

## **LBS.001**

5:30 p.m.

Outbreak of Immune Polyradiculoneuropathy in Workers Exposed to Porcine Neural Tissue.

*DH Lachance, PJB Dyck, SJ Pittock, Rochester, Minnesota, J Sejvar, Atlanta, Georgia, A Devries, Minneapolis, Minnesota, PJ Dyck, Rochester, Minnesota, R Lynfield, Minneapolis, Minnesota, V Lennon, Rochester, Minnesota*

We describe a novel neurological syndrome in 15 patients exposed to aerosolized brain tissue while butchering pig heads. In late 2007, we recognized a stereotypic neurological illness among workers at an Austin, MN, pork processing plant. By December, 12 cases were identified on Minnesota Dept of Health and Center for Disease Control criteria. Brain harvesting was voluntarily terminated. All were evaluated by Mayo Clinic neurologists. We report the clinical, laboratory, radiographic, serological, pathological and epidemiological correlations.

Criteria included exposure to swine slaughter, weakness on motor examination, electrodiagnostic evidence of neuropathy, and neuroimaging consistent with radiculitis, myelitis or encephalitis and/or elevated CSF protein. Thirteen patients met all criteria; two had a normal motor exam. All had evidence of polyradiculoneuropathy, often painful with nerve root irritation signs. One patient whose job was removing pig brains presented with transverse myelitis followed by polyradiculoneuropathy. All complained of some combination of generalized fatigue, weakness (usually mild to moderate) and positive sensory symptoms, mainly in the legs. Two had transient facial neuropathy at presentation. Electrophysiological testing showed a mixture of demyelinating and axonal features with prolonged motor and F-wave latencies suggesting pathology at root level and very distally in nerve. Quantitative sensory testing showed a mixture of large fiber and small fiber abnormalities. Ten of 12 patients had elevated CSF protein (mean 120 mg/dL, range 63-210). One had pleocytosis. In 10 of 12 patients, MRI showed enhancing, sometimes thickened, spinal roots. Sural nerve biopsies in three showed mild neuropathic abnormalities and mild perivascular inflammation. All patients had a novel profile of neural autoantibodies, including an IgG immunostaining pattern. The utility of this IgG as an epidemiological tool is under review. No infectious agent has been identified. Additional cases are being investigated.

This novel syndrome in workers at a swine processing plant is characterized by a polyradiculoneuropathy that is sensory greater than motor, occurring predominantly at the root and distal nerve level. This may have broad implications for the pathogenesis of idiopathic organ-specific autoimmunity as evidence to date supports induction of neurological autoimmunity by a unique environmental exposure.

**Disclosure:** Dr. Lachance has nothing to disclose. Dr. Dyck has nothing to disclose. Dr. Pittock has nothing to disclose. Dr. Sejvar has nothing to disclose. Dr. Devries has nothing to disclose.

## **LBS.002**

5:45 p.m.

Acute Severe Model of Anti-Muscle Specific Kinase (MuSK) Myasthenia in Lewis Rats.

*David P. Richman, Kayoko Nishi, Stuart Morell, Ricardo A. Maselli, Mark A. Agius, Davis, California*

**Objective:** To develop a model of anti-MuSK myasthenia (AMM) in order to analyze the pathogenic mechanisms in that disease.

**Background:** Forty percent of seronegative myasthenia gravis (MG) patients have antibodies (Abs) to the endplate receptor kinase MuSK and tend to exhibit a more focal form of weakness commonly associated with muscle atrophy. Relatively mild weakness has been produced in MuSK-immunized mice and rabbits, but only after repeated injections over an extended period. During our study of MuSK, we have identified two previously unknown exons involved in splice variants within the antigenically important extracellular portion of this protein.

**Design/Methods:** Four Lewis rats were immunized with one of the newly discovered isoforms of mouse MuSK in complete Freund's adjuvant and four were immunized with adjuvant alone. Animals were weighed and scored clinically every other day. Forearm muscle compound muscle action potentials (CMAP) were assessed in response to 3 Hz stimulation of median nerve and serum MuSK Ab titer determined by immunoblot assay.

**Results:** By day 21, the MuSK-immunized animals developed fatigable weakness and rapid weight loss. By day 25, these animals had severe weakness, kyphotic posture, marked axial muscle atrophy and ungroomed fur. The 3 animals immunized with 100ug MuSK died by day 26 and the single animal immunized with 50ug died on day 33. At day 26, CMAP decrement was 4% and 8%, whereas at day 33, it was 15%, with little correlation between decrement and muscle atrophy. All had MuSK Ab titers of >1:150,000. None of the 4 adjuvant controls had any of these findings ( $X^2=4.50$ ,  $p<0.05$ ).

**Conclusion/Relevance** This acute model of AMM, occurring after a single immunization with MuSK, is very severe and appears to mirror the findings observed in AMM, especially the muscle atrophy that distinguishes it from MG. The results support the hypothesis that the MuSK Abs are pathogenic in AMM and provide a potential system for analyzing the disease mechanisms involved at the neuromuscular junction in AMM.

**Study Supported By:** Myasthenia Gravis Foundation of California

**Disclosure:** Dr. Richman has nothing to disclose. Dr. Nishi has nothing to disclose. Dr. Morell has nothing to disclose. Dr. Maselli has nothing to disclose. Dr. Agius has received personal compensation for activities with Teva, Genentech, Biogen-Idee, Serono, and Berdex as a speaker and consultant.

