



阿茲海默症暨相關疾病生物標記國際研討會

隨著全世界失智症患者人數不斷的快速增長，其中罹患比例最高 (超過 60 %) 的阿茲海默症對全球社會的影響也日益加大，因此針對阿茲海默症的早期或臨床前診斷的研究就成為如何成功治療的重要關鍵。在不同的生物標記上，包括醫學成像，基因和生化檢測等檢驗方法，皆早已針對阿茲海默症的早期診斷或療效追蹤進行開發，近期更發展出創新的尖端技術，達成可能使用血液中的生物標記濃度來檢測出阿茲海默症的可靠方法。在世界各地，如美國，歐洲及亞洲的研究專家學者們，持續的在探索血液中可能的生物標記，及生物標記與其它檢測方法，如神經心理學，醫學成像和神經病理學之間的關係。即將於 **2016 年 10 月 26 日** 在台北舉行的阿茲海默症暨相關疾病生物標記國際研討會，邀請了國內外的知名專家，就他們本身團隊多年的研究成果提出寶貴的看法和發現，希望讓大家能夠了解到更多有關血液中的生物標記在阿茲海默症及相關疾病的臨床診斷上的潛在可能。

演講主題

阿茲海默症生物標記探討

血液生物標記在阿茲海默症預防治療及臨床治療上的應用

神經影像學與病理學在失智症的預防及診斷效益

地點

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組織委員會

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白明奇醫師，成大醫學院教授，台灣臨床失智症學會理事長

曾文毅醫師，臺大醫院分子生醫影像研究中心主任

Lih-Fen Lue, Research Prof., Neurodegenerative Disease Research Center,
Arizona State University, USA

陳達夫醫師，臺大醫院神經部主治醫師

楊謝樂博士，磁量生技 CEO



演講貴賓

Thomas G. Beach, M.D., PhD. Director, Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, USA.

- *Biomarkers for neurodegenerative disease: can they swing us across the valley?*

Kaj Blennow, M.D., PhD., Prof. of Clinical Neurochemistry, University of Gothenburg, Sweden.

- *Fluid biomarkers for Alzheimer's disease – moving from CSF to blood biomarkers.*

Kewei Chen, PhD., Sr. Scientist, Director, Image Research and Analysis Banner Alzheimers Institute, USA.

- *Neuroimaging and fluid biomarkers in the preclinical AD and prevention study.*

邱銘章醫師, 臺大醫學院教授, 神經部主治醫師/主任

- *Plasma biomarkers for discriminating various types of dementia.*

傅中玲醫師, 台北榮民總醫院一般神經科主治醫師

- *Plasma biomarkers on longitudinal cognitive changes in Taiwanese patients with Alzheimer disease*

李妮鍾醫師, 臺大醫院基因學部暨小兒部主治醫師

- *Amyloid and tau protein as biomarkers for the detection of early degeneration in Down syndrome – comparative study with Alzheimer disease in general population.*

Lih-Fen Lue, PhD., Research Prof., Neurodegenerative Disease Research Center, Biodesign Institute, Arizona State University, USA.

- *Plasma $A\beta_{42}$ and total tau levels combined attain high discriminatory sensitivity for Alzheimer's dementia: investigations in Sun City of Arizona and Taiwanese cohorts.*

Marwan Sabbagh, M.D., Director, Barrow Neurological Institute, USA.

- *Incorporation of novel biomarkers into clinical practice to improve the diagnostic confidence for Alzheimer's dementia.*



戴桓青博士, 台灣大學化學系助理教授

- *Synaptic pathology in Alzheimer's disease and its link to biomarker discovery*

主辦單位

臺大醫院神經部

協辦單位

台灣臨床失智症學會

臺大醫院分子生醫影像研究中心

贊助者

磁量生技股份有限公司



研討會時程

時間	活動與演講題目	演講者
8:30~9:00	註冊	—
9:00~9:30	開幕	
9:30~9:40	休息	—
9:40~10:20	<i>Fluid biomarkers for Alzheimer's disease – moving from CSF to blood biomarkers</i>	<i>Kaj Blennow M.D., PhD.</i>
10:20~11:00	<i>Plasma Aβ42 and total tau levels combined attain high discriminatory sensitivity for Alzheimer's dementia: investigations in Sun City of Arizona and Taiwanese cohorts</i>	<i>Lih-Fen Lue PhD.</i>
11:00~11:40	<i>Plasma biomarkers for discriminating various types of dementia</i>	<i>Ming-Jang Chiu M.D., PhD.</i>
11:40~13:00	午餐	-
13:00~13:40	<i>Incorporation of novel biomarkers into clinical practice to improve the diagnostic confidence for Alzheimer's dementia</i>	<i>Marwan Sabbagh M.D.</i>
13:40~14:20	<i>Neuroimaging and fluid biomarkers in the preclinical AD and prevention study</i>	<i>Kewei Chen PhD.</i>
14:20~15:00	<i>Amyloid and tau protein as biomarkers for the detection of early degeneration in Down syndrome – comparative study with Alzheimer disease in general population</i>	<i>Ni-Chung Lee M.D., PhD.</i>
15:00~15:15	休息	-



15:15~15:55	<i>Biomarkers for neurodegenerative disease: can they swing us across the valley?</i>	<i>Thomas G. Beach M.D., PhD.</i>
15:55~16:35	<i>Plasma biomarkers on longitudinal cognitive changes in Taiwanese patients with Alzheimer disease</i>	<i>Jong-Ling Fuh M.D.</i>
16:35~17:05	<i>Synaptic pathology in Alzheimer's disease and its link to biomarker discovery</i>	<i>Hwan-Ching Tai PhD.</i>
17:05~17:20	總結	<i>Marwan Sabbagh M.D.</i>

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Professional preparation:

*Medical degree (MD), Lund University, 1984
Registered doctor (Legitimerad läkare), 1986
Specialist competence in general psychiatry, 1993
Specialist competence in clinical chemistry, 1994
Doctor in Medical Science (PhD), Gothenburg, thesis in General Psychiatry, 1990.*

Appointments:

*The Torsten Söderberg Professorship in Medicine and the Royal Swedish Academy of Sciences, 2015-
Appointed the title "University Hospital Senior Physician", 2011-
Professor and Academic Chair in Clinical Neurochemistry, University of Gothenburg, 2003-
Senior Consultant and Head of the Clin. Neurochemistry Lab., Sahlgrenska University Hospital (1995-)
Post as Researcher at the Medical Research Council (MRC), Sweden, 1997-2002
Ass. Professor (Docent), University of Göteborg, 1994.*

