and 11 healthy controls that have completed the program. The data at baseline show that, ALD heterozygote carriers are weaker, with worse vibration sensation and walk more slowly than healthy controls. At baseline, imaging abnormalities are most predominant in the cervical spinal cord compared to the brain in carriers. Following the training intervention both ALD heterozygote carriers and healthy controls show significant gains in strength and walking measures, but not sensation. However, some individuals made more improvements than others, these will be discussed. Analyses show promising results for determining which measures may be most helpful in predicting intervention responsiveness. This data is important for better defining disability in women heterozygote carriers of AMN. In addition, these results will help to guide physicians and rehabilitation therapists in predicting who is likely to respond to rehabilitative interventions, as well as for optimizing outcomes for future neuroprotective pharmacological interventions.

**Supported by the ELA Research Foundation**

**S4-05**

**RESULTS OF THE CLINICAL TRIAL: “VALIDATION OF OXIDATIVE DAMAGE BIOMARKERS IN ADRENOLEUKODYSTROPHY USING THE COCKTAIL OF ANTIOXIDANTS N-ACETYLCYSTEINE, VITAMIN E AND LIPOIC ACID”**

Dr. Aurora PUJOL

**IDIBELL, Barcelona, Spain**

X-linked adrenoleukodystrophy is a rare, demyelinating and neurodegenerative disorder, due to loss of function of a very-long chain fatty acid transporter, the peroxisomal ABCD1 protein. Its most frequent phenotype adrenomyeloneuropathy (AMN), is characterized by axonal degeneration in spinal cord, and disabling spastic paraparesis. To date, there is no satisfactory treatment for the disease. Our work in the last ten years dissecting the physiopathological basis of the disorder, has uncovered a major role of oxidative stress early in the neurodegenerative cascade. In a preclinical trial we have identified an antioxidant cocktail that efficiently halts axonal damage and associated disability in the mouse model for the disease. On this molecular basis, we launched a pilot clinical
trial with the antioxidant cocktail N-acetylcysteine, lipoic acid and vitamin E, for validation of the previously identified oxidative lesion biomarkers, as a first step to a randomized versus placebo, multicentric and international trial. As secondary endpoints we included spasticity scales, timed walking tests, MRI, electromyographs and evoked potential tests. Preliminary results indicate a normalization of the oxidative lesion markers, while no effect was observed in the plasma VLCFA levels. Evaluation of clinical data is on progress.

 Supported by the ELA Research Foundation

S4-06

MD1003 IN ADRENOMYELONEUROPATHY: A RANDOMIZED DOUBLE BLIND PLACEBO-CONTROLLED STUDY

Dr. Frédéric SEDEL

MedDay Pharmaceuticals, Paris, France

Recently, preliminary data have shown that MD1003 (code name) could halt disease progression and improve symptoms in patients suffering from primary or secondary progressive multiple sclerosis (MS). Among 23 consecutive patients with progressive MS treated with MD1003 for a mean duration of 9.2 months, 21/23 patients (91.3%) improved. It is hypothesized that the positive effects of MD1003 are linked to increased energy production in demyelinated neurons and stimulation of myelin repair. Two phase-3 clinical trials are now running involving 250 patients with progressive MS with the goal of confirming the previous results. Adrenomyeloneuropathy (AMN) and progressive MS share similarities including secondary energy failure leading to progressive axonal degeneration. One patient suffering from AMN was treated for 5 months with MD1003 and showed clinical improvement comparable to the effects observed in progressive MS. The objectives of the trial are to evaluate the efficacy and safety of MD1003 in patients suffering from AMN. Sixty 60 male patients from 4 different centers (France, Spain, Germany) will be initially divided into 2 groups: one group of 20 patients will receive a placebo while a second group of 40 patients will receive MD1003. The placebo-controlled study will last 12 months followed by a 12 months extension phase during which all patients will be treated with MD1003. The primary efficacy endpoint will be the mean change of the 2 minutes walking test (2MWT) between M12 and baseline. Secondary efficacy judgment criteria will include the time to walk 25 feet test, the timed up and Go test, the Euroqol ED-5D quality of life questionnaire, the Qualiveen urinary function questionnaire and the MOS SF-36 quality of life questionnaire. In addition, exploratory analyses including MRI with non-conventional sequences, nerve conduction velocities and evaluation of muscle strength by the use of a dynamometer will be performed in a subset of centers.

 Supported by the ELA Research Foundation
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