### **LBS.003**

6:00 p.m.

Treatment with glatiramer acetate delays conversion to clinically definite multiple sclerosis (CDMS) in patients with clinically isolated syndromes (CIS)

*Giancarlo Comi, Massimo Filippi, Milan, Italy*

**Objective:** To evaluate the efficacy of early treatment with glatiramer acetate (GA, COPAXONE®) in delaying progression to CDMS in patients with CIS and a positive scan at screening MRI.

**Background:** GA reduced relapse rate and MRI-monitored disease activity in relapsing-remitting MS patients. This three years prospectively planned, randomized, controlled, multicenter trial, assesses the efficacy of GA therapy initiated shortly after the first clinical event suggestive of MS.

**Design/Methods:** Patients presenting with a first clinical event and at least two T2-weighted brain lesions, with a size of at least six mm were enrolled into the study (the PreCISe trial). Only patients with a unifocal disease manifestation were included. They were randomized to receive either sc 20mg/day GA or placebo. The primary efficacy outcome was time to CDMS, based on a second clinical attack. A preplanned interim analysis was performed on data accumulated from approximately 80% of the three-year study exposure.

**Results:** A total of 481 patients were randomized to receive GA (n=243) or placebo (n=238). Key baseline characteristics were: age (31.1±6.9 years), time from first event to randomization (74.0±14.9 days), corticosteroid use for first attack (64% of patients). EDSS (1.0±1.0), number (31.5±30.7) and volume (6.0±6.2ml) of T2 weighted lesions, and number (1.5±2.9) and volume (0.3±0.6ml) of gadolinium enhanced lesions; no difference between the study arms. Results from interim analysis showed that GA reduced the risk of developing CDMS by 45% compared to placebo. The 25<sup>th</sup> percentile time to CDMS was prolonged by 115% for GA to 722 days from 336 days for placebo; hazard ratio 0.55, p=0.0005). The proportion of patients converted CDMS was reduced from 43% in the placebo group to 25% in the GA group (p<0.0001). GA was well tolerated, with 16% overall withdrawals to the time of the interim analysis, and a safety profile similar to that observed in RRMS. Following the results of the interim analysis all subjects were offered open label therapy with GA and continued follow-up as planned in the original protocol.

**Conclusion/Relevance:** The results establish efficacy and safety of early treatment with GA in CIS patients.

**Disclosure:** Dr. Comi received personal compensation for activities with TEVA Pharmaceutical Industries, Merck Serono, Bayer-Schering as a consultant and member of the scientific advisory board; Novartis as a consultant; and Sanofi-Aventis and Biogen-Dompè as a consultant and speaker. Dr. Filippi has received personal compensation for activities with Merck-Serono, Genmab, Biogen-Dompe, Bayer-Schering, and Teva Pharmaceutical Industries as a consultant, speaker, and member of advisory board and other committees.

## **LBS.004**

6:15 p.m.

Interferon beta-1b 500mcg, interferon beta-1b 250 mcg and glatiramer acetate: primary outcomes of the Betaferon®/Betaseron® Efficacy Yielding Outcomes of a New Dose) study.

*Paul O'Connor, Toronto, Ontario, Canada, Barry Arnason, Chicago, Illinois, Giancarlo Comi, Massimo Filippi, Milan, Italy, Stuart Cook, Newark, New Jersey, Douglas Goodin, San Francisco, California, Hans-Peter Hartung, Düsseldorf, Germany, Douglas Jeffery, Winston-Salem, North Carolina, Ludwig Kappos, Basel, Switzerland, Francis Boateng, Timon Bogumil, Montville, New Jersey, Vitali Filipov, Maria Groth, Christoph Pohl, Berlin, Germany*

**Objective:** To compare the efficacy of interferon beta-1b (IFNB-1b) 500 mcg and 250 mcg with glatiramer acetate (GA) in patients with relapsing-remitting multiple sclerosis (RRMS).

**Methods:** RRMS patients with Expanded Disability Status Scale (EDSS) scores  $\leq 5.0$  were randomized (2:2:1 ratio) to subcutaneous IFNB-1b 500 mcg or 250 mcg every-other-day, or GA 20 mg daily for  $\geq 104$  weeks. The primary efficacy variable was relapse risk; supportive endpoints included: relapse rate, proportion of relapse-free patients, time to first relapse. Secondary outcome variables were time to confirmed EDSS progression and T1 black hole development. Other endpoints of interest included the number and volume of T2 lesions. Statistical testing followed a sequential null-hypothesis approach: IFNB-1b 500 mcg–IFNB-1b 250 mcg; IFNB-1b 500 mcg–GA; IFNB-1b 250 mcg–GA.