International projects:

- *President of the "the Society for CSF analysis and Clinical Neurochemistry", which started in 2015, and is an International Society to promote research and the use of CSF biomarkers in the clinic and in trials.*
- *Head of the project "The Alzheimer's Association QC program for CSF biomarkers", which started in 2009, and involves more than 90 CSF laboratories world-wide.*
- *Head of the International Federation of Clinical Chemistry (IFCC) working group on CSF proteins, with the aim to develop a reference method and reference material for CSF biomarkers (2012-).*
- *EC project "LipidiDiet", led by Prof. T. Hartman, Germany. The project involves 12 research teams in Europe, our lab is the neurochemistry/biomarker core.*



- *Member of the US AD Neuroimaging Initiative (ADNI) Resource Allocation Review Committee (2005-).*
- *Advisor in the NIA project "Alzheimer's disease prevention initiative" (API)*
- *Member of the Eur. Healthcare Innov. Leadership Network Alzheimer Dis. Working Group.*

Congresses:

- *Invited speaker for plenary lecture on 13 International Congresses, such as the AAIC, IPA, ECNP and ACNP congresses.*
- *Invited speaker and participant in 14 specialized meetings, such as the NIH Working Group on AD Biochemical Markers (1999), the Nature Medicine Translational Neuroscience Symposium (2009), the Nature Medicine Symposium on Neurodegeneration (2010), the Nature Medicine Global Alzheimer's Research Summit (2011), and the Keystone Symposia (2012).*

Research prizes:

- *The European College of Neuropsychopharmacology (ECNP) Award, Monte Carlo, 1991.*
- *The Collegium Internationale Neuro-Psychopharmacologicum (CINP) Award, Nice, 1992.*
- *The Ole J Rafaelsen Award in Biol. Psychiatry and Neuropsychopharmacology, Copenhagen, 1993.*
- *The International Psychogeriatric Association (IPA) Research Award, Berlin, 1993.*
- *Lundbeckfonden/Scandinavian Society of Psychopharmacology Scholarship, Copenhagen, 1994.*
- *Nordic Society for Research in Brain Aging (NORAGE) Research Award, Oslo, 1994.*
- *The Inga Sandeborgs Price, Swedish Medical Association, for Research in AD, Stockholm, 1996.*
- *The Alois Alzheimer Research Award, Munich, Germany, 2001.*
- *The European College of Neuropsychopharmacology (ECNP) Research Award, Amsterdam, 2010.*
- *The Henry Wisniewski Lifetime Achievement Award in AD Research, by the Alzheimer's Association, at the International Conference on Alzheimer's disease (AAICAD) 2011 in Paris, France.*
- *The David Ingvar Price, Swedish Med. Association, for research in Neuroscience, Stockholm, 2011.*
- *The Silviahemmet Price in Alzheimer research, presented by HM Queen Silvia, Stockholm, 2012.*
- *The Eric Forsgren Price in Alzheimer research, presented by Umeå University, Umeå, 2012.*
- *The Int. Foundation for Research in Alz. dis (IFRAD) European Grand Prix in Research, Paris, 2013.*
- *The Torsten Söderberg Professorship in Medicine and the Royal Swedish Academy of Sciences, 2015.*
- *The Söderberg Price in Medicine at the Swedish Medical Society, 2016.*



Publications:

- *About 750 original research papers and 120 reviews in peer-reviewed journals.*
- *Citation report on Scopus (June 2016) **h-index: 98***

Number of Papers: 861

Number of Citations: 41.662 (during 2015: 5.210)



Fluid biomarkers for Alzheimer's disease – moving from CSF to blood biomarkers

Kaj Blennow, MD, PhD

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Academy at University of Gothenburg, Mölndal, Sweden*

Fluid biomarkers for Alzheimer's disease (AD) and other neurodegenerative disorders are highly important for use as diagnostic tools in clinical routine and for enrichment purposes in clinical trials. In addition, fluid biomarkers show promise as theragnostic markers in clinical trials, to identify and monitor target engagement of the drug, and to identify downstream effects on neurodegeneration.

A panel of AD cerebrospinal fluid (CSF) biomarkers has been developed, including total tau (T-tau) reflecting the intensity of neuronal degeneration, phospho-tau (P-tau) correlating with brain tau pathology load, and β -amyloid (A β 42 or A β 42/40 ratio) reflecting cortical A β deposition. A high diagnostic performance of these core AD biomarkers have been well validated in numerous clinical studies, also to identify AD in the prodromal stage of the disease. Further, neurofilament light (NFL) protein shows promise as a biomarker for axonal degeneration, and the synaptic protein neurogranin as a measure of synaptic integrity.

Recent technological developments have given ultrasensitive analytical techniques (immunomagnetic reduction technology and single molecule array) that allows for quantification of brain specific proteins in blood (serum or plasma) samples. Plasma levels of A β 42 and the A β 42/A β 40 ratio were found to correlate with CSF levels and also with high amyloid ligand retention on amyloid PET scans. High tau levels in plasma was found in AD dementia, with longitudinal analyses showing associations between high baseline plasma tau and future rate of cognitive deterioration, progression of hippocampal atrophy on MRI, and reductions in hypometabolism on FDG-PET. High plasma levels of NFL were found in several neurodegenerative disorders, including AD, and show promise as a screening tool to identify neurodegeneration. In conclusion, new ultrasensitive assays may serve as the basis for clinically useful blood biomarkers for AD and other neurodegenerative disorders.



