S4-04 HOT TOPICS 2
WEDNESDAY, JULY 15, 2009
10:30 A.M. – 12:30 P.M.

S4-04-01 FRONTOTEMPORAL DEMENTIA WITH FUS PATHOLOGY

Ian R. Mackenzie[1], Manuela Neumann[2], Rosa Rademakers[3], David G. Munoz[4], *[1]University of British Columbia, Vancouver, BC, Canada; [2]University Hospital of Zürich, Zurich, Switzerland; [3]Mayo Clinic, Jacksonville, FL, USA; [4]St. Michael's Hospital, Toronto, ON, Canada*

Background: Frontotemporal dementia (FTD) is a clinical syndrome with heterogeneous molecular basis. Although the neuropathology associated with most FTD is characterized by abnormal cellular aggregates of either TDP-43 or tau protein, there remains a significant subgroup (~ 15%) characterized by ubiquitin-immunoreactive (ub-ir) inclusions that are negative for both tau and TDP-43. Missense mutations in the gene encoding the *fused in sarcoma* (FUS) protein (also known as *translated in liposarcoma*, TLS), on chromosome 16, have recently been identified as a cause of familial amyotrophic lateral sclerosis (ALS). The associated pathology is described as including neuronal inclusion bodies that are immunoreactive for FUS (FUS-ir) but negative for TDP-43. **Objective:** Because of the recognized clinical, genetic and pathological overlap between ALS and FTD, we investigated the possible role of FUS in FTD. **Methods:** Immunohistochemistry, double label immunofluorescence, immunoblotting, and molecular genetic analysis. **Results:** In all cases, FUS immunohistochemistry (IHC) demonstrated normal physiological staining of neuronal nuclei and cytoplasm and some glial nuclei. No FUS-ir pathology was identified in cases of FTD with TDP-43 or tau pathology, or TDP-43-positive ALS. However, in a significant proportion of cases with tau/TDP-43-negative FTD, FUS IHC labeled neuronal cytoplasmic and intranuclear inclusions of similar morphology, number and anatomical distribution as were demonstrated with ubiquitin IHC. The co-localization of FUS and ubiquitin in neuronal inclusions was confirmed with double label immunofluorescence. Neurons that contained inclusions retained at least some normal physiological FUS staining. FUS IHC also demonstrated previously unrecognized inclusions in glial cells. The pathological changes were demonstrated with multiple antibodies that recognize different epitopes across the entire FUS protein. Immunoblot analysis confirmed increased amounts of insoluble FUS in post-mortem brain tissue from these cases. All cases of FTD with FUS pathology were sporadic and molecular genetic analysis did not identify any mutations in the *FUS* gene or abnormal levels of *FUS* mRNA expression. **Conclusion:** These findings suggest that FUS is the pathological protein in a significant subgroup of sporadic FTD and reinforce the concept that FTD and ALS are closely related conditions.

S4-04-02 OVEREXPRESSION OF WILD-TYPE TDP-43 LEADS TO MOTOR NEURON DEGENERATION AND SPASTIC QUADRIPLEGIA IN GERMLINE TRANSGENIC MICE

Samir Kumar-Singh, Hans Wils, Gernot Kleinberger, Jonathan Janssens, Ivy Cuijt, Geert Joris, Christine Van Broeckhoven, *Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, University of Antwerp, Antwerp, Belgium*

Background: Missense mutations in the TDP-43 gene (TARDBP) have been associated with familial and sporadic amyotrophic lateral sclerosis (ALS). Furthermore, in the majority of ALS patients, with or without TARDBP mutations, TDP-43 aggregates as neuronal nuclear and cytoplasmic inclusions in affected brain regions. **Objective:** To generate and study transgenic mouse lines stably expressing human wild-type TDP-43 (hTDP-43). **Methods:** Multiple transgenic mouse lines were generated by pronuclear injection of hTDP-43 cDNA under the control of mouse Thy-1 promoter. Mice lines were analyzed for transgene expression, and were biochemically, histologically and behaviorally characterized. **Results:** We show here, in two transgenic mouse lines, that overexpression of hTDP-43 leads to a dose-dependent degeneration of specific neurons in the central nervous system, including motor neurons, and to spastic quadriplegia. The affected brain and spinal cord regions showed accumulation of full-length hTDP-43, a small proportion of which was also phosphorylated. In addition, we also observed carboxy-terminal hTDP-43 fragments that are currently implicated as the pathological substrates in TDP-43-mediated neurodegeneration. **Conclusion:** These data offer a novel ALS mouse model to study TDP-43 mediated neurodegeneration. Also, because copy number variations (CNV) such as gene duplications/triplications of the amyloid precursor protein gene (APP) or the alpha-synuclein gene (SNCA) have been shown to lead to familial forms of Alzheimer's or Parkinson's disease, our data also prompt for genetic screening of ALS patients for TARDBP CNVs or promoter polymorphisms.

