of Alzheimer's disease (AD). IVIG contains conformation-selective anti-amyloid antibodies and has immunomodulatory properties of potential relevance to treating AD. To better understand IVIG's mechanisms of action in AD, we measured plasma cytokine levels of AD subjects enrolled in a Phase 2 placebo-controlled IVIG clinical trial. We hypothesized that IVIG treatment alters cytokines involved in the inflammatory neuropathology of AD. **Methods:** 24 subjects with mild to moderate AD (MMSE 14-26) were randomly assigned to receive either placebo or Gammagard IVIG at one of four doses. Plasma samples were obtained prior the first infusion and one week after the month 6 infusion. A panel of 31 plasma cytokines was assayed using the Luminex platform. Evaluable data was obtained from 22 of 24 enrolled subjects. Every plasma sample was assayed twice and replicates were averaged. The significance of changes between baseline and six months was determined by t-test. Correlation analysis was used to explore relationship between cytokine alterations and clinical outcomes. **Results:** The expression of nine cytokines increased significantly following IVIG treatment compared to placebo including IL-1A, IL-4, IL-5, IL-6, IL-8, IL-13, GCSF, EGF and VEGF. Increases in 3 other cytokines (IL-17, MIP-1A and IL-12P70) trended towards significance. The magnitude of the cytokines changes varied with the dose of IVIG administered. Increases in IL-5 and IL-8 best correlated with 6 month cognitive, behavioral and functional outcomes while increases in IL-13 and GCSF correlated with the global outcome (CGIC). **Conclusions:** IVIG administration to AD patients for six months resulted in significant increases in 9 of 31 plasma cytokines tested. Since IVIG does not contain cytokines, these changes likely represent the immunologic consequences of IVIG treatment. Changes in three pro-inflammatory (Il-5, IL-8, GCSF) and one anti-inflammatory (IL-13) cytokine correlated with clinical outcomes at 6 months. These molecules are associated with TH-2 type immune responses. Although sample size was limited, this study provides evidence that plasma cytokines are altered in AD by chronic immunoglobulin administration. Immunomodulation by cytokines may be part of the therapeutic mechanism of action of IVIG in AD.

O4-06-02 EFFECTS OF HUMAN INTRAVENOUS IMMUNOGLOBULINS ON AMYLOID PATHOLOGY AND INFLAMMATION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

Lakshman Puli, Yuriy Pomeshchik, Malm Tarja, Jari Koistinaho, Heikki Tanila, *University of Eastern Finland, Kuopio, Finland.*

Background: Human intravenous immunoglobulin (hIVIG) preparation is indicated for treating several immunodeficiency disorders associated with impaired humoral immunity. hIVIG has been hypothesized to confer beneficial effects in Alzheimer's disease (AD). Here, we set out to determine the effects of hIVIG treatment on amyloid pathology and inflammation in vivo in APP/PS1 mouse model of AD. **Methods:** Four month old female APP/PS1 mice received weekly i.p injections of hIVIG (Gammagard, Baxter A/G) or saline for 8 months. At the end of treatment period mice brains were rapidly retrieved with one hemibrain fixed in 4% paraformaldehyde for immunostaining and the other hemibrain along with fresh serum samples were frozen to -70°C for biochemical assays of soluble and insoluble Aß40 and Aß42 species. Human IgG was detected with rabbit anti-human IgG HRP antibody. Human specific anti- Aß antibody (WO2) was used to visualize amyloid deposits. CD45, Iba-1a, GFAP, CD-68 antibodies were used for visualizing and quantifying glia-associated pathology. **Results:** Human IgG was able to penetrate into the mouse brain, and human IgG opsonization of amyloid deposits was noticed in both cortex and hippocampus. However,this opsonization did not induce any changes in amyloid plaque burden in hippocampus, except a biochemically detectable elevation in soluble Aß40 and Aß42 levels. Also, serum Aß40 levels did not change, indicating the absence of peripheral sink mechanism. Most immunohistochemical markers for inflammatory changes including GFAP, CD68 and Iba-1a did not change due to hIVIG treatment. However, we noticed a 30% decrease in hippocampal CD45 immunoreactivity in hIVIG treated group ($p = 0.0041$). More work related to RT-PCR analysis of inflammatory genes, and confocal analysis of CD45 positive microglial cells is underway. **Conclusions:** We found no evidence for a peripheral sink or microglia mediated clearance of amyloid load after hIVIG treatment. However, hIVIG altered soluble Aß40-42 levels and suppressed subset of microglial cells positive for CD45 antigen. These immunomodulatory effects of hIVIG may account for its beneficial effect in AD patients.

