Results: No differences in synaptic number or expression of synaptic markers were found in the cortex of 5XFAD mice at 6 months of age compared with control littermates. nNOS dimerization was disrupted in the 5XFAD cortex, accompanied by an increase in ROS production. Furthermore, the levels of p25, a CDK5 activator, increased significantly and it colocalized with nNOS in the 5XFAD cortex.

Conclusion: Taken together, our results demonstrate that nNOS dimers are disrupted in the 5xFAD cortex with CDK5 activation, may be involved in the disruption of nNOS dimerization and the development of AD.

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Keywords: Alzheimer’s disease, neuronal nitric oxide synthase, dimerization, cyclin-dependent kinase 5, p25

Abstract
Granulin (GRN) mutations were identified in patients with familial frontotemporal lobar degeneration (FTLD) with ubiquitin pathology in 2006 studies. GRN transcript haploinsufficiency has been proposed as a disease mechanism that leads to the loss of functional progranulin (PGRN) protein. GRN mutations were first found in tau-negative FTLD patients, however, recent findings indicate that these mutations are associated with other neurodegenerative disorders with tau pathology, including Alzheimer’s disease and corticobasal degeneration. Moreover, PGRN reduction in tau transgenic mice is associated with increasing tau phosphorylation and accumulation.

To investigate the influence of a decline in PGRN protein on other forms of neurodegenerative-related protein accumulation, four human GRN mutation cases (age at death; 54, 55, 56 and 78 years old) were investigated by histochemical and biochemical analyses.

The results showed neuronal and glial tau accumulation in all cases analyzed. Massive neuronal tau staining revealed pretangle forms and glial tau in both astrocytes and oligodendrocytes. Furthermore, phosphorylated α-synuclein-positive structures were also found in oligodendrocytes and the neuropil. Immunoblot analysis of fresh frozen brain tissues revealed that tau protein was present in the sarkosyl-insoluble fraction, which was composed of three- and four-repeat tau isoforms, resembling Alzheimer’s disease.

Our data suggest that PGRN reduction might be the cause of neuroenogial multiple proteinopathies, including TDP-43 proteinopathy, tauopathy and α-synucleinopathy, due to the accelerating accumulation of abnormal proteins.

Abstract
Neurodegenerative diseases are linked to tauopathy as a result of cyclin dependent kinase 5 (cdk5) binding to its p25 activator instead of its p35 activator and becoming over-activated. The overactive complex stimulates the hyperphosphorylation of tau proteins, leading to neurofibrillary tangles (NFTs) and stunning axon growth and development. It is known that the sigma-1 receptor (Sig-1R), an endoplasmic reticulum chaperone, is involved in axon growth by promoting neurite sprouting through nerve growth factor (NGF) and tropomyosin receptor kinase B (TrkB). It has also been previously demonstrated that a Sig-1R deficiency impairs the process of neurogenesis by causing a down-regulation of N-methyl-D-aspartate receptors (NMDArs). The study sought to understand the relationship between Sig-1R and tauopathy. It was discovered that the Sig-1R helps maintain proper tau phosphorylation and axon development by facilitating p35 myristoylation and promoting p35 turnover. Neurons that had the Sig-1R knocked down exhibited shortened axons and higher levels of phosphorylated tau proteins compared to control neurons. Here we discuss these recent findings on the role of Sig-1R in tauopathy and highlight the newly presented physiological consequences of the Sig-1R-lipid interaction, helping to understand the close relationship between lipids and neurodegeneration.

Abstract
Long-term Effect of Yokukansankachimpihange on Motivation in wild-type mice
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Methods: C57BL/6J mice were divided into two groups: YKSCH-containing chow and normal chow was administered. Mice were initially trained to press the lever to earn palatable food reward on a fixed ratio (FR) reinforcement schedule, then trained in a progressive ratio (PR) reinforcement schedule. The final ratio completed represented the break point (BP) and that was recognized as an index of instrumental motivation. YKSCH administration started at the beginning of the FR session. We examined the BP of both group until 40 weeks of age.

Results: We first tested whether two sessions per week was enough to maintain the acquired PR performance. Daily PR session was required to evaluate the short-term effect of western medicine, but daily session was laborious in the long-term evaluation of Kampo medication. We optimized the PR task parameter, and confirmed that the modified PR schedule that was conducted twice a week was able to maintain task performance over 6 months.
Averaged BP for each month consisting of 8 sessions was stable until the endpoint in control group. In the YKSCH group, averaged BP increased at 6 months of age and lasted.

**Conclusion:** YKSCH increased instrumental motivation in wild-type mice. It is valuable to test YKSCH effect on the decreased motivation of Alzheimer’s disease model.

