Autosomal dominant mutat####Ions#### in the presenilin 1 (PS1) gene are associated with familial, early-onset Alzheimers #########Disease#########. Although the pathogenic mechanism of these mutat####Ions#### is unclear, their common feature is that they ####Lead#### to an increased concentration of amyloid beta-peptide (Abeta) 42 in the plasma of early-onset patients, in the conditioned media of transfected cells, and in the brains of transgenic m####Ice#### that overexpress mutant PS1. To address the mechanism(s) by which the pathogenic PS1 mutat####Ions#### increase Abeta42, we constructed human cell lines expressing a doxycyclin (dox)-inducible antisense PS1 RNA and measured its effects on the levels of PS1, amyloid precursor protein (APP), and Abeta. In time course experiments, we observed a statistically significant ($p = 0.0038$) more than twofold elevation in secreted Abeta42 as early as 12 days after addition of dox. This correlated with an 80% decrease in the 46-kDa PS1 holoprotein and a 30% decrease in the 26-kDa N-terminal fragment (NTF). Furthermore, there was a significant fivefold ($p = 0.002$) increase in Abeta42 after 14-day dox treatment; this correlated with a >90% decrease in PS1 holoprotein and 60% decrease in NTF. At no time point did we observe significant changes in Abeta40, APP holoprotein, presenilin 2, or tubulin. Ten days after the removal of dox, we observed a return to constitutive levels for Abeta42, PS1 holoprotein, and NTF. These results suggest that in human cell lines, the reduction of normal PS1 activity results in the increased production of Abeta42. Furthermore, our results are consistent with a loss of function or dominant ne####GAT####ive mechanism for the pathogenic PS1 mutat####Ions####.

Regulator of G-####Protein S####ignaling 4 (RGS4) showed decreased mRNA levels in Alzheimers #########Disease######### in a large collection of human brain au####TOPS####ies from prefrontal cortex. The expression levels of three RGS4 spl####Ice#### variants were examined in the same samples, and the association between RGS4 ####Gene Expression#### and/or the #########Disease######### with single nucleotide polymorphisms located in this gene was explored. We show that all spl####Ice#### variants are down-regulated in patients. We also demonstrate that one rare haplotype (ATAG) is associated with decreased mRNA levels in both cases and controls. Our results suggest that an altered regulation in transcription initiation may be an important mechanism for low RGS4 protein levels in Alzeimers #########Disease#########.

Alzheimers #########Disease######### (AD) is a slowly ####progressin####g non-linear dynamic brain #########Disease########## in which pathophysiological abnormalities, detectable in vivo by biological markers, precede overt clinical symptoms by many years to decades. Use of these ####Biomarkers#### for the detection of early and preclinical AD has become of central importance following publication of two international expert working groups revised criteria for the diagnosis of AD ####Dementia####, mild cognitive impairment (MCI) due to AD, prodromal AD and preclinical AD. As a consequence of matured research evidence six AD ####Biomarkers#### are sufficiently va####LIDA####ted and partly qualified to be incorporated into operationalized clinical diagnostic criteria and use in primary and secondary prevention trials. These ####Biomarkers#### fall into two molecular categories: ####Biomarkers#### of amyloid-beta (Aß) ####DEPO####sition and plaque formation as well as of tau-protein related hyperphosphorylation and neurodegeneration. Three of the six ####Gold####-standard (####"C####ore feasible) ####Biomarkers#### are neuroimaging measures and three are ####CERE####bros####pinal#### fluid (CSF) analy####TES####. CSF

Aß1-42 (Aß1-42), also expressed as Aß1-42 : Aß1-40 ratio, T-tau, and P-tau Thr181 & Thr231 proteins have proven diagnostic accuracy and risk enhancement in prodromal MCI and AD ####Dementia####. Conversely, having all three ####Biomarkers#### in the normal range rules out AD. Intermediate condit####Ions#### require further patient follow-up. Magnetic resonance imaging (MRI) at increasing field strength and resolution allows detec####Tin####g the evolution of dis####Tin####ct types of structural and functional abnormality pattern throughout early to late AD stages. Anato####mica####l or volumetric MRI is the most widely used technique and provides local and global measures of ####Atrophy####. The revised diagnostic criteria for ####"p####rodromal AD" and "mild cognitive impairment due to AD" include hippocampal ####Atrophy#### (as the fourth va####LIDA####ted biomarker), which is considered an indicator of regional neuronal injury. Advanced image analysis techniques generate automatic and reproducible measures both in reg####Ions#### of interest, such as the hippocampus and in an exploratory fashion, observer and hypothesis-indedendent, throughout the entire brain. Evolving modalities such as diffusion-tensor imaging (DTI) and advanced tractography as well as res####Tin####g-state functional MRI provide useful additionally useful measures indica####Tin####g the degree of fiber tract and neural network disintegration (structural, effective and functional connectivity) that may substantially contribute to early detection and the mapping of progression. These modalities require further standardization and va####LIDA####tion. The use of molecular in vivo amyloid imaging agents (the fifth va####LIDA####ted biomarker), such as the Pittsburgh Compound-B and markers of neurodegeneration, such as fluoro-2-deoxy-D-####Glucose#### (FDG) (as the sixth va####LIDA####ted biomarker) support the detection of early AD pathological processes and associated neurodegeneration. How to use, interpret, and disclose biomarker results drives the need for optimized standardization. Multimodal AD ####Biomarkers#### do not evolve in an identical manner but rather in a sequential but ####TEMPO####rally overlapping fashion. Models of the ####TEMPO####ral evolution of AD ####Biomarkers#### can take the form of plots of biomarker severity (degree of abnormality) versus time. AD ####Biomarkers#### can be combined to increase accuracy or risk. A list of genetic risk factors is increasingly included in secondary prevention trials to stratify and select individuals at genetic risk of AD. Although most of these biomarker candida####TES#### are not yet qualified and approved by regulatory authorities for their intended use in drug trials, they are nonetheless applied in ongoing clinical studies for the following funct####Ions####: (i) inclusion/exclusion criteria, (ii) patient stratification, (iii) evaluation of treatment effect, (iv) drug target engagement, and (v) safety. Moreover, novel promising hypothesis-driven, as well as exploratory bioche####mica####l, genetic, electrophysiological, and neuroimaging markers for use in clinical trials are being developed. The current state-of-the-art and future perspectives on both biological and neuroimaging derived biomarker discovery and development as well as the intended application in prevention trials is outlined in the present publication.

Alzheimers ########Disease######### (AD) is a progressive neurodegenerative ########Disease######### affec####Tin####g mill####Ions#### of patients worldwide. Previous studies have demonstrated alterat####Ions#### in the lipid composition of lipid extracts from plasma and brain samples of AD patients. However, there is no consensus regarding the qualitative and quantitative changes of ####Lipids#### in brains from AD patients. In addition, the recent developments in imaging mass spectrometry methods are ####Lead####ing to a new stage in the in situ analysis of lipid species in brain tissue sl####Ice####s from human postmortem samples. The present study uses the matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS), permit####Tin####g the direct anato####mica####l analysis of ####Lipids#### in postmortem brain sect####Ions#### from AD patients, which are compared with the intensity of the lipid signal in samples from matched subjects with no neurological ########Disease#########s. The frontal cortex samples from AD patients were

classified in three groups based on Braaks histoche####mica####l criteria, ranging from non-cognitively impaired patients to those severely affected. The main results indicate a depletion of different sulfatide lipid species from the earliest stages of the ########Disease######## in both white and gray matter areas of the frontal cortex. Therefore, the decrease in sulfatides in cortical areas could be considered as a marker of the ########Disease#########, but may also indicate neuroche####mica####l modificat####Ions#### related to the pathogenesis of the ########Disease#########. This article is part of a Special Issue entitled: Membrane Lipid Therapy: Drugs Targe####Tin####g Biomembranes edited by Pablo V. Escribá.

In this review focus is on structural imaging in the Alzheimers ########Disease###### (AD) pre-sta####TES####, particularly cognitively normal (CN) persons at future ####Dementia#### risk. Findings in mild cognitive impairment (MCI) are described here only for comparison with CN. Cited literature evidence and co####MME####ntary address issues of structural imaging alterat####Ions#### in CN that precede MCI and AD, regional patterns of such alterat####Ions####, and the time relat####Ions####hip between structural imaging alterat####Ions#### and the appearance of symptoms of AD, issues re####levan####t to the conduct of future AD prevention trials. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative ##########Disease#########.

Extensive evidence has indicated that a high rate of ####Cholesterol#### biogenesis and abnormal neuronal energy ####Metabolism#### play key roles in Alzheimers ##########Disease######## (AD) pathogenesis. Here, for we believe the first time, we used osmo####Tin####, a plant protein homolog of mammalian ####Adiponec####Tin#########, to determine its therapeutic efficacy in different AD models. Our results reveal that osmo####Tin#### treatment modulated ####Adiponec####Tin######## receptor 1 (AdipoR1), significantly induced AMP-activated protein ki####nas####e (AMPK)/Sirtuin 1 (SIRT1) activation and reduced SREBP2 (sterol regulatory element-binding protein 2) expression in both in vitro and in vivo AD models and in Adipo-/- m####Ice####. Via the AdipoR1/AMPK/SIRT1/SREBP2 signaling pathway, osmo####Tin#### significantly diminished amyloidogenic Aß production, abundance and aggre####GAT####ion, accompanied by improved pre- and post-syn####APT####ic dysfunction, cognitive impairment, memory deficits and, most importantly, reversed the suppression of ####Long-term potentiation#### in AD m####Ice####. Interes####Tin####gly, AdipoR1, AMPK and SIRT1 silencing not only abolished osmo####Tin#### capability but also further enhanced AD pathology by increasing SREBP2, amyloid precursor protein (APP) and ß-secretase (BACE1) expression and the levels of toxic Aß production. However, the opposite was true for SREBP2 when silenced using small interfering RNA in APPswe/ind-transfected SH-SY5Y cells. Similarly, osmo####Tin#### treatment also enhanced the non-amyloidogenic pathway by activa####Tin####g the a-secretase gene that is, ADAM10, in an AMPK/SIRT1-dependent manner. These results suggest that osmo####Tin#### or osmo####Tin####-based therapeutic agents might be potential candida####TES#### for AD treatment.

OBJECTIVE: To investi####GAT####e the cognitive decline in ####Dementia#### with Lewy bodies (DLBs) and characterize the contribution of Lewy bodies (LBs) to cognitive impairment in the presence of concurrent ####Alzheimer ##########Disease######## (AD). METHODS: Cognitive deficits and ra####TES####

of progression attributable to DLB and AD neuropathology were investi####GAT####ed in three groups of participants from the longitudinal cohort of the ####Alzheimer ########Disease#################### Research Center at Washington University with au####TOPS####y-confirmed diagnoses of pure DLB (n = 9), mixed DLB/AD (n = 57), and pure AD (n = 66). ####factor A####nalysis was used to recover latent constructs in a comprehensive psychometric ####TES####t battery, analysis of variance was used to ####TES####t group differences on the observed dimens####Ions####, and random effects models were used to ####TES####t longitudinal ra####TES#### of cognitive decline. RESULTS: Patients with AD pathology performed worse on the verbal memory dimension. Patients with LB pathology performed worse on the visuospatial dimension. Combined pathology affected visuospatial performance but not verbal memory. The rate of cognitive decline in the DLB, DLB/AD combined, and the pure AD groups was equivalent. CONCLUS####Ions###: The comorbid presence of DLB and AD alters the cognitive presentation of visuospatial deficits in ####Dementia#### but does not alter ####Dementia#### progression. Both visuospatial and verbal abilities declined at similar ra####TES#### across the three patient groups. DLB diagnosis may be improved, particularly when there is comorbid AD, by using domain-specific ####TES########Tin####g.

In tau proteins, the hexa####Peptides#### in the R2 and R3 repeats are known to initiate tau fibril formation, which causes a class of neurodegenerative ########Disease#########s called the taupathies. We show that in R3, in addition to the presence of the hexa####Peptides####, the correct turn conformation upstream to it is also essential for producing prion-like fibrils that are capable of propa####GAT#####ion. A time-dependent NMR aggre####GAT####ion assay of a slow fibril forming R3-S316P peptide revealed a trans to cis equilibrium shift in the peptide-bond conformation preceding P316 during the growth phase of the aggre####GAT####ion process. S316 was identified as the key residue in the turn that confers templa####Tin####g capacity on R3 fibrils to accelerate the aggre####GAT####ion of the R3-S316P peptide. These results on the specific interact####Ions#### and conformational changes responsible for tau aggre####GAT####ion could prove useful for developing an efficient therapeutic intervention in Alzheimers ########Disease#########.

Alzheimers ########Disease######### (AD) is the most common cause of ####Dementia####, and currently there is no clinical treatment to cure it or to halt its progression. Aggre####GAT####ion and fibril formation of ß-amyloid ####Peptides#### (Aß) are central events in the pathogenesis of AD. Many efforts have been spent on the development of effective inhibitors to prevent Aß fibrillogenesis and cause disaggre####GAT####ion of preformed Aß fibrils. In this study, the conju####GAT####es of ####ferrocene#### and Gly-Pro-Arg (GPR) tripeptide, Boc-Gly-Pro-Arg(NO(2))-Fca-OMe (4, GPR-Fca) and Fc-Gly-Pro-Arg-OMe (7, Fc-GPR) (Fc: ####ferrocene####; Fca: ####ferrocene#### amino acid) were synthesized by HOBT/HBTU pro####tocol#### in solution. These ####ferrocene#### GPR conju####GAT####es were employed to inhibit Aß(1-42) fibrillogenesis and to disaggre####GAT####e preformed Aß fibrils. The inhibitory properties of ####ferrocene#### GPR conju####GAT####es on Aß(1-42) fibrillogenesis were evaluated by ####thioflavin T#### (ThT) fluorescence assay, and confirmed by atomic force microscopy (AFM) analysis. The interaction between the ####ferrocene#### GPR conju####GAT####es and Aß(1-42) was monitored by electroche####mica####l means. Our results showed that both GPR and GPR-Fca can significantly inhibit the fibril formation of Aß(1-42), and cause disaggre####GAT####ion of the preformed fibrils. As expected, GPR-Fca shows stronger inhibitory effect on Aß(1-42) fibrillogenesis than that of its parent peptide GPR. In contrast, Fc-GPR shows no inhibitory effect on fibrillogenesis

of Aß(1-42). Furthermore, GPR-Fca demonstra####TES#### significantly protection against Aß-induced cytotoxicity and exhibits high resistance to proteolysis and good lipophilicity.

