

BIOMARKERS FOR ALZHEIMER'S DISEASE AND BRAIN INJURY

[Ladenson, Jack](#), [Landt, Yvonne](#), [Laterza, Omar](#), [Modur, Vijay](#)

[Richards, Jennifer](#)

T-004414

Technology Description

Researchers in Prof. Jack Ladenson's laboratory have discovered biomarkers and associated antibodies for Alzheimer's disease (AD) that could be used for early/presymptomatic diagnosis or in clinical trials for AD drugs.

This patented technology is based on the initial finding that the neuronal protein VILIP-1 (visinin-like protein-1) is elevated in the cerebrospinal fluid (CSF) of patients with brain damage. Because VILIP-1 is a general markers for neuronal death, it could be useful (along with neurogranin and SNAP-25) for detecting and monitoring injuries from stroke, asphyxiation, surgery or traumatic brain injury (TBI). Furthermore, these biomarkers can detect the damage/neurodegeneration of Alzheimer's disease up to 15 years prior to clinically diagnosed dementia. VILIP-1 analysis can be combined with traditional markers of AD pathogenesis (e.g., amyloid and tau) to better manage the impact of AD on the patient and potentially to monitor the course of the disease after therapy. In addition, these markers may provide information about disease progression related to functional outcome to stratify patients or monitor therapeutic efficacy in AD clinical trials.

Validated in "DIAN" (Dominantly Inherited Alzheimer Network) Studies

Fagan, A. M., Li, Y., Todd, K., Herries, E. M., Henson, R. L., Schindler, S. E., ... & Shaw, L. M. (2018). [NOVEL CSF BIOMARKERS OF NEURONAL INJURY, SYNAPTIC DYSFUNCTION AND NEUROINFLAMMATION IN AUTOSOMAL DOMINANT ALZHEIMER DISEASE: VILIP-1, NEUROGRANIN, SNAP-25 AND YKL-40 IN THE DOMINANTLY INHERITED ALZHEIMER NETWORK \(DIAN\)](#). *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 14(7), P1059.

Applications

- **Clinical trials** for drugs to treat Alzheimer's disease:
 - patient risk stratification and monitoring
 - surrogate biomarker for efficacy
- **Diagnostics:**
 - early detection of Alzheimer's disease
 - may also be useful in the detecting and monitoring brain injury as a result of stroke, asphyxiation, surgery or traumatic brain injury (TBI)
- **Research** – analysis of patients with neuronal damage from disease or injury

Key Advantages

- **Early detection**

- VILIP-1 levels in the CSF are elevated up to 10-15 years prior to onset of clinical dementia
- could provide surrogate marker for preventative therapies that preserve brain function
- **Specific:**
 - diagnostic ability is comparable or superior to current “gold standard” amyloid- β_{1-42} and tau-based assays
 - increases are observed many years before cognitive changes

Patents

- Markers for brain damage (U.S. Patent Nos. [7,985,555](#) and [9,982,299](#) with additional foreign patents; WUSTL Technology T-004414)
- Alzheimer's diagnosis (U.S. Patent No. [8,481,277](#); WUSTL Technology T-006811)

Antibodies available for license

Analyte	Antibody code
Neurogranin	10E11 (WU-Ag-11) and 14D03 (WU-Ag-7.1))
Serpin E2	8H3 (WU-Ag8A)
Neuroserpin	9G04 (WU-Ag-2.1)
SNAP-25	6H7 (WU-Ag-4), 9E11 (WU-Ag-4), 2C12 (WU-Ag-4)
VILIP-1 (Visinin-like-protein-1)	3A8.1 (4399), 2B9.3 (4403)
Zygin-1 (Fasciulation and elongation protein Zeta-1)	1G4.4 (4554), 4G3.1 (4563 hamster)

Publications

VILIP-1

- Herries E, Brada N, Sutphen CL, Fagan AM, Ladenson, JH. Book Chapter: Brain Biomarkers: Follow up of RNA Expression Discovery Approach; CSF assays for Neurogranin, SNAP-25, and VILIP-1. 2019 Neuromethods book series: CSF biomarker analysis. Editors: Charlotte E. Teunissen and Henrik Zetterberg; Humana Press Springer Publishing; In Press
- Schindler SE, Li Y, Todd KW, Herries EM, Henson RL, Ladenson JH, et al. Emerging cerebrospinal fluid biomarkers in autosomal dominant Alzheimer's disease. *Alzheimer's & Dementia* 2019. 15(5): 655-665.
- Zhang H, Ng KP, Therriault J, Kang MS, Pascoal TA, Rosa-Neto P, Gauthier S, Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid phosphorylated tau, visinin-like protein-1, and chitinase-3-like protein 1 in mild cognitive impairment and Alzheimer's disease. *Translational Neurodegeneration*. 2018. 7:23
- Sutphen CL, McCue L, Herries EM, Xiong C, Ladenson JH, Holtzman DM, Fagan AM on behalf of ADNI (Alzheimer's Disease Neuroimaging Initiative). Longitudinal decreases in multiple cerebrospinal fluid biomarkers of neuronal injury in symptomatic late onset Alzheimer disease. *Alzheimer & Dementia*. 2018. 14(7): 869-879.
- Crimmins DL, Herries EM, Ohlendorf MF, Brada NA, Garbett NC, Zipfel GJ, Schindler SE, Ladenson JH. Double Monoclonal Immunoassay for Quantifying Human Visinin-Like Protein-1 in CSF. *Clin*

Chem. 2017. 63(2): 603-604.

