2014 Emerging Science Abstracts

The Emerging Science abstracts were presented at the 2014 AAN Annual Meeting. Abstracts qualify for Emerging Science presentations by having key aspects of research conducted after the October 28th abstract submission deadline and must be new and of sufficient scientific importance to warrant expedited presentation and publication. The Science Committee is committed to presenting the best neuroscientific research at the Annual Meeting; 10 abstracts were accepted for dual presentation and 14 were accepted as poster presentations. The last 2 abstracts were presented at the Clinical Trials Plenary Session.

Drisapersen treatment for Duchenne muscular dystrophy: results of a 96-week follow-up of an open-label extension study following two placebo-controlled trials

Nathalie Goemans, MD; Thomas Voit, MD PhD; Craig McDonald, MD; Carolyn Watson; John Kraus, MD, PhD; Katie Rolfe, MSc; Joanna Nakielny, MD, MRCPsych; Barbara Jeter; Rosamund Wilson, PhD; Giles Campion, MD, PhD

OBJECTIVE: To assess the long-term safety, tolerability, and efficacy (6MWD) of subcutaneously injected drisapersen (DRIS) 6 mg/kg/week. **BACKGROUND**: DRIS is a 2'-O-methylphosphothioate oligonucleotide designed to skip exon 51 of dystrophin pre-mRNA in subjects with Duchenne muscular dystrophy (DMD). Two placebo-controlled trials showed a treatment benefit favoring DRIS on 6-minute walk distance (6MWD) after 48 weeks' treatment (DMD114044, 10.3 meters; DMD114117, 35 meters). DMD114349 was an open-label extension of these studies. **DESIGN/METHODS:** Subjects with DMD (>=5 years; ambulant; steroid-treated; rise from floor <=7 sec [DMD114117 only]; dystrophin mutation correctable by exon-51 skipping) who completed the feeder studies were eligible. Safety (datacut June 2013) and efficacy (datacut October 2013) data are reported. **RESULTS:** Safety analysis (n=186) demonstrated that injection-site reactions, renal events, and thrombocytopenia were the most prominent findings. At 48 weeks of DMD114349, subjects who received DRIS (n=69) showed a clinically meaningful difference in 6MWD compared with those in the placebo/delayed-treatment arm (n=44; mean [95% CI] change, –66.8 [–96.6, –36.9] and –112.9 [–152.0, –73.8] meters for a total of 96 and 48 weeks of DRIS, respectively; mean difference, +46 meters). Subjects enrolled in DMD114044 had a 49-meter difference between DRIS (n=52) and placebo/delayed treatment (n=31) from original baseline. Those from DMD114117 had a 52-meter difference from original baseline between DRIS (n=17) and placebo/delayed treatment (n=13) in favor of DRIS; decline was only 5 meters in the DRIS arm. **CONCLUSIONS:** The long-term safety of DRIS appears similar to previous clinical trials, except for the occurrence of thrombocytopenia. A total of 96 weeks of DRIS treatment resulted in a clinically meaningful difference from placebo/delayed DRIS of 46 meters. This extension study suggests maintenance of benefit in a feeder study population with less severe disease, and a clinically meaningful benefit slower to emerge in a feeder study population that is, on average, more severely affected.

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Selective Inhibition of Meningeal Nociceptors by Botulinum Neurotoxin Type A (BoNT-A): Therapeutic Implications to Migraine and Other Pains

Rami Burstein, PhD; Xi Chun Zhang; Dan Levy, PhD; K. Roger Aoki, PhD; Mitchell Brin, MD, FAAN

OBJECTIVE: To understand the mechanism by which BoNT-A reduces chronic migraine. **BACKGROUND:** Migraine is a complex neurological disorder. While factors that predispose an individual to migraine attacks and those leading to attack initiation are not fully understood, it is generally believed that the headache depends on activation of trigeminal nociceptors supplying intracranial meninges. Accordingly, we hypothesized that effective peripherally-administered migraine prophylactics must reduce excitability of meningeal nociceptors. In this study, we assessed BoNT-A effects on different classes of naïve and sensitized meningeal nociceptors. **DESIGN/METHODS:** Using electrophysiological techniques, we identified 43 C- and 36 A-delta-meningeal nociceptors in the trigeminal ganglion, and measured their spontaneous and evoked firing before and after BoNT-A administration to intracranial dura and extracranial suture receptive fields. BoNT-A effects were studied in naïve units, in units sensitized by inflammatory soup (IS) prior to BoNT-A administration, and in units in which BoNT-A was administered hours before induction of sensitization by the IS. **RESULTS:** BoNT-A inhibited C- but not A-delta-meningeal nociceptors. When applied to naïve C-units, BoNT-A inhibited responses to mechanical stimulation of the dura with suprathreshold forces. When applied after IS-induced sensitization, BoNT-A reversed the mechanical hypersensitivity. When applied before IS, BoNT-A prevented the development of IS-induced mechanical hypersensitivity. When applied extracranially, to the suture branch of the meningeal nociceptor, BoNT-A inhibited the mechanical responsiveness of the suture branch but not dural axon. In contrast, BoNT-A did not inhibit C-unit responses to mechanical stimulation of the dura with threshold forces, or their spontaneous activity. **CONCLUSIONS:** The study provides direct evidence for BoNT-A ability to inhibit mechanical nociception in peripheral trigeminovascular neurons. The preferential suppression of responses to suprathreshold mechanical simulation suggests that BoNT-A inhibits high-threshold mechanosensitive ion channels linked to mechanical pain. We propose a mechanism whereby BoNT-A interferes with SNARE-mediated surface expression of relevant receptors, thus preventing fusion into the nerve terminal membrane.

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Asymptomatic carotid stenosis is associated with cognitive dysfunction

Moira C Dux, PhD; Gregory Kowalewski, BA; Limin Zhao, MBBS; Khalid AlMuhanna, MS; Siddhartha Sikdar, PhD; Brajesh Lal

OBJECTIVE: This cross-sectional data from our prospective cohort study is the first comparison of cognitive function between patients with asymptomatic atherosclerotic carotid artery stenosis (ACS) versus patients with similar vascular comorbidities but no stenosis, thus accounting for confounding vascular cognitive impairment (VCI). Furthermore, validated normative data was utilized to compute standardized scores allowing ascertainment of clinical significance of the results. **BACKGROUND:** The impact of ACS on cognitive function remains controversial. Existing information is based on comparisons with healthy controls, varied cognitive batteries, and inadequate standardization of scores. **DESIGN/METHODS:** 67 consecutive patients with ≥50% diameter-reducing ACS and 60 control patients with vascular co-morbidities without ACS underwent comprehensive cognitive testing. Stenosis was confirmed by duplex ultrasonography; asymptomatic status by neurologic and NIH Stroke Scale testing. Cognitive scores were adjusted for age, sex, education, and race using normative data. An overall index of cognitive function and five domain-specific composite scores were computed. Independent samples t-tests were used to compare groups, and Cohen's d was calculated to determine effect sizes. **RESULTS:** The two groups did not differ with respect to vascular risk factors (e.g., diabetes, hypertension, coronary artery disease). The ACS group performed worse on the overall neurocognitive composite score ($t=2.8$; $p\leq.01$; $d=.52$) and the motor/processing speed ($t=3.5$; $p\leq.01$; $d=.69$) and learning/memory ($t=2.6$; $p\leq.05$; $d=.48$) domain scores. A trend of poorer performance for executive function and attention/working memory emerged ($d= .35$ & $.26$, respectively). The groups did not differ on the language domain. **CONCLUSIONS:** We demonstrate, for the first time, that carotid stenosis without a neurologic deficit is not necessarily "asymptomatic" and is associated with greater cognitive impairment compared to patients with similar risk factors but no stenosis. This effect is driven primarily by poor motor/processing-speed and learning/memory, with deficits ranging from mild to moderate. Further studies will be needed to confirm these findings and to elucidate their mechanisms.

