THE 2015 ALZHEIMER'S DISEASE CONGRESS
ABSTRACTS

23rd - 25th June 2015
London, UK

EuroSciCon
This three day event will discuss aspects of Alzheimer’s Disease development and treatment in an informal academic setting. Topics for discussion include prediction and prevention strategies, vaccine development, drug discovery and care. With plenty of opportunity for networking and debate, this informal international meeting will bring you up to date with current research and thinking regarding Alzheimer's Disease.

This event has CPD accreditation

This abstract book will be finalised two weeks before the event
www.regonline.co.uk/Alz2015
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Oral Inflammation, Tooth Loss, Risk Factors, and Association with Progression of Alzheimer’s Disease

Dr Sim K. Singhrao, Oral & Dental Sciences Research Group, School of Medicine & Dentistry, University of Central Lancashire, Preston, UK

Periodontitis is a polymicrobial chronic inflammatory disease of tooth-supporting tissues with bacterial etiology affecting all age groups, becoming chronic in a subgroup of older individuals. It is the periodontal pathogenic bacteria that are implicated in the development of a number of inflammatory pathologies at remote organ sites, including Alzheimer’s disease (AD). The periodontal pathogens contribute to a source of low-grade, chronic infection and inflammation that follow daily episodes of bacteremia arising from everyday tasks such as brushing, flossing teeth, chewing food, and during dental procedures, but they also disseminate into the brain from closely related anatomical pathways. The long-term effect of inflammatory mediators, pathogens, and/or their virulence factors, reaching the brain systemically or otherwise would, over time, prime the brain’s own microglia in individuals who have inherent susceptibility traits. This eventually leads to a vicious cycle of sustained local inflammatory milieu resulting in the loss of cytoarchitectural integrity and vital neurons with subsequent loss of function (deterioration in memory).

Eye-drops of G-CSF Gene Ameliorate Brain Function in Preclinical Neurological Disorder

Dr Philip K. Liu, PhD, AA Martinos Center for Biomedical Imaging, Massachusetts General Hospital and the Harvard Medical School, Charlestown, MA, USA

Gene therapy has been used in clinical trial for neurodegenerative disorders. However, no meaningful assay has been appropriate to track its delivery, uptake and expression without biopsy. Granulocyte colony-stimulating factor (G-CSF) stimulates growth and differentiation of myeloid precursors; which has been proposed to treat neurodegenerative disorders. We have developed non-invasive methods to deliver, track its uptake and expression of human cDNA of G-CSF in preclinical models. Eye drop delivery of human G-CSF cDNA in ScAAV-type 2 adeno-associated virus after global brain ischemia in C57black6 mice lead to significant improvements in mortality rates, cerebral atrophy and neurological deficits; these observations including in vivo tracking of viral cDNA uptake and expression employed translatable magnetic resonance imaging (MRI). When facing a corner, C57black6 mice show 50% of left or right turn; mice after cerebral ischemia show 100% turn to one direction. Gene therapy of hG-CSF ameliorates such bias turn. Such approach should have applications as an effective treatment to reduce brain damage. We will discuss non-invasive thanrosanics approach to preclinical model of neurodegerative disorders.

Genome Damage/Repair Imbalance as a Common Basis in Neurological Diseases

Dr Muralidhar Hegde, Assistant Professor, Houston Methodist Hospital Research Institute, Houston, Texas, United States

Accumulation of genome damage including oxidized bases, single- and double-strand breaks, in affected brain cells has been linked to neurodegenerative diseases whose underlying cause(s) are not completely understood. We recently demonstrated that transition metals iron and copper that accumulate in neurodegenerative brain act as a double-edged sword by both increasing oxidative genome damage and preventing their repair and thus could play a role in accumulation of unrepaired genome damage in neurons leading to cell death (Hegde et al, J Biol Chem 2010: 285, 28812-25). Here, we provide evidence for the first time that RNA binding protein TDP-43, whose nuclear clearance and simultaneous cytoplasmic deposition is a hallmark feature in Amyotrophic Lateral Sclerosis (ALS) and other neurodegenerative diseases, is required for efficient DNA double strand break repair (DSBR) in neurons.

These results are consistent with the dramatic accumulation of unrepaired DSBs in postmortem brains of ALS-affected human patients and a distinct nuclear clearance of TDP-43 in these affected neurons. Thus deficiency in DNA strand break repair may be a key etiologic factor in neurodegenerative diseases. (Supported by Alzheimer’s Association and Muscular Dystrophy Association)

Is Alzheimer’s disease (AD) infectious?

Professor Frank O. Bastian, MD, Professor of Animal Science, LSU Agricultural center, Baton Rouge, LA & Professor of Pathology, Tulane Medical School, New Orleans, LA, US

Recent data suggest AD is infectious, although AD has not been transmitted. Creutzfeldt-Jakob disease (CJD), a human transmissible spongiform encephalopathy (TSE), is a bacterial infectious disease model for AD. Spiroplasma, a tiny wall-less bacterium, has been detected in CJD brains by morphological and molecular studies. Spiroplasma have been isolated into cell-free media from TSE-affected brains. Spiroplasma induce neurodegenerative brain disease in rodents and ruminants, with TSE-like...
neuropathology. Spiroplasma induce biofilm formation, wherein they produce curl fibers that transform host proteins into amyloid, explaining the prion phenomenon. Spiroplasma produce alpha-synuclein in tissue cultures indicating another link to the human neurodegenerative diseases.

**Alterations in the trafficking of the Amyloid Precursor Proteins result in endo-lysosomal defects and neuronal decline**

**Associate Professor Carmela Matrone**, Ph.D., Dept. of Biomedicine, Aarhus University, Aarhus, Denmark

Despite intense research efforts, the physiological function and molecular signaling of the Amyloid Precursor Protein (APP) have remained enigmatic. Emerging evidence indicates a pilot role for Y682 on the C-terminal Y682ENPTY687 domain of APP in regulating APP trafficking and signaling via its specific binding to adaptors. Herein, we describe how the Y682G mutation impacts the physiological trafficking and processing of APP, leading to neuronal deficits and premature decline. This new information on the function of the Y682ENPTY687 domain in the physiology of APP paves the way for potential therapeutic strategies.

**The emerging epidemic of dementia in Indigenous Australians**

**Associate Professor Robert Parker**, Director of Psychiatry, Top End Mental Health Services, Northern Territory Australia

Recent surveys have identified a significantly increased prevalence of dementia in Indigenous Australians with a prevalence of three times the rest of the Australian population. Reasons for this epidemic will be discussed.

**Tau promotes synaptic dysfunction in AD**

**Professor Alain Buisson**, Neuroscience, Université Joseph Fourier Grenoble, La Tronche, France

Tau is a microtubule-associated protein well-known for its stabilization of microtubules in axons. Recently, it has emerged that tau participates in synaptic function as part of the molecular pathway leading to Aβ-driven synaptotoxicity in the context of Alzheimer's disease (AD). In this presentation I will discuss of the physiological implication of tau in the profound functional synaptic modification associated with synaptic plasticity. I will also highlight how Human synthetic Aβ oligomers (Aβo) induced mislocalization of tau into the spines under resting conditions and abrogated subsequent activity-dependent synaptic tau translocation. In summary, I will promote the idea that tau synaptic role is a key event toward synaptotoxicity in neurodegenerative diseases.

**Oral Presentation Abstracts**

**THE BIOLOGICAL UNDERPINNING OF THE TOMM40 POLY-T: EFFECTS OF ALTERING TOM40 PROTEIN EXPRESSION ON MITOCOCHONDRIAL FUNCTION**

William Gottschalk\(^1\), Ornit Chiba-Falek\(^1\), Michael W. Lutz\(^1\), Kahlil Zeitlow\(^1\), Mirta Mihovilovic\(^1\), Allen D. Roses\(^1,2\),

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Mitochondrial dysfunction contributes to the etiology of many neurodegenerative diseases, including late-onset Alzheimer's disease (LOAD), ALS, Down syndrome, Huntington's disease, and Parkinson's disease. The causes of mitochondrial dysfunction in these diseases, and how it contributes to the pathogenesis of each is a matter of profound interest. A variable length deoxothymidine homopolymer, rs10524523 (hereinafter '523'), located within intron 6 of the TOMM40 gene (Chr 19:44,899,792 – 44,899,826, human genome reference assembly GRCh38/hg38) is a risk factor for LOAD and age of onset of LOAD\(^1\). The poly-T length alleles are categorized as Short (S: T ≤ 19 residues), Long (L: ≤ 20 T ≤ 29) or Very Long (VL: T ≥ 30). In Caucasians, APOE e4 is linked, predominantly, with the '523' L allele. In APOE e3/e4 subjects, in which APOE e4 is linked to the L allele and the VL or S is linked to APOE e3, the VL allele is associated with earlier age of LOAD onset than the S allele\(^1,2\). The e3/VL haplotype is also associated with impaired memory performance\(^3,4\) and reduced gray matter volume in regions that are affected early in AD\(^3\). Recently, we showed the VL allele is associated with greater TOMM40 and APOE gene expression than the S allele in human brain regions vulnerable to AD\(^5\).

TOMM40 encodes the main import channel through which nuclear encoded, cytoplasmically translated mitochondrial proteins enter mitochondria. We hypothesize the TOMM40 '523' poly-T modulates mitochondrial function through its effects on TOM40 protein expression, and the VL allele leads to relatively more mitochondrial dysfunction than the S allele. To test this hypothesis we compared three HeLa cell lines stably over-expressing human flag-tagged TOM40 (TOM cells), with control HeLa C cells transfected with a vector encoding only the selection marker. Levels of TOM40 in TOM M, TOM C8 and...
TOM C5 lines were ca. 2.3, 1.8 and 1.2X higher, respectively, than in HeLa C cells. Cell doubling times were lower in HeLa C cells than in TOM cells. The mitochondrial outer membrane proteins TOM20, TOM70 and VDAC were higher in TOM Cells than in controls, as were levels of OXPHOS complex I (inner membrane) and α-oxoglutarate dehydrogenase (matrix). By contrast, COX levels were the same in TOM and HeLa C cells. ROS levels were modestly higher in TOM M cells than in HeLa C cells following continuous exposure to 25 mM glucose. Twenty-four hours after shifting cultures from 25 mM to 5 mM glucose, ROS levels were elevated further in TOM M but not in HeLa C cells. Under basal conditions, TMRM fluorescence was ca. 30% higher in the TOM C8 over-expressing cells than in HeLa C cells but ATP levels were ca. 1.5-fold higher in the controls than in TOM C8 cells. Basal respiration rates in HeLa C cells were the same as those in TOM M and TOM 08 cells, and all three lines were equally sensitive to stimulation by FCCP and inhibition by oligomycin. When assayed at their respective FCCP EC_{50}'s, respiration rates were greater in TOM cells than in the HeLa C cells, and HeLa C cells were more sensitive to inhibition by rotenone (IC50s, mean, (95% CI), HeLa C, -7.74 (-7.8 - -7.62); TOM C8, -6.83 (-7.17 - -6.49); TOM M, -7.00 (-7.68 - -6.33)).

REFERENCES:

INTERNET-BASED INTERVENTIONS TO REDUCE DEMENTIA CAREGIVER BURDEN: A SYSTEMATIC REVIEW
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ABSTRACT

Background: Caregiving for dementia patients places a high burden of responsibility on informal caregivers which can negatively impact their quality of life. Interventions that directly support caregivers have been shown to reduce psychological distress and improve caregiver well-being and quality of life. Technology-based interventions have been increasingly developed and studied to reduce caregiver burden and help overcome access barriers to interventions due to the demands of caregiving. As part of a larger systematic review to assess the effectiveness of Internet-based interventions to reduce caregiver stress, we describe here the results relevant to dementia caregiving.

Methods: A systematic review was conducted using MEDLINE, EMBASE, PSYCINFO, and CINAHL using search terms caregiver and Internet-based interventions with open label or randomized controlled trial designs. All articles were independently reviewed by two investigators. Descriptive data for studies related to dementia caregivers are presented.

Results: Of 24 trials meeting study criteria, we identified 6 studies designed for dementia caregivers, including 3 open label and 3 randomized controlled studies. Internet-based interventions ranged from passive (online information, webcast sessions) to active (discussion boards, chat rooms, workshops, text) to face-to-face interaction (videoconference). All studies report positive results and improved outcomes for caregivers.

Conclusions: Internet-based interventions for dementia caregivers show promising strategies to reduce caregiver stress and burden. Further studies are needed to determine which interventions are most feasible and applicable to dementia caregivers.
Vascular mechanisms are increasingly recognized as important contributors to the Alzheimer's disease pathogenesis with rising identification of mixed pathologies, most commonly Alzheimer's disease and cerebral infaracts. Hypertension is one of the major risk factors for both cerebrovascular and Alzheimer's disease. We developed a mouse model of Alzheimer's disease associated with hypertension that reproduces more faithfully the human pathology. For this, we infused hypertensive doses of angiotensin II into transgenic APPPS1 mice overexpressing mutated human amyloid precursor and presenilin 1 proteins. We found that at 4.5 months, at the early stage of disease progression, only hypertensive APPPS1 mice presented impairment of temporal order memory performance in the episodic-like memory task. This cognitive deficit was associated with an increased number of cortical amyloid deposits (223 ± 5 vs 207 ± 5 plaques/mm², P < 0.05) and a two-fold increase in soluble amyloid levels in the brain and in plasma. We showed that early vascular alteration accompanies the neurological impairment in hypertensive APPPS1 mice. Indeed, we found a 25 % reduction in cerebral microvessel density, a 30 - 40 % increase in cerebral vascular amyloid deposits and a decrease in VEGF-A expression in the brain, compared to normotensive APPPS1 mice, as well as an impaired cerebral vasoreactivity in response to carbon dioxide. Moreover, the brain levels of nitric oxide synthase 1 and 3, and the nitrite/nitrate levels were reduced in hypertensive APPPS1 mice (by 49%, 34% and 33%, respectively, compared to wild type mice; P < 0.05). Our results indicate that hypertension-mediated impairment of vascular function may contribute to a faster development of neuropathology and cognitive deficit in hypertensive APPPS1 mice. This worsening of Alzheimer's disease-like pathology may not be attributable to the direct pro-inflammatory action of angiotensin II, as we found that gliosis and the production of pro-inflammatory cytokines have not been increased in hypertensive mice. Our results suggest that hypertension accelerates the development of Alzheimer's disease related structural and functional alterations without affecting significantly neuroinflammation.

NOVEL APTAMER TARGETED NEURON PRO SURVIVAL THERAPY IN ALZHEIMER'S DISEASE INTERVENTION

Joan Smith Sonneborn, Ph.D. Emeritus Professor Zoology & Physiology University of Wyoming, Laramie, Wyoming; 1226 E Curtis Street, 82072

Evolution of fundamental understanding of Alzheimer's disease (AD) pathology and effective intervention for prevention and treatment of AD is hampered by selective appropriate delivery vectors and unacceptable side effects. Aptamers (small molecule ligands or molecules with high affinity “specific” binding capacity) non-viral vectors can deliver therapeutic agents to AD markers, and avoid immune responses. Effective therapeutic anti-cancer and anti-infectious disease agents offer a reservoir for identification of gene expression interfering agents (like siRNA's and miRNA's) that can alter the path to cell death verses survival. Telomerase catalytic subunit protein TERT is a target molecule for therapy, as a master gene activator of pro-survival anti-aging pathways. However, in cancer and HIV, TERT has a dark side by protection against apoptosis of diseased cells, and TERT suppression is an effective therapeutic intervention, despite the unintended side effect of acceleration of aging. Targeted stimulation of pro-survival TERT expression in AD therapy offers therapy against βamyloid toxicity, AD neurofibrillary tangles, as well as protection of bystander neurons. Recent studies of others, using postmortem AD tissues, show that TERT localizes with mitochondria in AD hippocampal neurons. Those neurons expressing TERT did not show the pathological hyper phosphorylation of Tau (associated with AD tangles) or the increased ROS and oxidative damage found in TERT-deficient cells. Alternatively, aptamer-hormetic mimetic agents (small molecules that imitate environmental damage and stimulate pro-survival pathways in response to UV, exercise, or hibernation) offer another novel potential class of candidate AD therapeutic drugs.

BEHAVIORAL AND PSYCHOLOGICAL DISTURBANCES IN DEMENTIA

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OBJECTIVE
The purpose of this study was to evaluate behavioural and psychological symptoms associated in patients with dementia.
METHOD
We conducted a cross-sectional study in 30 patients from the Psychogeriatric and Psychiatric unit at the San Jorge’s Hospital. Neurodegenerative disease diagnoses included behavioral-variant frontotemporal dementia (n=14) (Rascovsky criteria), Alzheimer’s disease (n=12) (National Institute on aging and the Alzheimer’s Association Diagnostic Criteria); vascular dementia (n=3) (Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) with the Association Internationale pour la Recherche et l’Enseignement en Neurosciences NINDS-AIREN); Dementia with Lewy Bodies (DLB) (n=1) (Consortium on DLB Consensus Diagnostic Criteria).
All participants were assessed using the Functional assessment stages (FAST), Escala global del deterioro de Reisberg (GDS), Addenbrooke’s cognitive examination revised (ACE-R), Neuropsychiatric Inventory Questionnaire (NPI), Cambridge Behavioural Inventory Revised (CBI-R).