S4-04-03 NONINVASIVE DETECTION OF α-SYNUCLEIN DEPOSITS IN HUMAN BRAIN USING [^{11}C]BF227-PET

Nobuyuki Okamura[1], Akio Kikuchi[1], Atsushi Takeda[1], Shozo Furumoto[1], Manabu Tashiro[2], Katsutoshi Furukawa[3], Hiroyuki Arai[3], Yasuto Itoyama[1], Ren Iwata[2], Kazuhiko Yanai[1], Yukitsuka Kudo[4], *[1]Tohoku University School of Medicine, Sendai, Japan; [2]CYRIC, Tohoku University, Sendai, Japan; [3]Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan; [4]Innovation of New Biomedical Engineering Center, Tohoku University, Sendai, Japan*

Background: α-synuclein is a main component of Lewy bodies and glial cytoplasmic inclusions in α-synucleinopathy. However, no biomarker exists that can non-invasively detect α-synuclein deposits in human brain. **Objective:** The purpose of this study is to evaluate amyloid imaging probe [^{11}C]BF-227 as an agent for in vivo detection of α-synuclein deposits in the brains of α-synucleinopathy. **Methods:** In vitro binding of BF-227 to α-synuclein was examined using human brain sections and α-synuclein fibrils. Human PET study using [^{11}C]BF-227 was performed in 8 multiple system atrophy (MSA) patients and 3 dementia with Lewy bodies (DLB) patients, and compared with the study in 6 normal controls and 8 Alzheimer's disease (AD) patients. After intravenous injection of 211-366 MBq of [^{11}C]BF-227, dynamic PET images were obtained for 60 min with arterial blood samplings. Logan graphical analysis was applied to quantify the distribution volume (DV) and the ratio of the regional to cerebellar DV (DVR) of BF-227 in the brain using metabolite-corrected radioactivity in arterial plasma as input functions. **Results:** In vitro study indicated the binding ability of BF-227 to Lewy bodies and glial cytoplasmic inclusions in brain sections of DLB and MSA patients. In human PET study, DLB patients showed a tendency to accumulate BF-227 in the neocortex in a similar fashion to that we see in AD. BF-227 PET study in MSA patients further demonstrated significantly higher DV in the putamen than normal controls. MSA patients additionally showed higher DVR in the caudate, putamen, globus pallidus, substantia nigra, and primary motor cortex than normal controls and AD patients. **Conclusion:** These findings strongly suggest that [^{11}C]BF-227 have a potential to non-invasively detect α-synuclein deposits in the human brain.

S4-04-04 CLINICAL PRACTICES REGARDING MILD COGNITIVE IMPAIRMENT (MCI) AMONG NEUROLOGY SERVICE PROVIDERS

Scott Roberts[1], Wendy Uhlmann[1], Ronald Petersen[2], **Jason Karlawish**[3], Robert C. Green[4], *[1]University of Michigan, Ann Arbor, MI, USA; [2]Mayo Clinic, Rochester, MN, USA; [3]University of Pennsylvania, Philadelphia, PA, USA; [4]Boston University Schools of Medicine and Public Health, Boston, MA, USA*