O4-06-03 EVIDENCE ON THE ABILITY OF MOLECULAR CHAPERONES TO BIND AND NEUTRALIZE TOXIC PROTEIN OLIGOMERS AND MOLECULAR INSIGHT INTO THEIR MECHANISM OF ACTION

Fabrizio Chiti, *Università di Firenze, Firenze, Italy.*

Background: Protein aggregation is an underlying feature of Alzheimers's disease and is a complex process where a number of smaller protein oligomers form both during the process of protein aggregation or as products released from the fibrils. **Methods:** We have tested the effect of five molecular chaperones, namely Hsp70, aB-crystallin and the three known extracellular chaperones (clusterin, aptoglobin and a2-macroglobulin) on the toxicity of pre-formed misfolded oligomers by the amyloid b peptide as well as other model proteins. The suppression of oligomer toxicity by the chaperones was monitoredby measurables of cell viability, including the MTT reduction test, the detection of intracellular ROS, calcium influx, calcein release and caspase-3activity. **Results:** All chaperones were found to be effective in suppressing the toxicity of all types of toxic oligomers. Such an effect was found to be chaperone-dependent, as lysozyme and albumin were not ineffective. It was also found to be oligomer-dependent, as the chaperones did not suppress the toxicity of other stress-inducers, such as hydrogen peroxide. Importantly, the chaperones were found to significantly decrease oligomer toxicity even at 1:500 or 1:1000 chaperone: protein molar ratio, with the effect disappearing only at 1:2000 molar ratio. The ThT-binding of the preformed oligomers was not affected by the chaperones, indicating that the oligomers are not disassembled. The chaperones did not change the pyrene fluorescence at three critical positions within preformed HypF-N oligomers (involved in the difference between toxic and non-toxic oligomers), indicating that the chaperone did not cause a structural reorganization of the oligomers. Analyses performed with dot-blot assays, SDS polyacrylamide gel electrophoresis, intrinsic fluorescence and atomic force microscopy indicated binding between the oligomers and the chaperones, with subsequent clustering of the oligomersto form larger species. This suggests that the chaperone shield the reactive surfaces on the oligomers and promote their assembly. **Conclusions:** Overall the data present evidence on the generic ability of chaperones to bind and neutralize preformed toxic oligomers even at very low concentration. They offer molecular insight into their mechanism of action and put forward methods based on the exploit of chaperones as a basis for the design of novel therapeutics.

O4-06-04 IMPROVED COGNITIVE FUNCTION FOLLOWING TREATMENT OF ALZHEIMER'S PATIENTS WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) INTERLACED WITH COGNITIVE LEARNING TREATMENT

Jose Rabey, Evgenia Dobronevsky, Revital Gendelman Marton, Sergio Aichenbaum, Michael Khaigrecht, *Assaf Harofeh Medical Center, Zerifin, Israel.*

Background: Transcranial magnetic stimulation (TMS) is a technique for noninvasive painless brain stimulation. It generates a small electric current in the brain that induces, if applied repetitively (rTMS), amodulation in brain cortical excitability. rTMS has been explored as apotential novel therapeutic tool for different neuropsychiatric conditions. Early positive encouraging results of an open study with AD patients have been previously