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A negative florbetaben PET scan reliably excludes amyloid pathology as confirmed by histopathology in a large Phase 3 trial

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OBJECTIVE: Currently, a negative amyloid PET scan in a subject with cognitive impairment is regarded as the most important clinical information because it precludes Alzheimer's disease as the underlying etiology. The aim of this analysis was to assess the florbetaben diagnostic efficacy and its negative predictive value in a large histopathology cohort of subjects with ante mortem florbetaben PET imaging. **BACKGROUND:** The phase 3 study of florbetaben is the largest study to date, which demonstrates a strong correlation of tracer uptake and amyloid pathology. **DESIGN/METHODS**: Three independent readers visually assessed florbetaben PET scans from 74 end-of-life subjects (clinical diagnosis: 57 AD; 3 DLB; 8 non-demented volunteers; 6 other dementia) who underwent brain autopsy and final neuropathological diagnosis. The scan assessment was compared with the presence/absence of neuritic beta-amyloid plaques determined according to CERAD criteria. **RESULTS:** Presence of beta-amyloid was confirmed by histopathology in 47 cases: 44/57 AD subjects, 1/3 DLB patient, 1/6 other dementia subject and 1/8 non-demented volunteer. Florbetaben scans were correctly read as positive in 46 of these 47 cases. No Aß-plaques were found in 27 subjects, of these n=4 had no neurodegenerative pathologies and were correctly read PET-negative; and n=23 had other non-AD neurodegenerative pathologies like Parkinson's-disease, hippocampal sclerosis dementia, frontotemporal lobar dementia or multi-system neuronal and glial tauopathy or Pick's disease; 20 of these 23 scans were correctly read PET-negative.The resulting sensitivity and specificity of the majority read was 97.9% and 88.9%, respectively. The negative predictive value of florbetaben was 96%. **CONCLUSIONS:** Florbetaben imaging can reliably exclude amyloid pathology as demonstrated by the high negative predictive value. It is a valuable adjunct for the exclusion of Alzheimer's disease or differential diagnosis of dementia. A negative scan should encourage the physician to search for other causes of cognitive decline and tailor available treatment options.

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Coincident Alzheimer's disease modifies alpha-synuclein pathology in Lewy body disease

Jon Toledo; Kevin Raible; Erin Abner; David Irwin, MD; Johannes Brettschneider, MD; Steven Arnold, MD; Howard Hurtig, MD; Peter Nelson; Charles Adler, MD, PhD, FAAN; Thomas Beach; John Trojanowski, MD,PhD

OBJECTIVE: Study the different patterns of alpha-synuclein pathology distribution. **BACKGROUND:** Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common, frequently co-ocurring, neurodegenerative diseases. Dementia with Lewy Bodies (DLB) is defined by dementia with fluctuating cognitive symptoms and the appearance of a parkinsonian syndrome >1 year after dementia onset. Staging systems have been proposed for tau and Aβ deposits in AD as well as for alpha-synuclein pathology (ASP) in PD and DLB although no consensus has been reached. **DESIGN/METHODS:** We studied the distribution of ASP in DLB subjects with coincident AD (AD+DLB, n=313) and compared it to the distribution in PD cases without AD (PD, n=134) and with AD (PD+AD, n=71) from the University of Pennsylvania (UPenn) and the Banner Sun Health Research Institute. Cases were classified by ASP distribution into amygdala predominant, brainstem predominant, limbic (with/ without brainstem involvement) and neocortical using a modified Unified Staging System for Lewy Body Disorders scheme. Dopamine transporter immunohistochemistry was performed on a subset of the UPenn cohort. **RESULTS:** The amygdala predominant ASP category was present in AD+DLB cases and not PD cases. The limbic category presented a lower burden of brainstem, subcortical and frontal ASP in the DLB cases compared to the PD cases. In the neocortical category, PD only cases showed a lower burden of temporal and angular cortex ASP than the PD+AD and the DLB only cases. PD and PD+AD groups in the UPenn cohort showed a higher burden of ASP in the substantia nigra compared to the DLB only group. The nigro-striatal pathway, defined by dopamine transporter immunohistochemistry, was relatively preserved in the DLB+AD groups compared to the PD only and PD+AD groups. **CONCLUSIONS:** The presence of AD pathology modifies the burden and distribution of ASP in the alpha-synucleinopathies studied here.

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Results of a Phase 2 Study of ISIS-SMNRx in Children with Spinal Muscular Atrophy

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OBJECTIVE: This open-label, multiple ascending-dose study was conducted to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of ISIS-SMNRx (ISIS 396443) in children with Types 2 and 3 SMA. **BACKGROUND:** ISIS-SMNRx is an antisense oligonucleotide designed to alter splicing of SMN2 mRNA to increase the amount of functional SMN protein. Results from SMA mouse models indicate ISIS-SMNRx had a significant effect on functional and histological measures of neuromuscular health when delivered to the CNS. A Phase 1 single ascending-dose study in children with SMA had previously been completed, showing acceptable safety/tolerability. **DESIGN/METHODS:** Multiple doses of ISIS-SMNRx (3 dose levels) were delivered by intrathecal injection to medically stable SMA patients 2-15 years of age (n=25). Subjects were dosed 2-3 times over 3 months and then followed for 6 months post-dosing and monitored for drug safety and tolerability, CSF and plasma pharmacokinetics, CSF SMN protein levels, and clinical outcome measures. **RESULTS:** Overall, no safety or tolerability concerns related to ISIS-SMNRx were identified; the majority of adverse events were mild or moderate in severity and none were related to dose level of ISIS-SMNRx. No drug-related changes in neurological exams, laboratory assessments (including CSF safety), or systemic evaluations were reported. Repeated intrathecal injections were well tolerated in SMA children. CSF and plasma drug levels were dose-dependent predictable, and consistent with expected levels. HFMSE scores indicated an improvement in motor function at all doses levels, with a time and dose dependency. 6MWT and ULM functional tests also indicated improvement, although with limited data. Measurement of SMN protein levels in CSF indicated a significant increase at the highest dose (p=0.004), indicating biological activity of ISIS-SMNRx in SMA patients. **CONCLUSIONS**: Results from this study support continued development and further examination of ISIS-SMNRx in a Phase 2/3 controlled study in children with SMA.

Study Supported By: ISIS Pharmaceuticals

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Oral sialic acid extended release (SA-ER) stabilizes upper extremity muscle strength in human GNE myopathy: A phase 2 study.