RESULTS
Half of the subjects were females; the medium age was 69.17 years. Most of them (30%) were in a moderate stage (GDS=5, FAST=4). According to the education of the patients 27% have secondary studies, 43% primary education, 27% minimum schooling and 3% illiterate. Most of them live in their own house (60%) and the rest in a residence (20%) or with their family (20%).
The marital status: 56% were married, 41% widower and 3% single. The media of the ACE-R was 32,46.
The results showed that the prevalence of neuropsychiatric symptoms (> or = 1 symptom) reported was 100%. The most common symptoms were Apathy (80%) and Agitation (76%), the least was Hallucinations (33,6%).
The results on the NPI in Alzheimer’s disease showed a higher prevalence of apathy and aberrant motor behaviour (66%) and depression (50%). In the Frontotemporal dementia all of them had agitation, anxiety and appetite and eating disorders (100%).
In the CBI-R the intensity is measure from 0 to 4, the results on Alzheimer’s disease showed higher intensity in everyday skills (2,97), memory and orientation (2,57) and motivation (2,28).
In Frontotemporal dementia the higher intensity of the symptoms was found in motivation (2,63), eating habits (2,07) and everyday skills (1,87). In vascular dementia were everyday skills (4), self-care (3,88) and motivation (2,80) and in DCL were everyday skills (4), self-care (4) and memory and orientation (2,25).

CONCLUSIONS
The Frontotemporal dementia had more neuropsychiatric symptoms than the other dementias specially their characteristic lack of motivation and eating disorders, the Alzheimer’s disease had more difficulty on the everyday skills, memory and orientation and high levels of apathy.
This study remarks the high prevalence of neuropsychiatric symptoms in dementia; therefore it is very important to diagnose this symptomatology by using valid scales such as NPI and CBI-R which takes in account the information that the family or carers provide and can help to improve the management and care of the patients.

THE SPECIAL PHOSPHOLIPIDS PLASMALOGENS, WHICH HAVE BEEN REDUCED IN THE ALZHEIMERS DISEASE PATIENTS, FACILITATE HIPPOCAMPAL-DEPENDENT MEMORY BY MAINTAINING BDNF SIGNALING
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The special ether phospholipids Plasmalogens (Pls) are characterized by the presence of a vinyl ether linkage at the sn-1 position. The ethanolamine plasmalogens (EhPls) was found to be highly expressed in the hippocampus but its role was mostly elusive. It has been reported that advanced Alzheimer’s disease (AD) patients have a reduction of brain Pls, suggesting a possibility that Pls might function in the memory. To assess this hypothesis, we have reduced Pls in the adult mice by delivering specific sh-RNA against the Pls synthesizing enzyme, GNPAT (glyceronephosphate O-acyltransferase), directly in the hippocampus. Morris water maze studies showed a significant (P<0.001) reduction of spatial memory in the Pls-reduced mice which was associated with the reduction of BDNF and other memory related gene expression (e.g., Synapsin-1, PSD-95, c-Fos, Homer-1, CamKIIa, and Synaptotagmin-1). To assess the mechanism, we have screened the localization of Pls in the cell extracts by LC-MASS assays and found a strong abundance in the hippocampal tissue lipid rafts. Interestingly, in vitro reduction of Pls in the neuronal cell strongly reduced BDNF signaling and addition of Pls enhanced this signaling by recruiting more TrkB (a BDNF receptor) in the lipid rafts. These evidences suggest for the first time that Pls in the neuronal cell membrane modulates TrkB localization to accelerate BDNF signaling to enhance memory and the reduction of Pls can reduce this memory signaling. Furthermore, we have found that Pls-diet for 8 weeks enhanced the spatial memory
significantly in the adult mice which was associated with the enhanced BDNF signaling in the hippocampus. Electrophysiology studies showed an enhanced LTP (Long term potentiation) from the CA3-CA1 neuronal fibers of Pls-diet hippocampus. In the same mice, Golgi-Cox staining showed a significant (P<0.01) increase of dendritic spines in CA3 and CA1 neurons. In consistence with the laboratory animal studies, the preliminary clinical studies showed an improvement of memory performance among the AD patients who received oral ingestion of Pls daily for 6 months. We therefore propose that dietary supplement of Pls can improve our memory by improving the BDNF signaling by a unique mechanism which can be beneficial in the AD patients.

ISORHYNCHOPHYLLINE IMPROVES LEARNING AND MEMORY IMPAIRMENTS INDUCED BY SCOPOLAMINE IN MICE
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Abstract
Objectives: The present study aimed to investigate whether isorhynchophylline (IRN), an alkaloid isolated from Chinese herb Uncaria rhynchophylla, could reverse scopolamine (SCOP)-induced learning and memory impairments in mice and to evaluate its action mechanisms.

Methods: The cognitive-enhancing effect of IRN on amnesic mice induced by SCOP was investigated by the Morris water maze test. To elucidate the underlying mechanisms of memory enhancing effects of IRN, the activity of acetylcholinesterase (AChE) and neuroinflammatory parameters were measured.

Results: The results showed that IRN significantly improved the learning and memory functions in SCOP-treated mice. Mechanistically, IRN significantly decreased the protein and mRNA levels of interleukin (IL)-1β and the activity of AChE, but markedly accentuated the protein and mRNA levels of IL-10 and the level of acetylcholine in the brain of the SCOP-treated mice. Moreover, IRN also significantly suppressed the production of prostaglandin E2 and mRNA expression of cyclooxygenase-2 while markedly enhanced the protein level of phosphorylation of ERK1/2 in the brain of the SCOP-treated mice.

Conclusions: These results amply demonstrated that IRN was able to improve the learning and memory impairments induced by SCOP in mice, and the underlying mechanisms involved the inhibition of AChE activity and the amelioration of the neuroinflammatory processes via protecting ERK activity in the mice with SCOP-induced cognitive impairments. IRN is a promising chemical warranting further development into anti-AD therapeutic agent.

Chemical structure of isorhynchophylline.

Poster Presentation Abstracts
Poster abstracts will be finalised weeks before the event

RELIABILITY AND VALIDITY OF A NEW BEHAVIORAL SCALE TO MEASURE BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS IN DEMENTIAS (BPSD): LUTHRA’S BEHAVIORAL ASSESSMENT AND INTERVENTION RESPONSE (LUBAIR) SCALE
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ABSTRACT

Objectives: To establish the reliability and validity of LuBAIR Scale. It is also hypothesized LuBAIR will be less labour intensive, more comprehensive as well as offer improved categorization of behaviors into clinically meaningful categories.

Methods: Seven (7) Long Term Care Facilities (LTCF) in Ontario, Canada, were selected for the study. One hundred twenty (120) residents with a diagnosis of dementia were recruited for the study. Sixty residents exhibiting BPSDs were included in the study group and sixty participants not displaying BPSDs were in the control group. Pittsburg Agitation Scale was used to screen for presence of BPSDs. Two registered nurses (RN) completed LuBAIR Scale, BEHAVE-AD, and Cohen-Mansfield Agitation Inventory (CMAI) for each participant in the study group. This was done to establish inter-rater, Construct and Criteria Validity. Fourteen days later, the same RN completed LuBAIR Scale again for each participant for intra-rater reliability. A Clinical Utility Survey (CUS) was developed to evaluate the nurses’ viewpoints on the usefulness of LuBAIR Scale on three variables: less labor intensive, more comprehensive and better categorization of behaviors in clinical meaningful categories.

Results: Intra-rater reliability was established for 8 of the 12 behavioral categories. Inter-rater reliability was established for 10 of the 12 behavioral categories. LuBAIR scale had comparable Construct and Criteria Validity. CUS findings showed 23% of nurses found the LuBAIR Scale to be less labor intensive, 77% found LuBAIR Scale to be more comprehensive and an overwhelming majority, 98%, agreed the LuBAIR Scale helps understand behaviors in a clinically meaningful way.

Conclusions: LuBAIR Scale has acceptable inter- and intra-rater reliability and Construct and Criteria Validity. It is more comprehensive and is better able to categorize behaviors in clinically meaningful categories.

Keywords: Behavioral and Psychological Symptoms in Dementias (BPSDs), Luthra’s Behavioral Assessment and Intervention Response (LuBAIR)

QUERTEIN ATTENUATES OA-INDUCED TAU PROTEIN HYPERPHOSPHORYLATION IN HT22 CELLS

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ABSTRACT

Alzheimer’s disease (AD) is a common neurodegenerative disease mainly characterized by abnormal tau protein hyperphosphorylation, which eventually caused the formation of neurofibrillary tangles (NFT). NFTs played an important part in the development of AD and significantly associated with cognitive impairments and memory loss. Therefore, hyperphosphorylated tau protein was more and more concerned as a potential therapeutic target. Quercetin (QUE), a flavonoid compound, widely existed in fruits and vegetables. In present study, we found for the first time QUE markedly decreased OA-induced tau protein phosphorylation in HT22 cells. The results suggested that OA-induced tau protein hyperphosphorylation were effectively ameliorated at Ser396, Ser199, Thr231 and Thr205 sites. Further study indicated that QUE could inhibit cdk5 kinase activity by calcium-calpain-p25-cdk5 signaling pathway, which played a crucial role in regulating the state of tau protein. On a whole, these findings demonstrated that QUE could effectively decreased tau protein hyperphosphorylation and then attenuated neurotoxicity. Summarily, these discoveries highlight that QUE is a great potential agent for AD and other neurodegenerative tauopathy.

AMYLOID BETA UPTAKE BY AGED HIV-1-INFECTED BRAIN: RELATIONSHIP TO ALZHEIMER’S-LIKE DEMENTIA

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Due to the success of combination antiretroviral therapy (cART) which changed the clinical picture of HIV infection from an acute to a chronic disorder, there is a sharp increase in infected patients 50 years old and older. This increase in age of the HIV infected population constitutes a new challenge in the HIV epidemic in the affluent countries. Older HIV infected patients are more susceptible to neurocognitive impairments associated with the disease. HIV infected brains are characterized by increased deposition of amyloid beta
We hypothesized that lipid rafts and functional caveolae are critical structures involved in HIV-1-induced Aβ accumulation at the BBB and in human brain microvascular endothelial cells (HBMEC). Both silencing caveolin-1 (cav-1) and disruption of lipid rafts by pretreatment with beta-methyl-cyclodextrin (MCD) protected against Aβ accumulation in HBMEC. Exposure to HIV-1 and Aβ activated caveolae-associated Ras and p38. While inhibition of Ras by farnesylthiosalicylic acid (FTS) effectively protected against HIV-1-induced accumulation of Aβ, blocking of p38 with SB203580 did not have this effect. We also evaluated the role of caveolae in HIV-1-induced upregulation of the receptor for advanced glycation end products (RAGE), which regulates Aβ transfer from the blood stream into the central nervous system. In control cultures, RAGE immunoreactivity showed a distinct cytoplasmic staining pattern that appeared to imitate an intricate intracellular linear network. A 24 h exposure to HIV-1 resulted in a markedly stronger RAGE immunoreactivity with more detailed ramification of this staining pattern. Exposure of HBMEC to HIV-1-infected or control monocytes also resulted increased RAGE mRNA levels. Importantly, HIV-1 induced increase in RAGE expression was prevented by infecting HBMEC with cav-1 specific shRNA lentiviral particles or by pretreatment of cells with FTS.

Aβ not only accumulates in the cytoplasm of HIV-exposed cells but also enters the nuclei of HBMEC. Inhibition of dynamin by dynasore effectively attenuated this event via the EEA1 and TGF-β/Smad signaling. To further explore the possible mechanisms involved, we performed cDNA microarray analysis in order to examine changes in the transcriptional profile associated with this phenomenon. Gene network analysis indicated that inhibition of nuclear entry of Aβ resulted in enrichment in gene sets involved in apoptosis and survival, endoplasmic reticulum stress response, immune response, cell cycle, DNA damage, oxidative stress, cytoskeleton remodeling and TGFβ receptor signaling.

Using transgenic mice that express a chimeric mouse/human amyloid precursor protein and a mutant human presenilin 1, we next demonstrated that cerebrovascular toxicity of HIV-specific protein Tat is enhanced in mice with amyloid deposits in the brain. Indeed, exposure to Tat increased permeability across cerebral capillaries, enhanced disruption of ZO-1 tight junction protein, and elevated brain expression of MMP-9 in transgenic mice as compared to age-matched littermate controls. These changes were associated with increased leukocyte attachment and their transcapillary migration.

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NEUROPROTECTIVE EFFECT OF ACETYL-11-KETO-BETA-BOSWELLIC ACID ON LIPOPOLYSACCHARIDE INDUCED COGNITIVE IMPAIRMENT IN MICE: POSSIBLE INVOLVEMENT OF ANTIINFLAMMATORY AND ANTIGLUTAMATERIC PATHWAYS

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Background: Alzheimer's disease (AD) is a disabling progressive neurodegenerative disorder characterized by impairment of cognitive and motor functions. The disease is characterized by neuroinflammation accompanied by defects in some neurotransmitters and abnormal aggregation of amyloid-beta peptide (Aβ) extracellularly. *Boswellia Serrata* is among the well known anti-inflammatory herbal treatments. Its anti-inflammatory characteristic arises mainly from the unique inhibition of 5-lipoxygenase (5-LOX) enzyme. AKBA (3-acetyl-11-keto-β-boswellic acid) is proven to be the most potent 5-LOX inhibitor.

Objective: The aim of the current study was to investigate the effect of AKBA on blocking the ongoing increase in the glutamate, tumor necrosis factor alpha (TNF-α) and Aβ levels. These parameters were assayed after the administration of celecoxib, AKBA, memantine and the combination therapy of AKBA and celecoxib on the cognitive impairment induced by LPS injection of lipopolysaccharide (LPS).

Methodology: Animals were divided into 6 groups; Group 1: Saline (0.9%, i.p) once. Group 2: LPS (0.8mg/kg, i.p) once. All of the following groups were preinjected LPS at the same dose. Group 3: celecoxib (30mg/kg, i.p) for 4 days. Group 4: AKBA (5mg/kg, i.p) for 4 days. Group 5: Memantine (15 mg/kg, i.p) for 3 days. Group 6: AKBA (5mg/kg, i.p) and celecoxib (30mg/kg , i.p), both for 4 days. Behavioral tests as radial maze, Y maze and novel object recognition (NOR) were performed to evaluate different types of cognitive changes. Molecular changes were assessed by ex-vivo studies through measuring glutamate and TNF-α levels. Furthermore, immunohistochemical test was done to evaluate the Aβ levels in the brain.
Results: All treated groups showed significant improvement in cognitive functions and a decrease in TNF-α, glutamate as well as Aβ levels compared to LPS treated group. AKBA as a combination therapy with celecoxib showed better memory retrieval over some monotherapies in radial maze test as well as NOR test. The combination also showed significant decrease in TNF-α and Aβ levels compared to AKBA, celecoxib and memantine groups.

Conclusion: These finding showed that AKBA, the pentacyclic triterpene from Boswellia Serrata has an antiinflammatory, anti-glutamatergic and anti-amyloidogenic effect which suggest the possible incorporation of AKBA in clinical trials and development of a new therapeutic drug for prevention of AD progression. Moreover, the use of combination therapy of celecoxib and AKBA, as dual enzyme inhibitors, has slightly more beneficial effect over some monotherapies in limiting the progression and symptoms of AD.

Key words: Cognitive impairment, Lipopolysaccharide, AKBA, Radial maze, Glutamate, Tumor necrosis factor alpha, Amyloid- beta peptide.

MYELIN INJURY AND DEGRADED MYELIN VESICLES IN ALZHEIMER’S DISEASE
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Abstract

Objective: Myelin disruption is an important feature of Alzheimer’s disease (AD) that contributes to impairment of neuronal circuitry and cognition. In this study we characterize myelin injury in the brains of patients with AD compared with normal aged controls.

Methods: Myelin from patients with AD (n=13) was compared to matched controls (n=6). Myelin injury was examined by immunohistochemistry in frontal white matter (WM) for intact myelin basic protein (MBP), degraded MBP, the presence of myelin lipid and for PAS staining. The relationship of myelin injury and axonal injury was also assessed.

Results: Brains from patients with AD had significant loss of intact MBP, and an increase in degraded MBP in periventricular WM adjacent to a denuded ependymal layer. In regions of myelin injury, vesicles were identified that stained positive for degraded MBP, myelin lipid, and neurofilament but not for intact MBP. Most vesicles stained for PAS, a corpora amylacea marker. The vesicles were significantly more abundant in the periventricular WM of AD patients compared to controls (44.5±11.0 versus 1.7±1.1, p=0.02).

Conclusion: In AD patients degraded MBP is associated in part with vesicles particularly in periventricular WM that is adjacent to areas of ependymal injury.

DISTINCT 2-DRIBOSE-INDUCED APOPTOTIC RESPONSE DISTINGUISHES LYMPHOBLASTS FROM SPORADIC AND FAMILIAL ALZHEIMER’S DISEASE PATIENTS
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Objectives: We previously reported that control of cell cycle distinguishes lymphoblasts from sporadic and familial Alzheimer’s disease patients (SAD and FAD). We found significantly increased basal p21 levels and apoptotic response in SAD cells compared with FAD lymphoblasts. Since it is known that p21, besides controlling cell cycle, can regulate apoptosis, we checked whether p21 levels play a role in the cellular response of FAD and SAD cells to oxidative stress evoked by 2d-ribose (2dRib).