published (Journal of Neural Transmission, 2010). The objective of this study was to test the efficacy of using the Non Invasive Cortical Enhancement (NICE®, Neuronix Ltd., Israel) System, which provides rTMS interlaced with cognitive training (rTMS-COG), for the treatment of Alzheimer's disease (AD) patients compared with a sham device (double blind design) **Methods:** Twelve mild to moderate AD patients (6 treatment, 6control), [DSM-IVR criteria; Mini Mental Status Examination (MMSE) of 18 to 24], were recruited. Treatment patients were subjected to 30 daily sessions of rTMS while simultaneously performing COG tasks (45 minutes duration each; 6 weeks), followed by bi-weekly maintenance sessions for 3 more months. Six cortical brain regions (selected in each patient by brain MRI), were stimulated. COG was specifically developed according to the regions stimulated. Control patients followed the same potocol while exposed to a sham device. Treatment effects were assessed using: Alzheimer's Disease Assessment Scale - Cognitive (ADASCog (primary outcome), Alzheimer's Disease Assessment Scale - Activities of Daily Living (ADAS ADL), MMSE and Clinical Global Impression of Change scale (CGIC). **Results:** ADAS-cog results showed average improvements of -4.5points after 6 weeks in the treatment group compared to -0.87 in the control group and -3.93 points after 4.5 months in the treatment group compared to -0.12 in the controls ($p = 0.06$ and $p = 0.09$ respectively). Results showed baseline dependence in the treatment group ($r = 0.8$). No side effects were reported, and patient compliance remained high throughout the study). CGIC results of treatment patients at 6 weeks were 3.4 and controls 4.4, while at 20 weeks results of treatment patients were 3.6 and controls 4.6 and controls 4.6. **Conclusions:** Based on the above results, rTMS-COG (the NICE® system) seems to offer a valuable tool for the treatment of cognitive functions in ADpatients.

O4-06-05 PF-04447943: A PHASE II CONTROLLED CLINICAL TRIAL OF A SELECTIVE PDE9A INHBITOR IN ALZHEIMER'S DISEASE

Elias Schwam[1], Rebecca Evans[1], Timothy Nicholas[1], Robert Chew[1], Wendy Davidson[1], Darlene Ambrose[2], Larry Altstiel[1], *[1]Pfizer Inc, Groton, Conn, United States; [2]ExecuPharm Inc, Wethersfield, Conn, United States.*

Background: PF-04447943 is a potent, selective phosphodiesterase-9A (PDE9A) inhibitor that elevates cGMP in brain and CSF. PDE9A inhibition enhances synaptic plasticity and improves memory in preclinical cognition models, and prevents decreases in dendritic spine density in Tg2576 mice. PF-04447943 was well-tolerated in healthy young and elderly subjects in single and multiple dose Phase 1 studies. This multicenter study was designed to assess the efficacy, safety and PK of PF-04447943 in mild to moderate probable AD. **Methods:** Subjects 55-85 years old in overall good health with MMSE scores of 14-26 were randomized to 12 weeks treatment with PF-04447943 25 mg q12h ($n = 91$) or placebo ($n = 100$). Most mild, chronic stable conditions and concomitant medications not expected to adversely affect cognition, behavior or PK were permitted except cholinesterase inhibitors and memantine. The primary outcome was the ADAS-cog. The Neuropsychiatric Inventory (NPI) and Clinical Global Impression-Improvement scale (CGI-I) and standard safety measures were secondary outcomes. These outcomes and PK sampling were performed at 3 week intervals. **Results:** Baseline characteristics were similar between groups: both 64% female, mean age 74 and mean MMSE 20-21; percent mild AD 55% (PF-04447943) vs 49% (placebo); percent ApoE4 carriers 59% (PF-04447943) vs 51% (placebo). Mean ADAS-cog (21-22) and NPI scores (11-12) were also similar. Completion rates were similar, 87% PF-04447943 vs 92% placebo. At week 12 the mean baseline-adjusted decrease from baseline in the ADAS-cog was -1.91 vs -1.60 respectively. The corresponding values for the NPI were -2.86 vs -2.70. Neither these changes nor the distribution of CGI-I scores were statistically significantly different between groups. The incidence of serious AEs was similar between groups with 2 deaths in the placebo group. The PF-04447943 group reported more gastrointestinal AEs including diarrhea (5.5 vs 3%) and nausea (5.5 vs 1%) and had a higher rate of discontinuation due to AEs (6.6 vs 2%). **Conclusions:** Although generally safe and well-tolerated, 12 weeks PF-04447943 treatment did not improve cognition, behavior, and global change compared with placebo in these subjects with mild to moderate AD.