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OBJECTIVE/BACKGROUND: To assess safety and efficacy of SA-ER in GNE myopathy where no therapy is available. **DESIGN/METHODS**: Double-blind 48 week study in 47 patients who were randomized to placebo, 3 g or 6 g of SA-ER/day PO for 24 weeks, then placebo patients crossed to 3 g or 6 g for additional 24 weeks. The analyses compared change from baseline at week 24 for 6g or 3g versus placebo and for 48 weeks for combined 6 g vs. combined 3 g groups. Assessments included muscle strength by dynamometry [composites of upper extremity (UEC), lower extremity (LEC) muscles], 6 minute walk test (6MWT) test, an HIBM-specific patient reported outcome (GNEM-FAS) and safety. **RESULTS:** At 24 weeks, the UEC in the 6 g group showed a significant improvement over placebo (+2.33kg, p=0.04); at 48 weeks, the combined 6g group was improved over the combined 3 g groups (+3.44 kg, p=0.0033), especially in >200m baseline walking predefine subset (+4.70 kg, p<0.001). The LEC showed a similar pattern without a statistically significant difference. The 6MWT did not change. The GNEM-FAS measure showed a positive trend in total (p=0.087), mobility (p=0.087) and UE scores (p=0.096) in the combined 6 g vs 3 g groups at 48 weeks. SA-ER was well tolerated without serious adverse events. **CONCLUSIONS**: These are the first human clinical data suggesting that 6g/day SA-ER has a clinically meaningful effect of stabilizing UEC muscle strength over 48 weeks in GNE myopathy.

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Alemtuzumab Improves Brain MRI Outcomes in Patients With Active Relapsing-Remitting Multiple Sclerosis: 3-Year Follow-up of the CARE-MS Studies

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OBJECTIVE: Examine effect of alemtuzumab on magnetic resonance imaging (MRI) outcomes in the ongoing CARE-MS extension. **BACKGROUND:** In two phase 3, head-to-head trials in active relapsing-remitting multiple sclerosis (RRMS) patients (treatment-naive [CARE-MS I; NCT00530348] or relapsed on prior therapy [CARE-MS II; NCT00548405]), alemtuzumab proved superior to subcutaneous interferon beta (IFNB)-1a with respect to clinical efficacy, and the reduction in MRI activity and brain volume loss over 2 years. In an extension study, durable effects on clinical efficacy were still observed 1 year later. **DESIGN/METHODS:** Patients who received alemtuzumab (12 mg/day IV on 5 consecutive days and on 3 consecutive days 12 months later) in CARE-MS studies continued uninterrupted follow-up in an extension study (NCT00930553). They were eligible for alemtuzumab re-treatment on evidence of disease activity. MRI scans were acquired at

CARE-MS baseline, and at 12, 24, and 36 months. Lesion measurements included gadolinium (Gd)-enhancing lesions, T2-hyperintense lesions, and T1-hypointense lesions. **RESULTS:** 349 CARE-MS I (formerly treatment-naive) and 393 CARE-MS II (relapsed on prior therapy) alemtuzumab patients entered the extension; 18% and 20%, respectively, received re-treatment. At Month 36, the proportion of CARE-MS I alemtuzumab patients with new or active lesions was not statistically different from Month 24 for Gd-enhancing lesions (9.6% vs 7.1%), new/enlarging T2 lesions (27.4% vs 23.1%), and new T1 lesions (9.2% vs 7.7%). The proportions of CARE-MS II alemtuzumab patients with active scans were also comparable for all lesion types: Gd-enhancing lesions (13.5% vs 9.3%), new/enlarging T2 lesions (30.7% vs 24.3%), and new T1 lesions (10.6% vs 7.4%). **CONCLUSIONS:** The majority of alemtuzumab patients were free of new Gd, T2, and T1 lesions on scans obtained after 3 years of follow-up from their first course of treatment, even though most patients last received treatment 2 years earlier. These findings support the durable efficacy of alemtuzumab in RRMS.

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The Relationship Between Peripheral B-Cell Levels and MRI Disease Activity in Relapsing Remitting Multiple Sclerosis (RRMS)

Daren Austin, PhD; Immanuel Freedman, PhD; Richard Grove, MSc; Jerry Tolson, PhD; Susan Vanmeter, MD

OBJECTIVE: To evaluate the relationship between peripheral B-cells and brain MRI gadolinium-enhancing (GdE) lesions in RRMS subjects. **BACKGROUND:** B-cells have been implicated in the pathogenesis of disease in RRMS. Studies of supra-pharmacological anti-CD20 B-cell depletion have shown reduced disease activity but no relationship between B-cells and efficacy. OMS112831 is an ongoing Phase 2B placebo-controlled dose-ranging study of subcutaneous (SC) ofatumumab in RRMS. Headline safety and efficacy data are presented elsewhere (Presentations: S23.006, I7.1.007). The wide range of studied doses (3-180 mg) modulates B-cell depletion providing additional opportunities to explore relationships between B-cells and disease activity. **DESIGN/METHODS:** Study OMS112831 is evaluating the inhibition of new GdE lesions during a 12-week placebo controlled period. Weighted mean CD19 B-cell count for the period 4-12 weeks were correlated to the number of new GdE lesions on an individual patient basis (n=231). A non-parametric analysis was used to identify threshold effects and generalized linear models used to identify relationships between peripheral B-cell levels and MRI disease activity. **RESULTS:** Analysis of cumulative new GdE lesions showed disease activity was significantly reduced below a threshold CD19 count of 64 cells/uL for the period 4-12 weeks. A generalized linear model with underlying negative-binomial distribution accounting for over-dispersion of lesions across patients showed a highly significant linear relationship ($P<0.001$) with residual annualized disease activity of one new lesion per year and a threshold of approximately 32-64 cells/uL. **CONCLUSIONS:** This dose-response study of anti-CD20 therapy in RRMS demonstrates modulation of pharmacological and clinical effects. Relating peripheral B-cell pharmacology to appearance of new GdE lesions reveals a potential threshold of 32-64 cells/uL for significantly reducing MRI lesion activity. These results present a possible new target threshold for exploration of therapeutic benefit in RRMS patients undergoing anti-CD20 therapy.

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Prolonged-Release Fampridine Treatment and Walking Ability and Balance in Patients with Multiple Sclerosis: Results of the Randomized, Double-Blind MOBILE Study

Jan Lycke, MD; Christine Short; Claudio Gasperini, MD; Raymond Hupperts; Manjit McNeil; Rossella Medori; Lahar Mehta, MD; Jacob Elkins, MD

OBJECTIVE: To evaluate the effect of prolonged-release (PR) fampridine tablet (dalfampridine extended release in US) on self-assessed walking ability, dynamic and static balance, and quality-of-life (QoL) in patients with multiple sclerosis (MS). **BACKGROUND:** Walking impairment negatively impacts QoL and is one of the most commonly reported disabilities among MS patients. **DESIGN/METHODS:** MOBILE was a randomized, double-blind, multicenter, placebo-controlled study. Patients (18-70 years) with progressive or relapsing-remitting MS (revised McDonald criteria) and EDSS score of 4-7 were treated with PR-fampridine 10mg tablets or placebo twice daily for 24 weeks. Efficacy endpoints included change from baseline in the 12-item MS walking scale (MSWS-12), Timed Up and Go (TUG) test, Berg Balance Scale (BBS), 29-item MS impact scale (MSIS-29), and the EuroQol (EQ-5D-5L). MOBILE was designed to explore the effects of PR-fampridine on a range of walking-related endpoints. Post hoc statistical testing compared multiple thresholds of improvement between treatment groups for each of MSWS-12 and TUG using a logistic regression adjusted for baseline. **RESULTS**: 132 subjects were randomized at 24 sites worldwide. Over the 24-week study period, a higher proportion of subjects randomized to PR-fampridine vs. placebo experienced clinically meaningful improvements on the MSWS-12 (>=8 point mean improvement): 48.5% vs. 28.1% ($P=0.015$); and TUG speed (>=15% mean improvement): 47.1% vs. 30.2% ($P=0.026$), respectively. PR-fampridine treatment also resulted in greater (median) improvements from baseline on the MSWS-12 (-6.92 vs -2.89), TUG speed (12.26% vs 3.49%), BBS (2.93 vs 1.71) and MSIS-29 physical subscale (-4.96 vs -2.19) versus placebo. Safety findings were similar to previous studies. **CONCLUSIONS:** PR-fampridine treatment resulted in sustained, clinically meaningful improvement in walking ability and balance over the 6-month treatment period. These findings extend prior Phase 3 results to a longer treatment period and a broader range of objective and patient-reported measures of walking ability.