- Tarawneh R, D'Angelo G, Crimmins D, Herries E, Griest T, Fagan AM, Zipfel GJ, Ladenson JH, Morris, JC, Holtzman DM. The Diagnostic and Prognostic Utility of the Synaptic Marker, Neurogranin, in Alzheimer Disease. *JAMA Neurol.* 2016. 73(5): 561-71.
- Kester MI, Teunissen CE, Sutphen C, Herries EM, Ladenson JH, Xiong C., et al. Cerebrospinal fluid VILIP-1 and YKL-40, candidate biomarkers to diagnose, predict and monitor Alzheimer's disease in a memory clinic cohort. *Alzheimer's Res Ther.* 2015. 7(1): 59.
- Sutphen CL, Jasielc MS, Shah AR, Macy EM, Xiong C, Vlassenko AG, Benzinger TLS, Stoops EEJ, Vanderstichele HMJ, Brix B, Darby HD, Vandijck MLJ, Ladenson JH, Morris JC, Holtzman DM, Fagan AM. Longitudinal cerebrospinal fluid biomarker changes in preclinical Alzheimer Disease during middle age. *JAMA Neurol.* 2015. 72(9):1029-42.
- Tarawneh R, Head D, Allison S, Buckles V, Fagan AM, Ladenson JH, Morris JC, Holtzman DM. Cerebrospinal Fluid Markers of Neurodegeneration and Rates of Brain Atrophy in Early Alzheimer Disease. *JAMA Neurol.* 2015. 72(6): 656-65.
- Fagan AM, Xiong C, Jasielc MS, Bateman RJ, Goate AM, Benzinger TLS, Ghetti, B, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor, MN, Salloway S, Schofield PR, Sperling RA, Marcus D, Cairns NJ, Buckles VD, Ladenson JH, Morris, JC, Holtzman DM. Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's Disease. *Science Translational Medicine* 2014. March 5; 6(226):226ra30.
- Tarawneh R, Lee JM, Ladenson JH, Morris JC, Holtzman DM. CSF VILIP-1 predicts rates of cognitive decline in early Alzheimer's disease. *Neurology.* 2012. 78(10):709-19.
- Lee JM, Blennow K, Andreasen N, Laterza O, Modur V, Olander J, Gao F, Ohlendorf M, Ladenson JH. The brain injury biomarker VLP-1 is increased in the cerebrospinal fluid of Alzheimer's disease patients. *Clin Chem.* 2008. 54:1617-1623.

NEUROGRANIN

- Schindler SE, Li Y, Todd KW, Herries EM, Henson RL, Ladenson JH, et al. Emerging cerebrospinal fluid biomarkers in autosomal dominant Alzheimer's disease. *Alzheimer's & Dementia* 2019. 15(5): 655-665
- Willemse EAJ, DeVos A, Herries EM, Andreasson U, Engelborgh S, van der Flier WM, Scheltens P, Crimmins D, Ladenson JH, et al. Neurogranin as Cerebrospinal Fluid Biomarker for Alzheimer Disease: An Assay Comparison Study. *Clinical Chemistry.* 2018;. 64(6): 927-937
- Sutphen CL, McCue L, Herries EM, Xiong C, Ladenson JH, Holtzman DM, Fagan AM on behalf of ADNI (Alzheimer's Disease Neuroimaging Initiative). Longitudinal decreases in multiple cerebrospinal fluid biomarkers of neuronal injury in symptomatic late onset Alzheimer disease. *Alzheimer & Dementia.* 2018. 14(7): 869-879.
- Tarawneh R, D'Angelo G, Crimmins D, Herries E, Griest T, Fagan AM, Zipfel GJ, Ladenson JH, Morris, JC, Holtzman DM. The Diagnostic and Prognostic Utility of the Synaptic Marker, Neurogranin, in Alzheimer Disease. *JAMA Neurol.* 2016. 73(5): 561-71.
- Kester MI, Teunissen CE, Crimmins DL, Herries EM, Ladenson JH, Schelten P, van der Flier WM, Morris JC, Holtzman DM, Fagan AM. Neurogranin, as a CSF biomarker for synaptic loss in symptomatic Alzheimer's disease. *JAMA Neurol* 2015. Nov 1; 72 (11): 1275-80.

SNAP-25

- Schindler SE, Li Y, Todd KW, Herries EM, Henson RL, Ladenson JH, et al. Emerging cerebrospinal fluid biomarkers in autosomal dominant Alzheimer's disease. *Alzheimer's & Dementia* 2019. 15(5): 655-665
- Sutphen CL, McCue L, Herries EM, Xiong C, Ladenson JH, Holtzman DM, Fagan AM on behalf of ADNI (Alzheimer's Disease Neuroimaging Initiative). Longitudinal decreases in multiple cerebrospinal fluid biomarkers of neuronal injury in symptomatic late onset Alzheimer disease. *Alzheimer & Dementia*. 2018. 14(7): 869-879.
- Tarawneh R, D'Angelo G, Crimmins D, Herries E, Griest T, Fagan AM, Zipfel GJ, Ladenson JH, Morris, JC, Holtzman DM. The Diagnostic and Prognostic Utility of the Synaptic Marker, Neurogranin, in Alzheimer Disease. *JAMA Neurol*. 2016. 73(5): 561-71.