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Background: MCI is a research categorization that is entering clinical practice, but little is known about how it is being used. **Objective:** To assess how neurologists are diagnosing and treating patients with mild cognitive symptoms and how they view MCI as a clinical diagnosis. **Methods:** Members of the Geriatric and Behavioral Neurology sections of the American Academy of Neurology (AAN) were surveyed by the AAN Survey Department via mail and Internet. **Results:** Four hundred twenty providers (response rate = 48%) completed the survey. 88% reported at least monthly encounters with patients experiencing mild cognitive symptoms. Most respondents recognize MCI as a clinical diagnosis (90%) and use its diagnostic code for billing purposes (70%). When seeing this population, most respondents report routinely making recommendations for monitoring and follow-up (88%), counseling patients on physical (78%) and mental exercise (75%), and communicating about risk of dementia (63%). Relatively few respondents routinely provide information on support services (27%) or a written summary of findings (15%). Most (70%) prescribe cholinesterase inhibitors at least sometimes for this population, with memantine (39%) and ''other'' agents (e.g., vitamin E, gingko) prescribed less frequently. Respondents endorsed several benefits of making a clinical diagnosis of MCI: 1) labeling the problem is helpful (91%); 2) involving the patient in planning for the future (86%); 3) motivating the patient's risk reduction activities (85%); 4) helping the family with financial planning (72%); and 5) prescribing medications useful for treating MCI (65%). Some respondents noted potential drawbacks of MCI as a clinical diagnosis, including 1) it is too difficult to diagnose accurately or reliably (23%); 2) it is usually better described as early AD (21%); and 3) a diagnosis can cause unnecessary worry (20%). **Conclusion:** Patients with MCI are commonly seen by neurologists and prescribed various medications to address their symptoms. The MCI concept is generally viewed as a useful diagnostic category in clinical practice. Clinicians vary significantly in the education and support they provide or recommend for MCI patients, suggesting a need for practice guidelines in this area. Future research is needed to illuminate decision-making around MCI treatment. Funding source: Alzheimer's Association

S4-04-05 PBT2 FOR PRE-DEMENTIA ALZHEIMER'S DISEASE: ANIMAL AND CLINICAL EVIDENCE

Ashley I. Bush[1], Robert A. Cherny[1], David Finkelstein[1], Colin L. Masters[1], Rudolph E. Tanzi[2], Kevin J. Barnham[3], Craig Ritchie[4], Paul A. Adlard[1], *[1]Mental Health Research Institute, Parkville, Victoria, Australia; [2]Massachusetts General Hospital, Charlestown, MA, USA; [3]Bio21 Center, Parkville, Victoria, Australia; [4]Imperial College, London, United Kingdom*

Background: PBT2 is a zinc ionophore that restores cognitive performance and decreases interstitial brain Aβ in APP transgenic mice within days (1). A Phase IIa study for mild AD demonstrated a reduction in CSF Aβ42 with improved Executive Function performance within 12 weeks (2). The speed of these improvements suggested that PBT2 may also be correcting other aspects of synaptic dysfunction in early stage disease, such as the trans-synaptic movement of zinc. Presynaptic zinc is concentrated by ZnT3 and released with glutamate, and ZnT3-/- x Tg2576 progeny fail to develop amyloid pathology. The therapeutic relevance of zinc/copper ionophores such as PBT2 to prevent Aβ oligomers being attracted to zinc at glutamatergic synapses has been demonstrated with clioquinol (3). **Objective:** To investigate how PBT2 could be effective in early stage disease. **Methods:** We tested PBT2 on aged and cognitively impaired wildtype mice (C57Bl/6) with no amyloid burden. PBT2 treatment caused an almost complete normalization of Morris water maze performance within 11 days (ANOVA $p < 0.001$). Young mice were unaffected. We found that cortical ZnT3 levels fall with aging in humans and mice, which could inhibit the trans-synaptic movement of zinc. We hypothesised that amyloid may trap synaptic zinc, preventing it from reaching post-synaptic targets that mediate cognition such as TrkB, NMDAR, ZnR and p75(NTR) receptors. To test this, we studied ZnT3-/- mice and found that the cognitive aging phenotype is markedly accelerated in them, but that treatment with clioquinol (a PBT2 analogue) restores these deficits within 6 weeks. Levels of NR2A, NR2B and AMPA, which were decreased in the ZnT3-/- brain, were normalized with the treatment. **Conclusion:** Collectively these findings indicate that PBT2 can both decrease amyloid load, and as an ionophore be capable of restoring zinc homeostasis leading to an improvement in synaptic function. These data further support the prospect for effective treatment in Alzheimer's Disease.