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Bumetanide attenuates neuronal network hyperexcitability and improves survival in a mouse model of tuberous sclerosis

Hongyu Sun, MD, PhD; Delia Talos; June Goto; Hal Juul; John Dreier; Austin Coley; David Kwiatkowski; Frances Jensen, MD

OBJECTIVE: We propose to examine the potential benefits of bumetanide in a mouse model of tuberous sclerosis. **BACKGROUND:** Tuberous sclerosis complex (TSC) frequently manifests with refractory early life epilepsy, mental retardation and autism. The mechanism of epileptogenesis in TSC is poorly understood.We recently found that the Na+-K+-2Cl- transporter (NKCC1) is overexpressed relative to the K+-Cl- transporter (KCC2), and excitatory GABAARs are present in human TSC biopsy samples (Talos et al., 2012). Here we aim to examine the benefits of the NKCC1 inhibitor bumetanide in a Tsc1cc Nestin-rtTA+ TetOp-Cre+ (E12.5-14.5 doxy) mouse model. Bumetanide is currently being evaluated in a Phase I/II trial for neonatal seizures, based on our preclinical data (clinicaltrials.gov/NCT00830531). **DESIGN/METHODS:** NKCC1 and KCC2 expression were analyzed by Western blot. Perforated-patch clamp recordings were made to measure GABA reversal potentials. A sensitive mass spectrometry assay was performed to measure brain bumetanide levels. Field excitatory postsynaptic potential (fEPSP) was recorded to measure neuronal network excitability. **RESULTS:** Tsc1cc Nestin-rtTA+ TetOp-Cre+ mice showed a significant upregulation of NKCC1 protein expression and low KCC2 expression (pcc Nestin-rtTA+ TetOp-Cre+ mice (-52.7±3.1mV, n=7) was significantly higher than wild-type controls (-69.2±5.2mV, n=6, pAR mediated synaptic transmission. We next evaluate the beneficial effects of bumetanide treatment in TSC mutant mice. Oral supply of bumetanide provided a constant intake and achieved a brain bumetanide level (1.39±0.32ng/g, n=5) comparable to that of i.p injection of bumetanide. Importantly, bumetanide treatment beginning at P18-19 attenuates the increased fEPSP input-out function and significantly improved survival of Tsc1cc Nestin-rtTA+ TetOp-Cre+ mice ($p<0.05$, n=16) with no significant effects on body weight. **CONCLUSIONS:** These results suggest that excitatory GABAARs are critically involved in neuronal hyperexcitability in TSC and establish bumetanide as a potential adjuvant therapy for refractory epilepsy or infantile spasms in TSC.

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SPP1 rs28357094 genotype is neither a determinant of Duchenne muscular dystrophy (DMD) disease progression nor useful as a clinical trial outcome covariate: results from 3 controlled trials in DMD subjects amenable to exon 51 skipping

Sarah Glass, PhD; Pamela St Jean, PhD; Linda Briley; Dana Fraser; Carolyn Watson; John Kraus, MD, PhD

OBJECTIVE: Evaluate the effect of SPP1 rs28357094 on Duchenne muscular dystrophy (DMD) disease progression across subjects in the drisapersen clinical program. Determine

whether stratification of three different clinical trials by SPP1 rs28357094 would impact the trial outcome. **BACKGROUND:** Evidence in the literature observed that an osteopontin variant (SPP1 rs28357094) is a genetic modifier of disease severity in DMD (Pegoraro 2011). This variant was subsequently tested for an effect on functional measures over 12 months in DMD patients and was shown to be not only a disease modifier, but also relevant for selection of homogeneous groups of patients for future clinical trials (Bello 2012). Drisapersen is an antisense oligonucleotide designed to skip exon 51 in the dystrophin gene in development for the treatment of DMD. In the present evaluation, we assess the effect of the SPP1 rs28357094 on DMD disease progression and whether this variant has utility as a clinical trial stratification factor in subjects enrolled in the drisapersen program. **DESIGN/METHODS:** This was a GSK-funded evaluation (201188) in which 263 consented genetic samples from 290 subjects across 3 GSK-sponsored clinical trials (DMD114044, DMD114117, and DMD114876) were genotyped using the Affymetrix Axiom® Biobank plus Genotyping Array. An association analysis with >90% power to detect the published effect of SPP1 rs28357094 was performed. **RESULTS:** There was no statistical evidence that SPP1 rs28357094 was associated with disease progression ($p=0.96$). **CONCLUSIONS:** The results from this genetic evaluation of DMD subjects amenable to exon 51 skipping suggest that SPP1 rs28357094 is not associated with disease progression and thus do not provide evidence that SPP1 rs28357094 should be used in DMD clinical trial design.

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A Phase II study to assess safety and efficacy of olesoxime (TRO19622) in 3-25 year old Spinal Muscular Atrophy (SMA) patients

Eric Dessaud; Carole André; Bruno Scherrer; Patrick Berna; Rebecca Pruss, PhD; Valerie Cuvier; Wilfried Hauke; Enrico Bertini, MD

OBJECTIVE: Evaluation of olesoxime in patients with spinal muscular atrophy (SMA). **BACKGROUND:** Olesoxime (TRO19622) was identified as a potential treatment of SMA based on its beneficial effects in multiple preclinical neurodegeneration models. Olesoxime promotes neuron survival, neurite outgrowth, recovery from nerve injury and accelerates myelination or remyelination in models of demyelinating diseases. Maintaining motor neuron architecture and survival is highly relevant to SMA, a disease associated with progressive motor neuron compromise mainly affecting neuromuscular function. **DESIGN/METHODS:** 165 type 2 or non-ambulant type 3 SMA patients, aged 3-25 years old were recruited from 22 sites in 7 European countries beginning in November 2010. Patients were randomized to olesoxime, 10 mg/kg, administered as a liquid oral formulation or matching placebo in a 2:1 ratio and treatment duration was for 104 weeks. The last patient completed the study in November 2013. The primary outcome measure was the change in motor function using the MFM scale. The secondary outcome measures included the HFMS for SMA, electromyography, pulmonary function, and patient-reported outcomes as well as safety. **RESULTS:** Patients in the placebo arm of the study experienced a loss of motor function at a similar rate to that previously reported (Vuillerot et al. 2013); their MFM D1+D2 scores as a percent of the maximum score decreased from a mean of 39.0% at baseline to 37.1% after two years. Total MFM scores also decreased from 49.2% to 47.5%. The effects of olesoxime treatment on this primary outcome measure and other secondary outcomes will be presented. **CONCLUSIONS:** Results from this pivotal clinical trial will be used to assess the effectiveness of olesoxime in type 2 and type 3 non-ambulant SMA patients over a period of two years. The collected data will provide a valuable source of longitudinal data for motor function and potential prognostic biomarkers in a broad range of SMA patients.