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Education:

1973, B.S. Animal Husbandry, National Taiwan University, Taipei, Taiwan

1975, M.S. in Animal Husbandry, National Taiwan University, Taipei, Taiwan

1983, PhD. in Animal Science, Iowa State University, Ames, Iowa, USA

1985-1987, Postdoctoral Fellow, Department of Anatomy, Veterinary Medical College, Iowa State University, Ames, Iowa, USA

Professional career:

1975-1978: Research Scientist, Pig Research Institute, Tzu Nan, Mioli, Taiwan

1991-1995: Staff Scientist, Sun Health Research Institute, Sun City, AZ

1995-2000: Principal Scientist, Sun Health Research Institute, Sun City, AZ

2000-2007: Senior Scientist, Sun Health Research Institute, Sun City, AZ

2007-2015: Senior Scientist, Banner Sun Health Research Institute, Sun City, AZ

2015-present: Research Professor, NDRC, Biodesign Institute, ASU, Tempe, AZ

Expertise:

- *Research in neurodegenerative disease inflammatory mechanisms*
- *Blood biomarker development for neurodegenerative diseases*



- *Development of postmortem human brain cell models*
- *Use of human postmortem brain cells to model microglial activation in neurodegenerative diseases*

Professional services and lectures

Services:

- *Manuscript reviewer of many scientific journals; Grant reviewer of US Federal Funding Agents and International Funding Agents*
- *Scientific Member of Institutional Animal Care and Use Committee, Sun Health Research Institute, 1998-2008 and Banner Sun Health Research Institute, 2008-2014*
- *Student Internship Program Supervisor: Supervisors of high school and college student interns, Sun Health and Banner Sun Health Research Institute, 1996-present; Mentorship Program: Faculty of Undergraduate Biology Research Program of University of Arizona, 2013; Faculty of Undergraduate Student Research Program, Arizona State University, 2015-present*

Lectures:

Special Topic Lecturers in University of Nebraska Medical College, Omaha, Nebraska, USA, October, 2005; RIKEN Alzheimer's Disease Conference, October, 2006, Tokyo, Japan; National Cheng Kung Medical College, Tainan, and Sinica Academia, Taipei, 2008; The 22nd Biennial Meeting of the International Society of Neurochemistry/APS/N Joint Conference, Taipei, Taiwan, August, 2009; Neurobiology Department, Yang Ming Medical School, 2010; "New Frontiers of Medical Science", Science Museum of Phoenix, AZ, March, 2014.

Selected recent publications (over 70 peer-reviewed scientific publications)

1. **Lue LF**, et al., *TREM2 Protein Expression Changes Correlate with Alzheimer's Disease Neurodegenerative Pathologies in Post-Mortem Temporal Cortices.* *Brain Pathol.* 2014 Sep 3. doi: 10.1111/bpa.12190.
2. **Lue LF**, et al. *What happens to microglial TREM2 in Alzheimer's disease: Immunoregulatory turned into immunopathogenic?* *Neuroscience.* 2015 Aug 27;302:138-50. doi: 10.1016/j.neuroscience.2014.09.050. Epub 2014 Oct 2.
3. Walker DG, **Lue LF**. *Immune phenotypes of microglia in human neurodegenerative disease: challenges to detecting microglial polarization in human brains.* *Alzheimers Res Ther.* 2015 Aug 19;7(1):56.
4. **Lue LF**, et al., *Converging mediators from immune and trophic pathways to identify Parkinson disease dementia.* *Neurol Neuroimmunol Neuroinflamm.* 2016;3(1):e193.



5. Caviness JN, **Lue LF**, et al., *Cortical phosphorylated α -Synuclein levels correlate with brain wave spectra in Parkinson's disease.* *Mov Disord.* 2016 Apr 8. doi: 10.1002/mds.26621



Plasma A β 42 and total tau levels combined attain high discriminatory sensitivity for Alzheimer's dementia: investigations in Sun City of Arizona and Taiwanese Cohorts

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Background: Utility of plasma A β 42 and total tau (t-tau) levels in the clinical diagnosis of Alzheimer's dementia (AD) relies on the availability of highly sensitive assays that could detect narrow differences in low pg/ml concentration range. To overcome this issue, a novel technology using superconducting quantum interference device to detect immunomagnetic reduction (IMR) signals to assay biochemical levels of AD core proteins A β and t-tau have been developed. In last few years, the IMR assays for AD blood biomarker research have been intensively studied in the Taiwanese cohorts. To advance the utility of these assays in AD diagnosis, there is a need to assess how these assays performed in the cohort other than Taiwanese. Thus, we carried out the study to evaluate the ability of plasma A β 42 and total tau levels for identifying clinical AD in a cohort recruited from Sun City of



Arizona. The objective was to determine how the criteria of distinguishing AD from normal controls were comparable between Sun City and Taiwanese cohorts.

Methods: The study cohort was recruited from the clinic of Banner Sun Health Research Institute (BSHRI) in the Sun City of Arizona and the validation cohort was recruited from National Taiwan University Hospital (NTUH) in Taiwan. 16 non-demented controls (NCs) and 16 ADs were recruited at the BSHRI site, while 63 NCs and 31 ADs were enrolled at the NTUH site. Plasma levels of A β 42 and t-tau were measured by protein-specific IMR assays. Data from BSHRI cohort were analyzed for the best sensitivity and specificity for discrimination of AD from ND. The cut-off criteria for the levels of A β 42 and t-tau individually or combined as concentration product were applied to NTUH cohort to determine their ability of predicting AD.

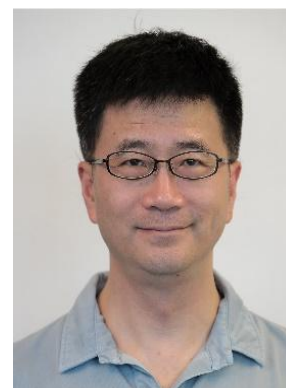
Results: The cut-off values obtained from BSHRI cohort were 23.99, 15.15, and 362.20 pg/ml for t-tau, A β 42 and the product of A β 42 and t-tau, respectively. The cut-off value of the product of A β 42 and tau provided the highest sensitivity (94%) for discriminating ADs from NCs. When we used this cut-off value in the NTUH cohort, sensitivity was 100% and specificity was 84%.

Conclusion: These findings support that plasma levels of A β 42 and t-tau protein measured by IMR technology hold the potentials as blood biomarkers for clinical diagnosis of the AD.