**Results:** 2244 patients were allocated to IFNB-1b 500 mcg (n=899), IFNB-1b 250 mcg (n=897) or GA (n=448). No difference in relapse risk was found (one-sided p=NS for all comparisons). The annualized relapse rate in each treatment arm fell by almost 80% compared with the year before study entry, but there were no inter-group differences. No difference was found in the proportion of relapse-free patients or time to first relapse, in accumulation of disability, or in most magnetic resonance imaging measures. However, the cumulative number of T2 lesions up to the last scan was greater in GA patients than in either the IFNB-1b 500 mcg (p=0.001) or IFNB-1b 250 mcg-treated patients (p=0.017). The relative increase in T2 lesion volume was also larger in GA patients than with IFNB-1b 500 mcg or 250 mcg (p=0.001 and p<0.001, respectively). All treatments were well-tolerated and the incidences of adverse events were within the established safety profiles of IFNB-1b 250 mcg and GA 20mg. Adherence to study drug was high in all groups, but a higher proportion of patients treated with IFNB-1b 250 mcg (82%) completed the course of study medication than those treated with IFNB-1b 500 mcg (73%) or with GA (78%).

**Conclusion:** For this early RRMS population, 250 mcg appears to be the optimal dose of IFNB-1b. The longer term significance, if any, of the observed differences in change in T2 lesion volume and number between IFNB-1b and GA is unclear.

**Study Supported By:** Bayer Schering Pharma AG, Berlin, Germany

**Disclosure:** Dr. O Connor has received compensation for activities with Biogen Idec, Cognosci, Serono, Teva, Berlex Labs, Genentech, Gnzyme, Novartis, Roche and Sanofi Aventis as a consultant. Dr Arnason has received compensation for activities with Berlex Inc. as a member of a scientific advisory board. Dr. Comi has received personal compensation for activities with TEVA Pharmaceutical Industries, Merck Serono, Bayer-Schering, Novartis, Sanofi-Aventis, Biogen-Dompè as a consultant and serving on a scientific advisory board. Dr. Filippi has received personal compensation for activities with Merck-Serono, Genmab, Biogen-Dompe, Bayer-Schering, and TEVA pharmaceutical Industries as a consultant, a member of the speakers bureaux, advisory, board and other committees. Dr. Cook has received research support from his participation with BEYOND Trail [ndash] Multicenter MS trail of Betaseron 500 vs. Betaseron 250 vs Copaxone. CLARITY Trail [ndash] Multicenter trail of Cladribine oral vs. placebo. Dr. Goodin received personal compensation for activities with Bayer, EMD Serono, and TEVA Neuroscience as honoraria. Dr. Hartung has received personal compensation for activities with Schering, Teva, Serono, Biogen. Dr. Jeffery has received personal compensation for activities with Berlex, Serono, Teva, Glaxo and Pfizer as an honoraria and consultant. Dr. Jeffery received research support from Berlex, Serono, Teva, and Pfizer. Dr. Kappos has received research support from Bayer-Schering Pharma, Bayhill, Biogen Idec, Centocor, Eisai, Genzyme, Merck-Serono, Novartis, Sanofi-Aventis, Roche, Teva, UCB Pharma, and Wyeth. Dr. Boateng has nothing to disclose. Dr Filipov has received personal compensation for activities with Schering AG, Berlin, Germany as an employee. Dr. Groth has received personal compensation for activities with Bayer Schering Pharma as an employee. Dr. Pohl has received personal compensation for activities with Schering AG, Germany as an employee. Dr. Bogumil has received personal compensation for activities with Bayer Healthcare Pharmaceuticals as an employee.

## **LBS.005**

6:30 p.m.

The LEADe Study: A Randomized, Controlled Trial Investigating the Effect of Atorvastatin on Cognitive and Global Function in Patients With Mild-to-Moderate Alzheimer's Disease Receiving Background Therapy of Donepezil.

*Howard Feldman, Vancouver, British Columbia, Canada, Roy W. Jones, Bath, United Kingdom, Miia Kivipelto, Stockholm, Sweden, Larry Sparks, Sun City, Arizona, Rachele Doody, Houston, Texas, David Waters, San Francisco, California, Judith Hey-Hadavi, Andrei Breazna, Rachel J. Schindler, Harry Ramos, New York, New York*

**Background:** There is growing evidence that elevated cholesterol levels in mid-life are associated with an increased risk of developing AD. Furthermore, statins may have a protective effect against AD. The LEADe Study (Atorvastatin/Donepezil in Alzheimer's Disease) is the first prospective clinical trial to assess the efficacy and safety of statin therapy in treating established AD. It tests the hypothesis that treatment with atorvastatin can benefit the longer term course of mild-to-moderate AD in patients receiving background therapy of donepezil.

**Methods: Design:** Multicenter, double-blind, randomized, parallel-group 72-week study with a further double-blind, 8-week atorvastatin withdrawal period. **Inclusion criteria:** Patients with mild-to-moderate "probable" AD (MMSE score 13-25), ages 50-90 years, Rosen Modified Hachinski Scale  $\leq 4$ , CT or MRI within previous 12 months consistent with AD, receiving donepezil 10 mg for at least 3 months prior to randomization, and low-density lipoprotein cholesterol levels (LDL-C) 95-195 mg/dL. **Exclusion criteria:** Subjects taking any medications affecting lipid metabolism or cholinesterase inhibitors other than donepezil within 3 months of screening, uncontrolled thyroid disease, significantly impaired renal or hepatic function, or any clinically significant or unstable medical condition. **Co-primary endpoints** are changes in cognition (ADAS-Cog) and global function (ADCS-CGIC), with a confirmatory end point of rate of change in MRI whole brain and hippocampal volumes. **Secondary end points** are changes in neuropsychiatric symptoms (NPI), function (ADFACS), global staging (CDR-SB), and MMSE.