Methods: Apoptosis was measured using flow cytometry (SubG1 level assessment, Annexin V staining and mitochondrial membrane potential). Cell viability after 2dRib and pifitrin (PFT-a) treatment were measured using MTT assay, mRNA levels were evaluated using real-time PCR and protein levels by immunoblotting. p21 levels in nuclear and cytosolic fractions were visualized using confocal laser scanning
Results: FAD lymphocytes were more resistant to 2dRib-induced cell death than control or SAD cells. In response to 2dRib FAD cells showed significantly increased p21 mRNA and protein levels and preferentially cytoplasmic location of p21 as compared to SAD cells. Transcriptional activation of p21 was shown to be dependent on p53, as it can be blocked by PFT-a.

Conclusions: The increase in p21 transcription in FAD lymphoblasts and its cytoplasmic localization confer these cells a survival advantage, since PFT-a sensitized FAD cells to 2dRib-induced apoptosis. Thus, as some cellular mechanisms seem to be different in FAD and SAD cells, our data suggest a possibility for differential diagnosis of FAD and SAD based on p21 and p53, and individualized therapeutic approach for SAD and FAD.

EFFECT OF LONG-TERM ADMINISTRATION OF LARD-ENRICHED DIET ON COGNITIVE AND MEMORY PROCESSES IN RATS AGED

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Abstract

The Alzheimer’s Disease (AD) is a multifactorial neurodegenerative disease characterized by the cognitive impairment, the increased memory loss, inflammatory processes, tau and beta-amyloid aggregation, and vascular damage. In the last years, recent studies have shown that high cholesterol levels, mid-life obesity and diabetes have been linked to the pathogenesis of AD. The aim of this work was to analyze the effects of the intake of lard in rats aged, a typical ingredient in many Mexican foods that is high in cholesterol and unsaturated fatty acids, in cognitive and memory processes. For 5 months after intake 33% lard-enriched diet plasma cholesterol levels and total weight were significantly enhanced compared to controls. Spatial memory was evaluated in an eight-arm radial maze, with a modified technique, and lard-treated animals significantly demonstrated an impaired learning and memory, which was confirmed with the novel object recognition test. In conclusion, our data demonstrated that the intake 33% lard-enriched diet in rats caused memory impairment, which looks AD-like pathology.

ABSENCE OF EFFECT OF RENAL IMPAIRMENT ON RIVASTIGMINE PHARMACOKINETICS IN PATIENTS WITH ALZHEIMER’S DISEASE

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Introduction: Alzheimer’s disease (AD) affects people mostly in old age (>65 years). People in this age group tend to develop renal impairment. Using a retrospective pharmacokinetic modelling analysis, we studied the effects of baseline renal impairment on steady-state concentrations of rivastigmine and its metabolite NAP226-90, following daily administration of rivastigmine transdermal patch (5, 10, 15 and 20 cm²) or capsule (3, 6, 9 and 12 mg).

Methods: Pharmacokinetic data were collected from IDEAL (Investigation of transDermal Exelon in AlzHeimer’s disease) study, a 24-week, multi-centre, randomised, double-blind, placebo and active-controlled (rivastigmine capsule), phase III trial conducted in patients with probable AD. Boxplots were constructed for the observed steady-state plasma concentrations of rivastigmine and NAP226-90 stratified by baseline renal-impairment (quantified by creatinine clearance [CLcr] and estimated glomerular filtration rate [eGFR]). Analyses were repeated with model-based estimates of plasma concentrations adjusted for bodyweight.

Results: When stratified by renal function, the two groups (mild or no renal impairment versus moderate, severe and end-stage renal impairment) were comparable for demographic covariates for all patient groups. There was no correlation between CLcr or eGFR and plasma concentrations of rivastigmine and NAP226-90, following daily administration of rivastigmine transdermal patch (5, 10, 15 and 20 cm²) or capsule (3, 6, 9 and 12 mg).

Conclusion: Rivastigmine can be safely administered to patients with renal impairment and does not require dose adjustment as there is no impact of renal impairment on steady-state plasma concentrations of either rivastigmine or its metabolite NAP226-90.
EFFICACY AND SAFETY OF HIGH-DOSE RIVASTIGMINE PATCH (13.3 mg/24h) IN ALZHEIMER'S DISEASE WITH AND WITHOUT CONCOMITANT MEMANTINE USE: RETROSPECTIVE ANALYSES OF THE OPTIMA AND ACTION STUDIES

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Introduction: The OPTIMA and ACTION studies have demonstrated the benefit and safety of 13.3 mg/24h rivastigmine patch on function and cognition in patients with mild-to-moderate and severe Alzheimer's disease, respectively. We report here the efficacy and safety of 13.3 mg/24h patch with and without concomitant memantine use.

Methods: Here we present data from retrospective analyses of OPTIMA and ACTION studies. These included patients who were randomised to receive 13.3 mg/24h patch in double-blind (DB) phase of OPTIMA study; patients declining and entering the DB phase, previously treated with 9.5 mg/24h patch alone, during the initial open-label phase (Sub-analysis 1, SA1; n=142) and patients who received ≥1 dose of concomitant memantine at or before the start of the DB phase and continued throughout the DB phase (SA2; n=130) of OPTIMA. These patients were matched 1:1 by means of propensity scores for both sub-analyses [9.5 or 13.3 mg/24h patch and concomitant memantine versus 13.3 mg/24h patch alone. Patients randomized to 13.3 or 4.6 mg/24h patch in ACTION study (SA3; n=716), were subdivided according to whether or not they had received ≥1 dose of concomitant memantine during the DB phase. Changes from baseline on ADCS-IADL and ADS-cog scores at Weeks 24 and 48 (OPTIMA) and on SIB and ADCS-ADL-SIV scores at Week 24 (ACTION) were compared using ANCOVA with treatment, country, memantine usage, and baseline as covariates. Safety evaluations included incidence of adverse events (AEs) and serious AEs.

Results: In SA1, patients treated with 13.3 mg/24h patch alone demonstrated significant benefits in function (ADCS-IADL) at Weeks 24 (p=0.005) and 48 (p=0.013) versus those treated with 9.5 mg/24h patch and concomitant memantine. ADAS-cog outcomes were comparable between both groups at Weeks 24 (p=0.691) and 48 (p=0.490). In SA2, no significant differences were observed in patients treated with the 13.3 mg/24h patch and concomitant memantine versus those receiving 13.3 mg/24h patch alone (Week 24 [IADL, p=0.121; ADAS-cog, p=0.104] and Week 48 [IADL, p=0.276; ADAS-cog, p=0.217]). In SA3, 13.3 mg/24h patch demonstrated significantly greater efficacy than 4.6 mg/24h patch (p<0.05) on SIB and ADCS-ADL-SIV in patients receiving concomitant memantine, and on SIB in those not receiving memantine. Safety was comparable across treatment groups, with no new or unexpected concerns in these retrospective analyses.

Conclusions: The data from these analyses suggest that the efficacy and tolerability of 13.3mg/24h rivastigmine patch is mostly unaltered irrespective of the use of concomitant memantine.

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Disclosures: Gil Lefèvre and Francesca Callegari are employees of Novartis Pharma AG, Basel Switzerland, and Yuan Xiong is employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

Disclosures: G Grossberg has served as a consultant for Accera, Avanir, Baxter Bioscience, Forest Labs/Actavis,, Genentech,Lundbeck, Novartis, Otsuka, Roche and Takeda; has received research support from Accera, Baxter, Elan, Forest, Janssen, NIH, Novartis, Noven, and Pfizer; and serves on a safety monitoring board for Merck and Neuron.

JL Molinuevo has provided scientific advice or has been an investigator or data monitoring board member or received consultancy fees from Bayer, Bristol-Myers Squibb, Eisai, GE Healthcare, GlaxoSmithKline, Innogenetics, Janssen-Cilag, Lundbeck, MSD, Merz Pharma, Novartis, Pfizer and Roche.

C Strohmaier is an employee of Novartis.
NEUROPROTECTIVE MECHANISMS OF N-ACETYLCYSTEINE AMIDE AGAINST AMYLOID BETA-PEPTIDE TOXICITY IN PRIMARY RAT CORTICAL CULTURES

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Abstract:
Amyloid beta-peptide (Aβ) aggregation is one of the major pathological hallmarks in Alzheimer’s disease (AD), which induces neuronal cell death. N-Acetylcysteine amide (NACA) is a novel thiol compound capable of serving as a glutathione precursor. NACA has a higher permeability through the cell membrane, thereby resulting in a lower effective dosage as compared to the traditional glutathione precursor, N-acetylcysteine (NAC). Previously NACA has been reported to play a neuroprotective role against Aβ1-42 toxicity. However, the detailed protective mechanisms of NACA against Aβ-induced neuronal death remain to be fully defined. To address this issue, we hypothesized that activation of nuclear factor kappa-B (NF-κB), a redox-sensitive transcription factor, with induction of its downstream target genes may mediate the neuroprotective effects of NACA against Aβ toxicity in cortical neurons. We found that NACA concentration-dependently, with the optimal dosage at 10 μM, protected rat cortical neurons against toxicity of 10 μM Aβ25-35 in a cotreatment paradigm for 48 h based on the MTT reduction assay. Counting of Hoechst-stained surviving cells with normal nuclear morphology revealed similar findings. Furthermore, immunocytochemistry using the antibody against microtubule-associated protein-2 (MAP-2), a neuronal dendrite marker, demonstrated that NACA restored neuronal morphology that was damaged by Aβ25-35, thereby confirming direct beneficial actions of NACA on cortical neurons. As an antioxidant, NACA also attenuated production of free radicals that were produced by Aβ25-35. In addition to the cotreatment paradigm, pretreatment of cortical cultures with NACA at 10 μM for 1-2 h, but not for a longer period of time at 4 h or 8 h, also rescued these cells from subsequent exposure to 10 μM Aβ25-35 for 48 h. Chromatin immunoprecipitation (ChIP) assay revealed that cotreatment of cortical cultures with NACA and Aβ markedly enhanced binding of NF-κB subunit p65 to the promoter region of the anti-apoptotic Bcl-2 gene as compared to the controls or the cultures treated with either reagent alone. Consistently, real-time reverse transcription polymerase chain reaction (RT-PCR) indicated that NACA/Aβ cotreatment substantially enhanced expression of Bcl-2 gene at mRNA levels. NACA/Aβ cotreatment also enhanced expression of Bcl-2 proteins as compared to control cultures. Consistently, Aβ25-35-induced cleavage of caspase-3 was attenuated by cotreatment with 10 μM NACA. Cotreatment of SN50, the specific peptide inhibitor of NF-κB, and the Bcl-2 peptide inhibitor both abolished NACA-mediated neuroprotective effects against Aβ25-35. Taken together, our results indicated that NF-κB-dependent induction of Bcl-2 contributes to the NACA-mediated protective effects against Aβ25-35 toxicity in cortical neurons.

Day 2:
Invited Speakers Abstracts

Development of allosteric activators of the Trk receptors for neuroprotection in AD
Nicholas Webster, Ph.D., M.A., Professor of Medicine, Chief, Division of Endocrinology and Metabolism, Associate Director for Shared Resources, Moores Cancer Center, University of California, San Diego, USA
The goal of our research is to develop new neuroprotective drugs that can prevent or reverse Alzheimer’s disease neuropathology. We have an ongoing project to develop libraries of novel, small-molecule enhancers of tyrosine kinase receptors that brings together multiple labs involved in chemical synthesis, neuroanatomy/pathology, in vitro screening and behavior. From these libraries of compounds, we have identified compounds that potentiate NGF activation of TrkA. These compounds are neuroprotective and improve spatial learning in a mouse Alzheimer’s Disease model, a mouse model for mild cognitive impairment, and improves motor function and recovery in a mouse model for traumatic brain injury.

ACAT1/SOAT1 as a therapeutic target for Alzheimer’s and other related neurodegenerative diseases
Ta Yuan Chang, PhD, Professor, Department of Biochemistry, Geisel School of Medicine at Dartmouth, Hanover, NH, USA
Acyl-CoA:Cholesterol acyltransferase 1 (A1) is a resident ER enzyme that prevents the built up of cholesterol in membranes by converting it to cholesteryl esters. Our laboratory had previously shown that A1 gene knockout or gene knockdown decreases amyloidopathy and rescued cognitive deficits in a mouse model for Alzheimer’s disease (AD). Here we show that A1 gene knockout or a specific A1 inhibitor K604...
stimulates autophagosome formation and lysosomal proteolysis in cultured microglia and neurons. Autophagy is needed to degrade misfolded proteins/peptides. Our results implicate that blocking A1 may provide a new way to beneﬁt multiple neurodegenerative diseases including AD.

Retro-inverso peptide inhibitors of β-amyloid oligomer formation as a novel treatment for progression of Alzheimer’s disease

Professor David Allsop, Professor of Neuroscience, Division of Biomedical and Life Sciences, Faculty of Health and Medicine, Lancaster University, Lancaster, United Kingdom

Inhibition of Aβ oligomer formation could have an impact on the progression of Alzheimer’s disease. This talk will describe retro-inverso (RI) peptides and RI-peptides attached to the surface of nanoparticles as therapeutically useful inhibitors of early-stage Aβ aggregation. The nanoparticle versions of our inhibitors have several advantages over free peptides for further development as a potential drug. These include biocompatibility, stealth properties, and the possibility of designing multi-ligand systems directed at more than one target. Our RI peptide and nanoparticle-based therapies are an alternative approach to more conventional drugs and could offer some hope for success in future human clinical trials.

Online information about the prevention of Alzheimer’s disease: The good, the bad, and the ugly

Dr. Julie Robillard, University of British Columbia, Djavad Mowafaghian Centre for Brain Health, Vancouver, BC, Canada

The dynamic environment of the Internet is reshaping health care, acting as a powerful new way for stakeholders to gather information. Over 80% of adults and older adults seek health information online and new resources are emerging to meet this demand. Information about Alzheimer disease in particular is widely shared through new new media and hosted on high-traffic websites. This talk will discuss recent research looking at the scientific validity and the ethical factors of online information about the prevention of Alzheimer disease, and will explore the implications of the online environment for physicians and researchers.

Treatment of Alzheimer with novel biologics

Dr Mourad Tayebi, Surrey University, Guildford, Surrey, UK

It was previously shown that plaque clearance did not stop the progression of dementia in Alzheimer patients administered with conventional anti-Aβ antibodies for monomeric Aβ, indicating that antibodies that would target the soluble oligomers and/or the fibrillar structures derived from monomeric Aβ might be a better therapeutic target. To that end, we administered PRIOC anti-oligomer mAbs or implanted PRIOC-secreting mesenchymal stem cells (MSCs) to Tg2576 or httau mice models in order to establish their therapeutic efficacy. PRIOC mAbs, unlike isotype control have shown substantial reduction of Aβ plaques and neuropathology and improvement of cognitive deﬁcits.

5-HT4 receptor agonists and multi-target directed ligands: novel promising agents for prevention of Alzheimer’s disease

Dr Sylvie Claeysen, PhD, HDR, Institut de Génomique Fonctionnelle, Université de Montpellier, Montpellier, France

5-HT4 agonists administration could represent an interesting and promising strategy for AD prevention. Chronic treatments promoting sAPPalpha release via the stimulation of 5-HT4 receptors clearly hinder plaque formation and Aβ load, while jointly attenuating inﬂammation processes and improving cognitive outcome in 5xFAD mice. In a collaborative effort with chemists, we developed Multi-Targets-Directed-Ligands (MTDL) presenting a double biologic activity: acetylcholinesterase inhibition and 5-HT4R activation. The drugs obtained would have dual-symptomatic properties and disease-modifying abilities. First outcomes of this modern MTDL approach will be presented.

Nanoliposomes for diagnosis and therapy of Alzheimer’s -Recent Progress

Professor Sophia G. Antimisiaris, University of Patras, Greece

Nanoliposomes (NL) for targeting Aβ peptides were developed and evaluated for diagnostic/ therapeutic purposes. Targets are the amyloid-peptide species (oligomers/aggregates/plaques). For brain targeting, anti-transferrin MAb (TfRMAb) and/or ApoE3 peptide derivative-decorated NL were evaluated in vitro, in vivo, and ex-vivo. For Aβ targeting, two types of curcumin-derivative ligands were used, as well as an anti-Aβ MAb (AβMAb). Also dually-decorated NLs to target both, the brain and Aβ species, were studied. The recent finding with all the NL-types will be presented.
New Cellular and Animal Models for Drug Discovery in Alzheimer's Disease
Dr Jordan L. Holtzman, University of Minnesota, USA

Currently Alzheimer's disease dementia is thought to be due to β-amyloid neurotoxicity. Yet, since β-amyloid is produced in everyone it is unclear why deposits are only seen in the elderly. We have found that in CSF the β-amyloid is kept in solution by N-glycosylation and binding two proteins, ERp57 and calreticulin. These endoplasmic reticulum (ER) proteins are molecular chaperones, which also catalyze the posttranslational processing of the synaptic membrane proteins necessary for memory. β-amyloid deposits indicate that the Alzheimer's dementia is due to a decline in the ER pathway catalyzing this processing. These findings suggest new targets for drug discovery.