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Academic background:

*1984, M.B. College of Medicine, National Taiwan University, Taipei, Taiwan
2000, PhD. Graduate Institute of Electric Engineering, National Taiwan University, Taipei, Taiwan*

Professional career:

*Attending Neurologists & Professor, 2014-
Director of the Diagnostic Neurophysiology Division 2009-
Graduate Institute of Brain and Mind Sciences / Graduate Institute of Psychology / Graduate Institute
of Biomedical Electronics and Bioinformatics, National Taiwan University*

Expertise:

*Board certificated neurologist
Board certificated physician in Sleep Medicine*

Professional services and honors:

- President of Taiwan Alzheimer's Disease Association. 2010-2015*

Recent main publications (Dr. Chiu has published more than 116 SCI papers):

- 1. Chiu MJ*. Systemic infection may cause cognitive decline and neurodegeneration. Critic Care Med 2014; 42:1282-1283. Invited editorial.*
- 2. YC Lin, YC Shih, WY I Tseng, YH Chu, MT Wu, TF Chen, PF Tang*, MJ Chiu*. Cingulum correlates of cognitive functions in patients with mild cognitive impairment and early*



- Alzheimer's disease - A diffusion spectrum imaging study. *Brain Topography* 2014 Jan 11.
3. Chen TF, Tang MC, Chou CH, **Chiu MJ**, Huang RF. Dose-dependent folic acid and memantine treatments promote synergistic or additive protection against A β (25-35) peptide-induced apoptosis in SH-SY5Y cells mediated by mitochondria stress-associated death signals. *Food Chem Toxicol.* 2013 Dec;62: 538-47. doi: 10.1016/j.fct.2013.09.015. Epub 2013 Sep 17
 4. LY Fan, **MJ Chiu***. Combotherapy and current concepts as well as future strategies for the treatment of Alzheimer's disease. *Neuropsychiatric Disease and Treatment* 2014 ; 10:439-451.
 5. CH Lin, TF Chen, **MJ Chiu**, RM Wu. Lack of C9orf72 repeat expansion in Taiwanese patients with mixed neurodegenerative disorders. *Frontiers in Neurology*, 2014 April
 6. Li HC, Chen YS, **Chiu MJ**, Fu MC, Huang GH, Chen CCH. (2014). Delirium, Subsyndromal Delirium, and Cognitive Changes in Individuals Undergoing Elective Coronary Artery Bypass Graft Surgery. *Journal of Cardiovascular Nursing*, in press.
 7. Y Sun, HJ Lee, SC Yang, TF Chen, KN Lin, CChi Lin, PN Wang, L Tang, **MJ Chiu***. A nationwide survey of mild cognitive impairment and dementia, including very mild dementia, in Taiwan, *PloS One*. Accepted 2014
 8. KY Tzen, SY Yang, TF Chen, TW Cheng, HE Horng, HP Wen, YY Huang, CY Shiue, **MJ Chiu***, Plasma A β but not tau related to brain PiB retention in early Alzheimer's disease. In revision. *ACS Neurosci* 2014.
 9. YL Chang, TF Chen, **MJ Chiu**, YC Shih, WYI Tseng, SH Yan, Regional Cingulum Disruption, Not Gray Matter Atrophy, Detects Cognitive Changes in Amnesic Mild Cognitive Impairment Subtypes. *J Alzheimers Dis.* 2015;44(1):125-38.
 10. Chang HT, **Chiu MJ**, Chen TF, Cheng TW, Hua MS, Distinct Patterns and Clinical Implications of Semantic Memory Deterioration Among Patients With MCI. *Alzheimer Dis Assoc Disord.* 2015 Apr-Jun;29(2):124-34.
 11. Kao HL, Lin MS, Wu WC, Tseng WY, Su MY, Chen YF, **Chiu MJ**, Wang SY, Yang WS, Tzen KY, Wu YW, Chen MF, Improvement of Cerebral Glucose Metabolism in Symptomatic Patients With Carotid Artery Stenosis After Stenting. *Clin Nucl Med.* 2015 Sep;40(9):701-7.
 12. Cheng YW, Lee MJ, Chen TF, Cheng TW, Lai YM, Hua MS, **Chiu MJ***. A single nucleotide TDP-43 mutation within a Taiwanese family – a multi-faceted demon. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2015, Sep. Accepted
 13. Fan LY, Sun Y, Lee HJ, Yang SC, Chen TF, Lin KN, Lin CC, Wang PN, Tang LY, **Chiu MJ***, Marital status, lifestyle and dementia: A nationwide survey in Taiwan. *PLoS One* 2015, Sep. Accepted
 14. Cheng YW, Chen TF, Cheng TW, Lai YM, Hua MS, Chen YF, **Chiu MJ***. Hippocampal Atrophy but not White-matter Changes predicts the Long-term Cognitive Response to Cholinesterase Inhibitors in Alzheimer's disease. *Alzheimer's Research & Therapy* 2015, Oct Accepted
 15. Shen CP, Lin JW, Lin FS, Lam AYY, Chen W, Zhou WZ, Sung HY, Kao YH, **Chiu MJ**, Leu FY, Lai



- FP. GA-SVM Modeling of Multiclass Seizure Detector in Epilepsy Analysis System Using Cloud Computing. Journal Soft Computing 2015, Oct Accepted.*
16. Tsai DFC, Hsu YR, Hwang TJ, Chen CY, **Chiu MJ**. Ethical Issues in the Treatment and Care for Dementia Patients. *Formosan J Med.* 2015;19:499-507. (In Chiese)
 17. Tsaih PL, **Chiu MJ**, Luh JJ, Yang YR, Hu MH. Effects of electromyographic biofeedback muscle training on motor function and cortical excitability in stroke patients. *Physiotherapy* 5/2015;101:e1538-e1539.
 18. Yu RL, Tang CH, Wu YR, Wu RM, **Chiu MJ**, Hua MS. Memory for gist and detail information in patients with Parkinson's disease. *BMJ Open* 11/2015;5(11): e009795.
 19. Yang SY, **Chiu MJ**, Lin CH, Horng HE, Yang CC, Chieh JJ, Chen HH, Liu BH. Development of an ultra-high sensitive immunoassay with plasma biomarker for differentiating Parkinson disease dementia from Parkinson disease using antibody functionalized magnetic nanoparticles. *J Nanobiotechnology.* 2016 Jun 8;14(1):41.



Plasma biomarkers for discriminating various types of dementia

Ming-Jang Chiu,^{1,2,3,4} Chin-Hsien Lin,¹ Ta-Fu Chen,¹ Che-Chuan Yang,⁵ and Shieh-Yueh Yang⁵

¹*Department of Neurology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei 100, Taiwan*