**Results:** There were 641 subjects randomized to the study. The baseline data included mean age  $74 \pm 8$  years, 53% women, MMSE  $22 \pm 3$ , ADAS-cog  $23 \pm 10$ , and ADFACS  $13 \pm 9$ . Mean prior donepezil treatment was  $409 \pm 407$  days, and mean baseline LDL-C levels were  $143 \pm 26$  mg/dL. Final study results will be presented.

**Conclusions:** The LEADe study provides much needed randomized, controlled trial data to address the compelling question of whether statins are a potentially useful treatment for AD.

**Disclosure:** Dr. Feldman has received personal compensation for activities with Astra Zeneca, Pfizer, Eisai, Novartis, Janssen, Servier, Targacept for consulting services, continuing medical education programs or advisory boards. Dr. Feldman has received personal compensation in an editorial capacity for Canadian STA communication and Canadian Alzheimer Review. Dr. Feldman has received research support from Pfizer, Eisai, Janssen, Lilly, Sanofi Synthelabo, Glaxo Smith Kline. Dr. Jones has received personal compensation for activities with Pfizer, Eisai, Lundbeck, Merz, Elan, Roche, Lilly, Nutricia, and Shire. Dr. Jones has received research support from Pfizer, Eisai, Elan, Lundbeck, Neurochem, Hunter Fleming, and Myriad. Dr. Kivipelto received personal compensation for activities with Pfizer and Elan for consulting services in advisory board and from Novartis and Janssen-Cilag for speaking. Dr. Sparks has received personal compensation for activities with Pfizer. Dr. Sparks has received research support from Pfizer. Dr. Doody has received personal compensation for activities with Astellas, BristolMeyersSquibb, Comentis, Debiopharm, Eisai, Epix, Forest, Medivation, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough as a consultant or honoraria for individual lectures. Dr. Doody holds stock and/or stock options in Medivation. Dr. Doody has received research support from Elan/Wyeth, GlaxoSmithKline, Myriad, and Pfizer/Eisai. Dr. Waters has received personal compensation for activities with Pfizer, Merck, Schering Plough, and Anthera. Dr. Hey-Hadavi has received personal compensation for activities with Pfizer as an employee. Dr. Breazna has received personal compensation for activities with Pfizer. Dr. Breazna has received personal compensation for activities with Pfizer as an employee. Dr. Schindler has received personal compensation for activities with Pfizer. Dr. Ramos has received personal compensation for activities with Pfizer.

**LB1.001**

7:00 a.m. to 10:00 a.m.

Autophagy independent suppression of CGG Repeat-Induced Neurodegeneration by HDAC 6 in a Drosophila Model of Fragile X Tremor Ataxia Syndrome

*Peter K Todd, Udai Pandey, J. Paul Taylor, Philadelphia, Pennsylvania*

Fragile X Tremor Ataxia Syndrome (FXTAS) is a recently described and potentially under-recognized inherited form of ataxia presenting in carriers of a “pre-mutation” length (55-200 repeat) CGG-trinucleotide expansion in the 5’UTR of the fragile X syndrome gene, FMR-1. FXTAS is thought to be an RNA mediated neurodegenerative disorder that is characterized pathologically by ubiquitin-positive nuclear inclusions. Research to date has focused on proteins that may be sequestered by the CGG-repeat expanded mRNA. Here we describe evidence in a drosophila model of FXTAS that the phenotype can be rescued by overexpression of HDAC 6, a class II histone deacetylase protein that is largely cytoplasmic and has recently been implicated in polyglutamine disease pathophysiology. Conversely, overexpression of a dominant negative mutant form of HDAC-6 worsens the phenotype. Similar phenotypic rescue was seen with overexpression of HDAC-11, a class IV HDAC that associates with HDAC-6 in vitro, but not with HDAC-3, a class I HDAC. Given previous data that implicated HDAC-6 in autophagy activation in a model of polyglutamine disease, we evaluated the effects of modification of autophagy pathways of CGG-repeat mediated neurodegeneration. Neither co-expression of siRNA directed against atg6 nor atg12 or pharmacological activation of autophagy by Rapamycin affected the CGG- repeat phenotype. Moreover, phenotypic rescue of the CGG-repeat mediated neurodegeneration by HDAC-6 was not affected by suppression of atg12 expression by siRNA, suggesting that this rescue was autophagy independent. Overexpression of p35, a caspase inhibitor, did not affect CGG-repeat mediated neurodegeneration, making a non-specific inhibition of apoptotic cell death an unlikely mechanism for HDAC-6 dependent rescue. Taken together, these results implicate HDACs 6 and 11 in CGG-repeat expansion induced neurodegeneration and have implications for therapeutic development in FXTAS

**Study Supported By:** R01 NS053825

**Disclosure:** Dr. Todd has nothing to disclose. Dr. Pandey has nothing to disclose. Dr. Taylor has nothing to disclose.

**LB1.002**

7:00 a.m. to 10:00 a.m.