Imaging Brain Injury in Diabetes
Assistant Professor Myria Petrou MA MBChB MS, Department of Radiology, Division of Neuroradiology, University of Michigan, Michigan, USA

Diabetes affects a large proportion of the population and a number of epidemiologic studies show that it is a risk factor for dementia. The mechanisms underlying the association between diabetes and dementia remain unclear. The talk will review MR and PET imaging findings which shed some light on the mechanisms responsible for diabetes related cognitive decline. We will also discuss current gaps in knowledge and ongoing research as well as how novel imaging methods can assist in the development and testing of novel therapies.

Oral Presentation Abstracts
Oral presentations will be added after the submission deadline

NEUTROPHILS INDUCE ALZHEIMER'S DISEASE-LIKE PATHOLOGY AND COGNITIVE DECLINE VIA A MECHANISM DEPENDENT ON LFA-1 INTEGRIN
Elena Zenaro, Enrica Pietronigro, Vittorina Della Bianca, Gennj Piacentino, Ermanna Turano, Bruno Bonetti, Gabriela Constantin

Department of Pathology and Diagnostics, University of Verona, Strada le Grazie 8, 37134, Verona, Italy

Inflammation is a pathological hallmark of Alzheimer's disease and understanding the underlying mechanisms may facilitate the development of new treatments. Our aim was to study the role of inflammation mechanisms in the pathogenesis of Alzheimer's disease.

Using mice with five familial Alzheimer's disease (5xFAD) mutations presenting amyloid pathology, and 3xTg-AD mice with both amyloid and tau pathology, we found increased expression of vascular adhesion molecules and neutrophils extravasating in areas with amyloid beta deposits. Interestingly, neutrophils released IL-17 and neutrophil extracellular traps (NETs) suggesting that NETosis may represent a potential neutrophil-dependent disease mechanism in AD. Using two-photon laser-scanning microscopy we observed that neutrophils crawl in blood vessels and transmigrate in areas with amyloid deposition in both AD-like models. Aβ42 peptide triggered the LFA-1 integrin high-affinity state and rapid neutrophil adhesion. Two-photon microscopy experiments showed that LFA-1 integrin controls neutrophil extravasation and intraparenchymal motility. Neutrophil depletion or the inhibition of neutrophil trafficking using an anti-LFA-1 antibody improved memory function in 5xFAD and 3xTg-AD mice compared to mice treated with a control antibody in Y maze and contextual fear conditioning tests. The role of LFA-1 integrin was confirmed by crossing 3xTg-AD animals with the LFA-1-deficient Itgal-/- strain. We found that the 3xTg-AD mice lacking LFA-1 integrin showed improved memory in cognitive tests compared to control animals. Interfering with neutrophil activity reduced microglial activation, amyloid deposition, tau phosphorylation and restored synaptic protein loss.

Notably, restoration of cognitive function in mice with temporary inhibition of neutrophil function during early disease was maintained also at later time points in aged animals.

To understand the relevance of our data in humans, we analysed human cortical brain samples from subjects with AD. In Alzheimer's patients, neutrophils adhered and spread inside brain venules or migrated into the parenchyma and released NETs in larger numbers than in control subjects.

In conclusion, our results demonstrate that neutrophils induce cognitive impairment and neuropathological changes suggesting that the inhibition of neutrophil trafficking may represent a new therapeutic strategy to address Alzheimer's disease.
objective Phosphodiesterase (PDE) / cyclic adenosine monophosphate (cAMP)/ cAMP response element binding protein (CREB) pathway plays an important role in the pathogenesis of Alzheimer's disease (AD), the purpose of this study is to investigate whether FA has the therapeutic effect on neuroinflammation AD through modulating PDE/ cAMP/CREB pathway.
Methods. Morris water maze was performed to measure memory enhancing effect of FA against lipopolysaccharide (LPS)-induced neuroinflammation in Sprague-Dawley (SD) rats. The immunohistochemistry staining was used to show the histological changes of neurons in the cortex and hippocampus of rat brains in different groups. In order to clarify the neuro-protective effect of FA against Aβ25–35 and LPS induced PC12 cellular damage, the superoxide production and the levels of inflammatory factors (TNF-α and IL-1β) in supernatant of PC12 cells were investigated. We further investigated the effects of FA against LPS induced changes in intracellular levels of cAMP and free Ca2+ ([Ca2+]i), the changes of [Ca2+]i was measured by laser scanning confocal microscope. The mRNA expressions of PDE4B were analyzed by quantitative real-time RT-PCR(Q-PCR), the protein expression of CREB and phospho-CREB were determined by immunoblotting. Furthermore, molecular docking was used to identify the interaction between the PDE4B and FA.

Results. FA significantly decreased time spent to find the hidden platform in Morris water maze test compared with the LPS treated group. HE staining showed that neurons in the cortex and hippocampus of the FA groups had much fewer karyopyknosis compared with LPS groups. FA significantly maintained cell viability, increased the levels of superoxide dismutase and inhibited production of TNF-α and IL-1β induced by Aβ25–35. Pretreatment with FA increased the intracellular levels of cAMP and decreased intracellular [Ca2+]i against LPS induced changes. Examination of PDE4B mRNA of N2a cells revealed a decrease in PDE4B, while immunoblotting showed up-regulation of CREB and phospho-CREB with FA pretreatment, these results are consistent with the increased levels of cAMP. The molecular docking results also showed that FA has a strong interaction with PDE4B, it indicated that FA has the potential to inhibit PDE4B activity.

Conclusion. Taken together, our results suggested that the beneficial property of FA might be conferred by inhibiting PDE and activating signaling pathway of PDE/cAMP/CREB, which might be a putative therapeutic intervention of neuroinflammatory diseases such as AD.

Key words. Ferulic acid, Phosphodiesterase, Alzheimer's disease, lipopolysaccharide

MEMORY GROUPS FOR MILD COGNITIVE IMPAIRMENT: WHAT IS THE BENEFIT?

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Background. Many people with amnestic mild cognitive impairment (aMCI), the pre-clinical stage of Alzheimer's disease, seek guidance about how best to manage everyday memory challenges. Following positive pilot study results, we investigated response to a six-week cognitive-behavioural intervention for aMCI. The LaTCH Memory Group Program provides knowledge about memory strategies and how to use such strategies in everyday activities. It is based on the expectation that people experiencing memory difficulties need assistance in learning and implementing effective compensatory strategies in everyday situations. This offers an alternative approach to 'brain training' or practice on computer-based memory tasks. We investigate multidimensional outcome following the memory group program and consider the relationship between different outcome measures.

Methods. In a randomised controlled trial, older adults diagnosed with aMCI (n = 108) were randomly allocated to an intervention or a wait-list control group. Over three years, trained allied health professionals delivered the intervention through memory groups at locations throughout Victoria, Australia. Outcome measures included (i) Memory Strategy Knowledge – Strategy Repertoire Test; (ii) Memory Strategy Use – Multifactorial Memory Questionnaire, Strategy subscale; (iii) Memory Ability – neuropsychological memory tests (CAMPROMPT and CVLT-II); and, (iv) Wellbeing – Multifactorial Memory Questionnaire, Contentment subscale.

Results. Following intervention, participants with aMCI significantly improved in (i) knowledge about memory strategies (aMCI: \( \eta^2 = .06 \)); (ii) use of memory strategies in everyday activities to prevent memory failures (aMCI: \( \eta^2 = .08 \)); and, (iii) contentment and self-efficacy about memory ability (aMCI: \( \eta^2 = .05 \)). Nevertheless, these significant changes were not reflected in neuropsychological tests.

Discussion. These findings suggest that unlike memory impairment (as measured by neuropsychological tests), memory disability in everyday life can be moderated by even brief intervention. The ability of participants with aMCI to demonstrate increased use of memory strategies to achieve self-determined memory-based goals after intervention was a critical outcome. It opens up opportunity for people to engage in more life activities, adding to the cycle of improving mental health. Choice of an outcome measure for cognitive training requires determining whether the focus is minimising disability by facilitating behaviour change and using compensatory strategies, or whether the focus is reducing memory impairment as measured by neuropsychological tests.
RESVERATROL IS SAFE AND WELL-TOLERATED IN INDIVIDUALS WITH MILD-MODERATE DEMENTIA DUE TO ALZHEIMER’S DISEASE

RS Turner, MD, PhD1, RG Thomas, PhD2, S Craft, PhD3, CH VanDyck, MD4, J Mintzer, MD5, B Reynolds, NP6, JB Brewer, MD, PhD2, RA Rissman, PhD2, R Raman, PhD2, PS Aisen, MD2 for the Alzheimer’s Disease Cooperative Study

(1) Department of Neurology, Georgetown University, Washington, DC, USA, (2) University of California, San Diego, CA, USA, (3) Wake Forest University, Winston-Salem, NC, USA, (4) Yale University, New Haven, CT, USA, (5) Roper St. Francis Healthcare, Charleston, SC, USA

Objective. We conducted a phase 2 randomized, placebo-controlled, double-blind, multicenter 12-month trial of resveratrol in individuals with mild-moderate Alzheimer’s disease. We examined safety and tolerability, pharmacokinetics, and change in volumetric MRI, plasma Aβ40 and Aβ42 and CSF Aβ40 Aβ42 tau, and phosphoTau181, and clinical outcomes.

Background. Similar to caloric restriction, resveratrol treatment reduces cognitive decline and neuropathology in animal models of Alzheimer’s disease - perhaps via activation of sirtuins and promotion of autophagy.

Methods. Subjects (N = 119) were randomized (1:1) to placebo or pure synthetic resveratrol 500 mg by mouth once daily (dose escalation by 500 mg every 13 weeks, ending with 1000 mg twice daily). Detailed pharmacokinetics were performed on a subset (N = 15) at baseline and weeks 13, 26, 39, and 52. After randomization there were no differences between groups (including AD severity) with the exception of longer disease duration in the placebo group compared to the treatment group (5.5 +/- 2.6 versus 3.9 +/- 2.3 years, mean +/- SD, p < 0.001). Brain MRIs and CSF collections were performed at baseline and again at week 52. A total of 104 subjects completed the study (12.6 % dropout). The primary efficacy analyses were based on intent to treat.

Results. Gastrointestinal symptoms were the most common drug-related adverse events (nausea, diarrhea, weight loss). Resveratrol and its major metabolites were measurable in plasma and CSF (with 3 % blood-brain barrier penetration of native resveratrol). CSF Aβ40 levels declined 14 % in the placebo group and 1 % in the resveratrol-treated group, resulting in a significant difference in mean change at week 52 (p = 0.002). A similar pattern was found with plasma Aβ40 (p = 0.024). No significant differences were found with CSF and plasma Aβ42, and CSF tau and phosphoTau181. Brain volume declined 3 % in the treatment group and 1 % in the placebo group (p = 0.03).

Conclusions. Resveratrol was safe and well-tolerated in individuals with mild-moderate AD. Further studies are needed to interpret the biomarker changes associated with resveratrol treatment. (NIA U01 AG010483; ClinicalTrials.gov NCT01504854; FDA IND 104205).

APE1/REF-1 IN ASSOCIATION WITH GINKGOLIDE B AUGMENTS MITOCHONDRIAL OXPHOS AGAINST Aβ(25-35)-INDUCED OXIDATIVE STRESS

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Post-mitotic neurons are prone to gather oxidized DNA base lesions potentially leading to progressive neurodegeneration and cognitive decline. Furthermore, ageing is a risk factor for neurodegeneration and accumulation of oxidative mitochondrial DNA damage is linked with various age-related disorders like Alzheimer’s disease (AD). Thus, manipulation of DNA repair mechanisms can be thought of as a putative approach to prevent neuronal loss in neurodegenerative disorders like AD. Ginkgo biloba has been used in traditional Chinese medicine for its potential effects on memory and cognition. In traditional Hindu medicine, Ginkgo extract is a constituent of an elixir called Soma. Recently, scientists have found out that Ginkgolide B, a terpenoid present in Ginkgo extract, has antioxidant, neuroprotective and cholinergic activities. In the present study we aimed: 1) to study the effect of Aβ(25-35) on mitochondrial ROS/RNS levels and activities of respiratory complexes (I, III, & IV) associated with OXPHOS; 2) to evaluate the neuronal survival mechanism(s) through over-expression of APE1 upon Aβ(25-35)-induced oxidative stress; and 3) to identify the neuro-modulatory role of phytochemical Ginkgolide B (G.B) on mitochondrial functions upon treatment with Aβ(25-35). The results of the present study demonstrated that ectopic expression of APE1 enhanced the capacity of human neuroblastoma SH-SYSY and IMR-32 cells to overcome accumulation of oxidative mitochondrial DNA damage is linked with various age-related disorders like Alzheimer’s disease (AD). Thus, manipulation of DNA repair mechanisms can be thought of as a putative approach to prevent neuronal loss in neurodegenerative disorders like AD. Ginkgo biloba has been used in traditional Chinese medicine for its potential effects on memory and cognition. In traditional Hindu medicine, Ginkgo extract is a constituent of an elixir called Soma. Recently, scientists have found out that Ginkgolide B, a terpenoid present in Ginkgo extract, has antioxidant, neuroprotective and cholinergic activities. In the present study we aimed: 1) to study the effect of Aβ(25-35) on mitochondrial ROS/RNS levels and activities of respiratory complexes (I, III, & IV) associated with OXPHOS; 2) to evaluate the neuronal survival mechanism(s) through over-expression of APE1 upon Aβ(25-35)-induced oxidative stress; and 3) to identify the neuro-modulatory role of phytochemical Ginkgolide B (G.B) on mitochondrial functions upon treatment with Aβ(25-35). The results of the present study demonstrated that ectopic expression of APE1 enhanced the capacity of human neuroblastoma SH-SYSY and IMR-32 cells to overcome...
the oxidative damage caused by Aβ(25-35). Upon Aβ(25-35) treatment, decrease in complex-I & IV activities were observed and increased activity of complex-III in both IMR-32 and SH-SY5Y cells. Endogenous APE1 level was found to be decreased in mitochondria upon treatment with Aβ(25-35) [up to 48 hr], and the APE1 level was restored and increased significantly upon pre-treatment with G.B. The pre-treatment with G.B and ectopic APE1 expression synergistically enhanced the activities of complex-I, III & IV as compared to Aβ(25-35) restoring mitochondrial OXPHOS. Our study for the first time provides new insights into how the phytochemical G.B helps synergistically in protecting neuronal cells by modulating or protecting APE1’s functions, and also advocating for further studies to carry out for development of therapeutic agents for treating AD from a new perspective, utilizing APE1.

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MICE DEVELOP B-LYMPHOCYTE DEPENDENT DELAYED COGNITIVE DEFICITS WEEKS AFTER STROKE
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Each year, ten million people worldwide survive the neurologic injury associated with a stroke. Importantly, stroke survivors have almost twice the risk of subsequently developing dementia. The link between stroke and the later development of dementia is not understood. For example, it is unknown how long inflammation persists after stroke. In this study, we tested the hypothesis that chronic inflammation in the brain contributes to the onset of dementia. We utilized a mouse model of stroke (DH, or Distal Hypoxic stroke) that generates a large cortical lesion and no immediate cognitive deficits. We characterized inflammatory responses (n=7-10 mice per group), long-term potentiation (n=6-9), and cognition (n=10) before and after stroke in wildtype C57BL/6j mice. We found that the inflammatory response to stroke persisted for months and was characterized by the presence of macrophages and B and T lymphocytes in the stroke lesion. Moreover, immunoglobulin was observed in the lesion and surrounding tissue, and there was prolonged inflammation in the area of Wallerian degeneration. We found that immunoglobulin accumulated in the hippocampus and mice developed a delayed deficit in hippocampal long-term potentiation and delayed short-term memory deficits one to seven weeks after stroke. Notably, delayed cognitive impairment was mitigated in C57BL/6j-μMT mice that lacked mature B lymphocytes and in wild-type mice treated with an anti-CD20 B cell-depleting antibody after stroke. Thus, the inflammatory response to stroke persisted for months in mice, and such mice developed a B lymphocyte-mediated autoimmune response that contributed to delayed cognitive dysfunction.

VIDEOPHONE CONVERSATION FOR PSYCHOLOGICAL STABILIZATION OF INDIVIDUALS WITH DEMENTIA
Kiyoshi Yasuda, Noriaki Kuwahara, Kazuhiro Kuwabara, Kazunari Morimoto, & Nobuji Tetsutani
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Background: Conversation is a common and enjoyable activity for most people. A remote reminiscence conversation system was created to provide opportunities for individuals with dementia (Kuwahara et al., 2010, Yasuda et al., 2013). This system incorporates a videophone with reminiscence photo sharing enabling individuals with dementia to remain stable during and after conversing with talking partners. Furthermore, it was very interesting to note that some individuals were even stable for more than 3 h after the conversation session ended. To our knowledge, this sustained psychological effect of conversation has not been reported. As the third experiment, we investigated whether psychological stability was again observed in other individuals while conversing with talking partners on the videophone than while watching TV programs. In this experiment, the remote photo sharing on the screen was not performed in order to understand the single effect of conversation.