S4-04-06 DIMEBON®: A CLINICALLY PROMISING DRUG FOR ALZHEIMER'S DISEASE, REGULATES AMYLOID-BETA METABOLISM IN CULTURED CELLS, IN ISOLATED NERVE TERMINALS, AND IN THE INTERSTITIAL FLUID OF THE LIVING RODENT BRAIN

Sam Gandy[1,2], John Cirrito*[3], John Steele*[1], Soong Ho Kim*[1], Gopal Thinakaran[4], David Westaway[5], Paul Fraser[6], Peter St George Hyslop[6], Mary Sano[1,2], Ilya Bezprozvanny[7], Michelle E. Ehrlich[1], David M. Holtzman[3], *[1]Mount Sinai School of Medicine, New York, NY, USA; [2]James J Peters VA Medical Center, Bronx, NY, USA; [3]Washington University, St Louis, MO, USA; [4]University of Chicago, Chicago, IL, USA; [5]University of Alberta, Edmonton, AB, Canada; [6]University of Toronto, Toronto, ON, Canada; [7]University of Texas Southwestern, Dallas, TX, USA*

Background: Recent evidence indicates that the retired Russian antihistamine Dimebon® (dimebolin) improves cognitive function in aged rodents and in humans suffering from mild to moderate Alzheimer's disease (AD). A recent screen against a set of biochemical targets indicated that Dimebon® inhibits alpha-adrenergic receptors (alpha-1A, alpha-1B, alpha-1D, alpha-2A), histamine H1 and H2 receptors, and serotonin 5-HT 2c, 5-HT 5A, and 5-HT 6 receptors with high affinity (Wu et al., Molec Neurodeg, 2008, 3: 15doi:10.1186/1750-1326-3-15). Dimebon® has also been shown to modulate Ca2+ flux, apoptosis, and mitochondrial stability. **Objective:** Given the clinical benefit, and given the known modulation of A-beta metabolism by neurotransmitters and by mitochondrial function, we assessed the ability of Dimebon® to modulate levels of APP metabolites including A-beta in a series of in vitro and in vivo experimental systems. **Methods:** Under control conditions or following Dimebon® treatment, we measured A-beta levels in either: (1) the conditioned media of SweAPP-overexpressing cultured N2a mouse neuroblastoma cells; (2) the releasate from isolated nerve terminals from TgCRND8 mice overexpressing Swe/Indiana APP, or (3) the interstitial fluid (ISF) of the brains of freely moving Tg2576 SweAPP-overexpressing transgenic mice. **Conclusion:** Acute treatment with Dimebon® increased A-beta levels in the releasate from TgCRND8 nerve terminals and in the ISF of freely moving Tg2576 transgenic mice. In media conditioned by SweAPP N2a cells overnight in the presence of drug, Dimebon® either had no effect on A-beta or lowered A-beta. Since questions have been raised regarding the nature of Dimebon® preparations, we performed these studies using Dimebon® from two independent vendors; both gave similar results. Elevation of A-beta release from isolated nerve terminals and elevation of ISF A-beta levels are unexpected phenomena to associate with a clinically beneficial AD drug. Further study is required to elucidate the molecular mechanism underlying the acute regulation of A-beta metabolism by Dimebon®. Chronic Dimebon® exposure also merits study. Dimebon® may be a useful chemical probe for advancing our understanding of the role of A-beta in AD and for identifying unexplored druggable mechanisms in the molecular pathogenesis of AD. *These authors contributed equally. Supported by Cure Alzheimer's Fund and National Institute on Aging.

S4-04-07 BACE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Johanna Fälting, Jan Neelissen, Fredrik Jeppson, Anki Radesäter, Susanna Eketjäll, Peter Söderman, Britt-Marie Swahn, Biljana Georgievska, *AstraZeneca R&D, Södertälje, Sweden*

Background: Beta-site amyloid precursor protein cleaving enzyme (BACE) and its homologue BACE2 are type I transmembrane aspartic acid proteases.