²*Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei 100, Taiwan*

³*Department of Psychology, National Taiwan University, Taipei 100, Taiwan*

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Different metabolic dysfunctions cause over expression or depletion of proteins in brain, and result in various types of dementia. These proteins of abnormal levels are conventionally assayed in cerebrospinal fluid (CSF). It is so difficult to assay these proteins in peripheral fluid, such as plasma, because that the concentrations of these proteins are ultra-low in peripheral fluid. Authors developed an ultra-sensitive assay technology, so-called immunomagnetic reduction (IMR), which showed the low-detection limit at the levels of pg/ml or fg/ml, depending on kinds of proteins. Furthermore, authors demonstrated the feasibility of differentiating patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or AD from healthy controls by assaying amyloid β ($A\beta$) and tau protein in human plasma. In this work, in addition to AD ($n=12$), patients with other types of dementia such as Parkinson disease dementia (PDD) ($n=13$), dementia with Lewy body (DLB) ($n=14$), frontotemporal dementia (FTD) ($n=12$) are recruited for exploring the concentrations of $A\beta_{1-42}$, tau protein, and α -synuclein in plasma by using immunomagnetic reduction. Healthy controls ($n=13$) show the concentrations of $A\beta_{1-42}$ and tau protein in plasma with (15.29 ± 1.60) and (16.16 ± 9.09) pg/ml, respectively. While ultra-low and wide-range concentrations from 0.04 fg/ml to 30 fg/ml are found for plasma α -synuclein with healthy controls. Patients with AD or FTD show the highest concentrations in plasma $A\beta_{1-42}$ or tau protein. The concentrations of plasma $A\beta_{1-42}$ or tau protein for PDD patients are



slightly higher than that of healthy controls. There is no significant difference in concentrations of plasma $A\beta_{1-42}$ or tau protein between DLB patients and healthy controls. In order to further differentiate AD from FTD, as well as DLB from healthy controls, the concentrations of plasma α -synuclein were detected. Clear differences in concentrations of plasma α -synuclein are found between AD and FTD, and between DLB and healthy controls. Hence, by using concentrations of $A\beta_{1-42}$, tau protein, and α -synuclein in plasma, AD ($n = 12$), FTD ($n = 12$), PDD ($n = 12$), DLB ($n = 14$), and healthy controls ($n = 13$) can be well discriminated.



Marwan Sabbagh, M.D.

Karsten Solheim Chair for Dementia

Professor of Neurology

Director, Alzheimer's and Memory Disorders Division

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Expertise:

Diagnosis, treatment and research of Alzheimer's disease, and other memory disorder conditions including dementia. Leading investigator for many prominent national Alzheimer's prevention and treatment trials, including Alzheimer immunotherapy studies.

Professional services and honors:



- *Student Summer Fellow, Arizona Cancer Society, 1988*
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- *Allistair Karmody Award Finalist, 1991*
- *Travel Fellowship Award Recipient, American Neurological Association, 1996*
- *Peter F Drucker Award Co-recipient, 1998*
- *Dystonia Doctor of Excellence, San Diego County, 2000*
- *Life Member of the National Registry of Who's Who #172142, 2001*
- *Arizona Business Journal, Healthcare Hero Finalist 2004*
- *Fellow of the American Academy of Neurology 2004*
- *WestMarc Innovator Award, 2015*

Recent main publications (Dr. Sabbagh has published more than 200 SCI papers):

1. *Gender Differences in Alzheimer Disease: Brain Atrophy, Histopathology Burden, and Cognition.*
Filon JR, Intorcio AJ, Sue LI, Vazquez Arreola E, Wilson J, Davis KJ, **Sabbagh MN**, Belden CM, Caselli RJ, Adler CH, Woodruff BK, Rapsack SZ, Ahern GL, Burke AD, Jacobson S, Shill HA, Driver-Dunckley E, Chen K, Reiman EM, Beach TG, Serrano GE. *J Neuropathol Exp Neurol.* 2016 Jun 12. pii: nlw047. [Epub ahead of print]
2. *Sex and post-menopause hormone therapy effects on hippocampal volume and verbal memory.*
Braden BB, Dassel KB, Bimonte-Nelson HA, O'Rourke HP, Connor DJ, Moorhous S, **Sabbagh MN**, Caselli RJ, Baxter LC. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* 2016 Jun 4:1-20. [Epub ahead of print] PMID: 27263667
3. *Impact of Training Method on the Robustness of the Visual Assessment of 18F-Florbetaben PET Scans: Results from a Phase-3 Study.*
Seibyl J, Catafau AM, Barthel H, Ishii K, Rowe CC, Leverenz JB, Ghetti B, Ironside JW, Takao M, Akatsu H, Murayama S, Bullich S, Mueller A, Koglin N, Schulz-Schaeffer WJ, Hoffmann A, **Sabbagh MN**, Stephens AW, Sabri OJ. *Nucl Med.* 2016 Jun;57(6):900-6. doi: 10.2967/jnumed.115.161927. Epub 2016 Jan 28. PMID: 26823561
4. *Graph theory network function in Parkinson's disease assessed with electroencephalography.*
Utianski RL, Caviness JN, van Straaten EC, Beach TG, Dugger BN, Shill HA, Driver-Dunckley ED, **Sabbagh MN**, Mehta S, Adler CH, Hentz JG.
Clin Neurophysiol. 2016 May;127(5):2228-36. doi: 10.1016/j.clinph.2016.02.017. Epub 2016 Mar 4. PMID: 27072094



5. *Cortical phosphorylated α -Synuclein levels correlate with brain wave spectra in Parkinson's disease.*

*Caviness JN, Lue LF, Hentz JG, Schmitz CT, Adler CH, Shill HA, **Sabbagh MN**, Beach TG, Walker DG.*

Mov Disord. 2016 Apr 8. doi: 10.1002/mds.26621. [Epub ahead of print]

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Incorporation of novel biomarkers into clinical practice to improve the diagnostic confidence for Alzheimer's dementia

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Background: Establishing the in-vivo diagnosis of Alzheimer's disease (AD) or other dementias relies on clinical criteria, although their accuracy can be limited. The diagnostic accuracy is 77% for a clinical diagnosis of AD, even amongst the experts.

Methods: We performed a comprehensive analysis of the specific modalities including Apo E, CSF, FDG PET, Amyloid PET, Tau-PET, SPECT, CT, MRI, screening labs (B12 and TSH) to determine the specificity and sensitivity of each test in the clinical diagnosis of AD. This was done through a review of PubMed. We added the Novel immunomagnetic reduction platform (MagQu Assay that provides ultra-sensitivity for measuring plasma Tau and amyloid beta 42) to assess to this analysis.

Results: The sensitivity of a diagnosis of AD is best rendered with invasive and expensive CSF testing. The sensitivity and specificity of the current diagnostic approach (structural CT or MRI with screening labs) remains low for clinical detection of AD and is still used to exclude other conditions mainly. The sensitivity and specificity of different PET modalities will be presented. Estimates of sensitivity and specificity of the ultrasensitive immunomagnetic reduction platform will be presented.