The neurotrophin ####Brain-Derived Neurotrophic Factor#### (BDNF) plays a critical role in neuronal survival, syn####APT####ic plasticity, and memory. Several recent studies have demonstrated altered BDNF serum levels in Alzheimers ########Disease######### (AD) patients. However, the association of BDNF serum levels with the rate of cognitive decline in AD patients is still unclear. We demonstrate that BDNF serum levels are significantly decreased in AD patients with fast cognitive decline [decrease of Mini-Mental State Examination (MMSE) score >4/yr; n=12] compared to AD patients with slow cognitive decline (decrease of MMSE score =4/yr, n=28) and show a significant correlation with the rate of cognitive decline during 1 yr follow-up. These results suggest that higher BDNF serum levels are associated with a slower rate of cognitive decline in AD patients. Further longitudinal studies are necessary to elucidate the kine####Tics#### and the potential role of serum BDNF as a surro####GAT####e marker of ########Disease######### progression in AD patients.

The effect of long-term treatment with ####Tacrine#### (tetrahydroaminoac####RID####ine) was studied in three Alzheimer patients (aged 57, 64, and 68 years) with mild ####Dementia####. All three patients had a Mini-Mental State Examination score of 24/30 and carried at least one apolipoprotein E (ApoE) epsilon4 allele. ####Tacrine#### was given in doses between 80 and to 160 mg daily for 13-31 months. A lower ####Tacrine#### concentration was observed generally in ####CERE####bros####pinal#### fluid (CSF) compared with plasma. The ####Acetyl####Choline########sterase activity in CSF tended to be increased following longer periods of ####Tacrine#### treatment, whereas the ####butyryl####Choline#########sterase activity was decreased. The three patients repeatedly underwent positron emission tomography investi####GAT####ion of ####CERE####bral blood flow, nico####Tin####ic receptors, ####CERE####bral ####Glucose#### ####Metabolism####, and electroencephalogram (EEG) and cognitive ####TES####ts. Positive influences on these parameters were observed following both short-term and long-term treatment with ####Tacrine####. Improvement of nico####Tin####ic receptors (measured as 11C-####Nico####Tin####e#### binding), ####CERE####bral blood flow, EEG, and some cognitive ####TES####ts (trail making ####TES####t, block design ####TES####t) occurred earlier after initiation of ####Tacrine#### treatment compared with the ####Glucose#### ####Metabolism####, which was increased after several months of ####Tacrine#### treatment. An improvement in attention (trail making ####TES####t) was observed following ####Tacrine#### as sign for frontal lobe activation (EEG). The functional effects of ####Tacrine#### in Alzheimer patients appeared to be related to both dose and length of ####Choline####sterase inhibitor treatment.

Alzheimers ########Disease######### pathomimetic toxicity could be induced in m#####Ice#### within one week after the intra####CERE####broventricular (i.c.v.) injection of an aggre####GAT####ed preparation of the highly toxic and endogenous amyloid-ß fragment Aß(25-35). It was recently reported that Aß(25-35) also provokes a modification of APP processing with accumulation of endogenous Aß(1-42). We here analyzed wh####Ether#### a ?-secretase inhibitor, BMS-299897, attenuated this Aß(25-35)-induced Aß(1-42) seeding and toxicity. The ####compound W#####as administered at 0.1-1 nmol/mouse, concomittantly with

Aß(25-35) (9 nmol) in male Swiss m####Ice###. After one week, the contents in Aß(1-42) and Aß(1-40), and the levels in lipid peroxidation were analyzed in the mouse hippocampus. M####Ice#### were submitted to spontaneous alternation, passive avoidance and object recognition to analyze their short- and long-term memory abilities. Aß(25-35) increased Aß(1-42) content (+240%) but failed to affect Aß(1-40). BMS-299897 blocked the increase in Aß(1-42) content and decreased Aß(1-40) levels significantly. The compound did not affect Aß(25-35)-induced increase in hippocampal lipid peroxidation. Behaviorally, BMS-299897 blocked the Aß(25-35)-induced deficits in spontaneous alternation or novel object recognition, using a 1h intertrial time interval. BMS-299896 failed to affect the passive avoidance impairments or novel object recognition, using a 24h intertrial time interval. These results confirmed that Aß(25-35) injection provoked an accumulation in endogenous Aß(1-42), an effect blocked by ?-secretase inhibition. This Aß(1-42) accumulation marginally contributed to the toxicity or long-term memory deficits. However, since the seeded Aß(1-42) affected short-term memory, the rapid Aß(25-35) injection Alzheimers ########Disease######### model could be used to screen the activity of new secretase inhibitors.

Some forms of familial Alzheimers ########Disease######### (FAD) are caused by mutat####Ions#### in presenilins (PSs), catalytic components of a ?-secretase complex that cleaves target proteins, including amyloid precursor protein (APP). ####Calcium#### (Ca(2+)) dysregulation in cells with these FAD-causing PS mutants has been attributed to attenuated store-operated Ca(2+) entry [SOCE; also called capacitative Ca(2+) entry (CCE)]. CCE occurs when STIM1 detects decreases in Ca(2+) in the endoplasmic reticulum (ER) and activa####TES#### ORAI channels to replenish Ca(2+) stores in the ER. We showed that CCE was attenuated by PS1-associated ?-secretase activity. Endogenous PS1 and STIM1 interacted in human ####Neuroblastoma#### SH-SY5Y cells, patient fibroblasts, and mouse primary cortical neurons. Forms of PS1 with FAD-associated mutat####Ions#### enhanced ?-secretase cleavage of the STIM1 transmembrane domain at a sequence that was similar to the ?-secretase cleavage sequence of APP. Cultured hippocampal neurons expressing mutant PS1 had attenuated CCE that was associated with destabilized dendritic spines, which were rescued by either ?-secretase inhibition or overexpression of STIM1. Our results indicate that ?-secretase activity may physiologically regulate CCE by targe####Tin####g STIM1 and that restoring STIM1 may be a therapeutic approach in AD.

As population-based epide####Miol####ogic studies may acquire images from thousands of subjects, automated image post-processing is needed. However, error in these methods may be biased and related to subject characteris####Tics#### re####levan####t to the research question. Here, we compare two automated methods of brain extraction against manually segmented images and evaluate wh####Ether#### method accuracy is associated with subject demographic and health characteris####Tics####. MRI data (n = 296) are from the Honolulu Asia Aging Study, a population-based study of elderly Japanese-American men. The intracranial space was manually outlined on the axial proton density sequence by a single operator. The brain was extracted automatically using BET (Brain Extraction Tool) and BSE (Brain Surface Extractor) on axial proton density images. Total intracranial volume was calculated for the manually segmented images (ticvM), the BET segmented images (ticvBET) and the BSE segmented images (ticvBSE). Mean ticvBSE was closer to that of ticvM, but ticvBET was more highly correlated with ticvM than ticvBSE. BSE had significant over (positive error) and underestimated (ne####GAT####ive error) ticv, but net error was relatively low. BET had large positive and very low ne####GAT####ive error. Method accuracy, measured in percent positive and ne####GAT####ive error, varied

slightly with age, head circumference, presence of the apolipoprotein eepsilon4 polymorphism, subcortical and cortical infracts and enlarged ventricles. This epide####Miol###ogic approach to the assessment of potential bias in image post-processing tasks shows both skull-stripping programs performed well in this large image dataset when compared to manually segmented images. Although method accuracy was statistically associated with some subject characteris####Tics####, the extent of the misclassification (in terms of percent of brain volume) was small.

A major question for gene therapy in brain concerns methods to administer therapeutic genes in a uniform manner over major port####Ions#### of the brain. A second question in neuroimmunology concerns the extent to which monocy####TES#### migrate to the CNS in degenerative disorders. Here we show that CD11b+ cells (largely monocy####TES####) isolated from the bone marrow of GFP (green fluorescent protein)-expressing donors spontaneously home to compacted amyloid plaques in the brain. Inject####Ions#### of these cells as a single pulse show a rapid clearance from ####Circulat####ion (90 min half-life) and tissue residence half-lives of approximately 3 d. The uptake into brain was minimal in nontransgenic m####Ice####. In transgenic m####Ice#### containing amyloid ####DEPO####sits, uptake was dramatically increased and associated with a corresponding decrease in monocyte uptake into peripheral organs compared to nontransgenic litterma####TES####. Tw####Ice#### weekly infus####Ions#### of the CD11b+ bone marrow cells transfected with a genetically engineered form of the pro####Tea####se ####Neprilysin#### completely arrest amyloid ####DEPO####sition in an aggressively ####DEPO####si####Tin####g transgenic model. Exploi####Tin####g the natural homing properties of peripherally derived blood cells to deliver therapeutic genes has the advantages of access to the entire CNS, expression largely restricted to si####TES#### of injury, low risk of immune reactivity, and fading of expression if adverse react####Ions#### are encountered. These observat####Ions#### support the feasibility of ####TES########Tin####g autologous monocy####TES#### for application of therapeutic genes in human CNS ########Disease########. Moreover, these data support the results from bone marrow grafts that ####Circulat####ing CD11b+ cells can enter the CNS without requiring the use of lethal irradiation.

Traumatic brain injury (TBI) is common, and is often the ####Lead####ing cause of disability and ####Death####. Complicat####Ions#### after TBI include increased risk for chronic central nervous system #########Disease#########, such as Alzheimers #########Disease########## (AD). However, the pathophysiology rela####Tin####g acute injury to neurodegeneration is unclear. Here we present a case of a patient whose cognition declined after TBI, and whose 18F fluoro####Deoxy####Glucose########## positron emission tomography scan showed an AD pattern.

Stages, as used in clinical pract####Ice#### and research, are defined, their value described, and criteria are proposed for their evaluation. The specific interest is in staging Alzheimers #########Disease######### (AD). Two staging systems, one based on the Global Deterioration Scale (GDS) and one based on the Mini-Mental State Exam (MMSE), are compared in terms of these criteria, as an illustration of the process involved. We propose that there is not one unique staging system, that different staging criteria might be appropriate to different research or clinical needs, depending on which part of the

####TEMPO####ral course of the ########Disease######### is of primary interest, and on wh####Ether#### the focus is on cognitive, functional, neurological, behavioral, economic, or other issues. GDS staging seems a better cho####Ice#### for the later stages of AD when the focus is on functional change. MMSE staging seems a better cho####Ice#### for tracking the earlier stages of AD when the focus is on cognitive change.

Patients with probable late-onset Alzheimers #########Disease######### (l-AD) had higher levels of serum ####alpha 1-Antichymotrypsin#### (alpha 1-ACT) than those found in patients with vascular ####Dementia#### (VD) and healthy elderly controls, when assessed by a competitive enzyme-linked immune assay. Serum alpha 1-ACT was also characterized by SDS PAGE electrophoresis. Western blot and computer-assisted optical density reading (OD). Using a polyclonal affinity-purified antibody specific for human alpha 1-ACT, one band with the apparent MW of 60 and another with 180 kD in sera from all subjects were clearly detectable. OD of both alpha 1-ACT bands from patients with l-AD was higher than that from VD patients, the 180-kD form being 2.65 times higher than that observed from patients with VD. Serum levels of other acute phase proteins from l-AD were comparable to those observed in VD patients. A slight but nonstatistical increment of serum IL-6 was noted in patients with l-AD. Serum alpha 1-ACT was purified from 3 of these l-AD patients by a two-step affinity chromatography technique. After Western blot, purified alpha 1-ACT showed two or three different bands which immune-reacted with an antibody specific for alpha 1-ACT. The apparent MWs were 60, 120 and 180 kD. In human sera the serpin was present mainly in a monomeric form, but it could also form SDS stable dimers and trimers. Both monomeric and SDS stable polymeric forms of alpha 1-ACT appeared to be increased in sera from patients with l-AD.

Sixteen residents in long-term care with advanced ####Dementia#### (14 women; average age = 88) showed significantly more constructive engagement (defined as motor or verbal behaviors in response to an activity), less passive engagement (defined as passively observing an activity), and more pleasure while participa####Tin####g in Mon####TES####sori-based programming than in regularly scheduled activities programming. Principles of Mon####TES####sori-based programming, along with examples of such programming, are presented. Implicat####Ions#### of the study and methods for expanding the use of Mon####TES####sori-based ####Dementia#### programming are discussed.

The FE65 protein binds to the intracellular domain of the beta-amyloid precursor protein (betaPP) and may modulate the internalization of betaPP. This gene is highly expressed in reg####Ions#### of the brain specifically affected in ####Dementia#### of the Alzheimer type (DAT). As a prelude to further investi####GAT########Ions#### of the role of FE65 in the ####Metabolism#### of betaPP and in the pathogenesis of DAT, we have determined the entire genomic structure and sequence of human FE65 and have discovered several polymorphisms in this gene. Human FE65 contains 14 exons ranging in size from 6 to 735 bp. All spl####Ice#### si####TES#### conform to consensus sequences except for the donor site of intron 10. The 5 end of FE65 mRNA was identified by rapid amplification of the cDNA 5 end and is 31 bp longer than the previously published cDNA sequence. The 5-flanking region of this gene is TATA-less and is very GC-rich with at least five putative Sp1 binding si####TES####. In comparison to the genomic rat FE65 sequence, the human FE65 5-untranslated

region is 134 bp longer and has an extra exon (exon 1, 86 bp). To identify mutat####Ions####/polymorphisms of the coding reg####Ions#### of this gene, we performed blinded analysis o####F 4####57 Caucasian case-control samples from a large epide####Miol####ogical study of sporadic DAT. Screening was conducted by single-strand conformation polymorphism. Four minor variants were found within the coding region, with frequencies between 0.002 and 0.015; two of the four result in amino acid substitut####Ions####. The more informative biallelic polymorphism (a trinucleotide deletion and a single base substitution) was found within intron 13 (84 bp), which interrupts two exons encoding the betaPP binding site. The frequency of the minor allele in this intron was 0.097 in DAT cases and 0.161 in controls (chi2=7.78, P=0.0054). Having at least one copy of the minor allele was associated with a decreased risk for DAT (chi2=9.20, P<0.005, odds ratio=0.49, 95% CI 0.31-0.77). Multivariate analysis showed that this association was independent of the APOE genotype. These results suggest that either FE65 itself or a closely linked gene influences the pathogenesis of sporadic DAT. The interaction of FE65 with betaPP and the association of a FE65 polymorphism with DAT lend credence to the hypothesis that the ####Metabolism#### of betaPP is central to the pathogenesis of common sporadic forms of DAT.

