December 9, 2019
Sysmex Corporation
Eisai Co., Ltd.

Sysmex Presents Academic Report with a View to Creating a Simple Method of Diagnosing Alzheimer's Disease Using Blood

- Presenting the Most Recent Data at
the 12th Clinical Trials on Alzheimer's Disease (CTAD) Conference -

Sysmex Corporation (HQ: Kobe, Japan; Chairman and CEO: Hisashi Ietsugu; "Sysmex") and Eisai Co., Ltd. (HQ: Tokyo, Japan; CEO: Haruo Naito; "Eisai") are pursuing a joint project to develop a method of diagnosing Alzheimer's disease (AD) using blood, presented two posters showing the most recent data from the project. The presentations took place at the 12th Clinical Trials on Alzheimer's Disease (CTAD) conference, from December 4 to 7, 2019, in San Diego, California. At CTAD, Sysmex demonstrated on behalf of the two companies the possibility of understanding amyloid pathology in the brain from the brain-derived amyloid beta (Aβ) in plasma measured using its protein measurement platform, the HISCL™ series of fully automated immunoassay analyzers.

The total number of those living with dementia across the world is projected to reach 82 million in 2030 and 152 million in 2050, with the total global societal cost of dementia stemming from direct medical and social care costs and lower productivity being estimated to reach 220 trillion yen in 2030.[1] In Japan, the number of those with dementia is thought to have reached approximately 4.62 million in 2012 and is projected to grow to 7.30 million in 2025[2], with the total societal cost of this disease being estimated to be equivalent to 4.1%[3] of the gross domestic product (GDP) in 2025 (25.8 trillion yen[4]). Of these sufferers, those living with AD is thought to account for more than 60% of those living with dementia.[2]

It is conceivable that AD is a disease that results in synaptic dysfunction and neuronal cell death due to the tau deposition in neurons triggered by Aβ aggregation on the outside of neurons. These brain changes cause the cognitive impairment and psychological and behavioral symptoms, suggesting that the Aβ aggregation and accumulation inside the brain is caused by AD before the presence of cognitive impairment appears, thus, it is believed that early diagnosis and early intervention is more effective in therapies targeting Aβ. Currently, amyloid PET and the plasma $Aβ_{1-42}$/ $Aβ_{1-40}$ ratio in cerebrospinal fluid (CSF) are used for detecting amyloid aggregates in the brain, but this puts significant burden on patients in terms of access, costs, and their physical wellbeing.[5]

In February 2016, Sysmex and Eisai signed a comprehensive non-exclusive agreement aimed at the development of new diagnostic tests in the field of dementia. By leveraging each other's technologies and knowledge, the objective has been to discover next-generation diagnostic reagents that will enable early diagnosis of dementia, selection of the most appropriate treatment options, and regular monitoring of the effects of such treatments.

At the Alzheimer's Association International Conference (AAIC) held in July 2019, Sysmex and Eisai presented their joint research on the correlation (Spearman's rank correlation coefficient (r_s)[6]=0.502, $p<0.001$) between the $Aβ_{1-42}$/ $Aβ_{1-40}$ ratio in CSF and the $Aβ_{1-42}$/ $Aβ_{1-40}$ ratio in plasma, and demonstrated that it may be possible to understand amyloid pathology in the brain by measuring the plasma $Aβ_{1-42}$/ $Aβ_{1-40}$ ratio. Subsequently, the two companies have examined the correlation between the plasma $Aβ_{1-42}$/ $Aβ_{1-40}$ ratio and amyloid PET.

Sysmex and Eisai are engaged in joint development aimed at creating a simple method of

diagnosing AD from a blood sample. At CTAD, Sysmex demonstrated that it may be possible to understand pathological processes in the brain by measuring the plasma $A\beta_{1-42}/A\beta_{1-40}$ ratio based on the analysis result of the plasma $A\beta_{1-42}/A\beta_{1-40}$ ratio measured with the HISCL™ series as a prediction factor for Aβ PET positivity. Also it was presented a technique for verifying that the HISCL™ measuring system correctly captures Aβ in plasma on that occasion.

Sysmex and Eisai are working to create new diagnostic technologies for the prevention and treatment of dementia. Accordingly, the overarching aim is to contribute to the advancement of healthcare and improve the quality of life for those living with the disease and their families.