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Elevated Neuroinflammatory Responses in a Mouse Model of Tuberous Sclerosis Complex (TSC)

Delia Talos, MD; Veronique Ruppe, PhD; Pelin Dilsiz; Austin Coley; Alexander Gill; Dennis Kolson, MD, PhD; Frances Jensen, MD; Hongyu Sun, MD, PhD

OBJECTIVE: We aimed to determine the extent of neuroinflammation and activation of cellular stress response pathways in a mouse model of TSC to identify new therapeutic targets for seizure suppression and epilepsy prevention. **BACKGROUND:** TSC is a multisystem autosomal dominant disorder due to inactivating mutations in TSC1 or TSC2 genes. Early onset epilepsy, cognitive dysfunction and autism are the most common neurological manifestations of the disease. We have recently demonstrated robust inflammation in human TSC brain lesions, suggesting that elevated neuroinflammation may contribute to disease progression. **DESIGN/METHODS:** Tsc1cc Nestin-rtTA+ tet-OP-cre+ mice were produced by timed Tsc1 inactivation in neuronal progenitor cells at E12.5-13.5 [PNAS 2011; 108 (45): E1070-9] and sacrificed at P30-P45 (n=18). We performed Western blot analysis of whole brain protein extracts for phospho-S6 (pS6), interleukin-1beta (IL1-β), IL1 receptor antagonist (IL1Ra), IL1 receptor I (IL1R1), NF-kB p50, ER chaperone binding immunoglobulin protein (BiP) and detoxifying enzyme heme oxygenase-1 (HO-1). We next determined the effect of IL-1β on neuronal excitability by measuring the field excitatory postsynaptic potential (fEPSP) and spontaneous excitatory postsynaptic currents (sEPSCs) in cortical slices. **RESULTS:** We observed a significant increase in pS6 ($p<0.0001$), IL1-β ($p<0.0001$), NF-kB ($p<0.05$), BiP ($p<0.05$) and HO-1 ($p<0.05$) in TSC mice. A trend of elevated IL1R1 was also observed ($p=0.07$). In contrast, IL1Ra expression was significantly lower in TSC mutant mice ($p<0.05$). Bath application of IL1-β significantly increased the slope of fEPSPs and the amplitude of sEPSC in cortical slices from TSC mice ($p<0.05$; $n=4$), while no significant effects were detected in wild type slices ($p>0.05$, $n=3$). **CONCLUSIONS:** Our results demonstrate a robust neuroinflammatory and cellular stress response in TSC mouse brain and enhanced cytokine responsiveness of TSC neurons. Our data suggests that neuroinflammation may mediate TSC pathogenesis and therefore justifies future studies evaluating the therapeutic potential of available FDA-approved immune modulators to improve neurological outcomes in TSC.

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Autosomal-dominant Parkinsonism With a Novel MAPT Gene Mutation in a Specific Population of Central Europe (South-Eastern Moravia, Czech Republic)

Petr Kanovsky, PhD; Katerina Mensikova, MD, PhD; Radek Vodicka, MD, PhD; Marek Godava, MD, PhD; Pavel Otruba; Radek Vrtel, MD, PhD; Lenka Mikulicova, MD; Michaela Kaiserova, MD; Miroslav Vastik, MD; Sandra Kurcova, MD; Tereza Bartonikova; Pavla Dudova

OBJECTIVE: To determine the type of mutation in families with autosomal-dominant parkinsonism with dementia. **BACKGROUND:** In an epidemiological study carried out in an isolated population of South-Eastern Moravia in the Czech Republic, a surprisingly high prevalence of parkinsonism was found, differingfrom the published prevalence rates in other European countries. **DESIGN/METHODS:** On the basis of a detailed genealogical examination of all the individuals with confirmed parkinsonism, the pedigrees were compiled and a DNA analysis of probands from each pedigree was subsequently initiated. A massive parallel sequencing method using Ion Torrent technology was used; the DNA sequence analysis was focused on the gene lociin which the causal mutations related to Parkinson's disease (PD) have been described. **RESULTS:** Three large pedigrees with an autosomal-dominant inheritance pattern with reduced penetration of parkinsonism were identified. None of the previously described pathogenic mutations associated with PD were found; rare variants or yet-undescribed mutations were also not found. In 5 of 10 examined probands, a novel missense Q230H mutation of the MAPT gene was detected. Polyphene and SIFT in silico predictors indicate this mutation as "probably damaging". **CONCLUSIONS:** Confirmation sequencing using an independent method is underway to examine the targeted MAPT mutation in other individuals from all three pedigrees and to compare it with healthy controls.

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A Novel Assay for Protein Analysis in Friedreich's Ataxia (FRDA): Implications for Diagnosis and Clinical Trial Design

Gabriela Raina; Claudia Perandones; Daniela Calvo, MD; Maria Elena Giuntini De Juarez; Santiago Faraj, PhD; Martin Radrizzani; Ralph Pikielny, MD; Federico Micheli, MD; Alejandro Ferrari, PhD; Javier Santos, PhD

OBJECTIVE: To develop a new assay to improve frataxin measurement as a second diagnostic step for patients with suspected FRDA. **BACKGROUND**: FRDA is the most common hereditary ataxia in Caucasians. The molecular defect in FRDA involves GAA trinucleotide expansion in the first intron of the frataxin-encoding gene (FXN). To date, only four studies have tried to quantify frataxin levels in FRDA carriers, controls and patients. **DESIGN/METHODS**: Patients. Twelve patients with classic FRDA phenotype (10 homozygous for GAA expansion and 2 harboring GAA expansion in compound heterozygosis with FXN point mutations carriers), and 10 healthy controls were enrolled. FXN determination. Frataxin was measured using an in-house competitive enzyme immunoassay. In contrast to other FXN measurement tests, the assay developed in our laboratory depends on a single specific sera (from rabbits), with no need of additional capture antibodies, thus resulting in a high-sensitivity and low-cost determination. Data analysis. FXN levels were determined interpolating each sample in a four-parameter standard curve, using Graph Pad Prism software. FXN levels were then normalized by total protein content, and expressed as fg of FXN/μg total protein. **RESULTS:** High levels of FXN (3.4?0.9 pg/mg of total protein) were found in controls, whereas FRDA patients had significantly lower levels (0.1?0.2 pg/mg). It is noteworthy that our data support whole blood as the source for FXN measurement. **CONCLUSIONS:** We developed a novel high-sensitivity assay for FXN measurement which allowed us to differentiate FRDA patients and healthy individuals. We are proposing this method for its use as an attractive biomarker for clinical trials and also prior to full FXN sequencing if genetic testing reveals heterozygous expansion, family history is non-informative, and/or clinical symptoms are not fully evident.