Conclusion: With limited diagnostic capabilities, physicians do not feel comfortable or skilled in rendering a clinical diagnosis of AD. Compounding this is the fact that inexpensive, minimally invasive diagnostics do not yet exist. There is a need for developing blood borne biomarkers that can aid in the clinical diagnosis of AD. One consideration is a tiered approach to a diagnosis.



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Professional services and honors:

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Recent main publications (Prof. Chen has published more than 260 SCI papers):

1. **Chen K**, Ayutyanont N, et al, the Alzheimer's Disease Neuroimaging Initiative, Characterizing Alzheimer's Disease using a Hypometabolic Convergence Index, Neuroimage (NIMG-10-2332), 2011
2. Anna et al. Summary metrics to assess Alzheimer's disease-related hypometabolic pattern with FDG-PET: head-to-head comparison, JNM, 2011
3. Schraml F, et al disease-related index and APOE e4 gene dose, PLOS-ONE, 2013



4. **Chen K**, et al., *Twelve-Month Metabolic Declines in Probable Alzheimer's Disease and Amnesic Mild Cognitive Impairment Assessed Using an Empirically Pre-Defined Statistical Region-of-Interest: Findings from the Alzheimer's Disease Neuroimaging Initiative* , pp654-664, *Neuroimage* 51(2), 2010 (PMC2856742)
5. **Chen K**, et al., *Correlations between FDG PET glucose uptake-MRI gray matter volume scores and apolipoprotein E4 gene dose in cognitively normal adults: a cross-validation study using voxel-based multi-modal partial least squares*, accepted by *Neuroimage*, 2012 (2/5/2012)
6. **Chen K**, et al., *Linking Functional and Structural Brain Images with Multivariate Network Analyses: A Novel Application of the Partial Least Square Method*, *Neuroimaging* 47 (2009) 602–610
7. **Chen K**. et al., *An Automated Algorithm for the Computation of Brain Volume Change from Sequential MRI's Using an Iterative Principal Component Analysis and Its Evaluation for the Assessment of Whole Brain Atrophy Rates in Patients with Probable Alzheimer's Disease*. *Neuroimage* 22/1: 134-143, 2004.
8. Napatkamon A, et al., *Twelve-month Whole-Brain Atrophy Rates and Estimated Power to Detect change in Alzheimer's Disease in Multi-center Trials Using Iterative Principal Component Analysis: Preliminary Findings from the Alzheimer's Disease Neuroimaging Initiative (BSP-NBE-2013-11)*, accepted by *Neuroscience and Biomedical Engineering (NBE)*, 2013
9. Spulber G. *Whole brain atrophy rate predicts progression from mild cognitive impairment to Alzheimer's disease* *Neurobiology of Aging*, (accepted 8/25/2008).
10. **Chen K**, et al., *Correlations Between Apolipoprotein E ϵ 4 Gene Dose And Whole Brain Atrophy Rates*. *Am J Psychiatry* 164: 713-720, 2007.
11. **K Chen**, et al, *Improved power to characterize longitudinal amyloid- β PET changes and evaluate amyloid-modifying treatments using a cerebral white matter reference region*, accepted by *Journal Nuclear Medicine*, 2014
12. Xia Wu, et al., *"The Receiver Operational Characteristic for Binary Classification with Multiple Indices and Its Application to the Neuroimaging Study of Alzheimer's disease"*, accepted by *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 2012
13. C Xiong, G Belle, **K Chen**, et al, *Combining Multiple Markers to Improve the Longitudinal Rate of Progression-Application to Clinical Trials on the Early Stage of Alzheimer's Disease* , *Statistics in Biopharmaceutical Research*, 2012
14. Jessica B Langbaum, et al., *An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease*, *Alzheimer's & dementia: the journal of the Alzheimer's Association* (Impact Factor: 14.48). 04/2014; DOI:10.1016/j.jalz.2014.02.002
15. Fleisher AS, **Chen K**, et al., *Associations Between Biomarkers and Age in the Presenilin 1*



E280A Autosomal Dominant Alzheimer Disease Kindred: A Cross-sectional Study, JAMA Neurology, 2014, accepted

Partial List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/kewei.chen.1/bibliography/48024756/public?sort=date&direction=ascending>



Neuroimaging and fluid biomarkers in the preclinical AD and prevention study

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Background: Cross-sectional and longitudinal studies using neuroimaging and fluid biomarkers such as florbetapir positron emission tomography (PET) for fibrillar amyloid- β (A β) burden, recently AV1451 for Tau protein, fludeoxyglucose (FDG) for glucose metabolism, T1-weighted magnetic resonance imaging (MRI) for volumetric changes and functional MRI for activation and connectivity have made significant impact on human brain functions and neurodegenerative diseases such as Alzheimer's disease (AD) at both preclinical (asymptomatic) and clinical stages. Focusing on AD using it as an example, this talk discusses various biomarkers based on these imaging and fluid measurements for their uses in diagnosis, potential treatment evaluation and the understanding of the mechanism/hypothesis of the diseases.

Methods: This discussion will be in the context of our 20-years long longitudinal studies on the Arizona cohorts with 0, 1 or 2 copies of apolipoprotein e4 allele, a genetic risk factor for AD, the recently launched Alzheimer Prevention Initiative (API) clinical trial on individuals with PS-1 mutation and a separate one on cognitively normal e4 homozygotes. In addition to the medical implications, emphasis will be on the analytic techniques to process, and the statistical tools to analyze the imaging data for each modality separately or jointly. One special hot topic is the use of different reference regions-of-interest (ROIs) in the computation of cerebral-to-reference ROI standard uptake value ratios (SUVRs) in longitudinal studies (clinical trial, e.g.).

Results: Using a newly introduced white-matter (WM) reference ROI permitted us to consistently detect significant longitudinal SUVR increases in the A β + AD, mild cognitive impairment (MCI), and normal control (NC) and normal APOE4 carrier sub-groups, to consistently detect significantly greater SUVR increases in these groups than in their respective A β - or non-carrier controls, and to detect an overall correlation between longitudinal SUVR increases and longitudinal Mini-Mental State Examination (MMSE) score declines. Using the WM reference ROI, we estimate the need for far fewer AD, MCI, A β + NC, and APOE4-carrying NC subjects to detect an amyloid-modifying treatment effect in a 12-month placebo-controlled trial.