INTRODUCTION: ####Cysteine#### pro####Tea####se are biological catalysts which play a pivotal role in numerous biological react####Ions#### in organism. Much of the literature is inscribed to their bioche####mica####l significance, distribution and mechanism of action. Many ########Disease#########s, e.g. Alzheimers #########Disease#########, develop due to enzyme balance disruption. Understanding of ####Cysteine#### pro####Tea####ses disbalance is therefor a key to unravel the new possibilities of treatment. ####Cysteine#### pro####Tea####se are one of the most important enzymes for protein disruption during progra####MME####d cell ####Death####. Wh####Ether#### protein disruption is part of cell ####Death####s is not enough clear in any cases. Thereafter, any tissue disruption, including proteolysis, generate more or less ####Inflammation#### appearance. REVIEW: This review briefly summarizes the current knowledge about pathological mechanisms that results in AD, with significant reference to the role of ####Cysteine#### pro####Tea####se in it. Based on the summary, new pharmacological approach and development of novel potent drugs with selective toxicity targe####Tin####g ####Cysteine#### pro####Tea####se will be a major challenge in years to come.

Identification of amyloid-beta and tau as the major ####Protein C####omponents of senile plaques and neurofibrillary tangles, respectively, led to an exponential increase in investi####GAT########Ions#### of these proteins and their corresponding ####Metabolic pathways#### in ####Alzheimer #########Disease#########(AD). The presumpt####Ions#### inherent in most studies and in the dogma of the amyloid cascade concept are that these hallmark les####Ions#### in AD brains contain molecules that drive the #########Disease########## process, and that the proteinaceous accumulat####Ions#### are themselves toxic. On the other hand, the les####Ions#### of AD are, by definition, end-stage, and their relat####Ions####hip to the clinical #########Disease########## is inconsistent; this has long been known but, generally, has not been acknowledged until relatively recently. Some recent attempts to address the etiology and pathogenesis of AD discard the pathology and focus on the interplay between invisible toxic intermedia####TES####, that is, amyloid-beta oligomers and the synapse. The concept that the hallmark les####Ions#### may be nontoxic (something we have long suggested) is slowly gaining acceptance. We favor the interpretation that senile plaques and neurofibrillary tangles represent a host

response to an upstream pathophysiologic process, and that the therapeutic targe####Tin####g of les####Ions####, including toxic intermedia####TES####, will succeed only in the event that the host response is directly deleterious. Therefore, renewed efforts aimed at elucida####Tin####g fundamental age-related processes such as oxidative stress and/or inflammatory mediators are warranted.

Relat####Ions####hips between measures of executive skills and neuropsychiatric and functional status were examined in a group of 31 patients with Alzheimers ########Disease#########. Deficits in four executive skills ####TES####ts were significantly associated with the Agitation/Disinhibition factor score and Total Neuropsychiatric score on the Neurobehavioral Ra####Tin####g Scale, as well as the Activities subscore on the Blessed ####Dementia#### Scale. The majority of these associat####Ions#### remained significant after covariance for Mini-Mental State Examination scores. Executive dysfunction is associated with clinically re####levan####t neuropsychiatric symptoms and functional impairment in Alzheimers ##########Disease##########. These associat####Ions#### may be independent of other cognitive deficits such as memory, language, and visuospatial skills, and may not be appreciated on rou###Tin####e clinical evaluat####Ions####. Executive skills deficits, neuropsychiatric symptoms, and functional disability may emerge from shared neurobiological mechanisms.

Silent brain infarcts and leucoaraiosis are frequently observed in patients with transient ischemic attack (TIA) and ischemic ####Stroke####. Patients with silent brain infarcts and leucoaraiosis at baseline are a high-risk group with an increased long-term risk for recurrent ####Stroke####, cognitive decline, and ####Dementia####. Effects on short-term outcomes are less clear, but leucoaraiosis appear to increase the risk of early infarct growth as determined by MRI in mismatch areas of the brain. After acute thrombolytic therapy, presence of silent ####CERE####brovascular ##########Disease######### increases the risk of intra##########CERE####bral ####Hemorrhage########, but the increased risk does not ne####GAT####e the overall benefit of this therapy. Similarly, presence of leucoaraiosis is associated with an increased risk of intra####CERE####bral bleeding during long-term anticoagulant therapy, but because the risk-benefit ratio has not been well delineated, degree of leucoaraiosis should not influence clinical decision-making at present. Carotid endarterectomy for symptomatic ####Carotid Stenosis#### appears equally effective across different degrees of baseline leucoaraiosis, despite an increased perioperative risk in those with moderate to severe leucoaraiosis. Long-term blood pressure lowering appears equally effective in patients with silent ####CERE####brovascular ##########Disease######### at baseline, and there is some support that blood pressure lowering may decrease the risk of progression of leucoaraiosis.

Analysis of serum ####Brain-Derived Neurotrophic Factor#### (BDNF) levels in Alzheimers ##########Disease######### (AD), amnestic mild cognitive impairment (aMCI) and controls with BDNF gene polymorphism and cognitive function were investi####GAT#####ed. The study recruited 63 AD patients, 15 aMCI and 63 age- and sex-matched healthy controls from All India Institute of Medical Sciences, New Delhi, India. Patients with AD (12268.3 ± 7099.9 pg BDNF/ml) and aMCI (10780 ± 4184.2 pg BDNF/ml) had higher serum levels than had the controls (9362.833 ± 5883.32 pg BDNF/ml). Significant difference in BDNF levels was not found between the three groups. No significant difference was obtained between BDNF genotype and allele distribution between AD patients, aMCI versus

controls; genotypic frequency: Chi-square = 3.21; p-value = 0.20 and allelic frequency: Chi-square = 0.412, p-value = 0.521, df = 1 (AD vs controls); Chi-square = 1.63, p-value = 0.201, df = 1 (aMCI vs controls). In conclusion, val66met polymorphism and BDNF serum level between the three groups and genotype did not significantly affect the serum BDNF level or age, Mini-Mental State Examination score in AD and aMCI. Further studies are necessary to elucidate the kine####Tics#### and the potential role of serum BDNF as a marker of ########Disease######### progression in AD patients.

Alzheimers ########Disease######### (AD) is known to be caused by the accumulation of deformed beta amyloid and hyperphosphorylated tau proteins resul####Tin####g into formation and aggre####GAT####ion of senile plaques and neurofibrillary tangles in the brain. Additionally, AD is associated with the accumulation of ####Iron#### or metal ####Ions#### in the brain which causes oxidative stress. ####Galantamine#### (Gal) is one of the therapeutic agents that has been approved for the treatment of AD, but still saddled with numerous side effects and could not address the issue of ####Iron#### accumulation in the brain. The use of metal chelators to address the ####Iron#### accumulation has not been successful due to toxicity and inability to address the aggre####GAT####ion of the plaques. We therefore hypothesize a combinatorial antioxidant-metal-chelator approach by formula####Tin####g a single dosage form that has the ability to prevent the formation of ####Free Radicals####, plaques and accumulation of ####Iron#### in the brain. This can be achieved by conju####GAT####ing Gal with apo-lactoferrin (ApoLf), a natural compound that has high binding affinity for ####Iron####, to form an apo-lactoferrin-####Galantamine#### proteo-alkaloid conju####GAT####e (ApoLf-Gal) as a single dosage form for AD management. The conju####GAT####ion is achieved through self-assembly of ApoLf which results in encapsulation of Gal. ApoLf changes its conformational structure in the presence of ####Iron####; therefore, ApoLf-Gal is proposed to deliver Gal and pick up excess ####Iron#### when in contact with ####Iron####. This strategy has the potential to proffer a dual neuroprotection and neurotherapeutic intervent####Ions#### for the management of AD.

####oleocanthal####, a ####Phenol####ic component of extra-virgin ####Olive Oil####, has been recently linked to reduced risk of Alzheimers ########Disease######### (AD), a neurodegenerative ########Disease######### that is characterized by accumulation of ß-amyloid (Aß) and tau proteins in the brain. However, the mechanism by which ####oleocanthal#### exerts its neuroprotective effect is still incompletely understood. Here, we provide in vitro and in vivo evidence for the potential of ###oleocanthal#### to enhance Aß clearance from the brain via up-regulation of P-glycoprotein (P-gp) and LDL lipoprotein receptor related protein-1 (LRP1), major Aß transport proteins, at the blood-brain barrier (BBB). Results from in vitro and in vivo studies demonstrated similar and consistent pattern of ####oleocanthal#### in controlling Aß levels. In cultured m####Ice#### brain endothelial cells, ####oleocanthal#### treatment increased P-gp and LRP1 expression and activity. Brain efflux index (BEI%) studies of (125)I-Aß40 showed that administration of ####oleocanthal#### extracted from extra-virgin ####Olive Oil#### to C57BL/6 wild-type m####Ice#### enhanced (125)I-Aß40 clearance from the brain and increased the BEI% from 62.0 ± 3.0% for control m####Ice#### to 79.9 ± 1.6% for ####oleocanthal#### treated m####Ice####. Increased P-gp and LRP1 expression in the brain microvessels and inhibition studies confirmed the role of up-regulation of these proteins in enhancing (125)I-Aß40 clearance after ####oleocanthal#### treatment. Furthermore, our results demonstrated significant increase in (125)I-Aß40 degradation as a result of the up-regulation of Aß degrading enzymes following ####oleocanthal#### treatment. In conclusion, these

findings provide experimental support that potential reduced risk of AD associated with extra-virgin ####Olive Oil#### could be mediated by enhancement of Aß clearance from the brain.

Our view of astrocy####TES#### in the operation of the brain is changing dramatically over the last 3 decades. Astroglial ####Calcium#### excitability controls the release of gliotransmitters, which can occur at the tripartite synapse. Astrocy#####TES#### not only modulate syn####APT####ic transmission by releasing and taking up transmitters, but also receiving neuronal signals that act upon astrocytic plasma membrane receptors. This process represents the bidirectional neurone-glia communication. Additionally, astrocy####TES#### play role in the regulation of blood flow as well as ion and ####Water#### homeostasis. Many of the brain dysfunct####Ions#### are primary astropathies, including ####Hepatic Encephalopathy#### and ####Alexander ########Disease#############, while other brain malfunct####Ions####, such as ####Epilepsy#### and ####Alzheimer ########Disease#############, may have substantial astrocytic contribution. Thus, these star-shaped cells by their roles in (patho)physiology of the brain seem to live up to the expectation one can have from their given name - astrocyte.

Selective neuronal vulnerability can be defined anato####mica####lly by the differential vulnerability of circuits and neuroche####mica####lly by the vulnerability of neurons that differentially express particular proteins. The anatomic perspective is exemplified by the vulnerability of the nigrostriatal projection in Parkinsons ########Disease######### (PD), the degeneration of upper and lower motor neurons in ####Amyotrophic Lateral ####Sclerosis######### (ALS), and the preferential loss of long corticocortical project####Ions#### in Alzheimers ########Disease######### (AD). The neuroche####mica####l perspective is reflected in the heightened vulnerability of neurons that normally express high somatodendritic levels of neurofilament (eg, entorhinal and association cort####Ice####s in AD, the s####pinal#### cord in a mouse model of ALS, and the re####Tin####a in a primate model of glau####Coma####), as well as the reduced vulnerability of neurons that express ####Calciu####-binding proteins (eg, neocortex of AD patients, the s####pinal#### cord and brainstem of ALS patients, and the s####pinal#### cord of a mouse model of ALS). By combining neuroche####mica####l and anatomic correla####TES#### of vulnerability, an integrated view of vulnerable neurons is emerging in which characteris####Tics#### of vulnerable neurons appear to transcend both brain region and ########Disease######### state, sugges####Tin####g that neurodegenerative disorders share common mechanisms of degeneration.

Regional levels of membrane phospho####Lipids#### [phosphatidyl####Ethanol####amine (PE), phosphatidyl####Inositol#### (PI), phosphatidyl####Choline#### (PC)] were measured in the brain of Alzheimers ########Disease######### (AD) and control subjects. The levels of PE-derived and PI-derived total fatty ####Acids#### were significantly decreased in the hippocampus of AD subjects. Here significant decreases were found in PE-derived s####Tea####ric, oleic and arachidonic and docosahexaenoic ####Acids####, and in PI-derived oleic and arachidonic ####Acids####. In the inferior parietal lobule of AD subjects, significant decreases were found only in PE and those decreases were contributed by s####Tea####ric, oleic and arachidonic ####Acids####. In the superior and middle ####TEMPO####ral gyri and ####CERE####bellum of AD

subjects, no significant decreases were found in PC-, PE- and PI-derived fatty ####Acids####. The decrease of PE and PI, which are rich in oxidizable arachidonic and docosahexaenoic ####Acids####, but not of PC, which contains lesser amounts of these fatty ####Acids####, suggests a role for oxidative stress in the increased degradation of brain phospho####Lipids#### in AD.

Alzheimers ########Disease######### (AD) is an age-related neurodegenerative disorder characterized by intelligence decline, behavioral disorders and cognitive disability. The purpose of this study was to investi####GAT####e ####Gene Expression#### in AD, based on published microarray data on Tg2576 m####Ice####. Hierarchical Cluster Analysis and Gene Ontology were employed to group genes tog####Ether#### on the basis of their product characteris####Tics#### and annotation data. Genes with prominent alterat####Ions#### were clustered into ####Apoptosis#### and ####Axon guidance#### pathways. Based on our findings and those of previous studies, we propose that the mitochondria-mediated apoptotic pathway plays a crucial role in the neuronal loss and syn####APT####ic dysfunction associated with AD. Furthermore, based on the findings of Positional Gene Enrichment analysis and Gene Set Enrichment analysis, we propose that the regulation of transcription of AD genes may be an important pathogenic factor in this neurodegenerative #########Disease#########. Our results highlight the importance of genes that could subsequently be examined for their potential as prognostic markers for AD.

Alpha-2-macroglobulin (A2M) is a protei####nas####e inhibitor that is present in senile plaques and may play a role in ####Metabolism#### of amyloid beta (A beta) peptide. Recently it was reported that inheritance of the deletion allele (A2M-2) confers increased risk for late-onset ####Alzheimer #########Disease######### (AD) with significance of this effect similar to the epsilon4 allele of apolipoprotein E (APOE). We examined the distribution of A2M genotypes and alleles in a cohort of 146 AD patients and 160 age-matched non-demented individuals. There was no evidence for association in the total sample or in subsets stratified by age or APOE epsilon4 status. These results suggest that this polymorphism is not a strong genetic risk factor for either early- or late-onset forms of the disorder. However, they do not exclude the possibility that an AD susceptibility allele is located elsewhere in A2M or a nearby gene.