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Brain Regeneration: Mechanistic and Functional Characterization of Axolotl Pallium Regeneration

Salman Bhai; Ryoji Amamoto; Dennis Sun; Paola Arlotta, PhD

OBJECTIVE: To characterize the molecular and cellular mechanisms underlying neuronal regeneration, determine whether the pallium (cerebral cortex homologue) reconstructs the distinct neuronal subtypes with fidelity, and assess the functional capacity of the regenerated tissue. **BACKGROUND:** The axolotl (Ambystoma mexicanum) has the ability to regenerate many of its organs, including the limb, heart, and the central nervous system. **DESIGN/METHODS:** First, we traced circuitry and built the first map of the resident neuronal subtypes within the axolotl pallium using retrograde tracing, immunofluorescence, and in situ hybridization of known murine subtype-specific markers. Then, the cellular and molecular dynamics of brain regeneration were characterized after pallium injury at 1, 2, 4, and 11 weeks post injury (wpi). Lastly, axolotls were trained through contextual fear conditioning, and performance was assessed after medial pallial resection and 11 wpi. **RESULTS:** Mapping neuronal subtypes identified cell cluster homologues of the murine cortex. Additionally, regeneration begins with periventricular repair, completing at 4 wpi, followed by a vast proliferation of BrdU+ cells populating the injured region. Interestingly, cells distal to the injury site, such as in the olfactory bulb, display rapid proliferation, indicating that extrinsic factors may mediate the increase in BrdU+ cells. Despite the increased number of proliferative cells in the pallium, very few new neurons (NeuN+BrdU+) are present 4 wpi; however, some NeuN+BrdU+ neurons are present 11 wpi. This parallels limb regeneration in that several markers are shared and a proliferative pool of blastema cells accumulates before differentiated cells repopulate the limb. Behaviorally, axolotls' baseline avoidance rate of 26% improved to 71% (p-value<0.001), falling to 20% after medial pallium resection. **CONCLUSIONS:** While further experiments are necessary to determine if the correct neuronal subtypes repopulate the pallium and whether regeneration restores previously learned behavior, this work lays the much-needed foundation to study the molecular mechanism underlying axolotl pallial regeneration.

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Mortality is greater in persons with non-amnestic than with amnestic mild cognitive impairment. The Mayo Clinic Study of Aging

Maria Vassilaki, MD, PhD, MPH; Rosebud Roberts, MD; Ruth Cha; Vernon Pankratz; Yonas Geda, MD; Michelle Mielke, PhD; David Knopman, MD, FAAN; Ronald Petersen, PhD, MD

OBJECTIVE: Assess the hazard of death in persons with amnestic and non-amnestic mild cognitive impairment (aMCI, naMCI) in the Mayo Clinic Study of Aging (MCSA). **BACKGROUND:** The relatively little information on mortality in MCI patients in population-based studies suggests higher mortality in MCI compared to cognitively normal individuals. However, mortality by MCI subtypes has not been investigated. **DESIGN/METHODS:** MCSA is an age/sex stratified random sample of Olmsted County residents, 70–89 years old on October 1, 2004, evaluated by a study nurse, a neurologic evaluation by a physician, and neuropsychological testing to assess cognitive function. Participants were followed at 15-month intervals. Deaths were determined from the Mayo Clinic databases at the time of follow-up. Mortality for MCI vs. cognitively normal subjects was estimated using proportional hazards models. **RESULTS:** Over a median follow-up of 5.8 years, 331 of 862 MCI cases and 224 of 1292 cognitively normal subjects died. Compared to cognitively normal individuals, mortality was elevated in persons with MCI (hazard ratio [HR] = 1.81; 95% CI: 1.45 to 2.25), and with both aMCI (HR = 1.68; 95% CI: 1.33 to 2.12) and naMCI (HR = 2.26; 95% CI: 1.66 to 3.09) after adjusting for potential confounders. Mortality was similar in persons with MCI who later developed dementia (HR =1.47; 95% CI: 1.07 to 2.03) and those who never developed dementia (HR =1.48; 95% CI: 1.14 to 1.92). Mortality was increased for single domain (HR =1.76; 95% CI: 1.37 to 2.28) and multiple domain aMCI (HR =1.49; 95% CI: 1.05 to 2.10), and for single domain (HR =2.31; 95% CI: 1.65 to 3.24) and multiple domain naMCI (HR =2.04; 95% CI: 1.14 to 3.66). **CONCLUSIONS:** Findings demonstrate that both aMCI and naMCI are associated with increased mortality, and this association is stronger in persons with naMCI.

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Effect of Adjunctive Perampanel on Cognition in Adolescents With Inadequately Controlled Partial-Onset Seizures

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OBJECTIVE: Compare the short-term effect on cognition of perampanel versus placebo when administered as adjunctive therapy in adolescents with refractory partial-onset seizures (POS). **BACKGROUND:** In epilepsy, cognition and behavior are considered 2 of the most crucial determinants of outcome following seizure control. Use of antiepileptic drugs (AEDs) has been shown to be associated with cognitive impairment. **DESIGN/METHODS:** Patients (12-<18 years, receiving 1-3 AEDs) with uncontrolled POS were randomized to once-daily placebo or perampanel (2-12 mg/day) in the Phase II study, which included: 1-week prospective baseline, 6-week titration, 13-week maintenance, and 4-week follow-up for patients not entering open-label extension. Primary endpoint was change from baseline (Week 0) to end of maintenance therapy (Week 19) in Cognitive Drug Research (CDR) System Global Cognition Score. Key secondary endpoints were changes from baseline in the 5 core CDR System domains: Power of Attention; Continuity of Attention; Quality of Episodic Memory; Quality of Working Memory; Speed of Memory. **RESULTS:** Cognition population consisted of 123 patients (placebo: n=44; perampanel: n=79). Mean age was 14.3 years; mean IQ score (Kaufman Brief Intelligence Test) was 100.5 for placebo and 101.5 for perampanel. Least squares mean differences in Global Cognition Score showed no evidence of an overall statistically significant effect of perampanel on cognitive function compared to placebo. These results were consistent across region, age, and gender subgroups. Although there were no effects on the composite, analysis of the 5 CDR System domains suggested possible benefits for perampanel on Quality of Episodic Memory and possible worsening with perampanel on Continuity of Attention and Speed of Memory compared with placebo. These results were supported by positive associations with perampanel drug concentration. **CONCLUSION:** Adjunctive perampanel therapy in adolescents with POS showed no significant overall short-term effects on cognition based on the CDR System Global Cognition Score.