Methods: Six outpatients with dementia (two males, four females) participated in this experiment. Their mean age was 75.8. Their mean MMSE score was 22.1. Furthermore, three males and three females of the same ages participated as talking partners. ABAB design was applied to investigate the effects of the conversation. In session A, the talking partner remotely booted Skype™ on the individual’s computer (videophone) and asked the individual to have a 30–40 min conversation. In session B, the individuals were requested to watch their favourite TV programs. The total period of sessions A and B lasted for two or three weeks. The talking partner for each individual was same in this period.

The 'different symptoms common in dementia' section of the Gottfries-Brane-Steen (GBS) scale was used to evaluate psychological stability while they were talking with the partner or while they were watching TV programs (concomitant evaluation). The caregiver graded the psychological stability on the GBS scale of 0–
**Results and discussion:** The average A score (conversing on the videophone) of the GBS scale was 0.6 in the concomitant evaluation and 0.42 in the delayed evaluation. The average B score (watching TV) was 0.93 and 0.86, respectively. In this scale, lower scores denote more psychological stability. Therefore, in both evaluations, individuals with dementia demonstrated more psychological stability while they were conversing on the video phone than while watching the TV programs. The stability was more apparent 3 h after the conversation ended, supporting our previous two experiments. Sufficient conversations in advance may prevent behavioural disturbances, such as evening syndromes. Remote conversation is a promising intervention for assisting individuals with dementia and for reducing caregivers’ burden in their daily lives.

**4Aβ1-15-DERIVED MONOCLONAL ANTIBODY REDUCES MORE Aβ BURDENS AND NEUROINFLAMMATION THAN HOMOLOGOUS VACCINE IN APP/PS1 MICE**

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**Abstract**

The common pathological hallmark of Alzheimer’s disease (AD) is β-amyloid plaque deposition. The ideal therapy would reduce the Aβ burden with a low inflammatory immune response. Passive immunotherapy is an advanced treatment that dramatically reduces brain Aβ pathologies in AD animal models. The objective of our study was to observe the effects of 5C8H5, a novel monoclonal antibody derived from 4Aβ1-15, on brain Aβ pathology in an APP/PS1 mouse model of AD. Six-month-old transgenic mice were administered 5C8H5, 4Aβ1-15 or IgG, and same-aged wild-type untreated C57Bl/6 mice were employed as controls. Inflammatory factors and Aβ40/42 levels were detected by ELISA, while Aβ plaques, microglial cell activation and neurogenesis were evaluated by immunohistochemical staining. Compared with 4Aβ1-15-treated mice, the mice in the 5C8H5 group induced more Aβ clearance with less microglial cell activation in a niche of Th2-polarized immune response. The levels of proinflammatory factors, including IL-1β, IL-6, TNF-α and IFN-γ, were significantly decreased in the CNS, while the level of anti-inflammatory IL-4 was increased. Moreover, the mice in the 5C8H5 group induced more neurogenesis and performed better in behavioral assays than did the 4Aβ1-15 group. In conclusion, the novel monoclonal antibody induces more Aβ clearance and less microglial cell activation in the absence of inflammation, accompanied by an increased Th2-polarized immune response, which makes it a more promising therapeutic strategy. These data provide evidence that passive immunity could alleviate pathologic Aβ alterations by modulating inflammation and should be pursued further for the treatment of AD.

**Keywords**

Alzheimer’s Disease, Behavior, β-amyloid, Inflammatory factors, Microglia activation, Neurogenesis

**Poster Presentation Abstracts**

Poster abstracts will be finalised weeks before the event

**COGNITIVE AND EXECUTIVE REHABILITATION IN ALZHEIMER PATIENTS: APOE AND SNAP-25 POLYMORPHISMS AS PREDICTORS OF OUTCOME**

Franca Rosa Guerini 1, Elisabetta Farina1, Francesca Baglio1, Andrea Saul Costa1, Francesca Lea Saibene1, Elena Calabrese1, Milena Zanzottera1, Elisabetta Bolognesi1, Raffaello Nemni1,2, Mario Clerici1,3

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**Introduction:** Alzheimer’s disease (AD) is a highly prevalent neurodegenerative disorder. Rate of decline and functional restoration in AD greatly depend on the capacity for neural plasticity within residual neural tissues; this is at least partially influenced by polymorphisms in genes that determine neural plasticity, including apolipoprotein E4 (APOE4) and synaptosomal-associated protein of 25 kDa (SNAP-25). We investigated whether correlations could be detected between APOE4 and SNAP-25 polymorphisms and the outcome of a multidimensional rehabilitative approach based on cognitive stimulation and behavioral and functional therapy (MST)

**Methods:** Fifty-eight AD with mild-to-moderate AD underwent MST for 10 weeks. Neuropsychological functional and behavioral evaluations were performed blindly by a neuropsychologist at baseline and after 10 weeks of therapy using MMSE, FLSA and NPI evaluation scales. SNPs were analyzed by molecular genotyping of APOE4 and SNAP-25 rs363050, rs363039, rs363043 SNPs. Results were correlated with DMMSE, DNPI and DFLSA scores by multinomial logistic regression analysis.
Results: Polymorphisms in both genes correlated with the outcome of MST. Thus, higher overall MMSE scores after rehabilitation were detected in APO e4- compared to APO e4+ patients, whereas the SNAP-25 rs363050(G) and rs363039(A) alleles correlated specifically with significant improvements in behavioural parameters after MST.

Conclusions: Polymorphisms in genes known to modulate neural plasticity predict the outcome of a multistructured rehabilitation protocol in AD. These data, although needing confirmation on larger case studies, could help optimizing the clinical management of individuals with AD, for example defining a more intensive treatment in those subjects with a lower likelihood of success.

**ALPHA ASARONE PREVENTS HYPOXIA INDUCED AMYLOIDOPATHY AND COGNITIVE DEFICITS IN RAT BRAIN**

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Alzheimer disease is an age related dementia which is characterized by increased oxidative stress leading to neuronal cell death. Hypoxia upregulates amyloid beta levels thereby playing role in AD pathogenesis. The present study was designed to test the protective role of alpha asarone, a plant derived antioxidant, on hypoxia induced amyloidopathy and hence neurodegeneration. The antioxidant and neuroprotective effects of alpha asarone against hypoxia induced neurotoxicity were investigated in male wistar rats. Rats exposed to hypoxia (10% O₂) for 3 days showed upregulation of amyloid beta, enhanced oxidative stress, neuronal death and and neurobehavioural impairments. However, pre-administration of alpha asarone(50 mg/kg of body weight), significantly ameliorated hypoxia-induced memory impairment as assessed by passive avoidance test and morris water-maze test and caused marked decrease in oxidative damage, as evidenced by decreased malondialdehyde and nitrite levels. Preadministration of alpha asarone was also accompanied by increased superoxide dismutase and catalase levels in hypoxia exposed rats. Furthermore, oral administration of alpha asarone prior to hypoxia also resulted in decreased neuronal death compared to hypoxia exposed rats. Hypoxic rats showed upregulated amyloid beta levels as evidenced by western blotting and immunohistochemistry. In contrast, rats pretreated with alpha asarone showed reduced amyloid beta levels compared to hypoxia exposed rats. This study highlights the neuroprotective effect of alpha asarone treatment against hypoxia induced ROS generation, amyloid plaque upregulation, memory impairment and apoptotic cell death in the rat brain thereby suggesting a possible prophylactic role of alpha asarone in mitigating the progression of AD.

**TERITARY TREPONEMATOSIS**

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With the recent polymerase chain reaction findings in Alzheimer’s disease that Borrelia burgdorferi (Lyme organisms) and oral treponemes are present in the affected brains, it is apparent that this disease is strikingly similar to tertiary syphilis caused by Treponema pallidum. The primary findings are in the skin or mucous membranes with syphilis demonstrating a chancre, Lyme disease a skin lesion (erythema chronicum migrans) and oral treponemes dental plaque. Secondary disease is not as well defined in Lyme disease or oral treponematosis as in syphilis, but tertiary is the same as neurosyphilis. We have shown the presence of biofilms made by these organisms with positive staining by PAS and Congo red histologic stains in brains from Alzheimer’s disease patients. We postulate how the amyloid that forms the infrastructure of all biofilms induces the formation of beta amyloid. We further postulate how this disease may be prevented by treatment anytime prior to clinical findings with a bactericidal antibiotic. This would also be similar to the situation in syphilis.

**EVENT-RELATED BRAIN ACTIVATION IN ALZHEIMER’S DISEASE**

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Abstract: Increasing prevalence of Alzheimer’s disease (AD), due to the aging of the population in developing countries, makes accurate diagnosis of AD a challenging problem. The AD is characterized by cognitive impairment, executive function impairment and stimuli evaluation in working memory attenuation. In this study, the brain sources localization of Evoked Related Potential (ERP) components, i.e., the Mismatch Negativity (MMN) and the P300, was investigated based on high-density
electroencephalogram (HD-EEG) data. The differences in the localization of the neuronal generators between control and AD were indentified in order to investigate whether they could serve as a biologic marker of mild AD. A simple auditory oddball experiment was conducted, involving 21 healthy elderly and 21 mild AD patients. The data were subjected to ERPs extraction, standardized LORETA and statistical analysis. The experimental results revealed significant AD-related differences to the latencies of the MMN ($p = 0.0125$) and the P300 ($p = 3 \cdot 10^{-4}$) and the topographic distribution of the HD-EEG amplitudes. Additionally, a shift in the maximum intensities was observed from frontal (BA 11) in controls to temporal lobe (BA 38) in AD in case of the MMN, and from superior temporal gyrus (BA 38) in controls to fusiform gyrus (BA 37) in AD in case of the P300. Finally, significant differences between groups were revealed in the response time of the subjects, finding AD patients response slower ($p = 1.6 \cdot 10^{-3}$) and far less accurate ($p = 8 \cdot 10^{-5}$). The findings reveal that brain source localization may increase the diagnostic value of ERP components in AD. Further investigation in mild cognitive impairment patients would facilitate the prognosis and the diagnosis of the progress of AD. These findings justify the enhanced potential of HD-EEG data to accurately reflect the brain activation and could have a great contribution in the investigation of neurodegenerative pathologies.

CONTINUOUS VACCINATIONS OF 4Aβ1-15 INDUCES SPECIFIC FLUCTUATION OF INFLAMMATORY FACTORS ACCOMPANY WITH PATHOLOGIC ALTERATIONS ALLEVIATION IN APP/PS1 MICE
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Abstract
The common pathological hallmark of Alzheimer's disease (AD) is β-amyloid plaques deposition. Immunotherapy is a revolutionary pharmacological treatment for AD, aiming at improving plaque clearance while concomitantly decreasing inflammation. Our previous study prepared antigen 4Aβ1-15 and found that it could alleviate pathologic alterations in APP/PS1 transgenic mice. The objective of our study was to research the changing processes induced by immunotherapy, including the inflammatory factor levels and microglial activation that is closely associated with Aβ burdens clearance. APP/PS1 mice were injected with 4Aβ1-15 six times. Each time, the inflammatory factors in sera were detected, and a specific fluctuation that first increased and then decreased was found, in which there was a turning point after the third injection. It prompted us to further detect the indicators in the brains after the third injection and the sixth injection. The results showed that the therapeutic effects for Aβ burdens and behaviors were continuously improved during the whole immune processes, whereas the inflammatory factor levels and microglial activation experienced similar specific fluctuations. The novel discovery may provide convenient methods for further detection and evaluation of immunotherapy in disease courses.

Keywords
Aβ burdens; APP/PS1 mice; continuous vaccinations; immunotherapy; inflammatory factors; microglial activation; spatial learning and memory ability; specific fluctuations

STRUCTURE MODIFICATION OF APOLIPROTEIN E4 TO RESTORE NORMAL FUNCTIONALITY
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ABSTRACT
Alzheimer disease is the most common form of dementia. Its pathogenesis incorporates many potential targets for treatment. Among the targets identified, Apolipoprotein E4 (apoE4) is especially interesting due to its catalytic role in the degradation and clearance of amyloid beta (Aβ), a risk factor for Alzheimer disease. ApoE exists in 3 isoforms which directly impact its functionality in the body. There are characteristic structural differences between the isoforms which result in loss of function in ApoE4. In ApoE4, ionic interactions exist between Arg-61 and Glu-255 residues, unlike the other isoforms. Hence interruption of this interaction by small molecular inhibitors may change the structure of ApoE4 to a more linear structure as observed in the other isoforms. Virtual screening of the NCI diversity set on an energy minimized protein virtual structure was performed to identify potential small molecule inhibitors and to gain further understanding of interactions that can be targeted to inhibit this protein.
AGE RELATED CHANGES IN ANXIETY, MOTOR PERFORMANCE AND SPATIAL MEMORY IN THE 5XFAD MOUSE MODEL OF ALZHEIMER’S DISEASE

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The 5xFAD mouse model of Alzheimer’s Disease (AD) has five mutations, three on the APP gene (Swedish, London and Florida), which are seen in humans with AD and two more on the Presenilin1 gene (PSEN1M146L and PSEN1L286V). Together these mutations increase Aβ42 synthesis to form intracellular plaques at 1.5 months and extracellular plaques at 2 months of age. Previous research using 5xFAD mice demonstrated impairments in spatial learning at six months of age, and increased deficits after 12 months of age, when motor impairments also became apparent. In addition, increased anxiety related behaviours were shown in the 5xFAD mice at 6 months of age. We used the Triple Test of Anxiety (TTA), Rotarod and the Hebb-Williams maze (HWM) to assess anxiety, motor performance and spatial learning and memory in 5xFAD mice at 6 and 12 months of age. The TTA is a combination of the open field, elevated plus maze and light-dark box, enabling us to compare the performance in each of those mazes without any carry over effects. We observed less time spent in the closed arms of the elevated plus maze of the TTA in the 5xFAD mice compared to the controls, yet they spent more time in the dark box of the TTA. We found motor deficits in the 12 month old 5xFAD mice on the Rotarod in both latency to fall from the rod and motor learning over 5 days. The HWM is an open field with start and goal boxes located at opposite corners. Barriers of various lengths are arranged to design different mazes that the mouse must solve in order to find food reward. The HWM has multiple levels of difficulty, with 12 maze designs in total, four in each group of easy, intermediate and hard mazes. We found no significant differences between 5xFAD and wild type control mice in the practice mazes of the acquisition phase. There was a significant maze difficulty effect in the hard mazes affecting both the WT and 5xFAD mice, and a trend suggesting that 5xFAD mice had more errors in all the mazes. In summary, our results show an increase in anxiety in the 5xFAD mice already present at 6 months of age, motor deficits at 12 months of age and suggest working memory deficits at 6 months of age. These results are important for evaluating the face validity of the 5xFAD mouse model, which is commonly used to study Alzheimer’s disease.

CHARACTERIZATION AND VALIDATION OF ALDH2-/- MICE AS AN AGE RELATED MODEL OF COGNITIVE IMPAIRMENT AND ALZHEIMER’S DISEASE

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Alzheimer’s disease (AD) currently affects 5.3 million Americans and 30 million people worldwide. However, the therapies available are unable to improve cognition deficits or reverse the degenerating disease. Despite showing promising results in preclinical trials, therapies targeting Aβ continue to fail in late clinical trials calling into question the identification of targets and the transgenic animal models used for preclinical evaluation. Current AD mouse models exhibit pathological changes dependent on overexpression of mutations linked with early onset familial AD which only accounts for a small amount of AD cases (1-5%). Therefore, the availability of an animal model that mirrors age-related cognitive impairments could become a valuable tool in assessing therapeutic strategies for improving memory and understand the underlying mechanisms of AD.

Oxidative stress has been suggested to be a driving force in AD pathogenesis in which aldehyde dehydrogenase 2 (ALDH2), an enzyme that detoxifies toxic aldehydes, has been seen to play a role. Our proposed mouse model lacks ALDH2 and has appearances of AD-like pathologies. We exhibited an increase in toxic aldehyde formation, age-dependent cognitive impairments, and dysregulation of AD related biomarkers. Aldh2-/- mice demonstrate key components of AD rarely seen in current mouse models such as development of classical characteristics of AD in parallel with biomarkers involved in neuronal and synaptic function and apoptosis. This proposed model for sporadic AD could expand the effectiveness of preclinical models and create greater predictability when shifted to human clinical trials.
Alzheimer’s disease (AD) is an age-related disease characterized by progressive neurodegeneration and dementia. Results from phase II clinical testing of methylene blue (MB) as a therapeutic agent for treatment of AD show that administration of MB significantly slowed disease progression in a large portion of individuals and improved cognitive function in AD patients after six months. MB has since been shown to mediate removal of amyloid-beta (Aβ) peptides (senile plaques) in a mouse model by increasing activity of the proteosome. In addition MB extends in vitro replicative lifespan of IMR90 human primary lung fibroblasts when present at low levels in growth media. An increase in cytochrome c oxidase and in the expression of phase II anti-oxidant defence enzymes were associated with this MB mediated delay in senescence. Many reports have linked oxidative damage to DNA and the associated avoidance and/or repair processes to ageing and neurodegeneration. Amnestic mild cognitive impairment (MCI) and AD are both associated with decreased base excision repair (BER) and increased accumulation of unrepaired oxidative DNA damage. BER is the main pathway for the repair of oxidative DNA lesions and is a potential target for treatment and/or prevention of AD. MB acts as a photosensitizer and when exposed to visible light (VL) leads to the formation of 7,8-dihydro-8-oxoguanine (8-oxoG) oxidative DNA lesions that are repaired by BER.