INTRODUCTION: Hypovitaminosis D has been associated with several chronic condit####Ions####; yet, its association with cognitive decline and the risk of ####Dementia#### and Alzheimers ########Disease######### (AD) has been inconsistent. METHODS: The study population consisted of 916 participants from the Three-City Bordeaux cohort aged 65+, nondemented at baseline, with assessment of ####Vitamin D#### status and who were followed for up to 12 years. RESULTS: In multivariate analysis, compared with individuals with 25(OH)D sufficiency (n = 151), participants with 25(OH)D deficiency (n = 218) exhibited a faster cognitive decline. A total of 177 ####Dementia#### cases (124 AD) occurred: 25(OH)D deficiency was associated with a nearly three-fold increased risk of AD (hazard ratio = 2.85, 95% confidence interval 1.37-5.97). DISCUSSION: This large prospective study of French older adults suggests that maintaining adequate ####Vitamin D#### status in older age could contribute to slow down cognitive decline and to delay or prevent the onset of ####Dementia####, especially of AD etiology.

We have investi####GAT####ed the subcellular distribution of presenilin-1 (PS1) and presenilin-2 (PS2) in a variety of mammalian cell lines. In ####iodixanol####-based density gradients, PS1 derivatives show a biphasic distribution, cofractiona####Tin####g with membranes containing ER-resident proteins and an additional population of membranes with low buoyant density that do not contain markers of the Golgi complex, ERGIC, COP II vesicles, ER exit compartment, COP II receptor, Golgi SNARE, trans-Golgi network, caveolar membranes, or endocytic vesicles. Confocal immunofluorescence and immunoelectron microscopy studies fully supported the fractionation studies. These data suggest that PS1 fragments accumulate in a unique subcompartment(s) of the ER or ER to Golgi trafficking intermedia####TES####. Interes####Tin####gly, the FAD-linked PS1 variants show a marked redistribution toward the heavier region of the gradient. Finally, and in contrast to PS1, PS2 fragments are detected preponderantly in more densely sedimen####Tin####g membranes, sugges####Tin####g that the subcellular compartments in which these molecules accumulate are dis####Tin####ct.

Neurodegeneration is characterized by the cell ####Death#### or loss of structure and/or function of neurons. Many neurodegenerative ########Disease########s including Parkinsons ########Disease######### (PD) and Alzheimers ########Disease######### (AD) are the result of neurodegenerative processes. ####Metals#### are essential for many life processes, but they are also culpable for several neurodegenerative mechanisms. In this review, we discuss the role of ####Metals#### in neurodegenerative ########Disease########s with emphasis on the utility of Caenorhabditis elegans (C. elegans) genetic models in deciphering mechanisms associated with the etiology of PD and AD.

Introduction: The Prospective and Retrospective Memory Questionnaire (PRMQ) is one of the most commonly used scales to assess both retrospective memory (RM) and prospective memory (PM) complaints. This study aimed to: 1/replicate the previous results concerning the PRMQ latent structure in a French version and 2/ provide its psychometric properties in a normal and clinical population. Method: This observational study included 488 participants divided into five subgroups. A sample of 168 healthy participants (no memory consultation sought), served as controls. Patients were recruited in a memory clinic: 98 "functional" patients (subjective memory complaints but no memory impairment), 83 amnestic-Mild Cognitive Impairment (a-MCI), 82 non-amnestic-MCI (na-MCI) and 57 ####Alzheimer ########Disease########## (AD) patients. Structure, validity, consistency, reliabilitiy and reproducibility of the PRMQ were calculated. Novelty, Area Under the Receiver-Opera####Tin####g Characteris####Tics#### (AUROC) curve, was used to determine the optimal cut-off, to dis####Tin####guish "functional" patients from control participants. Results: The optimal fit model of the French PMRQ was not a tri but a bi-partite model, with a RM and a PM subscale. The convergent validity showed significant correlation with cognitive difficulties (r = .82 and .78, respectively), anxiety (r = .44 and .48, respectively) and depression (r = .23) scales. Cronbachs alpha was good (a = .79 and .88), as well as the reproducibility (r = .71 and .80). The interaction [Subgroups of participants x PMRQ Subscales] was significant [F(4, 483) = 11.46; p < .001]. The power discrimination was adequate (AUROC = .71 and .74) for detec####Tin####g "functional" patients compared with controls, in particular for the PM subscale (sensitivity 66.6%, specificity 77.4%). Conclus####Ions####: The PMRQ, with minor changes, was va####LIDA####ted in its French form with

satisfactory psychometric qualities. This self-ra####Tin####g tool appears useful for identifying significant memory complaints in a normal population and may also be helpful in discrimina####Tin####g between functional/na-MCI and a-MCI/AD patients.

Alzheimers ########Disease######### (AD) is the most common neurodegenerative ########Disease######### in the world. The pathogenesis of AD is associated with beta-amyloid (Abeta) fibrillation. Nanoparticles have large surface area and can access the brain. But no investi####GAT####ion has been made to study the relat####Ions####hip between nanoparticles and AD. In our study, we observed Abeta fibril formation in the presence of six kinds of nanoparticles and found that TiO2 nanoparticles can promote Abeta fibrillation by shortening nucleation process, which is the key rate-determining step of fibrillation. Hereby the interaction between Abeta and nanoparticles may contribute to AD etiology.

####Ataxia#### telangiectasia (A-T) is a multisystemic ########Disease######### caused by mutat####Ions#### in the ATM (A-T mutated) gene. It strikes before 5 years of age and ####Lead####s to dysfunct####Ions#### in many tissues, including the CNS, where it ####Lead####s to neurodegeneration, primarily in ####CERE####bellum. Alzheimers ########Disease######### (AD), by contrast, is a largely sporadic neurodegenerative disorder that rarely strikes before the 7th decade of life with primary neuronal losses in hippocampus, frontal cortex, and certain subcortical nuclei. Despite these differences, we present data suppor####Tin####g the hypothesis that a failure of ATM signaling is involved in the neuronal ####Death#### in individuals with AD. In both, partially ATM-deficient m####Ice#### and AD mouse models, neurons show evidence for a loss of ATM. In human AD, three independent ind####Ice####s of reduced ATM function-nuclear translocation of histone deacetylase 4, tri####Methylation#### of histone H3, and the presence of ########Cell Cycle######### activity-appear coordinately in neurons in reg####Ions#### where degeneration is prevalent. These same neurons also show reduced ATM protein levels. And though they represent only a fraction of the total neurons in each affected region, their numbers significantly correlate with ########Disease######### stage. This previously unknown role for the ATM ki####nas####e in AD pathogenesis suggests that the failure of ATM function may be an important contributor to the ####Death#### of neurons in AD individuals.

For 11 AD cases and four normal elderly controls, post mortem volumes of the hippocampal subdivis####Ions#### were calculated by using magnetic resonance imaging and histological sect####Ions####. After at least six weeks of fixation in formalin, brains were examined on a 1.5-T Philips Gyroscan imager producing T1-weighted coronal images with a 3-mm sl####Ice#### thickness. Brains were then processed and embedded in ####Paraffin####. Serial coronal sect####Ions####, 3 mm apart and stained with ####cresyl violet####, were used for the planimetry and unbiased estimation of the total numbers of neurons in the hippocampal subdivis####Ions####. For a####LL 15#### cases, magnetic resonance imaging- and histology-based measurements were performed along the whole rostrocaudal extent of the hippocampal formation and included three subvolumes: (i) the hippocampus (CA1-CA4 and the dentate gyrus); (ii) hippocampus/subiculum; and (iii) hippocampus/parahippocampal gyrus. After controlling for shrinkage, strong correlat####Ions#### were found between magnetic resonance imaging and histological measurements for the hippocampus ($r = 0.97$, $P < 0.001$),

hippocampus/subiculum (r = 0.95, P < 0.001) and hippocampus/parahippocampal gyrus (r = 0.89, P < 0.001). We also calculated the total number of neurons in the hippocampus and hippocampus/subiculum subvolumes. Strong correlat####Ions#### between the magnetic resonance imaging subvolumes and neuronal counts were found for the hippocampus (r = 0.90, P < 0.001) and the hippocampus/subiculum subvolume (r = 0.84, P < 0.001). We conclude that very accurate volumetric measurements of the whole hippocampal formation can be obtained by using a magnetic resonance imaging pro####tocol####. Moreover, the strong correlat####Ions#### between magnetic resonance imaging-based hippocampal volumes and neuronal numbers suggest the anato####mica####l validity of magnetic resonance imaging volume measurements.

To clarify the profile of depressive symptoms in major depressive episodes in patients with Alzheimers ########Disease######### (AD-MD), we compared AD-MD with major ####Depressive Disorder#### in non-demented elderly patients (MDD) matched for age, using the 17-item Hamilton Ra####Tin####g Scale for Depression (HAM-D(17)). In addition, to clarify which depressive symptoms of AD patients respond to treatment with the selective ####Sero####tonin######### and norad####Renalin####e reuptake inhibitor (SNRI) ####Milnacipran####, we compared the HAM-D(17) average score and the score of each HAM-D item, the mini-mental state examination (MMSE) score, and GAF score according to the DSM-IV evaluation of AD-MD patients at baseline and at the endpoint (12 weeks). Depressive mood, loss of interest in hobbies and social activities and anxiety (psychic) scored the highest in both AD-MD and MDD groups, while psychomotor retardation scored significantly higher in AD-MD, and insomnia and anxiety (somatic) significantly did so in MDD. We also found that depressive mood, suicidal tendency, loss of interest, psychomotor retardation, anxiety (psychic), gastroin####TES########Tin####al symptoms, general somatic symptoms, and ####Hypochondriasis#### remarkably improved in patients of AD-MD treated with ####Milnacipran####. Our results suggest that in general the profiles of depression in AD-MD and MDD are similar, despite some different clinical features between both condit####Ions####. Our study also suggests that ####Milnacipran#### is promising to treat a broad range of depressive symptoms in AD-MD patients.

Alzheimers ########Disease#########, and ####Dementia####, represent a common cause of disability and one of the most re####levan####t challenges in the health world. In addition, these condit####Ions#### do not have, at moment, a pharmacological treatment that can stop the pathological progress. Mild cognitive impairment (MCI), defined as the borderline between normal aging and early ####Dementia####, represents a meaningful field of study because, in the transition to ####Dementia####, clinicians have defined a useful therapeutic window. Additionally, due to the lack of effective pharmacological intervent####Ions####, recent years have seen an increase in research into new technological solut####Ions#### to assess, stimulate, and assist patients afflicted with Alzheimers ########Disease#########. This review aims to outline the use of information and communication technologies in the field studying MCI. Particularly, the goal is to depict the framework and describe the most worthwhile research efforts, in order to display the current technologies available, describe the research objectives, and delineate prospective future researches. Regarding data sources, the research was conducted within three databases, PubMed Central, Web of Science, and Scopus, between January 2009 and December 2017. A total of 646 articles were found in the initial search. Accurate definition of the exclusion criteria and selection strategy allowed identification of the most re####levan####t papers to use for the study. Finally, 56 papers were fully evaluated and included in this review. Three major

clinical application areas have been portrayed, namely ####"C####ognitive Assessment," "Treatment," and "Assistance." These have been combined with three main technological solut####Ions####, specifically ####"S####ensors," ####"p#####ersonal Dev####Ice####s," and "Robots." Furthermore, the study of the publicat####Ions#### time series illustra####TES#### a s####Tea####dily increasing trend, characterized by the enrollment of small groups of subjects, and particularly oriented to the subjects assistance using robots companion. In conclusion, despite the new technological solut####Ions#### for people with MCI have received much interest, particularly regarding robots for assistance, nowadays it still owns vast room for improvement.

Genetic variation, both single-nucleotide variat####Ions#### and copy number variat####Ions#### (CNV), contribute to changes in ####Gene Expression####. In some cases these variat####Ions#### are meaningfully correlated with #########Disease######### sta####TES####. We hypothesized that in a genetically heterogeneous disorder such as sporadic Alzheimers #########Disease######### (AD), utilizing ####Gene Expression#### as a quantitative trait and CNVs as a genetic marker map within the same individuals in the context of case-control status may increase the power to detect re####levan####t loci. Using this approach an 8-kb deletion was identified that contains a PAX6-binding site on chr2q33.3 upstream of CREB1 encoding the cAMP responsive element-binding protein1 transcription factor. The association of the CNV to AD was confirmed by a case-control association study consis####Tin####g of the Texas Alzheimer Research and Care Consortium and NIA-LOAD Family Study data sets.

Five-year follow-up of a community-based, 77+ old cohort including incident ####Dementia#### cases was used to evaluate the impact of ####Dementia#### on the risk of ####Death####, taking into account other chronic condit####Ions#### potentially related to ####Death####, and contras####Tin####g Alzheimers #########Disease######### (AD), and vascular ####Dementia#### (VaD). In this population, 70% of the ####Dementia#### cases died during the five years after diagnosis, with a mortality rate specific for ####Dementia#### of 2.4 per 100 person-years. After controlling for sociodemographic variables and comorbidity, 14% of all ####Death####s could be attributed to ####Dementia#### with a risk of ####Death#### among demented subjects tw####Ice#### as high as that for non-demented people. Mortality risk ratios were 2.0 (95% confidence interval 1.5-2.7) for AD and 3.3 (95% confidence interval 2.0-5.3) for VaD. This study confirms that demen####Tin####g disorders are a major risk factor for ####Death####. Even in the oldest old (85+), ####Dementia#### shortens life, especially among women.