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The POEM Study: Testing the Impact of a Digital Health Platform in U.S. Veterans with Epilepsy

John Hixson, MD; Deborah Barnes, PhD, MPH; Karen Parko, MD, FAAN; Tracy Durgin, PharmD; Arianne Graham, MBA; Stephanie Van Bebber; Paul Wicks, PhD

OBJECTIVE: The purpose of the POEM (Policy for Optimal Epilepsy Management) study was to assess the impact of a digital health management platform PatientsLikeMe (PLM, www.patientslikeme.com) in a population of U.S. Veterans with epilepsy. The digital intervention included a social media forum, condition-specific tracking tools, and educational resources. **DESIGN/METHODS:** We conducted a pragmatic trial in U.S. Veterans with epilepsy that had not previously used the PLM platform. We utilized mixed recruiting techniques, including direct patient contact, mailing campaigns, and social media advertising. Patients registered through an online study website and completed informed consent and validation queries before entering the study. Participants initially completed two validated surveys representing the primary study outcomes: the Epilepsy Self-Management Scale (ESMS) and Epilepsy Self-Efficacy Scale (ESES), two measures of patient self-management practices. Upon completion, participants were directed to the PatientsLikeMe platform and engaged at their own discretion. After six weeks, study members were asked to complete the surveys again. An incentive was offered upon study completion. **RESULTS:** A total of 249 Veterans with epilepsy consented, were validated, and joined the online platform. The mean age was 50.2 years, 80.7% were male, and 75.1% were non-Hispanic white, consistent with U.S. Veteran demographics. 92 participants (36.9%) completed the second survey at the conclusion of the study. Scores improved over six weeks for both the ESMS (140 to 143 points, p=0.02) and ESES (244 to 254 points, p=.02) total scores. The greatest change was observed on the ESMS information management subscale (20 to 22 points, p<0.001). **CONCLUSIONS:** This first-time, pragmatic study of an online health management platform demonstrates statistically significant improvements in established epilepsy metrics of patient self-management and self-efficacy in more than one-third of veterans. This work demonstrates the potential impact of digital health solutions in epilepsy and serves as a foundation for further research.

Study Supported By: UCB Inc.

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The 2014 Certification of a Polio-Free India: Progress towards Global Polio Eradication

Farrah Mateen, MD; Roland Sutter, MD

OBJECTIVE: To officially announce the certification of a "polio free India" in Spring 2014 and provide a critical update on the transmission of the last 1% of poliovirus transmitted globally, including case numbers in armed conflict regions and polio-endemic zones. **BACKGROUND:** Wild-type poliovirus transmission has decreased by more than 99% since the World Health Assembly's 1988 resolution to eradicate poliomyelitis globally. In March 2014, India, as part of the WHO's South-East Asia Region, will be certified as "polio-free," making it the fourth WHO Region to be certified as polio-free, with India having the last case with poliovirus in this Region. **DESIGN/METHODS:** The global status of polio eradication is reported via an international network of collaborators and partner organizations who monitor acute flaccid paralysis and test stool samples for poliovirus in more than 150 countries. **RESULTS:** The last case of poliomyelitis was reported in India in January 2011. After an interval of 3 years with

sensitive surveillance, the Regional Certification Commission will likely be able to certify the Region as polio-free in Spring 2014. Globally, In 2013, there were 400 cases of poliomyelitis globally with 60% in non-polio endemic countries including Cameroon, Kenya, Somalia, Ethiopia, and Syria, representing a major shift since 2011 when most cases were within the polio endemic countries of Afghanistan, Pakistan, and Nigeria. In 2014, there have been 8 cases of poliomyelitis, now all in endemic countries. A rapid response to vaccination in Syria was required to contain transmission in the setting of conflict. **CONCLUSIONS:** Polio eradication in India, a country of more than 1 billion people, is a global public health success for vaccine-preventable neurological disorders. The lessons learnt in this decades-long challenge will instruct the eradication of other vaccine-preventable disorders and lead to eradication of poliomyelitis in the last remaining countries globally.

Study Supported By: Global Polio Eradication Initiative

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Longitudinal Change in Quantitative Spinal Cord MRI in Multiple Sclerosis Patients: Preliminary Results of a 2-year Study

Jiwon Oh, MD; Min Chen; Scott Newsome; Marie Diener-West, PhD; Kathleen Zackowski, PhD; Craig Jones; Peter Van Zijl; Jerry Prince, PhD; Daniel Reich, MD,PhD; Peter Calabresi, MD, FAAN

OBJECTIVE: To assess quantitative spinal cord (SC)-MRI measures over a median follow-up period of 2 years, and to characterize the relationship between changes in quantitative SC-MRI with clinical disability **BACKGROUND:** SC pathology is common in multiple sclerosis (MS). Prior studies have shown that quantitative SC-MRI measures, including diffusion-tensor and magnetization-transfer indices, and SC-cross-sectional area(CSA) correlate with MS-related clinical disability. To date, the evaluation of longitudinal change in quantitative SC-MRI in MS has been limited. **DESIGN/METHODS:** 74 MS patients underwent baseline and follow-up 3T cervical SC-MRI and clinical assessment including: expanded disability status scale(EDSS), vibration-sensation threshold(VST), and hip-flexion strength(HFS). Regions-of-interest circumscribing axial SC cross-sections at C3-C4 were used to obtain:CSA, fractional anisotropy(FA), mean, perpendicular, parallel diffusivity (MD, $\lambda\perp$, $\lambda||$,) and magnetization-transfer ratio(MTR). Mixed-effects regression incorporating subject-specific intercepts and slopes was utilized to assess longitudinal change in individual SC-MRI measures. Pearson's correlation coefficient(r) assessed relationships between subject-specific slopes and follow-up clinical measures. **RESULTS:** In 74 MS patients: MTR and SC-CSA decreased ($p<0.01$,$p=0.06$), while MD increased ($p=0.08$) over a median follow-up period of 726 days(inter-quartile range=372-754). There were moderately strong correlations between subject-specific slopes of individual SC-MRI indices and follow-up clinical measures. For EDSS: r with FA=-0.31($p<0.01$); MD=0.32($p<0.01$); $\lambda\perp$=0.34($p<0.01$); $\lambda||$=0.15($p=0.06$), MTR=-0.27($p<0.01$); SC-CSA=-0.44($p<0.01$), with comparable observations for HFS and VST. Individuals with accelerated SC MRI-index change vs. study population mean(based on subject-specific slopes) showed substantially stronger correlations with follow-up clinical measures for FA, MD, $\lambda||$, and MTR. **CONCLUSIONS:** In MS, quantitative SC-MRI indices change over a median follow-up period of 2 years, likely reflecting ongoing pathological processes. Of clinical relevance is that subject-specific trajectories of SC-MRI index change are relevant to disability at follow-up, suggesting that individual dynamics of change should be assessed in the interpretation of longitudinal SC-MRI measures, and to expand the practical utility of these techniques.

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Comparison and Correlation of Two Proposed PML Risk Stratification Biomarkers for Long-term Natalizumab Treatment, Anti-JCV Antibody Index and L-selection (CD62L): A Retrospective Study

Nicholas Schwab; Tilman Schneider-Hohendorf; Johanna Breuer; Antia Posevitz-Fejfar; Heinz Wiendl, MD; Anita Posevitz-Fejfar, PhD

OBJECTIVE: To compare and correlate PML risk stratification parameters during natalizumab therapy including the assessment of their relationship. **BACKGROUND:** Long-term treatment with and the presence of anti-JCV antibodies in serum is associated with the risk to develop-induced PML. Recent data suggest that the level of anti-JCV antibodies in serum (JCV antibody index>0.9) and/or the lack of L-selectin (CD62L) on cryopreserved CD4+ T cells (%CD62L+ cells of CD4+ T cells<16) could be biomarkers for higher PML risk. **DESIGN/METHODS:** Up to 1612 patients (number depending on data set completion) were analyzed for CD62L and JCV antibody index. Patient cohorts were grouped according to age, previous immune-suppression (IS), or JCV seropositivity and subsequently correlation between the two risk parameters 1) JCV index and 2) CD62L value was assessed. **RESULTS:** There was no difference in JCV antibody index, CD62L value, or age when patients were grouped according to their previous IS. CD62L and JCV antibody index only correlated in patients not previously IS (n=226; p=0.02). Risk stratification with the two markers alone set 54.2% at risk (JCV index>0.9), 66.5% (JCV index>0.9 and IS JCV+ patients), or 6.6% (CD62L<16). Synergy of the two markers reduced the percentage of patients at risk in our cohort (n=273) to 4.4%. **CONCLUSIONS:** This data set suggests a statistical correlation between CD62L and JCV index, indicating a possible biological link between the two parameters. However, this link only exists without previous IS, which is in line with the observation that IS patients do not have higher JCV indices before developing PML. For patients with previous IS CD62L therefore seems favorable for risk stratification. For non-IS patients, the presented correlation and synergy between the two markers might have implications for the research of biological mechanisms leading to PML and can also help to further individualize risk stratification in long-term natalizumab patients.