Improved symptom control with fixed dose levodopa/carbidopa/entacapone versus levodopa/carbidopa as first-line levodopa therapy in early Parkinson's disease (PD) patients

*Robert A. Hauser, Tampa, FL, Michel Panisset, Montreal, Quebec, Canada, Giovanni Abbruzzese, Genoa, Italy, Linda Mancione, Nalina Dronamraju, East Hannover, NJ, Algirdas Kakarieka, Basel, Switzerland*

**Objective:** To compare the symptomatic benefit of levodopa/carbidopa/entacapone (LCE) vs levodopa/carbidopa (LC) in early PD patients (pts) requiring initiation of levodopa.

**Background:** The benefit of LCE vs LC has been demonstrated in PD pts with wearing-off. LCE may also provide greater benefit in early PD pts starting levodopa therapy.

**Methods:** 423 early PD pts requiring levodopa were enrolled in this multicenter, double-blind, parallel-group trial. Exclusion criteria included treatment with dopamine agonists, levodopa or COMT inhibitors within 1 month of the study. Pts were randomized to fixed-dose LCE 100/25/200mg or LC 100/25mg 3-times daily for 39 wks. The primary outcome variable was change from baseline to Wk 39 in combined Unified PD Rating Scale (UPDRS) Part II-activities of daily living (ADL) and Part III-motor scores. Secondary outcome variables included changes in UPDRS subscores (Parts I-III, V and VI), patient- and investigator-assessed Clinical Global Impression (CGI), quality of life as assessed by the 39-item PD Questionnaire (PDQ-39), and the incidence of motor complications and AEs.

**Results:** 208 pts were randomized to LCE and 215 pts to LC. Mean age was 64.8 yrs and mean Hoehn & Yahr Stage was 2. At baseline, mean duration of PD was 1.16 yrs, total UPDRS Part II & III score was 34.3, and PDQ-39 score was 21.8. At Wk 39, the mean change from baseline in total UPDRS Part II & III scores was significantly greater for LCE-treated pts ( $p=0.045$ ), with an observed improvement of 10.0 vs 8.5 points for LCE vs LC. There were also significantly greater improvements in UPDRS Part II-ADL ( $p=0.025$ ), UPDRS Part VI-Schwab & England ADL (rater  $p=0.003$ , pt  $p=0.006$ ) and pt-assessed CGI ( $p=0.047$ ) for LCE vs LC. There were no significant differences in UPDRS Part III-motor, PDQ-39 and physician-assessed CGI. LCE was associated with a lower incidence of dyskinesia (5.3 vs 7.4%) and wearing-off (13.9 vs 20.0%), although this difference was not statistically significant. AEs were generally higher in the LCE-treated group, most commonly chromaturia (urine discoloration; 37.7 vs. 3.3%), nausea (26.6 vs 13.5%) and diarrhea (8.7 vs 2.8%); 11.6 vs 8.4% discontinued the study due to AEs. Serious AEs were reported in 6.3% vs 7.4% of pts.

**Conclusions:** LCE provides superior symptomatic benefit without an increase in motor complications compared with conventional LC in early PD patients requiring initiation of levodopa therapy.

**Study Supported By:** Novartis Pharma AG.

**Disclosure:** Dr. Hauser has received personal compensation for activities with Boehringer Ingelheim, Bertek, Centopharm, Genzyme, GlaxoSmithKline, Kyowa Pharmaceutical, Merck, Ortho McNeil, Pfizer, Schwarz Pharma, Schering, Valeant, Eisai Medical Research, Inc., IMPAX Laboratories, Inc., Novartis Pharmaceuticals, Prestwick, Bayer-Schering Pharma AG, Teva, Vernalis and Solvay Pharmaceuticals BV. Dr. Panisset has received personal compensation for activities with Teva, Novartis, Schwartz, Prestwick, Solvay. Dr. Panisset has received research support from Novartis, Teva, Schwartz, Kyowa, Elan, Eisai, Solvay, Boehringer Ingelheim. Dr. Abbruzzese has received personal compensation in an editorial capacity for Equilibrium-MLP. Dr. Mancione received personal compensation for activities with Novartis as an employee working on neuroscience clinical research projects. Dr. Dronamraju has received personal compensation for activities with Novartis. Dr. Kakarieka has received personal compensation for activities with Novartis.

**LB1.003**

7:00 a.m. to 10:00 a.m.

Abnormal Metabolic Brain Network in Parkinsonian Macaques: Modulation by Retinal Pigment Epithelial (RPE) Cell (Spheramine®) Implantation.

*Yilong Ma, Shichun Peng, David Eidelberg, Manhasset, New York, Joseph Flores, Doris J. Doudet, Vancouver, British Columbia, Canada, Michael Cornfeldt, Somerville, New Jersey, Branka Mitrovic, Richmond, California*

Objective: To assess the metabolic effects of RPE cell implantation in a primate model of Parkinson's Disease (PD).

Background: PD is associated with an abnormal pattern of regional metabolism on fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging. The expression of this network can be modulated by dopaminergic pharmacotherapy. Dopaminergic neurotransmission can also be enhanced by the implantation of RPE cells in the putamen. In this study, we used high resolution FDG PET to assess RPE cell-mediated changes in the expression of a parkinsonism-related metabolic pattern (PRP) in MPTP primates.