### PT584

**Peripheral inflammatory markers in Alzheimer’s disease and mild cognitive impairment**

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**Abstract**

**Objective:** Neuroinflammation has been recognized to play a role in progression of Alzheimer's disease (AD). Tumor necrosis factor (TNF-α) is one of the main proinflammatory cytokines that plays a central role in initiating and regulating the cytokine cascade during an inflammatory response. Interleukin (IL)-6 is a multifunctional cytokine that plays an important role in host defense, with major regulatory effects upon the inflammatory response. We measured serum levels of TNF-α and IL-6 in patients with AD, as compared to mild cognitive impairment (MCI) subjects and cognitively preserved older adults and analyzed its correlation with cognitive performance in these subjects.

**Methods:** The study included 92 subjects with AD (n=35), MCI (n=29) and normally cognitive function (n=28). The subjects’ overall cognitive functions and disease severity were measured using Korean version of the Mini-Mental State Examination (MMSE-K), the Clinical Dementia Rating (CDR), and the Global Deterioration Scale (GDS). The blood IL-6 and TNF-α levels were measured for subjects in all groups. The blood samples were stored in Vacutainer tubes containing citrate, were cooled with ice, and were immediately centrifuged at 3,000 rpm for 10 minutes. ANOVA was performed to analyze the statistical information of the serum IL-6 and TNF-α levels among all groups. The correlation between serum levels and several scores of cognitive function assessment was analyzed statistically.

**Results:** Among three groups, IL-6 levels in the AD group are significantly higher than MCI group and healthy controls (p=0.045). There is no difference of serum levels of TNF-α among all groups (p=0.082). MMSE-K score was negatively correlated with TNF-α (p=0.025) and IL-6 (p=0.006). GDS score was positively correlated with TNF-α (p=0.019) and IL-6 (p=0.007). TNF-α and IL-6 were positively correlated with each other (p<0.001).

**Conclusions:** The serum levels of IL-6 may be a candidate for identifying AD and its progression. AD. Our results suggested proinflammatory cytokine production seems, in part, to be implicated in neurological deleterious effects observed in the development and progression in AD.

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**References**

(1) Teunissen CE, de Vente J, Steinbusch HW, De Bruijn C. Biochemical markers related to Alzheimer’s dementia in serum and cerebrospinal fluid. Neurobiol Aging 2002;23 (4):485–508.
(2) Spooren A, Kolmus K, Laureys G, Clínckers R, De Keyser J, Hageman G, Gerlo S. Interleukin-6, a mental cytokine. Brain Res Rev 2011;67 (1–2):157–183.

### PT585

**Effect of Neuropsychiatric Symptoms on Mortality in Patients with Dementia: differences between Alzheimer’s dementia, subcortical vascular dementia, and frontotemporal dementia**

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**Abstract**

**Background:** Neuropsychiatric symptoms (NPS) have shown significant associations with mortality of dementia in several recent studies, although results have not been consistent. The purpose of this study was to compare the relationship of NPS and mortality between three common subtypes of dementia.

**Methods:** Database was derived from the Clinical Research for Dementia of South Korea (CREDOS), a multicenter longitudinal cohort study. Subjects aged over 65 years, diagnosed with AD, SVD, or FTD at baseline were selected. NPS were grouped into 4 clusters: the psychosis cluster (delusions and hallucinations), the hyperactivity cluster (agitation/aggression, disinhibition, and irritability/ability), the affect cluster (depression and anxiety), and the apathy cluster (apathy/indifference, sleep/night-time disturbances, and appetite/eating abnormalities). Kaplan-Meier plots, log-rank tests and time dependent Cox proportional hazard models were utilized with adjusting various covariates.

**Results:** 4,410 cases of AD, 829 cases of SVD, and 129 cases of FTD were selected, with 851, 248, and 26 individuals currently deceased from each respective group. The presence of the psychosis cluster symptom (p<0.05; mild symptom: HR=1.23, 95% CI 0.83–1.82; clinically significant symptom: HR=1.89, 95% CI 1.24–2.80) at baseline was a risk factor for mortality in SVD. In FTD, the presence of the affect cluster symptom (p<0.05; mild symptom: HR=9.89, 95% CI 1.93–50.60; clinically significant symptom: HR=4.92, 95% CI 0.62–39.27) at baseline was significantly associated with mortality. None of the clusters were associated with mortality in AD group.

**Conclusions:** These findings demonstrate that NPS may increase the risk of mortality in subjects with dementia, and that its effects may differ according to dementia subtype. This indicates that the screening and intervention of NPS may be an important preventive strategy to delay progression to death, and that symptoms should be considered differently with regard to dementia subtype.

### PT586

**Body Mass Index and Progression to Dementia in Patients with Mild Cognitive Impairment**

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**Abstract**

**Introduction:** Obesity has been proposed to lead to dementia. However, recent research found that being underweight also could increase the risk of dementia. We investigated the influence of body mass index (BMI) status at baseline on the development of dementia in mild cognitive impairment (MCI) patients.

**Methods:** For this study, we used a data derived from the Seouchoegi Support center for Dementia of which included people aged 60 years or older in whom diagnosed with MCI using for consortium to establish a registry for Alzheimer’s disease (CERAD) between 2012 and 2015. The longitudinal date of 702 MCI patients was used to investigate the relationships among...