In the present work we have examined the effect of culturing IMR90 cells and primary human skin fibroblasts in 100nM MB on BER of oxidative DNA lesions using a host cell reactivation (HCR) assay. The HCR assay utilizes a non-replicating adenovirus (AdCA35) expressing the bacterial β-galactosidase (β-gal) gene and MB+VL to induced 8-oxoG lesions in the viral DNA. HCR was examined in cells grown in the presence of 100nM MB for 2 to 8 population doublings and expression of the MB+VL-treated reporter gene was examined over a time course of 3 to 24 hours after infection with AdCA35. Consistent with an increase in BER capacity, a significant increase in expression of the oxidatively damaged β-gal reporter gene was observed in IMR90 fibroblasts grown in 100nM MB when scored at 12 hours after infection. However, Western blot analysis revealed no effect of growth in 100nM MB on the expression of the BER proteins APE1, CSB, DNA polβ and p53 in IMR90 cells. In addition, the growth of human skin fibroblasts GM8400 and GM9503 in 100nM MB resulted in a small increase in expression of the oxidatively damaged β-gal reporter gene when scored at 12 hours after infection, although this increase was not significant. The results presented here are consistent with increased BER in IMR90 lung fibroblasts due to growth in 100nM MB, suggesting enhanced repair is involved in extension of their in vitro lifespan and may play a role in the positive outcome of AD patients treated with MB. (Supported by funds from the Canadian Cancer Society)

**NOVEL THERAPEUTIC STRATEGIES TO TARGET ALZHEIMER’S DISEASE**

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Neurodegenerative disorders such as Alzheimer's disease are becoming more prevalent due to longer life expectancies. While pharmacological treatments can temporarily improve symptoms, there are no treatments available that can slow or stop the malfunction and death of neurons in the brain. One of the major problems associated with the treatment of neurodegenerative disorders is bioavailability as the blood brain barrier (BBB) is exceptional at preventing drugs from crossing into the brain. Several strategies have been proposed, such as disrupting the integrity, or inhibiting the drug efflux pumps on the BBB. However, these techniques will also allow other toxic substances access to the brain leading to potentially devastating side effects. A novel strategy is to use active transport mechanisms present on the BBB to transcytose, or slingshot, drugs into the brain. The transferrin receptor has been studied extensively for its potential to serve as a promising target for the delivery of a variety of drug vehicles. Aptamers have emerged as an alternative to conventional antibodies due to their safety profile, increased stability and minimal batch-to-batch variation. Here we describe the generation of nucleic acid aptamers to the transferrin receptor suitable for in vivo delivery of therapeutics across the BBB. The transferrin receptor aptamers were truncated and their specificity and sensitivity was confirmed against both transferrin receptor-positive and -negative cell lines. Their ability to be internalised was confirmed using confocal microscopy. Furthermore, colocalisation studies with a transferrin antibody confirmed a similar uptake, confirming receptor mediated endocytosis. Transcytosis was first studied in vitro, followed by examination of its capacity to cross the BBB in vivo in a mouse model. The results from this study confirm the potential for these aptamers to be utilised for therapeutic delivery of drugs across the BBB for the treatment of neurodegenerative disorders.
Nowadays, there is evidence that brain glucose metabolism and Alzheimer's disease (AD) are linked. Patients suffering from type II diabetes present a higher risk to develop AD while in Alzheimer's disease patients the brain glucose metabolism is reduced, leading to a general hypometabolism. This abnormal glucose metabolism can already be observed in genetically predisposed people before the expression of any clinical sign. It is therefore very important to better understand the link between brain utilization of glucose and AD. On the other hand, while beta-amyloid aggregates are one of the principal hallmarks of the disease, all strategies targeting these aggregates have failed until now to prove their efficacy. Targeting the amyloid precursor protein (APP) itself and its role in brain metabolism could bring some new insights and lead to novel therapeutic strategies. The aim of this project is to better understand the link between the expression and the processing of APP and brain glucose metabolism and its impact on neuronal activity and synaptic connections. This would provide new evidences in the pathological process of Alzheimer’s disease and diabetes. Experiments were carried out on the hippocampus of transgenic mice B6.129S7 having 2 (+/+, WT), 1 (+/−, HT) or 0 (−/−, KO) allele of the APP gene allowing the study of three levels of APP expression. This model has the advantage of excluding the possible role of beta-amyloid aggregates because the endogenous murine form of the beta-amyloid peptide does not aggregate into oligomers and fibers. The expression of APP gene and protein was evaluated by genotyping and Western-Blotting respectively. The correlation between APP expression level and metabolic activity in the hippocampus was evaluated by 1H-NMR spectroscopy and has allowed to discriminate each genotype on the basis of their metabolic profile. We observed a decrease in the level of glucose in the hippocampus of KO mice compared to WT mice. Creatine and phosphocreatine were also reduced in APP KO mice compared to HT and WT whereas the level of GABA increases in the hippocampus of KO mice. The interesting thing is that heterozygote mice (HT) present an intermediate level of each of these metabolites. The physiological impact of the interaction between APP and glucose was studied by extracellular electrophysiological recordings of cell excitability and synaptic activity in acute hippocampal slices. Slices were incubated with three different concentrations of glucose in the aCSF to assess their sensitivity to hypoglycaemia (10mM, normoglycemia; 5mM, mild hypoglycaemia; 2.5mM, severe hypoglycaemia). Preliminary results showed that the reduction of glucose level from 10mM to 5mM induced a large decrease of the synaptic response in WT mice (50 % of reduction) while the decrease in synaptic activity was much less important in KO mice (30% of reduction). Here again heterozygote mice presented an intermediate phenotype (40% of reduction). Moreover a higher decrease in glucose supply (2.5mM) further reduced the synaptic response, indicating that a more pronounced glucose hypometabolism has more deleterious consequences on neural viability. Finally ageing also seems to have an effect on the hippocampus. Indeed, 6 month-old mice showed a decrease in synaptic activity and excitability compared to 6 week-old mice. As we observed a modification of the expression of GABA, we studied the effect of disinhibition on electrical activity by adding picrotoxin (PTX) to the aCSF. In the normoglycemic condition the intensity of the epileptiform activity was higher in KO mice than in the other two groups. When the glucose was reduced to 2.5mM, we observed an extinction of the fEPSP in most of the WT slices compared to the KO slices, where epileptiform activity was still high. Once again HT mice presented an intermediate phenotype.

INTRAPERITONEAL TREATMENT WITH CAFFEEIC ACID PHENETHYL ESTER COUNTERACTS β-AMYLOID DAMAGE INDUCED IN A MURINE MODEL OF ALZHEIMER'S DISEASE

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Alzheimer’s disease (AD) is considered the most frequent neurodegenerative disease age-related and the main cause of dementia in elderly patients. AD is characterized by the progressive loss of cognitive capacities, in the beginning the short term memory ability and then all intellectual functions are involved. The principal morphological abnormalities that could be observed in the evolution of AD are the formation of neuritics plaques of β-amyloid (Aβ) protein and the intracellular neurofibrillary agglomerates of tau protein hyperphosphorylated, beyond microgliosis, dystrophic neuritis and neuronal and synaptic death. AD etiology is still unknown; the most common hypothesis involved the activation of amyloid cascade, where the crucial event may be an imbalance between production and degradation of Aβ peptide. Polyphenols are natural compounds that have already shown interesting neuroprotective properties, especially trough an antioxidant activity, and in AD, an anti-amyloidigenic property. The caffeic acid phenethyl ester (CAPE), located in propolis, have shown anti-inflammatory, immunomodulatory, antiproliferative, antioxidant and antimicrobial activities; that are all involved in the evolution of AD. The aim of the present study is to investigate the potential neuroprotective properties of CAPE in an experimental murine model of AD. We injected Aβ1-42 oligomers intracerebroventricularly in C57BL/6 mice, and the treatment with CAPE (10
Treatment animals were sacrificed and we analyzed the redox cell status through the evaluation of the reactive oxygen species (ROS) formation. Our data show that Aβ1–42 oligomers injection determines a consistent increment in ROS formation and CAPE is able to restore a physiological oxidative cellular status. We also evaluated glutathione (GSH) levels, one of the main endogenous antioxidant. Our results have shown the ability of the molecule of our interest to modify the GSH content slowing down its levels at basal values. In addition, we investigated the expression of the nuclear transcriptional factor Nrf2, able to control the transcription of several cellular systems of detoxification and defense. In our experimental model, we observed a significant increment of Nrf2 activation in animals lesioned and then treated with CAPE, showing a probable implication of this pathway in its neuroprotection mechanism of action. Finally we investigated synaptic activity and Aβ protein immunoreactivity by immunohistochemistry. Our results have shown increased synaptophysin reactivity in Aβ/CAPE group compared to Aβ/vehicle group and a decrease of Aβ protein deposition in the same group. In conclusion, our data show an interesting neuroprotective activity of CAPE, it is not only able to restore a physiological oxidative status and to interfere positively with Nrf2-pathway, but also to contribute to the improvement of synaptic functions.

**NUTRITIONAL STRATEGIES IN THE PREVENTION AND /OR MANAGEMENT OF ALZHEIMER'S DISEASE: 1ST PART OF A SYSTEMATIC REVIEW**

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**BACKGROUND:** Alzheimer’s disease (AD) is one of the main causes of dependency and disability in the elderly population. A number of investigations have being seeking its prevention and/or management, and in this context, it is important to highlight the role of modifiable lifestyle factors, such as nutrition. AIMS: The present study aims to conduct a systematic review and subsequent meta-analysis of clinical and epidemiological studies with respect to the use of food and/or nutrients in the prevention and treatment of AD. In this first part, we are presenting the main types of studied found.

**METHODS:** This work has been conducted based on the Cochrane Handbook for systematic reviews of interventions and the The PRISMA Statement for reporting systematic reviews and meta-analyses. We are consulting the electronic databases: MEDLINE/PubMed, CCTR, EMBASE, Virtual Health Library, Web of Sciences and website Alzheimer Disease International. The key words identified in the title and abstract of the texts were divided in three groups: a-) Clinical situation: #Alzheimer Disease, #Dementia Type Alzheimer; b-) Intervention: #Nutrient, #carbohydrate, #glucose, #lipids, #fatty acids, #Ωmega 3, #protein, #amino acids, #vitamin, #mineral, #zinc, #Selenium, #phytochemical, #antioxidant, #diet, #food, #dietary pattern, #mediterranean diet; c-) Type of study: #clinical trial, #randomized controlled trial, #epidemiological, #incidence study, longitudinal study, #follow-up study. We are consulting studies from the beginning of the database to the present, in Portuguese, English or Spanish. Unpublished studies have been directly obtained with the authors.

**RESULTS** of the 1st part: the whole research identified a total of 35327 studies, of which, 456 were directly related to dementia and nutrition and were repeated 5213 times in the total number of identified studies. From the 456 studies found, we excluded 274, because they were literature reviews and because they did not answer the systematic review’s questions. From the remained studies we found the following types of study: amino acids: 2 articles; carbohydrates: 2; lipids except w-3: 9; Ωmega 3: 23; antioxidants: 16; dietary patters and food: 38; micronutrients: 14; commercial supplements: 22; B-vitamins: 21; D-vitamin:5; Vitamin C+ E: 6; vitamin E: 16; vitamin E+B12+folic acid+ aspirin= 1; other substances: 6. From our data until now we observe most of the studies based on dietary patterns, instead of specific nutrients

Key-words: systematic review; meta-analysis; Alzheimer’s Disease.

**THE MOST FREQUENTLY USED TESTS FOR ASSESSING EXECUTIVE FUNCTIONS IN AGING**

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Introduction: There are numerous neuropsychological tests for assessing executive functions in aging, which vary according to the different domains assessed. Objective: To present a systematic review of the most frequently used instruments for assessing executive functions in older adults with different educational levels in clinical and experimental research. Methods: Articles published in the last five years
were searched, using the PubMed database with the following terms: “neuropsychological tests”, “executive functions”, and “mild cognitive impairment”. There was no language restriction. Results: 25 articles fulfilled all the inclusion criteria. The seven neuropsychological tests most frequently used to evaluate executive functions in aging were: [1] Trail Making Test (TMT) Form B; [2] Verbal Fluency Test (VFT) - F, A and S; [3] VFT Animals category; [4] Clock Drawing Test (CDT); [5] Digits Forward and Backward subtests (WAIS-R or WAIS-III); [6] Stroop Test; and [7] Wisconsin Card Sorting Test (WCST) and its variants. The domains of executive functions most frequently assessed were: mental flexibility, verbal fluency, planning, working memory, and inhibitory control. Conclusion: The study identified the tests and domains of executive functions most frequently used in the last five years by research groups worldwide to evaluate older adults. These results can direct future research and help build evaluation protocols for assessing executive functions, taking into account the different educational levels and socio-demographic profiles of older adults in Brazil.

This work was supported by the CNPq – Brazil

THE ASSOCIATION BETWEEN CORTISOL LEVELS, COGNITIVE AND CARDIOVASCULAR FUNCTIONS IN PATIENTS WITH ALZHEIMER DISEASE AND VASCULAR ENCEPHALOPATHY

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OBJECTIVE:
To investigate the association between cortisol level and cognitive and cardiovascular functions in Alzheimer disease (AD) and vascular encephalopathy (VE).

METHODS:
In 32 patients with AD, 43 patients with VE and in age-matched 28 healthy subjects the parameters of visual evoked potentials (VEP), characteristics of blood pressure, heart rate and cognitive tests performance as well as the level of salivary and blood cortisol were examined. The analysis of correlation between cognitive and cardiovascular characteristics and cortisol levels was performed.

RESULTS:
The blood and saliva cortisol in the AD and VE patients were 1.5-2.0 times higher than in the healthy subjects. In the healthy subjects the amplitude of VEP P3 component showed positive correlation with blood cortisol level, while in the AD patients the amplitude of VEP P3 component showed negative correlation. In VE subjects the salivary cortisol level increased significantly during the performance of cognitive tasks. Baseline cortisol level correlated with diastolic blood pressure recorded during the performance of Luria's memory test.

CONCLUSIONS:
In patients with AD cortisol influences cortical information processes, whereas in patients with VE cortisol affects the regulation of blood pressure. Studies of association of cortisol with physiological processes may be informative for finding locus minoris susceptible to stress.

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EFFECTS OF LOW FORMAL EDUCATION ON COGNITION, FUNCTIONALITY AND FRAILTY IN ELDERLY: A COMMUNITY-BASED STUDY

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Aim: This study aimed to examine the effects of low education (0-4 years) on cognition, functional abilities and frailty in elderly community dwellers.

Methods: Participants: elderly residents under the primary health care system of Sao Carlos, Brazil. 594 addresses recorded elderly dwellers, which were contacted for the study. Of all contacted families, 541 participants fulfilled criteria: elderly (≥60), with low education (≤4 years); 123 were excluded for different reasons (loss of contact/change of address; death, etc). Data were collected during home visits in the period from April to November 2014. Instruments included: cognitive screening (Mini Addenbrooke's Cognitive Examination, M-ACE, cut off 21/30); functional abilities (Lawton Index for Activities of Daily Living – IADL, cut off 7/17 and 20/21); frailty (Fried's phenotype, defined as a syndrome of unintentional weight loss, fatigue, muscular weakness, walking slowness and decrease in the practice of physical activity,
Results: The sample had a similar proportion of males and females (44.1%, 55.9%), average age 72 years. The participants had an average of 13 points in the M-ACE, 20.7% were independent, 75% were partial dependent and 4.3% were dependent to the functional abilities, 27.6% categorized as frail, 52.2% as pre-frail and 20.2 as non-frail. The regression analyses revealed that level of education is a significant factor on cognitive scores, disability and frailty. Each year of education improves 1.87 (p<0.01; 95% CI) points on the M-ACE, 0.57 (p<0.01; 95% CI) points on the IADL scale and reduces frailty by 0.15 (p<0.01; 95% CI). The strongest effects were seen in the cognitive scores.

Conclusion: Low education had an important influence on cognitive scores, functional abilities and frailty in this sample of Brazilian elderly with low levels of education. This study demonstrates that elderly with lower levels of education are potentially at greater risk of dependence and frailty, and should be potentially targeted for early interventions to minimize greater disability.

EXPRESSION OF REGULATORY PROTEINS IN CHOROID PLEXUS CHANGES IN EARLY STAGES OF ALZHEIMER’S DISEASE
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ABSTRACT
The role of choroid plexus in Alzheimer’s disease (AD) is being increasingly recognized. Recent studies suggest that the choroid plexus has a more important role in physiological and pathological brain functions than previously appreciated. To obtain additional insight on choroid plexus function, we performed a proteomic analysis of choroid plexus samples from AD stages I-II (n = 16), III-IV (n = 16), and V-VI (n = 11), and 7 age-matched control subjects. We used differential 2D electrophoresis (2-D DIGE) coupled with mass spectrometry to generate a complete picture of changes in choroid plexus protein expression occurring in AD patients. We identified 6 proteins: 14-3-3 δ, αB-crystallin, PSME1, annexin V, and aldehyde dehydrogenase (ALDH), which are significantly regulated in AD pathology (p<0.05, >1.5-fold variation in expression comparing with control samples), with central physiological functions, including mitochondrial dysfunction and apoptosis regulation, and able to model key pathological events. The data presented here contribute additional significance to the emerging importance of molecular and functional changes of choroid plexus function in the development of AD pathology.

