the naturalhistory of small vessel diseases, evaluated in a large cohort of postmortem brains from the Newcastle Institute for Ageing and Health (Newcastle University, UK). This provides a score from 0 to 20 (no to severe vascular burden) and is in good agreement previous neuropathological standards. Nevertheless, the clinical relevance of this score has not yet been evaluated, and this was this study's aim. **Methods:** Post mortem AD brains from Lille Neurobank (Lille, France) were scored according this cerebrovascular scale, blinded to clinical and neuroimaging data. Patients had been prospectively followed up with a standardized clinical examination, neuropsychological tests, and structural brain imaging. Correlation with the clinical diagnosis of vascular contribution, age at onset, disease duration, imaging white matter lesions visual scoring scale (Fazekas et al. 1987), vascular risk factors, Mini Mental State Examination score and Dementia Rating Scale score at first visit were analyzed with non-parametric tests. **Results:** Eleven patients were included. Four of them had a neuropathological cerebrovascular score < 10, all these 4 patients were clinically diagnosed as pure AD. Six of the 7 patients with a score $= 10$ were considered to have no significant cerebrovascular contribution to their dementia. Higher scores were associated with a longer disease duration ($p = 0.05$) andtended to be associated with a higher Fazekas score. **Conclusions:** There is an urgent need to establish a reproducible and standardized quantitative assessment of the cerebrovascular burden in post mortem brains. In this small study, we used an original neuropathological cerebrovascular staging system which seems to be relevant enough to identify the clinical and imaging correlates of the cerebrovascular burden in clinicopathological series. In this limited number of cases, the clinical contribution of cerebrovascular lesions was largely underestimated. Further inclusions are needed to confirm our findings.

P4-005 QUANTITATION OF BETA-AMYLOID IN TRANSGENIC MICE USING WHOLE SLIDE DIGITAL IMAGING AND IMAGE ANALYSIS SOFTWARE

Robert Dunstan, Thierry Bussiere, Diana Fahrer, Catherine Quigley, Xueli Zhang, Marian Themeles, Tom Engber, Ken Rhodes, Mahim Arastu, Mingwei Li, *Biogen Idec Inc., Cambridge, Massachusetts, United States.*

Background: Defining the effects of biological manipulation on beta-amyloid in mouse models requires quantifying treatment-induced changes. The gold standard remains microscopic quantitation of beta-amyloid in histologic sections; however, there is no consistency how this is performed. This presentation describes methods for defining the area of vascular and parenchymal beta-amyloid in transgenic mice. **Methods:** Methods were established on Tg2576 mice. All sections used formalin-fixed, paraffin embedded tissues sectioned at 5um. Sectioning focused on capturing both the cortex and the hippocampus and for each brain, 300 consecutive sections were produced. An immunohistochemical (6E10) and histochemical stain (thioflavin-S) defined the presence of beta-amyloid. Staining with 6E10 antibody used diaminobenzidine and Fast Red as chromogens. Slides were scanned on an Aperio XT. Thioflavin S staining was performed by hand and slides were scanned on an Aperio FL. Images were hand-annotated to define the cortex and hippocampus and analyzed using algorithms to separate tissue from non tissue, and vascular from parenchymal plaques. **Results:** Critical analysis of the methods to quantify beta-amyloid demonstrated four major areas of variability:1) variation in tissue processing; 2) variation in pipetting; 3) chromogen (use of Fast Red is preferred to distinguish melanosis from brown DAB staining of beta amyloid); and 4) poor focus of scanned image. In order to use the same algorithm throughout large studies, it was necessary to critically review all slides, scanned images and processed images. In general, bright field images were easier to define the area of interest but more difficult to differentiate vascular amyloid from parenchymal plaques. **Conclusions:** Inter-animal variability requires that large numbers of animals be used to define a biological effect in amyloid reduction studies. Thus, whole slide digital imaging and sophisticated image analysis software represent a major improvement in efficient and consistent quantification of beta amyloid in tissues. However, this is not a"set it and forget it process" and requires constant review during all stages to produce consistent results. In our experience, the quality of the scanners and the software to quantify morphologic changes on these digital images are associated with much less variability than the slides being evaluated.