[Data sheet]

Blood diagnosis P75	Prediction of amyloid pathology by the plasma Aβ(1-42)/Aβ(1-40) ratio measured with a fully automated immunoassay system (HISCL™ series) Poster presentation: December 4 (Wed.) to December 5 (Thu.)
In the presentation (P75), to create a simple blood diagnostic test for AD, the result of the receiver operating characteristic (ROC) analysis of the plasma $A\beta_{1-42}/A\beta_{1-40}$ ratio, measured using the HISCL™ series, was used as a prediction factor for Aβ-PET positivity. The HISCL™ system enables an automated immune assay to be completed in 17 minutes with sample volumes as small as 10-30μL, and it was demonstrated that the Aβ assay in plasma had sufficient sensitivity and high reliability. In addition, it was confirmed that the Aβ assay system using the HISCL™ series had a high correlation with IP-MS methods reported in Poster 81. The samples from 192 persons living with the disease with mild cognitive impairment (MCI) and AD associated with amyloid PET results were used for investigation with the HISCL™ series. Using the plasma $A\beta_{1-42}/A\beta_{1-40}$ ratio, amyloid PET positivity can be predicted with a sensitivity of 73% and a specificity of 71% (AUC0.74), and it was confirmed that sensitivity and specificity were improved (AUC0.82) by adding factors such as age and APOE4, a gene associated with a greatly increased risk of developing AD. This preliminary result indicates the plasma $A\beta_{1-42}/A\beta_{1-40}$ ratio measured with the HISCL™ series could be used as a prescreening method for amyloid PET. To further assess its clinical utility, additional sample sets will be evaluated.	

Blood diagnosis P81	Clinical utility of plasma amyloid beta measurements by immunoaffinity enrichment and LC-MS/MS Poster presentation: December 4 (Wed.) to December 5 (Thu.)
In the presentation (P81), the development of high-sensitivity peptide ($A\beta_{1-42}$ and $A\beta_{1-40}$) measurement technology using mass spectrometry was described. With this technology, it is possible to measure the peptides in a liquid sample in two hours with a small sample volume of 250μL, and it was confirmed that the amounts of $A\beta_{1-42}$ and $A\beta_{1-40}$ in CSF and plasma could be measured. In addition to the presentation on the measurement performance (dynamic range, sensitivity, reproducibility, etc.) of this method under pure conditions, a good correlation between the CSF $A\beta_{1-42}/A\beta_{1-40}$ ratio and plasma $A\beta_{1-42}/A\beta_{1-40}$ ratio in elderly persons with normal cognition and those living with MCI and AD (44 people in total) was confirmed.	

1 World Alzheimer Report 2018

2 Promotion of Comprehensive Measures against Dementia, Ministry of Health, Labour and Welfare

3 Study on Economic Impact of Dementia in Japan, 2014 Health Labour Sciences Research Grant Annual Report

4 Estimated by Sysmex based on Japan's Medium-term Economic Outlook (February 2018), Daiwa Institute of Research

5 Aβ, a peptide consisting of amino acid residues, is generated by excision from the

amyloid precursor protein. $A\beta_{1-40}$ consists of 40 residues, is the dominant substance, and does not fluctuate significantly as AD progresses. In contrast, $A\beta_{1-42}$, which consists of 42 residues, has high aggregability and a reduction in $A\beta_{1-42}$ is detected from the early stage of AD. There are individual differences in the absolute value of Aβ as well as intra-individual variabilities, therefore, it has been reported that there is a high correlation between the $A\beta_{1-42}/A\beta_{1-40}$ ratio in CSF and amyloid PET.

6 The correlation coefficient indicates the strength of the relationship between the two sets pf data from the two quantitative data distributions. In this analysis, Spearman's rank correlation coefficient (r_s), which is an index of correlation obtained from rank data, is calculated.

Contacts for inquiries

Johji Hayashi, Akinobu Seko IR & Corporate Communication Sysmex Corporation 1-5-1 Wakinohama-Kaigandori, Chuo-ku, Kobe 651-0073 Tel: 078-265-0508	Public Relations Department Eisai Co., Ltd. Tel: 03-3817-5120