Day 3:
Invited Speakers Abstracts

Aberrant cell cycle in Alzheimer’s disease lymphocytes: diagnostic prospects
Professor Urszula Wojda, Head of the Laboratory of Advanced Preclinical Research Neurobiology Center, Nencki Institute of Experimental Biology, Warsaw, Poland
In Alzheimer’s disease (AD) some molecular changes are observed not only in patients’ neurons but also in peripheral cells. Among such changes is aberrant regulation of the cell cycle and apoptosis. The dysregulation of the cell cycle was reported, among others, in AD blood lymphocytes. These findings provide support for the cell cycle hypothesis of AD pathogenesis and open perspectives for the application of easily accessible blood cells in studies on AD pathogenesis. Moreover, based on the aberrant cell cycle regulatory molecules in AD lymphocytes new diagnostic methods and marklers might be developed.

Clusterin: a garbage disposal system you can’t do without
Professor Mark R Wilson, School of Biological Sciences, Faculty of Science, Medicine & Health, University of Wollongong, Wollongong, Australia
 Previous studies have identified changes in the clusterin (CLU) gene as the second highest risk factor for Alzheimer’s disease (AD). CLU is a normally secreted chaperone that appears to also be actively involved in the turnover of misfolded/aggregating proteins inside the cell. Multiple lines of evidence indicate that CLU can enter the cytosol and there influence vesicle trafficking and protein degradation pathways. CLU has recently been shown to affect Tau aggregation and toxicity in cell and animal models. This talk will describe
Interspecies comparative gene expression profiling revealed impaired insulin production and insulin signaling in Alzheimer's disease brains: The Hisayama Study

Dr Yusaku Nakabeppu, DVM, D.Sc. Distinguished Professor and Director of Research Center for Nucleotide Pool, Division of Neurofunctional Genomics, Department of Immunobiology and Neuroscience, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan

To identify molecular pathological alterations in Alzheimer's disease (AD) brains, we performed interspecies comparative microarray analyses using RNA prepared from postmortem human brain tissues donated for the Hisayama study, and hippocampal RNAs from the triple-transgenic mouse model of AD (3xTg-AD). We found altered expression of genes involved in insulin production, insulin signaling and mitochondrial function in AD brains. Mitochondrial dysfunction is considered to have a pivotal role for developing AD, we further examined effects of human mitochondrial transcriptional factor A (hTFAM) transgene, which plays important roles to maintain mitochondrial homeostasis, on the pathology of 3xTg-AD mice.

Various phenotypes of Alzheimer's disease and management strategies

Chuang-Kuo Wu, M.D., Ph.D., FANA, Director, Alzheimer’s Disease Program, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas, USA

As Alzheimer’s disease becomes prevalent in the world, patients and caregivers are both suffering. The recent advances in biomarker research indeed have offered high hopes. We can diagnose Alzheimer’s disease at the earliest stage with confidence. In 2014, the International World Group utilized the proper biomarkers to set up sets of criteria for the various phenotypes of Alzheimer’s disease, including the typical one, atypical phenotypes and mixed type. This particular classification is quite useful. I will present the clinical cases to illustrate all phenotypes of Alzheimer’s disease. I will discuss the management strategies for each phenotype of Alzheimer’s disease.

Reduction in Antipsychotic Medication Use Among US Nursing Home Residents: Regulation Revisions and a National Partnership

Professor Jane R. Mort, Pharm.D., Associate Dean for Academic Programs, Professor of Pharmacy Practice, College of Pharmacy, South Dakota State University, USA

The United States Centers for Medicare & Medicaid Services established a partnership (May, 2012) and revised regulations (May, 2013) to decrease the percentage of residents in nursing homes receiving an antipsychotic agent. This goal emanated from concerns including the large percentage of residents taking antipsychotic agents, the questionable use of antipsychotics, the high cost of inappropriate antipsychotic use, and reported toxicity in patients with dementia. The features of these national efforts, rationale, and impact on antipsychotic medication use patterns will be discussed.

Caregiver burden in dementia in rural Australia

Ms Kaye Ervin, Researcher and Lecturer Rural Health, University of Melbourne, Vic, Australia

Caring for a person with dementia, predisposes carers in rural areas to high levels of stress and depression. In a study conducted in rural Victoria, Australia, more than half of the carers of people with dementia reported high levels of stress and depression. Behavioural and psychological symptoms of dementia, exhibited by care recipients, such as agitation, anxiety, aggression and nocturnal disturbance, showed a relationship to the level of stress reported by the carer. In addition carers did not use services available in the community to help them in their caring role, indicating that referral pathways are poor.

Diagnosis of mild cognitive disorders in older adults: the usefulness of evaluation of Activities of Daily Living

Dr Patricia De Vriendt, Vrije Universiteit Brussel & University college Artevelde Ghent, Belgium

With the high prevalence and incidence of dementia, the ability to detect Alzheimer’s Disease, in its prodromal phase will remain an important research topic. Early detection is a strategic intervention point in the clinical management of AD. However, although traditional biomarkers are strongly promoted, to date there are no guidelines to use them routinely in clinical practice. Therefore sensitive clinical measures that are associated with biomarkers of AD, but easy and inexpensive to administer, are needed. We developed a measurement to evaluate the ‘advanced’ Activities of Daily Living, which showed promising results for identifying mild cognitive disorders.
Driving quality care for people with dementia in nursing homes: The impact of large scale interprofessional student clinical placements.

Dr Andrew Robinson RN, MNS, PhD, Professor of Aged Care Nursing, School Of Health Sciences., Wicking Dementia Research and Education Centre., University of Tasmania, Hobart, Tasmania, Australia

The Wicking Dementia Research and Education Centre has prototyped Teaching Aged Care Facilities in six Australian aged care nursing homes. The project deploys a whole of organization change approach to facilitate large-scale, high quality inter-professional student placements, and build organisational and leadership capability. The project findings highlight positive outcomes for students learning and knowledge of dementia, as well as evidence of improved care outcomes and quality of life for people with dementia resident in the nursing homes.

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline

AUTOMATIC VERSUS EXECUTIVE SEMANTIC MEMORY IMPAIRMENT IN EARLY ALZHEIMER’S DISEASE: A POSSIBLE DIAGNOSTIC TOOL?
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Background: A decline in semantic memory (SM) is experienced earlier on in Alzheimer’s disease (AD). This impairment can be tracked through linguistic tasks that require semantic processing, such as the picture naming test which is widely used in the assessment of dementia. In a healthy brain, semantic functioning relies on two components, semantic representation and semantic control. Our aims were to devise novel instruments to determine the nature of impairment present in early AD and to improve the identification of people at risk of developing AD.

Methodology: The test included 40 novel photographed pictures (20 living and 20 non-living) which allowed for the assessment of the different aspects of SM. Half of the pictures consisted of whole objects (semantic representation) while the other half contained part of an object (semantic control). A group of healthy older adult participants and a group of patients with mild cognitive impairment (MCI) (amnestic and non-amnestic) were tested with this newly devised confrontation naming test. In both cases participants were required to recognise and name the presented pictures. The difference in performance on both sets of pictures was analysed.

Findings: There was a significant difference in performance between the healthy and the MCI groups with the latter being able to name fewer items. The difference was more prominent on the task that required semantic control. A difference in performance was also reported between the amnestic and non-amnestic MCI subgroups. Therefore the test is able to discriminate between healthy ageing and early AD as well as differentiate between the non-amnestic and the amnestic form of MCI.

Conclusions: The novel picture naming test increases sensitivity of confrontation naming to SM impairment. Furthermore, it contributes to the understanding of the memory impairment present in early AD and might be useful to detect abnormalities earlier than current tests do. Earlier detection of abnormal cognitive decline will have implications for the management and care of the disease as well as the testing of possible disease modifying drugs.

PROGRESSION PATTERN OF BRAIN MINERAL DEPOSITION AS A DIFFERENTIAL INDICATOR OF COGNITIVE DECLINE
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Background: Brain mineral deposition is associated with cognitive decline and is a proposed mechanism in the pathogenesis of Alzheimer’s Disease (AD) [1,2]. We investigated prevalence of basal ganglia mineral deposition (BGMD) and brain microbleeds on individuals of cognitive status ranging from cognitively normal to early/late mild cognitively impaired – these being differentiated by results from the Wechsler Memory Scale Logical Memory II [3] - and AD patients.
Methods: All MRI scans available from the ADNI2 database (adni.loni.usc.edu) that had the required sequences for analysing brain mineral deposition (i.e. T1- and T2*-weighted sequences) at the time the database was accessed (January 2015) were analysed, blind to any clinical or cognitive information. Only 20 individuals had the relevant MRI datasets for 3 consecutive years. Microbleeds were identified in this sample using the BOMBS guidelines[4], their count and volumes were obtained using a semi-automatic method [1] and BGMD was assessed fully automatically[2]. From the same database, 200 other datasets were identified to have the relevant MRI sequences at least once. The same measurements were cross-sectionally analysed in this subsample. We examined distribution and load of mineral deposition in relation to cognitive status using Mann-Whitney U test. Intracranial volumes were adjusted for in the statistical analyses.

Results: In the longitudinal analysis 3/20 individuals were cognitively normal (CN), 12/20 had early mild cognitive impairment (EMCI), and 5/20 had late cognitive impairment (LMCI). Cognitive status did not change during the 3 years. Despite slight variations in microbleed count, it was higher in LMCI than EMCI (p=0.677) and CN individuals (p=0.863). A consistent pattern of temporal lobe vessel mineralisation was found, most predominately in patients with MCI (2/3 CN, 6/12 EMCI, 5/5 LMCI). When extended to a larger sample of 58 CN, 78 EMCI, 49 LMCI and 15 AD patients, microbleeds were significantly lower in CN patients compared to EMCI (p=0.017) and LMCI patients (p=0.002). There was no significant difference in number of microbleeds between CN and AD patients (p=0.416). The temporal lobe vessel mineralisation was observed more evenly across the cognitive groups: in 21% CN, 27% EMCI, 37% LMCI, and 20% AD patients.

In the longitudinal analysis, BGMD was present in all cognitive groups (median(IQR): 0.20(0.26)ml in year 1, 0.17(0.50)ml in year 2 and 0.19(0.34)ml in year 3), absent in 1/3 CN individual and absent in the baseline scan of 2/12 EMCI patients. Whilst the median volume of BGMD increased in EMCI patients from years 1 to 3 (0.16ml → 0.17ml → 0.21ml), it decreased in LMCI patients (0.26ml → 0.11ml → 0.08ml). BGMD of predominantly iron content followed the same pattern: 0.14ml → 0.16ml → 0.20ml for EMCI patients and 0.20ml → 0.11ml → 0.07ml for LMCI patients. Whilst volume of mineralised clusters also increased in EMCI patients from years 1 to 3 (0.005ml → 0.007ml → 0.009ml), a clear pattern was not observed amongst the CN individuals (0.01ml → 0.02ml → 0.0ml) and neither amongst the LMCI patients(0.02ml → 0.003ml → 0.01ml). The same pattern (i.e. higher load of BGMD in MCI patients with respect to CN and AD) was observed in the larger sample.

Conclusions: Microbleeds and BGMD may be useful indicators of mild cognitive impairment. A novel finding of a trend in the progression of mineralisation and microbleed load amongst patients from CN to LMCI and gradual decrease towards AD could be of potential use as a differential indicator in the diagnosis of AD if replicated in a larger sample.

References

NEUROPSYCHIATRIC SYMPTOMS AND DEMENTIA IN PARKINSON’S DISEASE
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Background
Neuropsychiatric symptoms, particularly apathy, negatively affect quality of life of PD patients who developed these symptoms. Apathy refers to a combination of behavioural, emotional and cognitive features that lead to reduced interest and participation in daily life activities. Apathy is considered one of the most common neuropsychiatric symptoms in Parkinson’s Disease (PD). The prevalence of apathy in PD is approximately 40%. Few studies have investigated the cognitive performance of apathy in PD. From apathy studies in Alzheimer’s disease and other neurological disorders we expected to find dysfunctions in abilities of executive function and memory.

Materials and Methods
Sixty Five PD patients in the early stages of the disease (25 with apathy and 40 without apathy) underwent extensive neuropsychological screening (To assess multiple cognitive domains e.g. executive function, memory, attention, abstract reasoning and visuospatial), neuropsychiatric assessment using the Neuropsychiatric Inventory and neurological examination. An independent T-test was carried out to compare the two group of patients (with apathy and without apathy) using SPSS software.

Results
Patients with apathy had lower scores in all cognitive tests. However, significant impairments were found in tests assessing executive functions (Letter Fluency Test and Stroop Test) and a trend-level significant difference was observed in memory tests (Rey 15-word Memory Test and Category Fluency Test) in patients with apathy when compared with patients without apathy.
**Discussion**

Apathy was associated with overall lower level of cognitive performance, particularly in executive function and memory skills. These findings are in line with results from studies of other neurological conditions. For instance, a similar pattern of executive dysfunction has been reported in apathetic patients with PD with dementia and apathetic patients with Alzheimer disease. Apathy appears to be a risk factor for cognitive impairments in PD and might be a useful clinical indicator of dementia risk in PD.

**ARE SYMPTOMS OF DEPRESSION AND ANXIETY PREDICTIVE OF THE INCIDENCE OF ALZHEIMER’S DISEASE? FINDINGS FROM THE AUSTRALIAN IMAGING, BIOMARKERS & LIFESTYLE (AIBL) STUDY OF AGING**

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While depressive symptomatology has in some studies been shown to occur co-morbidly with and potentially predict the incidence of Alzheimer’s disease (AD), anxiety has received relatively little attention in the research literature to date. It was here hypothesised that depression and anxiety scores at baseline would predict i) deterioration in age-related cognitive function and ii) a shift in diagnostic category from healthy aging towards AD. 633 cognitively healthy individuals at baseline (mean age = 70 years) completed a 36-month AIBL follow-up assessment. Across the 3-year course of the study, depressive symptomatology at baseline predicted a decline in attention span at follow-up while anxiety symptoms at baseline significantly predicted a decline in episodic memory. Depressive and anxiety symptomatology did not significantly predict conversion from healthy aging to mild cognitive impairment or Alzheimer’s disease. Given the observed relationship between emotion dysregulation and age-related cognitive change, further longitudinal studies over more extended time frames are clearly warranted to determine whether cognitive deterioration in older individuals influences progression to AD.

**RED BLOOD CELLS: A NEW PLAYER IN ALZHEIMER’S DISEASE PATHOGENESIS**

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Alzheimer’s disease (AD) is the most common form of dementia. It progresses quite slowly, and is clinically manifested in a gradual loss of memory and cognitive function. There have been no significant advancements in the diagnostics or causative factors for AD for over a century. This lack of progress is mainly due to the invalidity of the currently active doctrines of the origin of the disease: its brain localization, and amyloid hypothesis of the pathogenesis. AD affects about 30 million people worldwide. However, it is impossible to predict and prevent the illness, because the pathogenic mechanisms of AD are unknown to date. At the disease incidence of such a large scale, it is imperative to investigate the pathogenic factors involved in this disease in order to find the effective therapeutics targeted towards this devastating disease. Here we report a new model based on the red blood cell (RBC) interaction with amyloid 1-42 beta peptide (Abeta). Firstly, through different experimental methodologies, we have studied the properties of RBC’s membrane following to soluble Abeta exposure at different times, in order to characterize specific alterations induced by Abeta. Secondly, considering that RBC membrane contains, among blood elements, higher membrane AChE (acetylcholinesterase) levels, we can assume that there is a mechanism similar to the one which occurs at the neuronal level leading to an increase of Abeta toxicity mediated by the binding with RBC AChE. Similar to non-neuronal acetylcholine (Ach), Abeta following to AChE binding, is capable to affect RBC morphology and functionality. Lastly, since mechanical properties of RBC membrane are regulated by a number of molecular components of signaling and/or regulatory pathways, of these, we have shown the role played by protein band 3, protein kinase C isoenzymes (PKC), endothelial nitric oxide synthase (eNOS), caspase 3 and pentose phosphate pathway in the mechanism responsible for RBC morphology alterations induced by Abeta. Thus the entire signaling cascade which is associated with Abeta dependent-morphology alterations of RBC, responsible ultimately in a reduced oxygen delivery to brain causing hypoxia, include: a) AChE membrane as...
Abeta receptor; b) intracellular steps involving antioxidant imbalance, PKC, eNOS and caspase3, responsible for cytoskeleton alterations. Therefore, oxidative stress from Abeta-altered RBC may outflow and damage adjacent cells and tissues, accelerating the progression of AD.

References:
Carelli-Alinovi, C., Giardina, B., and Misiti, F. (2015), Cell Biochem Funct. in press

BETA-AMYLOID Oligomerization IS ASSOCIATED WITH THE GENERATION OF A TYPICAL PEPTIDE MODIFICATION FINGERPRINT WHICH CAN BE SPECIFICALLY TARGETED USING NOVO-EPITOPE ANTIBODIES.
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Background: Beta-amyloid (abeta) oligomers account for the decline in synaptic plasticity and loss of memory associated with dementia and therefore represents an early diagnostic and therapeutic target for the treatment of Alzheimer's disease (AD). Oligomers are collectively defined as a group of neuro-toxic abeta aggregates of pre-fibrillar morphology and reflect the initial, early events of abeta misfolding associated with AD pathology. Therefore, the presence of toxic abeta oligomeric species found in cerebrospinal fluid (CSF) or blood of AD patients may highlight the onset of AD pathology. In order to elucidate the mechanisms of peptide misfolding in the early stages of AD pathogenesis, it is important to develop specific and sensitive assays to identify and monitor key molecular triggers and biological markers before the development of clinical symptoms.