Design/Methods: Nine macaques with bilateral MPTP lesions underwent unilateral surgery (1): six received putaminal RPE cell implantation; three received microcarriers alone (sham). All animals were scanned with FDG PET 6 months to 5 years after surgery. FDG PET scans from six normal animals served as controls. Metabolic images were spatially normalized into a macaque brain template. Scans from untreated MPTP and control hemispheres were analyzed using a voxel-based network approach to identify a significant PRP metabolic pattern. PRP expression was computed prospectively in operated hemispheres (RPE and sham). Network values were compared using paired Student t-tests.

Results: Network analysis revealed a significant PRP that was characterized by relative sensorimotor, thalamic, and cerebellar hypermetabolism and posterior parietal hypometabolism. PRP expression was elevated in untreated MPTP hemispheres relative to controls ( $P < .0005$ ). PRP expression in the implanted MPTP hemispheres was lower ( $P < .005$ ) than in the untreated hemispheres. Differences in network expression were not present in sham-operated animals or in the one treated animal who did not exhibit PRP elevation at baseline.

Conclusions/Relevance: This primate PET study suggests that RPE cell implantation can suppress abnormal parkinsonism-related network activity, resulting in clinical improvement. These results suggest the presence of a dopaminergic mechanism for RPE cell implants. Changes in network expression may be useful to assess the efficacy of this intervention in PD patients. <sup>1</sup> Doudet et al. (2004) *Exp. Neurol.* 89:361-368.

**Study Supported By:** Bayer HealthCare Pharmaceuticals, Inc.

**Disclosure:** Dr. Ma has nothing to disclose. Dr. Peng has nothing to disclose. Dr. Eidelberg has received personal compensation for activities with Bayer Pharmaceuticals, Boehringer Ingelheim, and Neurologix, Inc. Dr. Flores has nothing to disclose. Dr. Doudet has received personal compensation for activities with Bayer Healthcare. Dr. Doudet has received research support from Bayer Healthcare Pharmaceuticals and Schering Bayer Pharma. Dr. Cornfeldt has nothing to disclose. Dr. Mitrovic has received personal compensation for activities with Bayer HealthCare Pharmaceuticals.

**LB1.004**

7:00 a.m. to 10:00 a.m.

Efficacy of Donepezil in CADASIL: A model of Subcortical Vascular Cognitive Impairment.

*Stephen Salloway, Providence, Rhode Island, Martin Dichgans, Munich, Germany, Hugh Markus, London, United Kingdom, Margaret Moline, Qin Wang, Ridgefield Park, New Jersey, Holly Posner, New York, New York, Hugues Chabriat, Paris, France*

Introduction: Cholinergic deficits may contribute to cognitive impairment in vascular dementia. CADASIL is an early-onset genetic form of subcortical ischemic vascular dementia unlikely to be mixed with Alzheimer type pathology. Therefore CADASIL is well-suited to test the efficacy of cholinesterase inhibitors in vascular cognitive impairment.

Objective: To evaluate the efficacy and safety of donepezil in patients with CADASIL who have cognitive impairment.

Design: 18-week, double-blind, randomized, multi-national study of 10 mg donepezil versus placebo (1:1). Cognitive inclusion criterion required an MMSE score of 10-17 or a Trail Making Test (TMT) B time score 1.5 SD below the mean after adjustment for age and education. Primary endpoint was change from baseline in the V-ADAS-cog (ADAS-cog plus number cancellation and maze tests; ITT-LOCF population). Secondary endpoints included ADAS-cog, MMSE, TMT A & B, Exit 25, CLOX, Stroop, Disability Assessment for Dementia (DAD), and Clinical Dementia Rating – Sum of Boxes (CDR-SB).

Results: 168 patients (mean age 54.8 years [27-71]) were randomized. Completers included 89.0% on placebo and 84.9% on donepezil. At week 18, the donepezil group showed no difference versus placebo on the primary endpoint. There was a significant treatment effect favoring donepezil on the following secondary outcomes: TMT B, p=0.005; TMT A, p=0.01; Exit 25, p=0.02. Donepezil was generally well tolerated, with typical adverse events related to cholinesterase inhibition. Discontinuations due to AEs were 7.3% in placebo and 10.5% in donepezil subjects.

Conclusions: Donepezil had no effect on the V-ADAS-cog in CADASIL patients with cognitive impairment. However, significant improvement compared to placebo was noted on several measures of executive function. These findings may have implications for future trial design in subcortical vascular cognitive impairment. (ClinicalTrials.gov number, NCT00103948).

**Study Supported By:** Eisai Medical Research Inc. (Ridgefield Park, NJ)

**Disclosure:** Dr. Salloway has received personal compensation from Eisai, Pfizer, Forest, Janssen, Myriad, Elan, sanofi-aventis, and Merck as a consultant. Dr. Salloway has received research support from Eisai, Pfizer, Forest, Janssen, Myriad, Elan, Neurochem, Wyeth, and Cephalon. Dr. Dichgans has received personal compensation for activities with Eisai as a consultant. Dr. Dichgans has received research support from Eisai. Dr. Markus has received personal compensation for activities with GE as a consultant. Dr. Markus has received personal compensation in an editorial capacity for Stroke Journal. Dr. Markus has received (royalty or license fee or contractual rights) payments from FSI. Dr. Moline has received personal compensation for activities with Eisai as an employee. Dr. Wang has received personal compensation for activities with Eisai as an employee. Dr. Posner has received personal compensation for activities with Eisai as an employee. Dr. Chabriat has received personal compensation for activities with Lundbeck, J&J Pharmaceutical Research & Development as a consultant.