O4-06-07 IMAGING AND CEREBROSPINAL FLUID BIOMARKER RESULTS OF A PHASE II DOSE-RANGING STUDY OF ELND005 (SCYLLO-INOSITOL) IN MILD-TO-MODERATE ALZHEIMER'S DISEASE

Anton Porsteinsson[1], Reisa Sperling[2], Stephen Salloway[3], Ron Keren[4], Christopher van Dyck[5], Pierre Tariot[6], Douglas Arnold[7], Gerald Crans[8], Ramon Hernandez[8], Earvin Liang[8], Menghis Bairu[8], Jesse Cedarbaum[9], Aleksandra Pastrak[10], Susan Abushakra[8], *[1]University of Rochester Medical Center, Rochester, N.Y., United States; [2]Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Boston, Massachusetts, United States; [3]The Warren Alpert Medical School of Brown University, Providence, Rhode Island, United States; [4]University Health Network Memory Clinic, Toronto, Ontario, Canada; [5]Departments of Psychiatry and Neurobiology, Yale University School of Medicine, New Haven, Connecticut, United States; [6]Banner Alzheimer's Institute, Phoenix, Arizona, United States; [7]NeuroRx Research, Montreal, Quebec, Canada; [8]Elan Pharmaceuticals, Inc., South San Francisco, California, United States; [9]Cytokinetics, Inc., South San Francisco, California, United States; [10]Transition Therapeutics, Toronto, Ontario, Canada.*

Background: ELND005 (scyllo-inositol) is being investigated as a potential disease modifying oral agent for the treatment of Alzheimer's disease (AD). ELND005 inhibits aggregation of beta-amyloid (Abeta) and decreases plaque burden intransgenic TgCRND8 mice (McLaurin et al., 2006). In addition to clinical outcomes, this study investigated the effects of ELND005 on volumetric MRI measures (vMRI) and cerebrospinal fluid (CSF) biomarkers. **Methods:** Of 353 mild/moderate patients randomized to ELND005 (250, 1000, or 2000mg) or placebo twice daily for 78weeks, 351 received study drug. Brain ventricular volume (VV) was designated as the key imaging biomarker; exploratory endpoints included whole brain volume, average hippocampal volume, and cortical ribbon thickness. MRIs were performed in all patients at baseline and every 24 weeks. CSF samples from a subset of patients at baseline, 24 weeks, and 78 weeks were tested for Aß40, Aß42, tau, and p-tau_{181} levels. All primary anaylses were performed using a mixed-effects model repeated measures analysis. **Results:** After elective discontinuation of the 2 high-dose groups due to safety findings, the primary analysis compared the 250mg and placebo groups. In the overall population, the VV increase at week 78 was greater for ELND005 than placebo (VV increase of $3.2cm^3$;$p = 0.049$; $n = 84/82$ in 250mg/placebo), while other brain volume measures were not significant. In mild patients, who showed a positive trend on this study's primary cognitive endpoint (Salloway et al, submitted), the VV increase of $0.3cm^3$ was not significant. In mild/moderate patients, CSF biomarker changes were not significant at 24 weeks, but CSF Aß42 was significantly decreased at 78 weeks ($p = 0.009$, $n = 19/14$ in 250 mg/placebo), other CSF biomarker changes were not significant. **Conclusions:** Patients treated with ELND005 250mg demonstrated a significant decrease in CSF Aß42 levels and a small, but significant,increase in ventricular volume after 78 weeks of treatment. Similar MRI findings have been reported in clinical trials with other amyloid-targeted therapies. The time course of CSF Aß42 reduction may reflect a gradual decrease in brain amyloid pathology, consistent with the effects of scyllo-inositol in transgenic mice.

O4-06-08 SAFETY AND TOLERABILITY OF BMS-708163 IN A PHASE II STUDY IN MILD-TO-MODERATE ALZHEIMER'S DISEASE

Stephen Salloway[1], Vlad Coric[2], Mark Brody[3], Niels Andreasen[4], Christopher van Dyck[5], Hilkka Soininen[6], Stephen Thein[7], Thomas Shiovitz[8], Sandeep Kumar[9], Gary Pilcher[10], Susan Colby[2], Linda Rollin[2], Howard Feldman[2], Robert Berman[2], *[1]Butler Hospital, Providence, R.I., United States; [2]Bristol-Myers Squibb, Wallingford, Connecticut, United States; [3]Brain Matters Research, Delray Beach, Florida, United States; [4]Karolinska Universitetssjukhuset Huddinge, Stockholm, Sweden; [5]Yale University School of Medicine, New Haven,*