The aggre####GAT####ion of the amyloid ß peptide (Aß) into amyloid fibrils is a defining characteristic of Alzheimers #########Disease#########. Because of the complexity of this aggre####GAT####ion process, effective therapeutic inhibitors will need to target the specific microscopic steps that ####Lead#### to the production of neurotoxic species. We introduce a strategy for genera####Tin####g fibril-specific antibodies that selectively suppress fibril-dependent secondary nucleation of the 42-residue form of Aß (Aß42). We target this step because it has been shown to produce the majority of neurotoxic species during aggre####GAT####ion of Aß42. Star####Tin####g from large phage display libraries of single-chain antibody fragments (scFvs), the three-stage approach that we describe includes (i) selection of scFvs with high affinity for

Aß42 fibrils after removal of scFvs that bind Aß42 in its monomeric form; (ii) ranking, by surface plasmon resonance affinity measurements, of the resul####Tin####g candidate scFvs that bind to the Aß42 fibrils; and (iii) kinetic screening and analysis to find the scFvs that inhibit selectively the fibril-catalyzed secondary nucleation process in Aß42 aggre####GAT####ion. By applying this approach, we have identified four scFvs that inhibit specifically the fibril-dependent secondary nucleation process. Our method also makes it possible to discard antibodies that inhibit elon####GAT####ion, an important factor because the suppression of elon####GAT####ion does not target directly the production of toxic oligomers and may even ####Lead#### to its increase. On the basis of our results, we suggest that the method described here could form the basis for rationally designed immunotherapy strategies to combat Alzheimers and related neurodegenerative ########Disease########s.

Amyloid-ß oligomers (AßOs) are the most important toxic species in the brain of Alzheimers ########Disease######## (AD) patient. AßOs, therefore, are considered reliable molecular ####Biomarkers#### for the diagnosis of AD. Herein, we reported a simple and sensitive electroche####mica####l method for the selective detection of AßOs using ####Silver#### nanoparticles (AgNPs) as the redox reporters and PrP(95-110), an AßOs-specific binding peptide, as the receptor. Specifically, ad####aman t####ine (Ad)-labeled PrP(95-110), denoted as Ad-PrP(95-110), induced the aggre####GAT####ion and color change of AgNPs and the follow-up formation of a network of Ad-PrP(95-110)-AgNPs. Then, Ad-PrP(95-110)-AgNPs were anchored onto a ß-cyclodextrin (ß-CD)-covered electrode surface through the host-guest interaction between Ad and ß-CD, thus producing an amplified electroche####mica####l signal through the solid-state Ag/AgCl reaction by the AgNPs. In the presence of AßOs, Ad-PrP(95-110) interacted specifically with the AßOs, thus losing the capability to bind AgNPs and to induce the formation of an AgNPs-based network on the electrode surface. Consequently, the electroche####mica####l signal decreased with an increase in the concentration of AßOs in the range of 20 pM to 100 nM. The biosensor had a detection limit of 8 pM and showed no response to amyloid-ß monomers (AßMs) and fibrils (AßFs). On the basis of the well-defined and amplified electroche####mica####l signal of the AgNPs-based network architecture, these results should be valuable for the design of novel electroche####mica####l biosensors by marrying specific receptors.

Phospholipase C (PLC, EC 3.1.4.11) is the major star####Tin####g point in the phosphatidyl####Inositol#### pathway, which genera####TES#### intracellular signals that regulate protein ki####nas####e C and intracellular ####Calcium#### concentration. To date, three major types of phosphoinositide-specific PLC species named beta, gamma and delta, have been characterized. This article reviews recent studies on isozymes delta of PLC. Four such isozymes have been cloned and termed delta1-4. Their structural organization, regulation of activity and the interaction with membrane ####Lipid A####re considered. The intracellular localization of delta isozymes and distribution in various tissues are presented. Attention is given to the pathological condit####Ions#### in which an abnormal protein level of PLC delta or its activity have been observed.

INTRODUCTION: Dual-specificity ty####rosin####e phosphorylation-regulated ki####nas####e 1A (DYRK1A) is a eukaryotic ####Serine####-####Threonine####

protein ki####nas####e belonging to the CMGC group. DYRK1A hyperactivity appears to contribute to the development of a number of human malignancies and to cognitive deficits observed in ####Dow####N ####Syndrome########### and Alzheimers ########Disease#########. As a result, the DYRK1A ki####nas####e represents an attractive target for the synthesis and optimization of pharmacological inhibitors of potential therapeutic interest. Like most ty####rosin####e ki####nas####e inhibitors developed up to the market, DYRK1A inhibitors are essentially ac####Tin####g by compe####Tin####g with ATP for binding at the catalytic site of the ki####nas####e. Areas covered: This paper reviews patent activity associated with the discovery of synthetic novel heterocyclic molecules inhibi####Tin####g the catalytic activity of DYRK1A. Expert opinion: Despite the important role of DYRK1A in biological processes and the growing interest in the design of new therapeutic drugs, there are only few patented synthetic DYRK1A inhibitors and most of them were and are still developed by academic research groups, sometimes with in####Dust####rial partners.

MicroR####nas#### (miR####nas####) are a group of small noncoding R####nas#### that regulate ####Translation####al repression of multiple target mR####nas####. The miR####nas#### in a whole cell regulate greater th####AN 3####0% of all protein-coding genes. The vast majority of presently identified miR####nas#### are expressed in the brain in a spatially and ####TEMPO####rally controlled manner. They play a key role in neuronal development, differentiation, and syn####APT####ic plasticity. However, at present, the pathological implicat####Ions#### of deregulated miRNA expression in neurodegenerative ########Disease#########s remain largely unknown. This review will briefly summarize recent studies that focus attention on aberrant miRNA expression in Alzheimers ########Disease######### brains.

Morphological changes of dendritic spines are strongly associated with syn####APT###ic development and syn####APT####ic plasticity, which underlies learning and memory. These changes are driven by alterat####Ions#### of F-ac####Tin#### dynamics under the control of Rho GTPases or by syn####APT####ic trafficking and insertion of glutamate receptors. Understanding the molecular events that occur during the formation and stabilization of dendritic spines, and the signaling pathways regula###Tin####g these processes, provides insights into the mechanisms of learning and memory. In this review, we discuss the recent advances on these postsyn####APT####ic signaling pathways, in particular, we discuss the specific signaling events that couple the cell-surface receptors to intracellular targets. In addition, we discuss the deregulation of these signaling pathways and their subsequent impact on syn####APT####ic dysfunction in Alzheimers ########Disease#########.

P300 and ####CERE####bros####pinal#### fluid neurotransmitter metaboli####TES#### and amino ####Acids#### were examined in 10 patients with Alzheimers ########Disease#########, 9 patients with vascular ####Dementia#### and 10 healthy controls. A ne####GAT####ive correlation between P300 amplitude and MHPG concentration, ne####GAT####ive correlation between P200 and N200 latencies and nor####Epinephrine#### concentration, positive correlation between N200 latency and ####Lysine#### concentration and positive correlation between N100 amplitude and ty####rosin####e concentration were statistically

significant. These findings suggest that the noradrenergic system influences P300 amplitude, and that multiple systems may influence P300 components.

Our goal was to ascertain, among normal elderly and individuals with mild cognitive impairment, which ####TEMPO####ral lobe neocortical reg####Ions#### predicted decline to ####Dementia#### of the Alzheimers type (DAT). Individuals received an MRI at baseline and a clinical and cognitive evaluation at baseline and follow-up. By using the baseline MRI we assessed the anato####mica####l subdivis####Ions#### of the ####TEMPO####ral lobe: anteromedial ####TEMPO####ral lobe (hippocampus and parahippocampal gyrus), medial occipito####TEMPO####ral (fusiform) gyrus, middle and inferior ####TEMPO####ral gyri, and superior ####TEMPO####ral gyrus. We studied two groups of carefully screened age- and education-matched elderly individuals: 26 normal elderly (NL) and 20 individuals with mild cognitive impairment (MCI). Fourteen individuals (12 from the MCI group and two from the NL group) declined to DAT within the 3.2-year follow-up interval. We used logistic regression analyses to ascertain wh####Ether#### the baseline brain volumes were useful predictors of decline to DAT at follow-up after accoun####Tin####g for age, gender, individual differences in brain size, and other variables known to predict DAT. After accoun####Tin####g for age, gender, and head size, adding the volume of the anteromedial ####TEMPO####ral lobe (the aggre####GAT####e of hippocampus and parahippocampal gyrus) and an index of global ####Atrophy#### raised the accuracy of overall classification to 80.4%. However, the ability to detect those individuals who declined (sensitivity) was low at 57%. When baseline medial occipito####TEMPO####ral and the combined middle and inferior ####TEMPO####ral gyri were added to the logistic model, the overall classification accuracy reached 95.6% and, most importantly, the sensitivity rose to 92.8%. These data indicate that the medial occipito####TEMPO####ral and the combined middle and inferior ####TEMPO####ral gyri may be the first ####TEMPO####ral lobe neocortical si####TES#### affected in AD; ####Atrophy#### in these areas may herald the presence of future AD among nondemented individuals. No other clinical baseline variables examined predicted decline with sensitivities above 71%. The apolipoprotein APOE epsilon4 genotype was not associated with decline.

AIMS: Abnormal sleep is a common feature of Parkinsons ########Disease######### (PD) and prodromal disorders of sleep are frequent (e.g. ####Restless Legs ####Syndrome######### and rapid eye movement sleep behaviour disorder). However, the exact pathological basis of disturbed sleep remains as yet undefined. METHODS: To investi####GAT####e this further, 32 PD cases were stratified into three groups: (1) PD with disturbed sleep, PD(S); (2) PD with ####Dementia#### (PDD) and disturbed sleep, PDD(S); and (3) PD without disturbed sleep, PD(nS). The extent of a-synuclein (aSyn) and ####Alzheimer ########Disease######### (AD)-type pathology [amyloid ß peptide (Aß) and tau] was assessed in 15 reg####Ions#### of the PD brain. RESULTS: The results demonstrate a significant association between disturbed sleep in PD and aSyn pathology in specific brainstem [locus coeruleus (P?=?0.006) and raphe nuclei (P?=?0.02)], hypothalamic [paramammillary nuclei (P?=?0.04) and posterior nucleus (P?=?0.02)], subcortical/limbic [amygdala (P?=?0.03), thalamus (P?=?0.01)] and cortical [entorhinal cortex (P?=?0.01)] reg####Ions####. A statistically significant increase of tau pathology was observed in the amygdala (P?=?0.03), CA2 sector of the hippocampus (P?=?0.01) and entorhinal cortex (P?=?0.04) in PD cases with disturbed sleep. CONCLUS####Ions####: Pathological changes in these structures, residing in the brain circuitry rela####Tin####g to sleep physiology, strongly predict the presence of sleep disturbances in PD.

Intra####CERE####bral injection of brain extracts from Alzheimers ########Disease######## (AD) patients into appropriate mouse models was previously found to drastically accelerate the ####DEPO####sition of Aß amyloid in the recipient animals indica####Tin####g a prion-like activity. In this study we show that this prion-like activity can be also identified by using a cell culture model of Aß plaque formation. Analysis of bioche####mica####l fract####Ions#### of AD brain extract indicate that the seeding-activity correlated with the presence of Aß peptide and Aß-derived aggre####GAT####es. In vitro-formed fibrils were also active but their activity was low and depending on the fibril structure and condit####Ions#### of fibril formation. Our data indicate a conformational basis of the observed seeding effect and suggest the utility of our cell model for further studies on the prion-like activity of AD extracts.

Traumatic brain injury (TBI) contribu####TES#### to the increased ra####TES#### of suicide and post-traumatic stress disorder in military personnel and veterans, and it is also associated with the risk for neurodegenerative and psychiatric disorders. A cross-phenotype high-resolution polygenic risk score (PRS) analysis of persistent post-concussive symptoms (PCS) was conducted in 845 U.S. Army soldiers who sustained TBI during their deployment. We used a prospective longitudinal survey of three brigade combat ####Tea####ms to assess deployment-acquired TBI and persistent physical, cognitive, and emotional PCS. PRS was derived from summary statis####Tics#### of large genome-wide association studies of Alzheimers ########Disease####, Parkinsons ########Disease#########, ####Schizophrenia####, ####Bipolar Disorder####, and major ####Depressive Disorder#### (MDD); and for years of schooling, college completion, childhood intelligence, infant head circumference (IHC), and adult intracranial volume. Although our study had more than 95% of statistical power to detect moderate-to-large effect sizes, no association was observed with neurodegenerative and psychiatric disorders, sugges####Tin####g that persistent PCS does not share genetic components with these traits to a moderate-to-large degree. We observed a significant finding: subjects with high IHC PRS recovered better from cognitive/emotional persistent PCS than the other individuals (R2?=?1.11%; p?=?3.37?×?10-3). Enrichment analysis identified two significant Gene Ontology (GO) terms related to this result: GO:0050839~Cell adhesion molecule binding (p?=?8.9?×?10-6) and GO:0050905~Neuromuscular process (p?=?9.8?×?10-5). In summary, our study indicated that the genetic predisposition to persistent PCS after TBI does not have substantial overlap with neurodegenerative and psychiatric ########Disease#########s, but mechanisms related to early brain growth may be involved.

OBJECTIVE The double transgenic mouse model (APPswe/PS1dE9) of Alzheimers ########Disease######### (AD) has been widely used in experimental studies. ß-Amyloid (Aß) ####peptide I####s excessively produced in AD mouse brain, which affects syn####APT####ic function and the development of central nervous system. However, little has been reported on characterization of this model. The present study aimed to characterize this mouse AD model and its wild-type counterparts by bioche####mica####l and functional approaches. METHODS Blood samples were collected from the transgenic and the wild-type m####Ice####, and radial arm ####Water#### maze behavioral ####TES####t was conducted at the ages of 6 and 12 months. The m####Ice#### were sacrif####Ice####d at 12-month age. One hemisphere of the brain was frozen-sectioned for immunohistochemistry and the other hemisphere was dissected into 7 reg####Ions####. The levels of Aß1-40, Aß1-42

and 8-hydroxy####Deoxy####Guanosine######### (8-OHdG) in blood or/and brain samples were analyzed by ELISA. Secretase activities in brain reg####Ions#### were analyzed by in vitro assays. RESULTS The pre-mature ####Death#### rate of transgenic m####Ice#### was approximately 35% before 6-month age, and high levels of Aß(1-40) and Aß(1-42) were detected in these dead m####Ice#### brains with a ratio of 1:10. The level of blood-borne Aß at 6-month age was similar with that at 12-month age. ####BES####ides, Aß(1-40) level in the blood was significantly higher than Aß(1-42) level at the ages of 6 and 12 months (ratio 2.37:1). In contrast, the level of Aß(1-42) in the brain (160.6 ng/mg protein) was higher than that of Aß(1-40) (74 ng/mg protein) (ratio 2.17:1). In addition, the levels of Aß(1-40) and Aß(1-42) varied markedly among different brain reg####Ions####. Aß(1-42) level was significantly higher than Aß(1-40) level in ####CERE####bellum, frontal and posterior cortex, and hippocampus. Secretase activity assays did not reveal major differences among different brain reg####Ions#### or between wild-type and transgenic m####Ice####, sugges####Tin####g that the transgene PS1 did not ####Lead#### to higher ?-secretase activity but was more efficient in producing Aß(1-42) ####Peptides####. 8-OHdG, the biomarker of DNA oxidative damage, showed a trend of increase in the blood of transgenic m####Ice####, but with no significant difference, as compared with the wild-type m####Ice####. Behavioral ####TES####ts showed that transgenic m####Ice#### had significant memory deficits at 6-month age compared to wild-type controls, and the deficits were exacerbated at 12-month age with more errors. CONCLUSION These results suggest that this mouse model mimics the early-onset human AD and may represent full-blown ########Disease######## at as early a####S 6####-month age for experimental studies.