## **LB2.001**

11:30 a.m to 2:30 p.m.

Results from a Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled Study of the Safety and Efficacy of Myozyme, Recombinant Human Acid alpha-Glucosidase (rhGAA), for the Treatment of Pompe Disease in Juveniles and Adults

*A.T. van der Ploeg, Rotterdam, The Netherlands, P. Clemens, Pittsburgh, Pennsylvania, D. Corzo, S. Lake, A. Skrinar, Cambridge, Massachusetts, D. Escolar, J. Mayhew, Washington, D.C., J. Florence, A. Pestronk, St. Louis, Missouri, P. Laforet, Paris, France, B. Rosenbloom, Beverly Hills, California, M. Wasserstein, New York, New York*

**Background:** Pompe disease (also known as acid maltase deficiency) is a rare, genetic, metabolic myopathy caused by a deficiency of lysosomal acid  $\alpha$ -glucosidase (GAA), an enzyme that degrades intralysosomal glycogen. In juveniles and adults, the disease is relentlessly progressive and leads to wheelchair dependency and respiratory failure.

**Methods:** Patients were >8 years old, ambulatory, free of invasive ventilation, and had quantifiable respiratory and lower extremity muscle weakness. Patients were randomized 2:1 to biweekly alglucosidase alfa (Myozyme®) 20 mg/kg IV or placebo for 78 weeks at 8 centers in the US and Europe. Distance walked in the six minute walk test (6MWT) and % predicted forced vital capacity (FVC) were co-primary endpoints.

**Results:** 90 patients (45 male, 45 female; 93% Caucasian; age range 10-70 years) were randomized. Baseline mean 6MWT distance was 327.4±128.0 meters (50.1% predicted) and mean FVC was 54.6±14.8% predicted, indicating considerably impaired walking ability and pulmonary function. By last evaluation (78 weeks), estimated mean absolute differences of 28.1±13.1 meters in 6MWT distance ( $p=.03$ ) and 3.4±1.2% in % predicted FVC ( $p=.003$ ) were observed in favor of Myozyme vs. placebo. The frequency of adverse events and infusion associated reactions were comparable between Myozyme and placebo. Three patients in the Myozyme treatment group experienced hypersensitivity reactions, two of whom discontinued treatment. One patient in the Myozyme group died from causes unrelated to treatment. All evaluable patients in the Myozyme group ( $n=59$ ) developed IgG antibodies to rhGAA (mean time to seroconversion: 5.6 weeks). A trend toward decreasing IgG titers was observed over time (median peak titer: 6,400, range 200 to 819,200; median last titer :1,600, range 0 to 819,200).

**Conclusions:** In this first placebo-controlled study of rhGAA conducted in juveniles and adults with Pompe disease, Myozyme was shown to improve walking and pulmonary outcomes when compared to placebo. Follow-up data collection continues under an open-label extension study.

**Study Supported By:** Genzyme Corporation, Cambridge, MA, USA

**Disclosure:** Dr. van der Ploeg has received personal compensation for activities with Genzyme as a consultant and member of the advisory board. Dr. van der Ploeg has received research support from Genzyme. Dr. Clemens has received research support from Genzyme. Dr. Laforet has received personal compensation for activities with Genzyme. Dr. Corzo has received personal compensation for activities with Genzyme as an employee. Dr. Corzo has received compensation for serving on the board of Genzyme. Dr. Corzo holds stock and/or stock option in Genzyme, which sponsored research in which Dr. Corzo was involved as an investigator. Dr. Corzo holds stock and/or stock options in Genzyme. Dr. Corzo has received research support from Genzyme. Dr. Wasserstein has nothing to disclose. Dr. Skrinar has received personal compensation for activities with Genzyme as an employee. Dr. Skrinar holds stock and/or stock option in Genzyme. Dr. Florence has received personal compensation for activities with PTC and Amicus as a consultant. Dr. Rosenbloom has received personal compensation for activities with Genzyme as a consultant. Dr. Rosenbloom has received research support from Genzyme. Dr. Mayhew has received personal compensation for activities with Genzyme as a consultant. Dr. Escolar has received personal compensation for activities with Genzyme, Faust Pharmaceuticals, SAIC, Athena Diagnostics, Gerson Leman's Group, and MEDA as a consultant. Dr. Escolar has received research support from Genzyme. Dr. Lake has received personal compensation for activities with Genzyme as an employee. Dr. Lake holds stock and/or stock option in Genzyme. Dr. Pestronk has received personal compensation for activities with Athena as a speaker. Dr. Pestronk has received (royalty or license fee or contractual rights) payments from Athena. Dr. Pestronk holds stock and/or stock option in Genzyme, which sponsored research in which Dr. Pestronk was involved as an investigator. Dr. Pestronk holds stock and/or stock option in Johnson & Johnson. Dr. Pestronk has received research support from Genzyme, Wyeth, Inmed, and PTC.

**LB2.002**

11:30 a.m. to 2:30 p.m.