Conclusion: *neuroimaging techniques provide a great opportunity for testing the AD hypothesis, and an efficient approach for evaluating the effectiveness of early intervention and treatment of the disease.*



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Professional services and honors:

- 2005 Travel Award. 1st Congress on Asian Society for Pediatric Research (ASPR). November 24-26, 2005 in Tokyo, Japan
- 2014 Young Investigator Award. 218th biannual meeting of Taiwan Pediatric Association. April 26-27, 2014 in Taipei, Taiwan
- 2015 Annual Best Reviewer Award, Journal of Formosa Medical Association, Taipei, Taiwan
- PI of research projects supported by Ministry of Science and Technology, Taiwan, since 2009

Recent main publications:

1. **Lee NC**, Chien YH, Hwu WL. Integrated care for Down syndrome. *Congenit Anom (Kyoto)*. 2016 Feb 11.
2. Liu YN, Liu TT, Fan YL, Niu DM, Chien YH, Chou YY, **Lee NC**, Hsiao KJ, Chiu YH. Measuring propionyl-CoA carboxylase activity in phytohemagglutinin stimulated lymphocytes using high performance liquid chromatography. *Clin Chim Acta*. 2016 Jan 30;453:13-20.
3. Li MJ, **Lee NC**, Yang YL, Yen HJ, Chang HH, Chien YH, Lu MY, Jou ST, Lin KH, Hwu WL, Lin DT. Long-term outcome for Down syndrome patients with hematopoietic disorders. *J Formos Med Assoc*. 2016 Feb;115(2):94-9.
4. **Lee NC**, Muramatsu SI, Chien YH, Liu WS, Wang WH, Cheng CH, Hu MK, Chen PW, Tzen KY, Byrne BJ, Hwu WL. Benefits of neuronal preferential systemic gene therapy for neurotransmitter deficiency. *Mol Ther. Mol Ther*. 2015 Oct;23(10):1572-81.
5. **Lee NC**, Chien YH, Wong SL, Sheen JM, Tsai FJ, Peng SF, Leung JH, Chao MC, Shun CT, Hwu WL. Outcome of early-treated type III Gaucher disease patients. *Blood Cells Mol Dis*. 2014 Sep;53(3):105-9.
6. **Lee NC**, Chien YH, Hu MH, Liu WS, Chen PW, Wang WH, Tzen KY, Byrne BJ, Hwu WL. Treatment of congenital neurotransmitter deficiencies by intracerebral ventricular injection of an AAV9 vector. *Hum Gene Ther*. 2014 Mar;25(3):189-98.
7. **Lee NC**, Shieh YD, Chien YH, Tzen KY, Yu IS, Chen PW, Hu MH, Hu MK, Muramatsu S, Ichinose H, Hwu WL. Regulation of the dopaminergic system in a murine model of aromatic L-amino acid decarboxylase deficiency. *Neurobiol Dis*. 2013 Apr;52:177-90.
8. Chen YC, Chien YH, Chen PW, Leung-Sang Tang N, Chiu PC, Hwu WL, **Lee NC**. Carnitine uptake defect (primary carnitine deficiency): risk in genotype-phenotype correlation. *Hum Mutat*. 2013 Apr;34(4):655. (Corresponding author)
9. Hwu WL, Muramatsu S, Tseng SH, Tzen KY, **Lee NC**, Chien YH, Snyder RO, Byrne BJ, Tai CH, Wu RM. Gene therapy for aromatic L-amino acid decarboxylase deficiency. *Sci Transl Med*. 2012 May 16;4(134):134ra61.



Amyloid and tau protein as biomarkers for the detection of early degeneration in Down syndrome – comparative study with Alzheimer disease in general population

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Background: Abnormal concentrations of β -amyloids and tau had been noted in patients with Alzheimer's disease (AD) and Down syndrome (DS) with AD. However, reports about the changes of these biomarkers in early stage of regression such as behavioral and psychological symptoms of dementia (BPSD) in DS are sparse.

Methods: Seventy-eight healthy control, 62 AD, 35 DS without degeneration, 16 DS with degeneration (DS_D) including 9 BPSD and 7 DS with dementia were enrolled. β -amyloid-40 ($A\beta$ -40), β -amyloid-42 ($A\beta$ -42) and tau protein from blood were analyzed using antibody-labelled functionalized magnetic nanoparticles by measuring superconducting quantum interference device (SQUID) magnetometer. Adaptive Behaviour Dementia Questionnaire (ABDQ) was used to evaluate clinical status of degeneration.

Results: Baseline $A\beta$ -40 and tau is higher but $A\beta$ -42 and $A\beta$ -42/ $A\beta$ -40 ratios are lower in DS compared with healthy subjects (all $p < 0.001$). In DS_D, a lower $A\beta$ -40 with higher $A\beta$ -42 and $A\beta$ -42/40 ratio were observed compared with DS without degeneration (all $p < 0.001$). ABDQ score is negatively correlated with $A\beta$ -40 level ($\rho = -0.556$; $p < 0.001$) and tau protein level ($\rho = -0.509$; $p = 0.003$) and positively correlated with $A\beta$ -42 ($\rho = 0.621$; $p < 0.001$) and $A\beta$ -42/40 ratio ($\rho = 0.544$; $p < 0.001$). Of the markers, $A\beta$ -40, $A\beta$ -42 and $A\beta$ -42/ $A\beta$ -40 ratio are good indicators for early detection of degeneration in DS.



Conclusion: Baseline $A\beta$ -40 and tau elevated in DS patients may indicate the chronic neurotoxicity in young DS. $A\beta$ -42 and $A\beta$ -42/40 ratio increased in DS patients with degeneration, indicating the $A\beta$ -42 could be a biomarker for regression in DS subjects. The elevation of baseline tau but decrement in demented DS patients may reflect the burn-out phenomenon in neurodegeneration.