P4-006 THE ROLE OF BRAIN MACROPHAGES ON THE CLEARANCE OF AMYLOID PLAQUES FOLLOWING THE TREATMENT OF TC2576 WITH BIIB037

Robert Dunstan[1], Thierry Bussiere[1], Tom Engber[1], Paul Weinreb[1], Marcel Maier[2], Jan Grimm[2], Ken Rhodes[1], Mahim Arastu[1], Mingwei Li[1], Xueli Zhang[1], [1]*Biogen Idec Inc., Cambridge, Massachusetts, United States;* [2]*Neurimmune, Schlieren, Switzerland.*

Background: Effective passive immunotherapy of anti-beta amyloid antibodies with effector function might require antibody Fc domain-mediated brain macrophage activation with subsequent phagocytosis of Abeta. Herein we report that BIIB037, a murine chimeric antibody with Fc effector function, appears to require brain macrophage activation for amyloid plaque clearance. **Methods:** BIIB037, a murine chimeric IgG2a that recognizes a conformational epitope to human, fibrillar Abeta was administered intraperitoneally to Tg2576 mice and compared to PBS-treated controls. The area and morphology of vascular amyloid and parenchymal plaques and changes in brain macrophage area and distribution were assessed with immunohistochemistry. Defining Abeta in vessels and parenchymal plaques used the mouse anti-human Abeta monoclonal antibody 6E10. Brain macrophages were defined by a rabbit anti-macrophage polyclonal antibody to ionized calcium-binding adaptor molecule-1 (IBA-1). Samples were examined visually and quantified using Visiopharm software. **Results:** Treatment with BIIB037 resulted in amyloid reduction. Amyloid plaques in treated animals were less abundant and smaller than in controls. In addition, the plaques were generally discrete,consisting of a circular dense core. Many of the plaques in untreated animals were "multicored" and surrounded by more diffuse amyloid material. In both treated and controls,brain macrophages adjacent to parenchymal plaques were more densely distributed and larger than those scattered randomly throughout the neuropil, suggesting Ab caused a state of macrophage activation regardless of treatment. However, brain macrophages in treated animals often encircled the plaques and were less dendritic. In neither treated nor controls was the number or size of macrophages increased around leptomeningeal vessels. **Conclusions:** Treatment with BIIB037 results in amyloid load reduction and the plaques present have a different morphology than controls: they are smaller and rounder, often consisting of dense cores of Abeta. These cores are often ringed by brain macrophages, a feature rarely noted in the brains from treated animals. This pattern suggests amyloid load reduction is associated with phagocytosis in BIIB037 treated animals. Finally, the paucity of activated macrophages around vessels suggest that BIIB037 does not affect vascular amyloid in leptomeningeal vessels.

P4-007 ASSOCIATION BETWEEN NEUROPATHOLOGICAL FEATURES OF ALZHEIMER'S DISEASE AND DEMENTIA IN THE VERY OLD VERSUS THE YOUNG OLD

Jose Farfel[1], Lea Grinberg[2], Renata Ferretti[1], Renata Leite[1], Claudia Suemoto[1], Carlos Pasqualucci[1], Ricardo Nitrini[1], Wilson Jacob-Filho[1], [1]*University of Sao Paulo, Sao Paulo, Brazil;* [2]*University of California San Francisco, San Francisco, California, United States.*

Background: A recent study by Middleton & Colleagues demonstrated a less predictive role of neuropathological features towards the diagnosis of Alzheimer's disease (AD) in the oldest-old compared to the young-old.