The frequency of autoantibodies (AAbs) was surveyed in several neurodegenerative ########Disease#########s, other neurological ########Disease#########s, and controls using antigen-specific EIAs for neurofilament heavy subunit, tubulin, glial fibrillary acidic protein, S100 protein, tau, beta-amyloid peptide, myelin basic protein, and heparan sulfate proteoglycan. High frequencies of sera and ####CERE####bros####pinal#### fluid tubulin AAbs were found in ####Alzheimer ########Disease############ (62% and 69%, respectively), Parkinson ########Disease######## (27% and 70%), ####Amyotrophic Lateral ####Sclerosis######## (54% and 67%), and in sera from multiple ####Sclerosis#### (50% and 67%), optic ####Neuritis#### (85%), Guillain-Barré ####Syndrome#### (88%), and vascular ####Dementia#### (52%). High frequencies of neurofilament heavy subunit AAbs were detected in Guillain-Barré ####Syndrome####, chronic peripheral neuropathy (88%) and optic ####Neuritis#### (62%); whereas, some Alzheimers ########Disease######### (33%) and vascular ####Dementia#### (44%) patients had glial fibrillary acidic protein AAbs. Lower frequencies of other AAbs were found in patient groups. AAb results were also compared to functional assessment of blood-brain barrier integrity in Parkinsons ########Disease######### and Alzheimers ########Disease#########. The re####levan####ce of these AAbs to pathogenesis and/or course of neurologic ########Disease#########s merits further study with particular reference to subgrouping and prognosis.

BACKGROUND: Epide####Miol####ogic evidence has emerged to reveal an association of ####Albuminuria#### and low estimated glomerular filtration rate (eGFR) with ####Dementia####, but the findings are inconsistent. In addition, there are limited studies addressing the association between ####Albuminuria#### and ####Alzheimer ########Disease######### (AD). METHODS AND RESULTS: A total of 1562 community-dwelling Japanese subjects aged =60 years without ####Dementia#### were followed up for 10 years. The outcomes were incidence of

all-cause ####Dementia#### and its subtypes, namely, AD and vascular ####Dementia#### (VaD). The hazard ratios for the outcomes were estimated according to urine albumin-####Crea####Tin####ine#### ratio (UACR) and eGFR levels using a Cox proportional hazards model. During the follow-up, 358 subjects developed all-cause ####Dementia#### (238 AD and 93 VaD). Higher UACR level was significantly associated with greater multivariable-adjusted risks of all-cause ####Dementia#### (hazard ratios [95% confidence intervals]: 1.00 [reference], 1.12 [0.78-1.60], 1.65 [1.18-2.30], and 1.56 [1.11-2.19] for UACR of =6.9, 7.0-12.7, 12.8-29.9, and =30.0 mg/g, respectively), AD (1.00 [reference], 1.20 [0.77-1.86], 1.75 [1.16-2.64], and 1.58 [1.03-2.41], respectively), and VaD (1.00 [reference], 1.03 [0.46-2.29], 1.94 [0.96-3.95], and 2.19 [1.09-4.38], respectively). On the other hand, lower eGFR level was marginally associated with greater risk of VaD, but not AD. Subjects with UACR =12.8 mg/g and eGFR of <60 mL/min per 1.73 m2 had 3.3-fold greater risk of VaD than those with UACR <12.8 mg/g and eGFR of =60 mL/min per 1.73 m2. CONCLUS####Ions####: ####Albuminuria#### is a significant risk factor for the development of both AD and VaD in community-dwelling Japanese elderly. Moreover, ####Albuminuria#### and low eGFR are mutually associated with a greater risk of VaD.

Alzheimers ########Disease######### (AD) is the most prevalent cause of ####Dementia#### in humans. This ########Disease######### is characterized by the presence of amyloid beta (Ab) ####DEPO####sits in the parenchyma (also known as amyloid plaques or senile plaques) and in the ####CERE####bral vasculature. Though Ab formation and ####DEPO####sits are strongly correlated with cognitive impairment, the mechanisms responsible for the syn####APT####ic dysfunct####Ions#### and loss of neurons in AD remain largely unknown. Many studies have provided evidence that microglial cells are attracted to amyloid ####DEPO####sits both in human samples and in rodent transgenic models that develop this ########Disease#########. We have recently found that blood-derived microglia and not their resident counterparts have the ability to eliminate amyloid ####DEPO####sits by a cell-specific phagocytic mechanism. These bone marrow-derived microglia have consequently a great therapeutic potential for AD patients. Molecular strategies aiming to improve their recruitment could ####Lead#### to a new powerful tool for the elimination of toxic Ab and improve cognitive funct####Ions####. However, numerous limitat####Ions#### have to be taken into consideration before recom####MEND####ing such a cellular therapy and these are discussed in the present review.

beta-Secretase (memapsin 2, BACE1) is an attractive target for the development of inhibitor drugs to treat Alzheimers ########Disease######### (AD). Not only does this pro####Tea####se function at the first step in the pathway ####Lead####ing to the production of amyloid-beta (Abeta), its gene deletion produces only mild phenotypes. In addition, beta-secretase is an aspartic pro####Tea####se whose mechanism and inhibition are well known. The development of beta-secretase inhibitors, actively pursued over the last seven years, has been slow, due to the difficulty in combining the required properties in a single inhibitor molecule. S####Tea####dy progress in this field, however, has brought about inhibitors that contain many targeted characteris####Tics####. In this review, we describe the strategy of structure-based inhibitor evolution in the development of beta-secretase inhibitor drug. The current status of the field offers grounds for some optimism, in that beta-secretase inhibitors have been shown to reduce brain Abeta and to rescue the cognitive decline in transgenic AD m####Ice####, and an orally available beta-secretase inhibitor drug candidate is in clinical trial. With this knowledge base, it seems reasonable to expect that more drug candida####TES#### will be ####TES####ted in

human, and then successful ########Disease#########-modifying drugs may ultimately emerge from this target.

A computation docking study of the highly potent, non-####Nitrogen#### containing, ####Acetyl####Choline#########sterase inhibitor (+)-####arisugacin#### A is presented. The model suggests that (+)-####arisugacin#### A is a dual binding site covalent inhibitor of AChE. These findings are examined in the context of Alzheimers #########Disease#########-modifying therapeutic design. (+)-####arisugacin#### As revealed mode of action is unique, and may serve as a basis for the development of AD therapeu####Tics#### capable of trea####Tin####g the symptomatic aspects of AD, while being neuroprotective with long term efficacy.

In postmenopausal women, both the aging process and the hypoestrogenism due to the loss of ovarian function seem to be related to the progressive impairment of cognitive funct####Ions#### and to a higher risk of developing Alzheimers ########Disease######### (AD). This paper reviews the potentially beneficial effects of hormonal replacement therapy (HRT) on cognition and on the risk of developing AD. Articles re####levan####t to the topic were selected by reviewing MEDLINE data and references of previous published reviews on this subject. Epide####Miol####ogical studies on the effects of HRT on cognitive functioning have yielded disparate results, perhaps because of varying methodology and designs. However, the available data suggest that the use of HRT could be associated with a lower risk for AD. This conclusion should be interpreted with caution, since most of the studies were case-control studies, and thus subjected to several sources of bias. Further well-designed and conducted clinical trials and longitudinal studies would be required to clarify the effects of ####Estrogens#### on cognition and AD.

In Alzheimers ########Disease#########, histoche####mica####lly visualized ####Choline####sterases with altered pH optimum for activity and inhibitable by ####indole########Amines#### and the pro####Tea####se inhibitor ####Bacitracin#### emerge in association with plaques and tangles. It has been suggested that these ####Choline####sterases may participate in the pathologic process. However, it is not known wh####Ether#### the properties of ####Choline####sterases observed in Alzheimers ########Disease######### are due to requirements of histoche####mica####l procedures or actual bioche####mica####l properties of these enzymes. Using bioche####mica####l assays of ####Acetyl####Choline#########sterase and ####butyryl####Choline#########sterase activities, we demonstrate here that ####Sero####tonin######### and ####Bacitracin#### result in a significantly greater and dose-dependent inhibition of ####Choline####sterases in Alzheimers ########Disease######### cortex when compared with age-matched controls. In contrast, variat####Ions#### in pH did not dis####Tin####guish ####Choline####sterases in Alzheimers ########Disease######### and control cortex. We also confirmed significant reduction of ####Acetyl####Choline#########sterase activity in Alzheimers ########Disease######### cortex and increased ####butyryl####Choline#########sterase activity that only approached significance. We conclude that inhibition by ####indole########Amines#### and ####Bacitracin#### is a bioche####mica####l characteristic of a proportion of ####Choline####sterases in Alzheimers ########Disease######### that most likely

represents the pool associated with plaques and tangles. Most of the available ####Choline####sterase inhibitors are relatively incapable of inhibi####Tin####g ####Choline####sterases associated with plaques and tangles. The findings of the present investi####GAT####ion open the way for attempts to isolate ####Choline####sterases associated with plaques and tangles and design or discovery of inhibitors specifically targeted to ####Choline####sterases in these les####Ions####.

Previous research has hypothesized an association between Alzheimers ########Disease######### and the amyloid precursor protein (APP) gene found on chromosome 21. We report the case of ####A 7####8-year-old woman with Downs ####Syndrome#### with partial ####Trisomy#### 21 [46,XX,rec(21)dup q, inv(21)(p12q22.1)]. No evidence of Alzheimers ########Disease######### was found on neuropsychological, magnetic resonance imaging, and neuropathological assessment. The gene sequence for APP was present in only two copies. This case further supports the hypothesis that Alzheimers ########Disease######### is associated with ####Trisomy#### for proximal chromosome 21q, including the APP gene.

Prior functional magnetic resonance imaging (fMRI) studies have found increased activity-related blood ####Oxygen#### level-dependent (BOLD) signal in cognitively normal persons at genetic risk for Alzheimers ########Disease######### (AD). This has been interpreted as a compensatory response to incipient AD pathology. We studied the effects of fully penetrant familial Alzheimers ########Disease######### (FAD) mutat####Ions#### and apolipoprotein E (APOE) genotype on BOLD fMRI during a novelty encoding task in presymptomatic subjects. Twenty-three Mexican or Mexican-American persons at-risk for inheri####Tin####g FAD mutat####Ions#### performed a block design novelty encoding task, and activation exhibited by FAD mutation carriers (MCs) was contrasted with that of noncarriers (NCs) and among APOE genotype groups. FAD MCs (n = 14) showed decreased BOLD activation in the anterior cingulate gyrus relative to 9 NCs. No increased activation was seen in MCs relative to NCs. Four APOE e3/4 carriers demonstrated increased BOLD signal compared with 14 e3/3 carriers in the occipital and perisylvian cort####Ice####s bilaterally. There were no areas where e3/3 carriers activated more than e3/4 carriers. Our findings of increased fMRI activation associated with APOE genotype but not with FAD mutat####Ions#### suggest that APOE exerts an effect on the BOLD signal that is not readily explained as a compensatory phenomenon.

BACKGROUND: Data on ####Dementia#### from low- and middle-income countries are still necessary to quantify the burden of this condition. This mult####Ice####nter cross-sectional study aimed at estima####Tin####g the prevalence of ####Dementia#### in 2 large cities of Central Africa. METHODS: General population door-to-door surveys were conducted in the districts of Bangui (Republic of Central Africa) and Brazzaville (Congo) in elderly aged = 65 years. The subjects were screened with the Community Screening Interview for ####Dementia#### and the Five-Words ####TES###t. Diagnosis of ####Dementia#### was made according to the DSM-IV criteria and to the clinical criteria proposed by the NINCDS-ADRDA for Alzheimers ########Disease#########. RESULTS: We enrolled 496 subjects in Bangui and 520 in Brazzaville. The prevalence of ####Dementia#### was estimated at 8.1% (95% CI = 5.8-10.8) in Bangui and 6.7% (95% CI = 4.7-9.2) in Brazzaville. CONCLUSION: The prevalence of

####Dementia#### in urban areas of Central Africa is close to those observed in high-income countries.

Neuropsychological ####TES####ts are useful for diagnosing Alzheimers ########Disease########## (AD), yet for many ####TES####ts, diagnostic accuracy statis####Tics#### are unavailable. We present diagnostic accuracy statis####Tics#### for seven variables from the Neuropsychological Assessment Battery (NAB) that were administered to a large sample of elderly adults (n = 276) participa####Tin####g in a longitudinal research study at a national AD Center. ####TES####ts included Driving Scenes, Bill Payment, Daily Living Memory, Screening Visual Discrimination, Screening Design Construction, and Judgment. Clinical diagnosis was made independent of these ####TES####ts, and for the current study, participants were categorized as AD (n = 65) or non-AD (n = 211). Receiver opera####Tin####g characteris####Tics#### curve analysis was used to determine each ####TES####ts sensitivity and specificity at multiple cut points, which were subsequently used to calculate positive and ne####GAT####ive predictive values at a variety of base ra####TES####. Of the ####TES####ts analyzed, the Daily Living Memory ####TES####t provided the grea####TES####t accuracy in the identification of AD and the two Screening measures required a significant tradeoff between sensitivity and specificity. Overall, the seven NAB sub####TES####ts included in the current study are capable of excellent diagnostic accuracy, but appropriate understanding of the context in which the ####TES####ts are used is crucial for minimizing errors.