**Oral Dexamethasone Pulse Therapy Versus Daily Prednisole in Subacute Inflammatory Myopathies: A Randomized Clinical Trial**

*Janneke van de Vlekkert, J. de Haan, M. de Visser, Amsterdam, Netherlands, J.E. Hoogendijk, A. Algra, J. van der Tweel, W.L. van der Pol, E.V. Uijtendaal, Utrecht, Netherlands*

**Background:** Treatment of subacute inflammatory myopathies consists of daily high-dose prednisone. Major drawbacks of long-term prednisone are its side-effects. Pulsed treatment may have fewer side-effects. In an open-label short-term study on myositis pulsed oral dexamethasone was effective. We compared effectiveness and safety of prednisolone and pulsed dexamethasone in newly diagnosed adult patients with dermatomyositis or non-specific myositis.

**Methods:** Sixty-two patients were assigned to 28-day cycles of oral high-dose dexamethasone (n=30) or daily high-dose prednisolone (n=32) in a long-term, prospective, multicenter, double-blind randomized controlled clinical trial. Primary outcome measures determined at 18 months' follow-up included a composite score composed of six clinically relevant outcomes (Rank 0-1, remission within 3 months, no relapse, Medical Research Council sum score at least 138 out of 140, visual analogue scale for muscle pain 0-2, no Cushingoid appearance); and time-to-remission and time-to-relapse. Secondary outcome measures included side effects.

**Results:** Because of a low inclusion rate, a group sequential analysis was done. No difference between both treatment groups on the composite score was found, justifying a premature termination of the study after inclusion of 62 instead of the planned 80 patients. There were also no statistically significant differences in the other primary outcome measures. Side effects, notably diabetes mellitus, hypertension, mood changes, weight gain, gastric symptoms (and almost every side effect) were found in fewer patients treated with dexamethasone than in patients with prednisolone (any side effect: 79% versus 97%; 95% CI of the risk difference, -36 to -1%).

**Conclusion:** Pulsed high-dose dexamethasone is an alternative for daily prednisolone as first-line treatment of subacute inflammatory myopathies, especially in patients with a high risk of side effects.

**Study Supported By:** Prinses Beatrix Fonds (The Hague, The Netherlands)

**Disclosure:** Dr. van de Vlekkert has nothing to disclose. Dr. Hoogendijk has nothing to disclose. Dr. de Haan has nothing to disclose. Dr. van der Tweel has nothing to disclose. Dr. Algra has received personal compensation for activities with Boehringer Ingelheim as a presenter. Dr. Algra has received research support from Boehringer Ingelheim. Dr. van der Pol has nothing to disclose. Dr. Uijtendaal has nothing to disclose. Dr. de Visser has nothing to disclose.

**LB2.003**

11:30 a.m. to 2:30 p.m.

Splice mutation in the iron-sulfur cluster scaffold protein ISCU causes myopathy with exercise intolerance

*Fanny Mochel, Karen Ayyad, Ronald G. Haller, Dallas, Texas, Melanie A. Knight, Wing-Hang Tong, Dena Hernandez, Andrew Singleton, Tracey A. Rouault, Kenneth H. Fischbeck, Bethesda, Maryland, Tanja Taivassalo, Montreal, Quebec, Canada, Peter M. Andersen, Umea, Sweden*

A myopathy with severe exercise intolerance and myoglobinuria has been described in patients from northern Sweden, with associated deficiencies of succinate dehydrogenase (SDH) and aconitase in skeletal muscle. We found a common region of homozygosity in three patients from three families originating from northern Sweden, and confirmed a founder haplotype. Within that interval, we further identified a single intronic mutation in the gene for the iron-sulfur cluster scaffold protein, ISCU. This homozygous mutation strengthens a weak splice acceptor site and results in reduced levels of ISCU mRNA and protein. The protein levels of the iron regulatory protein IRP1 were also low in patient muscle, suggesting a destabilization of iron-sulfur proteins due to the loss of iron-sulfur clusters. In addition, histochemical studies showed a notable increase in iron staining in patient muscle fibers compared to controls. This iron overload was observed exclusively in SDH negative fibers, where ISCU is likely to be most depleted. Therefore, we have shown that myopathy with deficiency of succinate dehydrogenase and aconitase is an autosomal recessive metabolic disease caused by mutations in the ISCU gene. Frataxin physically interacts with ISCU, and this interaction likely facilitates delivery of iron from frataxin to nascent iron-sulfur clusters on ISCU. The interaction of frataxin with ISCU and the biochemical and histological features associated with this ISCU mutation indicate that this myopathy is caused by defects in iron-sulfur cluster assembly and intracellular iron metabolism similar to Friedreich ataxia, but with different tissue specificity.

**Disclosure:** Dr. Mochel has nothing to disclose. Dr. Hernandez has nothing to disclose. Dr. Tong has nothing to disclose. Dr. Taivassalo has nothing to disclose. Dr. Singleton has nothing to disclose. Dr. Andersen has nothing to disclose. Dr. Fischbeck has nothing to disclose. Dr. Rouault has nothing to disclose. Dr. Knight has nothing to disclose. Dr. Haller has received personal compensation for activities with Edison Pharmaceuticals as a consultant. Dr. Ayyad has nothing to disclose.