Results: We have identified key molecular changes associated with abeta peptide oligomerization using targeted and quantitative mass spectrometry. This finding has enabled us to design new epitope targets (novo-epitope) for anti-abeta antibodies, which allow to specifically target a population abeta bearing these "diagnostic modifications" at the early stage of peptide oligomerization, without binding to the monomeric, non-toxic form of the peptide. Our targeted MS analysis of abeta oligomers indicate that, aggregation associated peptide modification gives rise to the formation of a stable entity with toxic oligomers, which can be specifically targeted using our novo-epitope antibodies. Screening of human post-mortem brain tissue and CSF samples from AD patients and non-demented control subjects revealed that these molecular changes of abeta peptide are a highly relevant feature found in AD patients.

Conclusion: Our findings show that the use of "novo-epitope "antibodies offers a new analytical and diagnostic tool for the identification of early molecular seeds of abeta oligomers in human CSF and post-mortem brain tissue extracts. We believe that these findings are crucial not only for understanding and targeting abeta peptide aggregation but also for monitoring disease associated changes in levels of abeta found in human biofluids. The development of precise analytical assays for the identification of antecedent biomarkers is not only crucial for an early diagnosis of AD pathology, but also serves as an indispensable analytical tool for monitoring changes in disease progression during the clinical testing of novel therapeutic compounds.

FUNCTIONAL MEMORY DISORDER- AN IMPORTANT DIFFERENTIAL DIAGNOSIS IN THE MEMORY CLINIC- KEY FEATURES AND REVIEW OF DIAGNOSTIC CRITERIA
Daniel Blackburn, Chris Elsey, Danielle Jones, Sarah Wakefield, Kirtsy Harkness, Annalena Venneri, Paul Drew, Markus Reuber

OBJECTIVE:
To create a diagnostic conversational profile of dementia within memory clinics

BACKGROUND:
Memory problems are a very common reason for presenting to primary healthcare practitioners and the early and accurate distinction of dementia from functional or non-progressive memory complaints is of great importance if appropriate treatment is to be delivered in a timely manner. Increased government and media interest aiming to increase diagnosis rates of dementia appears to have increased the number of people seeking help for memory problems. An increasing number of these presentations do not have dementia. There is a need to develop better cognitive screening tools that can detect functional memory problems as well as dementia.
One approach is to use conversation analysis. This technique has been used to study patient-doctor interactions and has been used to successfully distinguish epilepsy from non-epileptic attacks.

DESIGN/METHODS:
We have recruited 100 new attendees to a memory clinic and video and audio recorded the encounters. Transcripts were made and conversation analysis methods were successfully applied to doctor-patient interactions, focusing particularly on their interactional structure, dynamics and organisation.

RESULTS:
Conversation analysis profiles from 15 people with dementia and 15 people with Functional Memory Disorder have shown distinct profiles. Examples of features seen in people with dementia include head turn, failure to follow compound questions, length of turns and speed of response. Profiles of people with functional memory problems include speed and detail in describing cognitive complaints, no requirement for help from care-partners and being more concerned about their memory problem than the care-partner.

CONCLUSIONS:
Profiles from conversation analysis checklist may help primary care doctors screen, refer and treat people with memory complaints more effectively. Greater awareness of functional memory disorders with appropriate terminology and diagnostic criteria are required.

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DESIGN OF MEMORY AIDS AGENT SERVICE BASED LOCATION AND TIME FOR PEOPLE WITH DEMENTIA
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Purpose With dementia’s disease, this risk for wandering not only increases family burden and caregivers but it also reduces the independence of the person with the disease1. The effective way to keep the cognitive ability is suggested by keeping the cognitive impairment them in the social relationship with the others. But it has difficulty because of the family relationship has changed, so individual has less time for other relatives, friends and family1. Based on the social background, agent service which assists the dementia people has provided. For example, Pollack2 has proposed the conversational humanoid agent for people with dementia. This system recommends individual’s daily plan using AI-management technology. However, existing research/technology does not approach to assist with dementia based on whose current context (e.g. time and location) as far as we know. If agent service could assist using based on the current individual’s context, it will increase the independence for people with dementia.

Proposal In this research, we propose the memory aids service based on time and location for people with dementia. The service consists of three services, location detection service, forget-things registry service and agent service. This service aims to assist the individual based on individual’s context (i.e. schedule and current location). Moreover, this service could interact with a conversation for example if the person goes to the hospital the service assists that “Do you have proof of insurance?” and so on. Following we describe each feature of services. The location detection service aims to find where the dementia is in the home. So using such information, we can provide the suitable information for the location where the dementia people move. This service obtains the rough individual’s location information using some electronic device, so as to detect where the dementia people are in the house. So the sensor should easily to take a log at short intervals, but it does not require the high accuracy. Secondly, forget-things registry service which stores the usual schedule for the people with dementia. So, the caregivers or families could register the schedule such as daycare. Moreover, they register the information when the dementia people go out. Based on the registered information, the service reminds not only notify the schedule, but also could prevent from wandering around in the midnight. Finally, agent service enables people with both voice and text interaction that enables to easily understand and confirm to prevent forget-things. Concretely speaking, when the individual goes to hospital, the service displays the list of forget-things (e.g. insurance, wallet) on the screen and also confirms to the individual with a voice.

Result In this research, we have designed the memory aids service framework based on the location and time for people with dementia. Our proposed service consists of three services, location detection service, forget-things registry service and agent service.

References
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**Poster Presentation Abstracts**
Poster abstracts will be finalised weeks before the event

**THE PREVALENCE AND INFLUENCING FACTORS OF FEEDING PROBLEMS AMONG RESIDENTS WITH DEMENTIA**
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**ABSTRACT**

**Objectives:** The purpose of this study was to examine the prevalence of feeding difficulty and associated factors.

**Methods:** A cross-sectional research design was used. The subjects were recruited in long-term care facilities in Taiwan. Two hundred and thirteen residents with dementia participated in this study. An observational study was used in order to examine the prevalence of feeding difficulty and associated factors.

**Results:** The prevalence rate of feeding difficulty measured by FDI was 55.4%. The predictors of feeding difficulties during lunch were ADL and eating time ($\beta = -0.022$ and $0.097$). The predictors during dinner were cognition ($\beta = -0.082$), light level ($\beta = -0.003$), sound level ($\beta = 0.138$), talking with caregivers ($\beta = 0.626$) and eating time ($\beta = 0.096$).

**Conclusions:** The prevalence of the feeding difficulty among residents with dementia in long-term care was high and associated with multiple factors including physical function, psychological factors, social interactions, dining environment and culture issues. Training nurses or nursing assistants to notice feeding problems in order to provide adequate assistance is important for preventing malnutrition among residents with dementia in long-term care facilities.

**Keywords:** Dementia, Feeding difficulty, Long-term care

**CHINESE CALLIGRAPHY WRITING AS MEANS FOR AUGMENTING ATTENTION AND WORKING MEMORY AMONG PATIENTS WITH MILD COGNITIVE IMPAIRMENT – INTERIM RESULTS**
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**Abstract**

This study aims at investigating clinical usefulness of an eight-week calligraphy training for augmenting cognitive functions of patients with mild cognitive impairment (MCI). Different from previous studies, Chinese calligraphy writing was used to specifically train orienting attention and working memory processes. The writing involved visually transforming the script of a Chinese character from "Kai" to "Hang" style, of which the latter were written in black ink with a brush pen. Taking a mnemonic approach, the transformation process has four stages. First, the character is to be broken down into individual strokes (orienting attention). Second, individual "Kai" style stroke is to be visually transformed into a "Hang" style stroke (orienting attention). Third, the "Hang" style strokes of the character are maintained and composed in visual working memory (visual working memory). Forth, the "Hang" style character image is written via motor execution (visual working memory). A total of 84 patients with mild cognitive impairment were randomized into experimental (n=41) and control group (n=43) (Age: Mean=68-69 years; MoCA: Mean=24). The experimental group received eight weeks of Chinese calligraphy writing training; while the control group received the same duration of training the use of electronic personal device. Both interventions contain writing of Chinese characters (writing "Kai" style characters with pen for the control group) and use of IPad (practicing writing "Hang" style characters with finger tracing). Assessment of cognitive functions was conducted at the baseline and by end of the interventions (i.e. at 9th week). The results indicated that the MCI patients in the experimental group showed significant post-intervention improvements in attention and visual scanning function (Symbol Digit Modalities test), working memory function (digit backward test), and self-perceived physical function (SF-36), than those in the control group. Among the experimental group, qualities of the writing scripts were significantly correlated with the post-intervention attention and visual
scanning functions of the patients. These findings suggest that intervention specific to augmenting orienting attention and working memory would be useful for patients with MCI. The mnemonic-based approach appears to be useful for adaptation to daily or cultural activities for the patients. The full study is to deliberate on the long-term effects of Chinese calligraphy writing and potential generalization of such effects.

DEMENTIA VILLAGE SINGAPORE: VISIONS OF THE FUTURE
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Introduction
Velocious development and urbanization in the past century has led to a wave of 'silver tsunami” sweeping over the developed world, with the number of dementia patients expected to double to 75.6 million by 2030. Emphasis on improving the quality of life of our seniors has never been so pertinent. In place of traditional nursing homes, the Netherlands has pioneered the first dementia village in the world, the De Hogeweyk, a 1.5-hectre self contained model village in Amsterdam. We imagine how a similar–styled village can be built in Singapore, and its feasibility.

Objectives
The principle of the dementia village would be to create a safe environment for dementia patients to live, as normal a life as they could. We want to preserve their freedom, accord them dignity and respect, and maintain a good quality of life.

The Dementia Village
Land scarce Singapore would be the perfect setting for a block of condominium-style apartments, with each flat furnished to a high standard and personalized according to the senior's liking. The rest of the compounds will be situated within a gated premise, replete with pavements, streets, cycling paths and gardens. Residents will be given the independence to walk around as they please.

The village will be helmed by a myriad of healthcare staff who will "live" in the same community. They will patrol the village in their own street clothes and look after the villagers in a discreet manner. For the patients' safety, security cameras will also be situated around the compounds. The village will be self-equipped with its own facilities. There will be a grocery store, gym, hair salon, restaurant, chapel and a GP clinic. There will also be a community town hall, where villagers can mingle and have classes such as cooking, chess, dancing and art therapy. Villagers will manage their own households with the help of staff if they require. Families are strongly encouraged to visit. Residents can participate in the community, be it as gardener in the compounds, or the leader in their religious community, or even the assistant cook in the kitchen.

Limitations
The cost of building and maintaining the compounds will be the main consideration, as well as manpower recruitment and training. Staff has to be passionate about serving the elderly, and contribute to creating a pleasant and harmonious village atmosphere. To make it affordable to the public, the costs of staying in the village will have to be reasonable, and might require subsidies from the government. It can be foreseen that demand for places in the village will be high, hence criteria has to be put in place to ensure the ones who will benefit from it the most will be selected.

Conclusion
A dementia village is a novel concept, which would result in a more active, comprehensive and humane way for dementia patients to live, without being handicapped by their condition.

ATTITUDES, PSYCHOLOGICAL AND BEHAVIOURAL IMPACTS OF GENETIC SUSCEPTIBILITY TESTING FOR ALZHEIMER'S DISEASE IN ASIAN ELDERLY
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Background: The only susceptibility gene for Alzheimer's disease (AD) that has been consistently replicated across studies is the Apolipoprotein E (APOE) gene. Compared with those possessing the common ε3/ε3 genotype, individuals with the ε3/ε4 or ε4/ε4 genotype have a three or eight-fold increased risk of developing AD respectively. Current clinical guidelines do not recommend APOE genotyping for prognostication because possession of the ε4 allele is neither sufficient nor necessary to cause or prevent AD, and might cause undue psychological distress. However, studies suggest that disclosure of ε4-positive status when conducted with adequate protocols does not appear to cause psychological harm. Moreover, ε4-
Therefore, the finding of some ongoing because of their neurodegenerative involvement of glial 1.

The Background:
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Acknowledgments.

Advancement of knowledge in these neurological disorders, but in order to demonstrate their possible pathological potential. It would be important to approach similar for Alzheimer's disease. Therefore, the efficient treatment. Since we have been able to demonstrate a relevant role of astroglia in prion diseases, we process has widely delayed the understanding of these pathologies and the neurodegeneration of these diseases.

Relevance has been pro individual contributions provided in the frame of Alzheimer's, just like Parkinson's or Huntington's diseases are being nowadays considered as prion-like disorder: Alzheimer's disease.

To our knowledge, the absence of studies at cellular level on these disorders is mainly taken very little into account in relation with them. Despite gliosis constitutes one of the histopathological changes typically found in affected brains, no enough relevance has been probably pinpointed to the components of glial population in the characteristic neurodegeneration of these diseases. To our knowledge, the absence of studies at cellular level on these processes has widely delayed the understanding of these pathologies and therefore, the finding of some efficient treatment. Since we have been able to demonstrate a relevant role of astroglia in prion diseases, we would like to approach in the same sense for Alzheimer's disease. Therefore, the involvement of glial population in the neuronal progressive deterioration of this disease is here assessed by morphological studies in order to demonstrate their possible pathological potential. It would not only mean a significant advance of knowledge in these neurological disorders, but it might open up new therapeutic strategies.

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GLIA IN A PRION-LIKE DISORDER: ALZHEIMER'S DISEASE
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Alzheimer's, just like Parkinson's or Huntington's diseases are being nowadays considered as prion-like disorders since they seem to share molecular basis and mechanisms of propagation. Consequently, all contributions provided in the frame of prion knowledge result relevant for other neurodegenerative diseases.

Pathogenesis is mostly unknown in all these neurodegenerative diseases and as consequence, to date it has been impossible to develop preventive and/or palliative treatments against all of them. In our opinion, individual protective response has been maybe taken very little into account in relation with them. Despite gliosis constitutes one of the histopathological changes typically found in affected brains, no enough relevance has been probably pinpointed to the components of glial population in the characteristic neurodegeneration of these diseases. To our knowledge, the absence of studies at cellular level on these processes has widely delayed the understanding of these pathologies and therefore, the finding of some efficient treatment. Since we have been able to demonstrate a relevant role of astroglia in prion diseases, we would like to approach in the same sense for Alzheimer's disease. Therefore, the involvement of glial population in the neuronal progressive deterioration of this disease is here assessed by morphological studies in order to demonstrate their possible pathological potential. It would not only mean a significant advance of knowledge in these neurological disorders, but it might open up new therapeutic strategies.

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AN AUDIT OF THE COGNITIVE DISORDERS CLINIC, MATER DEI HOSPITAL, MALTA
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Background:
The Cognitive Disorders Clinic was set up in November 2012. It is a neurology specialist service that provides assessment and management of patients referred with cognitive impairment. The clinic receives referrals of patients presenting with memory, concentration and attention problems as well as behavioural changes and new-onset difficulties of performing activities of daily living. Following this new service, an audit was carried out to study and identify current practice and any need for improvement.

The purpose of the audit was two-fold:
1. to study the referral tickets sent to the clinic and to identify if screening is done at the time of referral...
2. To examine preliminary assessment of patients in the clinic, investigations and services offered, as well as care plans provided to the patient and relatives.

Method used:
51 patients who were appointed at the clinic in 2013, were recruited retrospectively. Data was collected from the patients' records, PACS, iSoft Clinical Manager.

Results:
- Out of the 51 patients studies, 44 patients turned up for the appointment.
- 34 referral tickets were found in the medical records, 31 of these had a clear indication for referral.
- Only 5 patients from the total number of those referred had a formal assessment of cognitive function before being referred.
- On referral, only 8 and 5 patients had been screened for possible medical and psychiatric causes for cognitive impairment, respectively.
- During the visit, 33 patients had a definite diagnosis documented; of those who had no diagnosis, 7 were still being worked up, the remaining 4 had no documentation.
- 30 patients were investigated with blood investigations which comprised of a full dementia screen.
- 27 patients had imaging investigations carried out. The majority had CT scanning as first-line imaging modality.
- 14 patients had been investigated with EEG modality.
- 5 patients had already been started on treatment before the first cognitive clinic visit, whereas 12 patients were started on treatment at the clinic.
- 17 patients were referred for further assistance by other healthcare professionals.
- 41 patients had a care plan provided.

Conclusions:
From the audit, a number of recommendations were identified, primarily the need to establish formal referral pathways and criteria for referrals. Teaching to doctors working in primary care as well as secondary care can help increase awareness of easily available tools and improve earlier screening of cognitive impairment. Opening joint clinics with psychiatrists can also aid in the assessment of patients, since psychiatrists were mostly involved for further follow-up and evaluation of patients. There is a demand for more opportunities and training about conditions associated with cognitive impairment; for example having specialised nurses working in the clinic can aid in the preliminary assessment of the patient.