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Perception of Analgesia in Narcotic Users with Chronic Pain: A Multi-Center Cross-Sectional Study Comparing Genotype to Pain VAS (P.A.I.N. Study)

Tobore Onojjighofia, MD; Brian Meshkin; Si Van Nguyen, MD; Dan Schwartz, MD; Bilikis Akindele, MD; John Hubbard; Derrick Holman, MD; Juetong Chen

OBJECTIVE: To evaluate whether genotype can help objectively stratify patient perception of pain among chronic pain patients taking narcotics. **BACKGROUND:** Various studies have explored modalities for objectively evaluating pain perception, including functional MRI and genotype. In this study, researchers evaluated 2721 patients from 48 clinical sites and conducted a cross-sectional analysis of genotype with Pain VAS. **DESIGN/METHODS**: Subjects diagnosed with chronic pain and currently taking prescription opioid pain medications were genotyped using a RealTime PCR TaqMan assay from Proove Medical Laboratories (Irvine, CA). The following single nucleotide polymorphisms (SNPs) were evaluated: COMT (Rs4680), DRD2 (Rs1800497), DRD1 (Rs4532), and OPRK1 (Rs1051660). All 2721 patients completed a Pain VAS rating their perception of pain on a scale from 0 to 10. Subjects with no pain (Pain VAS) were excluded from the study. Low pain perception was defined as a score of 1, 2 or 3 (n=249, 9.2%). Moderate pain perception was defined as a score of 4, 5, or 6 (n=1259, 46.2%). High pain perception was defined as a score of 7, 8, 9 or 10 (n=1,213, 44.6%). A multinomial logistic regression analysis was performed using SPSS. **RESULTS:** The DRD1 variant was found to be more prevalent in the low pain perception population compared to high pain perception population ($p<0.043$, OR 1.334 PPV 84.44 %.) Among subjects with a moderate pain perception, the COMT and OPRK variants were more prevalent compared to those with high pain perception (COMT: $p<0.007$, OR 1.25 PPV: 52.41%, OPRK: $p<0.032$, OR 1.19, PPV 51.09%). Among subjects with a high pain perception, the DRD2 variant was more prevalent compared to subjects with moderate pain perception ($p<0.041$, OR 1.25, PPV 52.61%). **CONCLUSIONS**: This retrospective analysis provides a potential genotypic analysis to stratify pain perception, and a more objective method to define subjective Pain VAS perceptions.

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CGRP Monoclonal Antibody LY2951742 for the Prevention of Migraine: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study

David Dodick, MD; Peter Goadsby, MD, PhD; Egilius Spierings, MD,PhD; Joel Scherer, MD; Steven Sweeney; David Grayzel, MD

OBJECTIVE: We evaluated the efficacy and safety of LY2951742, a fully humanized monoclonal antibody to Calcitonin Gene Related Peptide for migraine prevention. **BACKGROUND:** Migraine remains poorly treated with few effective preventive medications available. **DESIGN/METHODS:** Subjects with 4-14 migraine headache days (MHD) per month were enrolled in a double-blind, randomized, 12-week placebo-controlled trial of biweekly subcutaneous injections of LY2951742 (150 mg) versus placebo. The primary endpoint was the change in number of MHD per 28 day period assessed at 12 weeks; secondary end points were the change in headache days, migraine attacks, and responder rate. **RESULTS:** A total of 217 subjects were randomized and received LY2951742 (107) or placebo (110). The mean change in MHD at 12 weeks when compared to baseline was -4.2 (62.5% decrease) vs. -3.0 (42.3% decrease) for LY2951742 and placebo respectively ($p<0.003$). LY2951742 was superior to placebo for all secondary endpoints including headache days -4.9 vs. -3.7 ($p<0.0117$), migraine attacks -3.1 vs. -2.3 ($p<0.0051$), and responder rate 70% vs. 45% (OR 2.88 [CI 1.78 to 4.69]). An exploratory endpoint of complete responders (100% reduction in MHD) was 33.3% vs. 17.3% for LY2951742 and placebo respectively. Adverse events seen more frequently with LY2951742 than placebo included injection site pain, upper respiratory tract infections, and abdominal pain. **CONCLUSION:** In subjects with frequent migraine headache, treatment with LY2951742 resulted in a significant decrease in the number of migraine headache days, headache days, and migraine attacks when compared to placebo. LY2951742 was safe and well tolerated. The safety and robust efficacy results in this study are promising and justify the conduct of larger, randomized, placebo-controlled, phase 3 studies and the expression of cautious optimism that a new era of mechanism-based migraine prevention is beginning.

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Randomized, Double-blind, Placebo-controlled Trial of ALD403, an anti-CGRP peptide antibody in the prevention of frequent episodic migraine

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OBJECTIVE: To evaluate the efficacy and safety of ALD403, a genetically engineered humanized anti-CGRP antibody (IgG1), for migraine prevention. **BACKGROUND:** Calcitonin gene-related peptide (CGRP) is crucially involved in the pathophysiology of migraine. **DESIGN/METHODS:** Patients with 5 to 14 migraine days per month were randomized to receive a single intravenous dose of ALD403 1000mg or placebo in a double-blind fashion. The primary endpoint was the mean change in frequency of migraine days from baseline to migraine days during to weeks 5-8. Patients were followed for 24 weeks for additional safety and efficacy analyses **RESULTS:** Of 174 patients randomized, 163 patients received either ALD403 (81) or placebo (82). There were no significant differences in baseline demographics or characteristics between the two treatment groups. The mean change in migraine days between weeks 5-8 and baseline was -5.6 days (66% decrease) for ALD403 vs. -4.6 days (52% decrease) for placebo (one-sided $p = 0.03$). The proportion of patients with a 50%, 75%, and 100% reduction in migraine days at 12 weeks for ALD403 and placebo was 60% vs 33% ($p < 0.001$); 32% vs 9% ($p < 0.001$); and 16% vs 0% ($p < 0.001$), respectively. There were no differences in the type or frequency of adverse events, vital signs, or laboratory safety data between the two treatment groups **CONCLUSIONS**: A single intravenous dose of ALD403 1000mg demonstrated efficacy for the preventive treatment of migraine in patients with a high monthly frequency of migraine days. ALD403 was generally safe and well tolerated. These results support the conduct of larger randomized, placebo-controlled studies and may potentially represent a new era in disease-specific and mechanism-based preventive therapy for migraine.

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