Converging evidence from clinical and pathological studies indicate the presence of important relat####Ions####hips between the ongoing deterioration of brain lipid homeostasis, vascular changes and the pathophysiology of sporadic Alzheimers ##########Disease########## (AD). These associat####Ions#### include the recognition of ####Cholesterol#### transporters apolipoprotein E (APOE), APOC1 and APOJ as major genetic risk factors for common AD and observat####Ions#### associa####Tin####g risk factors for cardiovascular ##########Disease########## such as high midlife plasma ####Cholesterol####, diabe####TES####, ####Stroke####, ####O####BES####ity#### and ####Hypertension#### to ####Dementia#####. Moreover, recent clinical findings lend support to the notion that progressive deterioration of ####Cholesterol#### homeostasis in AD is a central player in the ##########Disease######### pathophysiology and is, therefore, a potential therapeutic target for ##########Disease########## prevention.

Two recent studies have identified that a rare coding variant (p.R47H) in exon 2 of triggering receptor expressed on myeloid cells 2 (TREM2) gene is associated with Alzheimers ##########Disease########## (AD) susceptibility in Caucasians. This association was not successfully replicated in Han Chinese, where this variant was rare or even absent. Previously, we resequenced TREM2 exon 2 to investi####GAT####e wh####Ether#### additional rare variants conferred risk to AD in our cohort. Although several new variants had been identified, none of them was significantly associated with ##########Disease########## susceptibility. Here, to ####TES####t wh####Ether#### TREM2 is truly a susceptibility gene of AD in Han Chinese, we extend our previous study by sequencing the other four exons of TREM2 in 988 AD patients and 1,354 healthy controls. We provided the first evidence that a rare coding variant (p.H157Y) in TREM2 exon 3 conferred a considerable risk of AD in our cohort (Pcorrected = 0.02, odds ratio = 11.01,

95% confidence interval: 1.38-88.05). This finding indica####TES#### that rare coding variants of TREM2 may play an important role in AD in Han Chinese.

BACKGROUND: Protein aggre####GAT####ion plays important roles in several neurodegenerative disorders. For instance, insoluble aggre####GAT####es of phosphorylated tau and of Aß ####Peptides#### are cornerstones in the pathology of Alzheimers ########Disease#########. Soluble protein aggre####GAT####es are therefore potential diagnostic and prognostic ####Biomarkers#### for their cognate disorders. Detection of the aggre####GAT####ed species requires sensitive tools that efficiently discriminate them from monomers of the same proteins. Here we have established a proximity li####GAT####ion assay (PLA) for specific and sensitive detection of Aß protofibrils via simultaneous recognition of three identical determinants present in the aggre####GAT####es. PLA is a versatile technology in which the requirement for multiple target recognit####Ions#### is combined with the ability to translate signals from detected target molecules to amplifiable DNA strands, providing very high specificity and sensitivity. RESULTS: For specific detection of Aß protofibrils we have used a monoclonal antibody, mAb158, selective for Aß protofibrils in a modified PLA, where the same monoclonal antibody was used for the three classes of affinity reagents required in the assay. These reagents were used for detection of soluble Aß aggre####GAT####es in solid-phase react####Ions####, allowing detection of just 0.1 pg/ml Aß protofibrils, and with a dynamic range greater than six orders of magnitude. Compared to a sandwich ELISA setup of the same antibody the PLA increases the sensitivity of the Aß protofibril detection by up to 25-fold. The assay was used to measure soluble Aß aggre####GAT####es in brain homogena####TES#### from m####Ice#### transgenic for a human allele predisposing to Aß aggre####GAT####ion. CONCLUS####Ions####: The proximity li####GAT####ion assay is a versatile analytical technology for proteins, which can provide highly sensitive and specific detection of Aß aggre####GAT####es - and by implication other protein aggre####GAT####es of re####levan####ce in Alzheimers ########Disease######### and other neurodegenerative disorders.

Alzheimers ########Disease######### is a debilita####Tin####g neurological ########Disease######### placing significant burden on health care budgets around the world. It is widely believed that accumulation of amyloid-beta (Aß) in the brain is a key event that initia####TES#### neurodegeneration, thus the clearance of Aß from brain could be a key therapeutic strategy. Aß exists in an equilibrium in healthy individuals, and recent research would suggest that dysfunction in the clearance pathways is the driving force behind its accumulation. One mechanism of clearance is proteolytic degradation by enzymes, and increasing the expression of these enzymes in animal models of Alzheimers ########Disease######### has indeed shown promising results. This approach could be challenging to translate into the clinic given the likely need for genetic manipulation. We hypothesize that stimula####Tin####g the activity of these enzymes (as opposed to increasing expression) through pharmacological agents will enhance degradation or at least prevent amyloid ####DEPO####sition, and is therefore another potentially novel avenue to manipulate Aß levels for therapeutic purposes. We discuss the recent research suppor####Tin####g this hypothesis as well as possible drawbacks to this approach.

BACKGROUND: Expression of neuronal thread protein (NTP), which is considered to be related to neuritic sprou####Tin####g and neuronal ####Death####, may be

elevated in brain tissue, ####CERE####bros####pinal#### fluid, and even urine in patients with Alzheimers ########Disease######### (AD). OBJECTIVE: In this study, we analyzed the correlation between urine AD-associated NTP (AD7c-NTP) level, and amyloid-ß (Aß) ####DEPO####sition, and clinical symptoms in AD and mild cognitive impairment (MCI). METHODS: Twenty-two patients with mild to moderate AD and 8 subjects with MCI were recruited. Aß ####DEPO####sition was measured with [11C]-labeled Pittsburgh compound B (PiB)-positron emission tomography (PET) in all participants. Urine AD7c-NTP levels were measured using enzyme-linked immunosorbent assay. Mini-Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI) were used to evaluate cognitive function and behavioral psychological symptoms, respectively. RESULTS: Fourteen (63.6%) of AD patients and 2 (25.0%) of MCI subjects were Aß positive on PiB-PET. There was a significant difference in urine AD7c-NTP level between Aß positive (2.27±2.22?ng/ml) and ne####GAT####ive (0.55±0.60?ng/ml) subjects (p?=?0.018). Using 1.46?ng/ml as a cut-off value, 68.8% of Aß positive subjects showed elevated urine AD7c-NTP level, and 92.9% of Aß ne####GAT####ive subjects showed normal urine AD7c-NTP level. There were no relat####Ions####hips between urine AD7c-NTP level and MMSE and total NPI scores. However, AD7c-NTP level positively correlated with agitation score on NPI. CONCLUS####Ions####: Urine AD7c-NTP had high specificity and moderate sensitivity in predic####Tin####g Aß ####DEPO####sition among patients with cognitive impairment. Furthermore, urine AD7c-NTP level strongly correlated with the symptom of agitation.

We aimed to determine wh####Ether#### presence of AD neuropathology predicted cognitive, gait and balance measures in patients with idiopathic normal pressure ####Hydrocephalus#### (iNPH) after shunt surgery. This is a prospective study of gait and balance measured by Timed Up and Go (TUG) and ####Tin####etti ####TES####ts, and cognitive function measured by Mini Mental Status Exam (MMSE), before and after shunt surgery in participant####S 6####5 years and older with iNPH at the Johns Hopkins University. Random effects models were used and adjusted for confounders. 88 participants were included in the analysis with a median (IQR) time of 104 (57-213) days between surgery and follow-up. 23 (25%) participants had neuritic plaques present (NP+) and were significantly older [76.4 (6.0) years], but were otherwise similar in all demographics and outcome measures, when compared to the group without neuritic plaques (NP-). NP- and NP+ participants equally improved on measures of TUG (ß = -3.27, 95% CI -6.24, -0.30, p = 0.03; ß = -2.37, 95% CI -3.90, -0.86, p = 0.02, respectively), ####Tin####etti-total (ß = 1.95, 95% CI 1.11, 2.78, p<0.001; ß = 1.72, 95% CI 0.90, 2.53, p<0.001, respectively), -balance (ß = 0.81, 95% CI 0.23, 1.38, p = 0.006; ß = 0.87, 95% CI 0.40, 1.34, p<0.001, respectively) and -gait (ß = 1.03, 95% CI 0.61, 1.45, p<0.001; ß = 0.84, 95% CI 0.16, 1.53, p = 0.02, respectively), while neither NP- nor NP+ showed significant improvement on MMSE (ß = 0.10, 95% CI -0.27, 0.46, p = 0.61, ß = 0.41, 95% CI -0.27, 1.09, p = 0.24, respectively). In summary, 26% of participants with iNPH had coexis####Tin####g AD pathology, which does not significantly influence the clinical response to shunt surgery.

The prevalence of Alzheimers ########Disease######### (AD) has grown progressively over the past 100 years. The present study monitored the evolution of AD incidence in relation to several factors known as favoring it, in a county in Romania, between 1980 and 2006. The annual incidence of AD in our clinic over a period of 27 years was determined along with 17 here####DITA####ry, medical, sociodemographic and env####Iron####[####MME#####ntal parameters. The results show a relatively s####Tea####dy curve until 1994, followed by a doubling of the incidence with a tendency to con####Tin####uous growth. During this period, none of the known

pathogenic factors--medical, psychological or sociodemographic--suffered any mathematically significant transformation. The only significant change for this population was the access to in####Dust####rialized and preserved food and fizzy drinks which came from the western world, i####MME####diately after the borders had opened (1989). Therefore, the cause of the increased AD incidence must be looked for in food hygiene, and we must accept the notion of an ecologically caused ########Disease#########.

Disruption of the postsyn####APT####ic density (PSD), a network of scaffold proteins located in dendritic spines, is thought to be responsible for syn####APT####ic dysfunction and loss in early-stage Alzheimers ########Disease######### (AD). Extending our previous demonstration that derangement of the PSD by soluble amyloid-beta (Abeta) involves pro####Tea####somal degradation of PSD-95, a protein important for ionotropic glutamate receptor trafficking, we now show that Abeta also disrupts two other scaffold proteins, Homer1b and Shank1, that couple PSD-95 with ionotropic and metabotropic glutamate receptors. Treatment of fronto-cortical neurons with soluble Abeta results in rapid (within 1 h) and significant thinning of the PSD, decreased syn####APT####ic levels of Homer1b and Shank1, and reduced syn####APT#####ic mGluR1 levels. We show that de novo ####Protein S####ynthesis is required for the declustering effects of Abeta on Homer1b (but not Shank1) and that, in contrast to PSD-95, Abeta-induced Homer1b and Shank1 cluster disassembly does not depend on pro####Tea####some activity. The regulation of Homer1b and Shank1 by Abeta diverges in two other respects: i) whereas the activity of both NMDAR and VDCC is required for Abeta-induced declustering of Homer1b, Abeta-induced declustering of Shank1 only requires NMDAR activity; and ii) whereas the effects of Abeta on Homer1b involve engagement of the PI-3K pathway and calcineurin phosphatase (PP2B) activity, those on Shank1 involve activation of the ERK pathway. In summary, soluble Abeta recruits discrete signalling pathways to rapidly reduce the syn####APT####ic localization of major components of the PSD and to regulate the availability of mGluR1 in the synapse.

μ-Cal####Pain#### is a ####Calcium#####-dependent ####Cysteine#### pro####Tea####se, which is activated by μM concentration of ####Calcium#### in vitro. Disrupted intracellular ####Calcium#### homeostasis ####Lead####s to hyper-activation of μ-cal####Pain####. Hyper-activated μ-cal####Pain#### enhances the accumulation of ß-amyloid ####peptide B####y increasing the expression level of ß-secretase (BACE1) and induces hyper-phosphorylation of tau along with the formation of neurofibrillary tangle by media####Tin####g p35 cleavage into p25, both of which are the major mechanisms of neurodegeneration in Alzheimers ########Disease######### (AD). Hence, inhibition of μ-cal####Pain#### activity is very important in the treatment and prevention of AD. In this study, conju####GAT####ed ####Lin####Oleic Acid######### (CLA), an eighteen-####Carbon#### unsaturated fatty acid, was discovered as a μ-cal####Pain####-specific inhibitor. CLA showed neuroprotective effects against ####Neurotoxins#### such as H2O2 and Aß1-42 in SH-SY5Y cells, and inhibited Aß oligomerization/fibrillation and Aß-induced Zona Occludens-1 degradation. In addition, CLA decreased the levels of proapoptotic proteins, p35 conversion to p25 and tau phosphorylation. These findings implicate CLA as a new core structure for selective μ-cal####Pain#### inhibitors with neuroprotective effects. CLA should be further evaluated for its potential use as an AD therapeutic agent.

BACKGROUND: ####CERE####bral ####Amyloid angiopathy#### (CAA) is classified as type 1 with capillary amyloid ß (Aß) or type 2 without capillary Aß. While it is known that CAA activa####TES#### complement, an inflammatory mediator, there is no information on the relat####Ions####hip between capillary Aß and complement activation. METHODS: We evaluated 34 au####TOPS####y brains, including 22 with CAA and 12 with other neurodegenerative ##########Disease##########s. We assessed the vascular density of CAA by analyzing the expression of complement (C1q, C3d, C6, C5b-9), macrophage scavenger receptor (MSR), and apolipoprotein E (ApoE). RESULTS: Capillary immunostaining for C1q, C3d, MSR, and ApoE was identified almost exclusively in CAA-type1 brains. There was intense expression of C1q, C3d, MSR, and ApoE, as well as weaker expression of C5b-9 and C6 in the arteries/ arterioles of both CAA subtypes, but not in control brains. C5b-9 and C6 were preferentially expressed in arteries/arterioles with subcortical ####Hemorrhage#### or cortical superficial ####Siderosis####. Triple immunofluorescence revealed that C1q, C3d, and ApoE were colocalized with Aß in CAA brain capillaries. CONCLUSION: Complement, MSR, and ApoE were only coexpressed in the presence of Aß accumulation in capillaries, sugges####Tin####g a role for complement activation in the propa####GAT####ion of Aß. Additionally, C5b-9 expression may be associated with hemorrhagic brain injury in CAA.

BACKGROUND: Apathy and depression are the most frequent behavioural and psychiatric disorders in Alzheimers ##########Disease##########, and may both have a ne####GAT#####ive impact on the progression of the illness. OBJECTIVES: To examine the clinical correla####TES#### of apathy in Alzheimers ##########Disease########## (AD), and to determine wh####Ether#### apathy is a significant predictor of more rapid cognitive, functional and emotional decline. METHODS: Using a structured psychiatric evaluation, we examined a consecutive series of 354 subjects mee####Tin####g clinical criteria for AD. Apathy was assessed by the Apathy Scale, and diagnosed using standardised criteria. Additional measurements included scales for depression, functional impairment, and global cognitive funct####Ions####. A follow up evaluation was carried out in 247 patients (70% of the total sample) between 1 and 4 years after the baseline evaluation. RESULTS: Apathy was significantly associated with older age ($p = 0.009$), and a higher frequency of minor and major depression ($p < 0.0001$). Apathy at baseline was a significant predictor of depression at follow up ($p = 0.01$), and was associated with a faster cognitive ($p = 0.0007$) and functional decline ($p = 0.006$). CONCLUS####Ions####: Apathy in AD is a behavioural marker of a more aggressive ####Dementia####, characterised by a faster progression of cognitive, functional, and emotional impairment.