Although a large population was evaluated in this study, the diagnosis of AD was gathered exclusively through clinical information and neuropathological features typical of vascular and Lewy bodies dementia were included in the analysis. The objective of the current study was to examine whether the association between neuropathological features related to AD and dementia varies in the very-old group (age = 80 years) compared to the young-old group (age = 79 years). **Methods:** A post-mortem study evaluating individuals = 60 years, included in the Brazilian Aging Brain Study. Cognitive evaluation was gathered with a semi-structured interview with the next of kin informant using the CDR and the IQCODE. Individuals were classified as cognitively normal if the CDR = 0 and the IQCODE < 3.20 and as demented if the CDR = 2 and the IQCODE > 3.80. Neuropathological examinations were carried out based on accepted criteria, using immunohistochemistry. All subjects were classified according to Braak & Braak staging, CERAD and the NIA-RI criteria. ROC analysis were preformed to evaluate the predictive value of each neuropathological feature in both intervals of age. **Results:** We examined 360 individuals. Of the participants 52.5% were female, 66.4% were classified as CDR = 0, 12.5% as CDR = 2 and other 21.1% as CDR = 3 and 41,1% were = 80 years. The relationship between AD-type neuropathological features and dementia were not different among the Young-old compared to the very-old group. Braak & Braak staging was considered the most predictive feature in both groups (ROC area under the curve 0.75, 0.61-0.89, $p < 0.01$ for the very-old and 0.73, 0.52-0.93, $p = 0.04$ for the young-old group). The NIA-RI (ROC area 0.59, 0.43-0.73 and 0.67, 0.46-0.87 for the very-old and young-old, respectively) and the CERAD criteria (ROC area 0.53, 0.36-0.70 and 0.66, 0.45-0.87 for the very-old and young-old, respectively) did not reach statistical significance as predictors. **Conclusions:** Neruopathological features related to AD demonstrate the same predictive value for dementia in the very-old compared to the young-old. Braak & Braak staging is the most predictive neuropathological feature in both groups of age.

P4-008 LIVING LONGER WITHOUT ALZHEIMER'S DISEASE: A NEUROPATHOLOGICAL STUDY OF THE INDIVIDUALS AGED ≥ 90 YEARS.

Jose Farfel[1], Lea Grinberg[2], Renata Ferretti[1], Claudia Suemoto[1], Renata Leite[1], Carlos Pasqualucci[1], Ricardo Nitrini[1], Wilson Jacob-Filho[1], *[1]University of Sao Paulo, Sao Paulo, Brazil; [2]University of California San Francisco, San Francisco, California, United States.*

Background: The oldest old (≥90 years) are the fastest growing demographical population. However there are few neuropathological studies in this group and many clinicians keep the concept that Alzheimer's disease (AD) is a paradigm of longevity. Studies including oldest old individuals focus on demented individuals but fail to characterize the healthy individuals who spare clinical and neuropathological features of AD. The objective of the current study is to characterize the oldest old free of cognitive impairment and of neurofribrillary tangles and neuritic plaques and to compare demographical, clinical, neuropathologic data and apoE genotype between nonagenarians and octogenarians. **Methods:** A post-mortem study evaluating individuals, aged 80 years or older, included in the Brain Bank of the Brazilian Aging Brain Study from University of Sao Paulo. Cognitive evaluation was gathered with a semi-structured interview with the next of kin informant using the Clinical Dementia Scale (CDR) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Subjects were classified as cognitively normal if the CDR = 0 and the IQCODE < 3.20 and as demented if the CDR ≥ 2 and the IQCODE > 3.80. Neuropathological examinations were carried out based on accepted criteria, using immunohistochemistry. Alzheimer's disease was diagnosed if the subject presented moderate or high likelihood for AD base in the NIA-RI criteria. ApoE genotyping was performed in subgroup of patients (10 nonagenarians and 46 octogenarians randomly selected). **Results:** Twenty-five individuals ≥ 90 years were included, mean age 93.3 years (90-102 years), being 64% females. From this sample, 44.0% were free of clinical and neuropathological features of AD. A total of 121 individuals of 80 to 90 year were included, mean age 83.7 (80-89 years), being 64.2% females and 45.5% were totally free of AD There were no differences between the two groups regarding gender ($p = 0.98$), education ($p = 0.37$), systemic hypertension ($p = 0.97$), diabetes ($p = 0.27$), presence of microinfarcts ($p = 0.23$), hyaline atherosclerosis ($p = 0.31$), prevalence of AD-related neuropathological features through the fulfillment of moderate and high likelihood criteria of the NIA-RI ($p = 0.85$). There was significant differencea between the groups regarding the presence of apolipoprotein e4 (37% in octogenarians and 0% in nonagenarians, $p = 0.03$). **Conclusions:** There is no difference in the prevalence of AD between octogenarians and nonagenarians. Nonagenarians may present a favorable genetic profile protecting them against dementia and balancing the effects of aging.

P4-009 DECREASE OF PTEN EXPRESSION LEVELS AMONG NORMAL, SYMPTOMATIC AND ASYMPTOMATIC ALZHEIMER'S DISEASE (AD) SUBJECTS, MEASURED IN HIPPOCAMPUS, TEMPORAL AND ENTORHINAL CORTICES.

Ana Cecília Feio dos Santos[1], Aderbal Silva[1], Lea Grinberg[2], Jose Farfel[3], Renata Ferretti[4], Maria Dirlei Ferreira Begnami[1], Rafael Rocha[1], Fernando Soares[1], Helena Brentani[4], *[1]A C Camargo Hospital, São Paulo, Brazil; [2]UCSF, San Francisco, California, United States; [3]University of Sao Paulo, São Paulo, Brazil; [4]University of São Paulo Medical School, São Paulo, Brazil.*

Background: PTEN negatively regulates intracellular levels of PIP3 and antagonizes the PI3K signaling pathway important for tumor suppressor, modulating cell apoptosis. In hippocampus, PTEN deficiency causes defects in synaptic structure and plasticity. In AD brain, recent studies showed decreased levels and altered distribution of PTEN along with, suggesting that a loss of PTEN contributes to neurodegeneration in AD. **Methods:** This study measured distribution of PTEN in postmortem human brain tissue (hippocampus - H, entorhinal - EC andtemporal cortices - TC) through the tissue microarray technique. We compared three groups: symptomatic AD (sAD) -with dementia and AD pathology; asymptomatic AD (asAD) - with AD pathology but without dementia; and normal elderly subjects (N) - without dementia and AD pathology, accounting 61 subjects. Asemi-quantitative analysis was employed. Statistical analysis was performed by chi-square. **Results:** Statistically significant decrease was found when we analyzed samples by absence/presence of AD pathology, in all brain regions together (Normal versus sAD+asAD)($x^2 = 29.97$ and p-value <0.0001), and analyzing the regions separately (EC - $x^2 = 14.00$ and p-value = 0.003; and H - $x^2 = 13.13$ and p-value = 0.004). However, nostatistically difference in PTEN levels was found at TC ($x^2 = 5.911$ and p-value = 0.116). When we analyzed separated by absence/presence of dementia (aAD versus sAD) statistical difference was found ($x^2 = 16.62$ and p-value = 0.0008) at all regions, and at TC ($x^2 = 10.81$ and p-value = 0.012), but no at EC ($x^2 = 6.881$ and p-value = 0.075) and H ($x^2 = 3.39$ and p-value = 0,334). At 42.5% of TMA cores showed prominent cytoplasmatic staining, but there was not statistical difference. **Conclusions:** Publications on the role of PTENin AD are still controversial. Our results corroborates some papers in the literature that showed decrease in PTEN levels when we analyzed samples by absence/presence of AD pathology (Normal vs sAD+aAD). Literature have no previous data that have measured and compared PTEN levels in asymptomatic ADindividuals, and the differences found when individuals were separated by the absence/presence of dementia (aAD versus sAD) is an unpublish 2nd data. Others authors showed decreasing PTEN levels in EC, TC and H. Regarding the cytoplasmatic immunoreactivity, this localization is in agreement with data from other studies reporting that PTEN is ubiquitously expressed in CNS and is both nuclear and cytoplasmatic.