OBJECTIVES: To study the prevalence rate of ####Dementia#### and its subtypes in Japan and to investi####GAT####e the relat####Ions####hip of risk factors, such as demographic features and ##########Disease########## history, to the prevalence of Alzheimers ##########Disease########## or vascular ####Dementia####. DESIGN: A prevalence study within a longitudinal cohort study. SET####Tin####G: The o####rigin####al Adult Health Study (AHS) cohort consisted of atomic-bomb survivors and their controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. Since 1958, the AHS subjects have been followed through biennial medical examinat####Ions####. PARTICIPANTS: Subjects were 637 men and 1585 women aged 60 years or older in the AHS cohort. Forty-eight subjects resided in hospitals and institut####Ions####. MEASUREMENTS: In addition to the biennial medical examinat####Ions#### ongoing since 1958, a screening ####TES####t for cognitive impairment (CASI) was conducted by trained nurses

between September 1992 and September 1996. The prevalence of ####Dementia#### and its subtypes was assessed in 343 subjects suspected to have ####Dementia#### and in 272 subjects with high CASI scores who were selected randomly. RESULTS: The prevalence of ####Dementia#### based on D####SM II####I/R criteria, using neurological examination, the IQCODE, and CDR > or = 1, was 7.2%. The prevalence of Alzheimers ########Disease######## was 2.0% in men and 3.8% in women, and the prevalence of vascular ####Dementia#### was 2.0% in men and 1.8% in women. The relat###Ions####hip of risk factors to Alzheimers ########Disease######## or vascular ####Dementia#### was investi####GAT####ed by the multivariate logistic linear regression analysis. Odds ratios of Alzheimers ########Disease######## for age (in 10-year increments), attained education (in 3-year increments), history of head trauma, and history of cancer are 6.3, 0.6, 7.4, and 0.3, respectively. Odds ratios of vascular ####Dementia#### for age, history of ####Stroke####, and history of ####Hypertension#### are 2.0, 35.7, and 4.0, respectively. Neither type of ####Dementia#### showed any significant effect of sex or radiation exposure. CONCLUSION: This study is the first study of Japanese ####Dementia#### ra####TES#### carried out with a pro####tocol#### similar enough to that of a US study to allow meaningful comparisons. The prevalence ra####TES#### demonstrated are more similar to US ra####TES#### than were found in many previous reports in Japan.

In spite that the use of naturally occurring neurotrophic factors like NGF, BDNF, CNTF, GDNF and others for treatment of neurodegenerative disorders seems promising because of their pharmacological properties, until now no large scale clinical trials have been published. One of the reasons is that these molecules are unable to penetrate through the blood brain barrier, making invasive application strategies like intra####CERE####broventricular infusion necessary. Another one is the fact that in first clinical studies, several undesirable side-effects like ####Hyperalgesia#### or ####Weight Loss#### have been reported. Major efforts are now put into development of improved application procedures and in treatment pro####tocol####s for avoiding the known side-effects. Already 7 years ago it has been demonstrated that ####CERE####brolysin, a peptidergic drug, produced from purified brain proteins by standardized enzymatic breakdown, containing biologically active ####Peptides####, is exer####Tin####g ####Nerve Growth Factor#### like activity on neurons from dorsal root ganglia. Still ongoing investi####GAT########Ions#### are showing growth promo####Tin####g efficacy of this drug in different neuronal populat####Ions#### from peripheral and central nervous system. The current findings are in accordance with several older publicat####Ions####, enabling now a more clear interpretation of these findings. In addition to the direct neurotrophic effect, the drug also shows clear neuroprotective properties after different types of lesion in vitro and in vivo, resembling the pharmacological activities of naturally occurring ####Nerve Growth Factor####s. Neurotrophic and neuroprotective efficacy has been shown with a broad variety of methods in different models and it is remarkable that all bioche####mica####l and morphological drug dependent alterat####Ions#### are resul####Tin####g in improvements of learning and memory. Because of these experimental results, clinical trials using ####CERE####brolysin in Alzheimers patients have been performed, demonstra####Tin####g a quick improvement in the overall state of the patients, particularly enhancing the cognitive performance. It is remarkable that these effects are long las####Tin####g after cessation of the active treatment procedure. Even 6 months after stop of drug application improvements in AD-patients are detectable. Therefore it is concluded that ####CERE####brolysin is able to induce repair phenomena, resul####Tin####g in long term stabilization. In contrast to the naturally occurring growth factors, tolerability of this drug is extremely high, without any reports about serious side-effects in these clinical studies.

####Heparan Sulfate ####Proteoglycans######### (HSPGs) have been suggested to play an important role in the formation and persistence of senile plaques and neurofibrillary tangles in ####Dementia#### of the Alzheimers type (DAT). We performed a comparative immunohistoche####mica####l analysis of the expression of the HSPGs agrin, ####perlecan####, gly####Pica####n-1, and syndecans 1-3 in the les####Ions#### of DAT brain neocortex and hippocampus. Using a panel of specific antibodies directed against the protein backbone of the various HSPG species and against the glycosaminoglycan (GAG) side-chains, we demonstrated the following. The basement membrane-associated HSPG, agrin, is widely expressed in senile plaques, neurofibrillary tangles and ####CERE####bral blood vessels, whereas the expression of the other basement membrane-associated HSPG, ####perlecan####, is lacking in senile plaques and neurofibrillary tangles and is restricted to the ####CERE####bral vasculature. Gly####Pica####n and three different syndecans, all cell membrane-associated HSPG species, are also expressed in senile plaques and neurofibrillary tangles, albeit at a lower frequency than agrin. Heparan sulfate GAG side chains are also associated with both senile plaques and neurofibrillary tangles. Our results suggest that glycosaminoglycan side chains of the HSPGs agrin, syndecan, and gly####Pica####n, but not ####perlecan####, may play an important role in the formation of both senile plaques and neurofibrillary tangles. In addition, we speculate that agrin, because it contains nine pro####Tea####se-inhibi####Tin####g domains, may protect the protein aggre####GAT####es in senile plaques and neurofibrillary tangles against extracellular proteolytic degradation, ####Lead####ing to the persistence of these ####DEPO####sits.

A recent study showed modest evidence for an increased frequency of the ####Bleomycin#### hydrolase (BH) V/V genotype in Alzheimers ########Disease######### (AD) patients compared with non-demented controls. To ####TES####t this hypothesis, we examined this polymorphism in 621 rigorously evaluated patients and 502 control subjects (all caucasian) but were unable to detect an association between BH and AD even after controlling for age, gender, and apolipoprotein E (ApoE) genotype. We conclude that this polymorphism does not account for inherited susceptibility to AD in the populat####Ions#### represented in this sample.

####CERE####bros####pinal#### fluid samples from a total of 157 subjects consis####Tin####g of 55 patients with sporadic Alzheimers ########Disease######### (AD), 34 normal controls, 23 patients with non-AD ####Dementia####, and 45 with other neurological ########Disease##########s were examined by ELISA of tau, A beta 1-40, and A beta 1-42(43). The AD group had a significantly higher level of tau than the normal control group ($P < 0.001$), and the diagnostic sensitivity was 31% and specificity was 94%. CSF A beta 1-40 levels did not show any significant differences. Although the level of A beta 1-42(43) was decreased significantly in the AD group compared to the control group ($P < 0.005$), the overlap of A beta 1-42(43) levels among all groups meant that none of the AD samples exceeded the cut-off value, the mean 2SD of normal control subjects. Reduction of A beta 1-42(43) levels in AD resulted in a significant increase in the ratio of A beta 1-40 to A beta 1-42(43) (A beta ratio) as an improved marker. The diagnostic sensitivity and specificity of A beta ratio were 51% and 82% respectively. The three indexes, using the tau level and A beta ratio (tau or A beta ratio, deviation score and tau x A beta ratio), showed better sensitivity (58%, 67%, 69%) and specificity (82%, 86%, 88%) than previously reported methods. Combination assay for CSF tau, A beta 1-40 and A

beta 1-42(43) in CSF is a biological marker of AD and may be useful to bioche####mica####lly monitor subjects under treatment.

Missing data are frequent in Alzheimers ####Disease######## (AD) trials due to the age of participants and the nature of the ####Disease#########. This can ###Lead#### to bias and decreased statistical power. We assessed the level and causes of missing data in a 2-year randomised trial of an AD patient management program (PLASA study), and conducted sensitivity analyses on the primary endpoint (functional decline), using various methods for handling missing data: complete case, LOCF, Z-score LOCF, longitudinal mixed effects model, multiple imputation. By 2 years, 32% of the 1131 subjects had dropped out, with the commonest reasons being ####Death#### (28% of dropouts) and refusal (22%). Baseline cognitive and functional status were predictive of dropout. All sensitivity analyses led to the same conclusion: no effect of the intervention on the rate of functional decline. All analyses demonstrated significant functional decline over time in both groups, but the magnitude of decline and between-group (intervention versus usual care) differences varied across methods. In particular, the LOCF analysis substantially underestimated 2-year decline in both groups compared to other methods. Our results suggest that data were not "missing completely at random", meaning that the complete case method was unsuitable. The LOCF method was also unsuitable since it assumes no decline after dropout. Methods based on the more plausible "missing at random" hypothesis (multiple imputation, longitudinal mixed effects models, z-score LOCF) appeared more appropriate. This work highlights the importance of considering the validity of the underlying hypotheses of methods used for handling missing data in AD trials.

When emerging from the ####Ribosome####s, new poly####Peptides#### need to fold properly, eventually translocate, and then assemble into stable, yet functionally flexible complexes. During their lifetime, native proteins are often exposed to stresses that can partially unfold and convert them into stably misfolded and aggre####GAT####ed species, which can in turn cause cellular damage and propa####GAT#####e to other cells. In animal cells, especially in aged neurons, toxic aggre####GAT#####es may accumulate, induce cell ####Death#### and ####Lead#### to tissue degeneration via different mechanisms, such as ####Apoptosis#### as in Parkinsons and Alzheimers ######Disease#####s and aging in general. The main cellular mechanisms effectively controlling protein homeostasis in youth and healthy adulthood are: (1) the molecular chaperones, ac####Tin####g as aggre####GAT####e unfolding and refolding enzymes, (2) the chaperone-####GAT####ed pro####Tea####ses, ac####Tin####g as aggre####GAT####e unfolding and degrading enzymes, (3) the aggresomes, ac####Tin####g as aggre####GAT####e compac####Tin####g machineries, and (4) the auto####Phagosome####s, ac####Tin####g as aggre####GAT####e degrading organelles. For unclear reasons, these cellular defences become gradually incapacitated with age, ####Lead####ing to the onset of degenerative ######Disease#########s. Understanding these mechanisms and the reasons for their incapacitation in late adulthood is key to the design of new therapies against the progression of aging, degenerative ######Disease#########s and cancers.

BACKGROUND: Our purpose was to assess the safety and tolerability of extended-release ####Galantamine#### (GAL-ER), using a 1-week dose titration in

Alzheimers patients. METHODS: An open-label, 12-week, mult####Ice####nter study was performed (n = 82). Results were compared with findings from a placebo-controlled trial using a 4-week titration of GAL-ER and i####MME####diate-release ####Galantamine####. The primary analysis compared incidences of adverse events (AEs). RESULTS: Although not statistically significant, more patients in the 1-week titration study experienced an AE. More patients with a 1-week titration had at least one prespecified gastroin####TES########Tin####al (GI) AE. These findings correlated with a higher baseline incidence of GI disturbances. Four patients experienced serious AEs; no ####Death####s occurred. Mean Mini-Mental State Examination scores improved by 1.8 and 1.9 points at weeks 4 and 12, respectively. CONCLUS####Ions####: A 1-week titration of GAL-ER was generally safe and well tolerated, with a potential risk of more GI side effects. A 1-week titration may permit dosing flexibility and promote increased adherence to medication regimens.

INTRODUCTION: There are dozens of drugs in development for AD with bill####Ions#### of dollars invested. Despite the massive investment in AD drugs and a burgeoning pipeline, there have been more setbacks and failures than treatment successes. Areas covered: The classes of drugs that have failed to date include the monoclonal antibodies, the gamma secretase inhibitors, dimebon, neuroche####mica####l enhancers, and one tau drug. Data for these compounds were sought through a PubMed search and a clinicaltrials.gov search. Expert opinion: The obvious question to be posed is: Why are they failing? Is the treatment of symptomatic ####Dementia#### too late? Are the therapeutic targets incorrect? Are the clinical methodologies imprecise, mis####Lead####ing, or inaccurate? This review summarizes the drugs that have failed during 2010-2015 and offers possible theories as to why they have failed.

OBJECTIVE: The study assessed the effects on global cognitive function and mood of a reduction of brain ####Sero####tonin######### by means of acute ####Tryptophan#### depletion in 16 patients with ####Dementia#### of the Alzheimer type and in 16 cognitively intact comparison subjects. METHOD: In a double-blind, crossover design, subjects received a ####Tryptophan####-free amino acid drink to induce acute ####Tryptophan#### depletion and, on a separate occasion, a placebo drink containing a balanced mixture of amino ####Acids####. On each occasion, ra####Tin####gs of depressed mood were made at baseline and 4 and 7 hours later, and the Modified Mini-Mental State was administered at baseline and 4 hours later. RESULTS: Patients with ####Dementia#### of the Alzheimer type had a significantly lower mean score on the Modified Mini-Mental State after acute ####Tryptophan#### depletion than after receiving placebo. The comparison group showed no difference in mean score on the Modified Mini-Mental State after acute ####Tryptophan#### depletion and after receiving placebo. No significant changes in mood were found in either group. CONCLUS####Ions####: Acute ####Tryptophan#### depletion significantly impaired cognitive function in patients with ####Dementia#### of the Alzheimer type. Compromised serotonergic function, in combination with ####Choline####rgic deficit, may make an importaant contribution to cognitive decline in ####Dementia#### of the Alzheimer type.