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Professional career:

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1997-present: Director, Civin Laboratory for Neuropathology, Banner Sun Health Research Institute

Expertise:

Neuropathology of Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases

Assessment of CSF, imaging and biopsy biomarkers

Tissue banking operating procedures

Professional services and honors:

British Columbia Post-Secondary Scholarship 1986-1987

British Columbia Health Care Research Fellowship 1986-1989

British Columbia Gerontology Association Student of the Year 1988

Arizona Business Journal, Researcher/Scientist of the Year 2006

Westmarc "Best of the West" 2007 (Western Maricopa County Business Association)



Editorial Board member, Acta Neuropathologica, 2012-2015

Associate Editor, Journal of Alzheimer's Disease, 2012-present

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Recent main publications:

1. **Beach TG**, Corbille A-G, Letournel, F et al. Multicenter assessment of immuno-histochemical methods for pathological alpha-synuclein in sigmoid colon of autopsied Parkinson's disease and control subjects. *Journal of Parkinson's Disease*, in press.
2. **Beach TG**, Thal DR, Zvanette M et al, Detection of striatal amyloid plaques with [18F]flutemetamol: Validation with postmortem histopathology. *J Alzheimers Dis.* 2016 31;52(3):863-73.
3. Adler CH, Dugger BN, Hentz JG, et al...**Beach TG**, Peripheral synucleinopathy in early Parkinson's disease: Submandibular gland needle biopsy findings. *Mov Disord.* 2016 31(2):250-6.
4. **Beach TG**, Schneider JA, Sue LI et al, Theoretical impact of Florbetapir (18F) amyloid imaging on diagnosis of Alzheimer dementia and detection of preclinical cortical amyloid. *J Neuropathol Exp Neurol* 2014; 73(10):948-53.
5. Adler CH, **Beach TG**, Hentz JG et al. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. *Neurology.*2014 83(5):406-12.
6. Adler CH, Dugger BN, Hinni ML et al ... **Beach TG**, Submandibular gland needle biopsy for the diagnosis of Parkinson disease. *Neurology* 82(10):858-64.
7. Maarouf CL, **Beach TG**, Adler CH et al, Quantitative appraisal of ventricular cerebrospinal fluid biomarkers in neuropathologically diagnosed Parkinson's disease cases lacking Alzheimer's disease pathology. *Biomark Insights.* 2013;8:19-28
8. **Beach TG**, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol.* 2012 Apr;71(4):266-73.



Biomarkers for Neurodegenerative Disease: Can they Swing us Across the Valley?

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Broadly defined, biomarkers have a wide range of disease specificity. Measures of the severity and nature of a patient's impairment, in terms of cognition and movement, are the usual inclusion criteria and drug efficacy endpoints in clinical trials for Alzheimer's disease (AD), Parkinson's disease (PD) and dementia with Lewy bodies (DLB), but are critically hampered by their lack of disease sensitivity and specificity. Due to the high failure rate of clinical trials, regulatory approval for efficacious new drugs has stagnated in the past few decades, with the gap between basic science discovery and clinical application metaphorically termed the "Valley of Death". While the causes for this are probably multiple and complex, the usage of biomarkers as surrogate endpoints, particularly when they are molecularly-specific for the disease, has achieved some success in cancer trials and it is likely that neurodegenerative disease trials would benefit from the same approach. As dementia and parkinsonism are not disease-specific clinical syndromes, trials have been flawed by reliance on clinical diagnosis and clinical endpoints. Molecularly-specific biomarkers are urgently needed, to improve diagnostic accuracy, disease-tracking and accounting for comorbid disease. Even when a molecularly-specific biomarker is found, such as amyloid imaging for AD, it may not reflect the entire molecular disease repertoire and may not serve equally well in the different roles of preclinical detection, diagnostic confirmation and surrogate endpoint, foreshadowing the future usage of two, three or more biomarkers, deployed in series or in parallel. We have contributed to the calculation of baseline clinical diagnostic accuracy as well as to the development of imaging, CSF and biopsy biomarkers. We suggest that tau biomarkers may be most useful for the earliest AD detection and prevention trials, amyloid (A β) biomarkers may be best suited to later prodromal detection and prevention, while both will be essential for testing specific anti-tau and anti-amyloid agents. As effective synuclein biofluid and PET biomarkers remain elusive, biopsy of the peripheral nervous system is currently the most promising approach for improving PD and DLB clinical trials while REM



sleep behavior disorder is the best prodromal indicator of latent PD and DLB. Avenues of potential progress include greater molecular biofluid dissection of tauopathies and synucleinopathies and “big data” mining to develop risk algorithms. Cortical needle biopsy needs to be reconsidered, in those with clinically-manifest disease, if we are ever to achieve “precision medicine” comparable to that being developed for cancer.



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2008-now Board member of Asian Society against Dementia Congress

2009-2012 President of Taiwan Dementia Society

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Expertise:

Biomarkers study of Alzheimer disease, Cohort study of dementia, behavioral and psychological symptoms of dementia, Parkinson disease dementia

Professional services and honors:

- 1. Millenium Best Essay Award, Cerebrovascular Disease Prevention Foundation, 2000*
- 2. Award of the Best Poster, 2nd Asian Society against Dementia Congress & 3rd Taiwan Dementia society Annual Meeting, 2008*
- 3. Top Cited Papers in International Psychogeriatrics*
- 4. Outstanding physician, Veterans Affairs Commission, Executive Yuan, ROC, 2010.*
- 5. Outstanding physician, Veterans Affairs Commission, Executive Yuan, ROC, 2015.*



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Recent main publications (Dr. Fuh has published more than 280 SCI papers):

1. Lin HF, Chern CM, Chen HM, Yeh YC, Yao SC, Huang MF, Wang SJ, Chen CS, **Fuh JL ***-Validation of NINDS-VCI Neuropsychology Protocols for Vascular Cognitive Impairment in Taiwan. *PLoS One*. 1;11(6):e0156404, 2016.
2. Lee WJ, Wu SL, Li JY, Chen CC, Lin JJ, Peng GS, Lin TK, Wang SJ, Chen RS, Yang YH, Tsai CH, Hsu JL, Liao YC, Chen SP, **Fuh JL ***. PDD-5S: A Useful Screening Tool for Parkinson's Disease Dementia. *Parkinsonism & Related Disorders* 25:85-90, 2016.
3. Hsu JL, Lee WJ, Liao YC, Lirng JF, Wang SJ, **Fuh JL ***. Posterior atrophy and medial temporal atrophy scores are associated with different symptoms in patients with Alzheimer's disease and mild cognitive impairment. *PLoS One* 10(9):e0137121, 2015.
4. Tsai CF, Lee YT, Lee WJ, Hwang JP, Wang SJ, **Fuh JL ***. Depression of family caregivers is associated with disagreements on life-sustaining preferences for treating patients with dementia. *PLoS ONE* 10(7):e0133711, 2015
5. Liao YC, Lee WJ, Hwang JP, Wang YF, Tsai CF, Wang PN, Wang SJ, **Fuh JL ***. ABCA7 gene and the risk of Alzheimer's disease in Han Chinese in Taiwan. *Neurobiology of Aging* 35(10):2423.e7-2423.e13, 2014.
6. Lee WJ, Chang YY, Lin JJ, Sung YF, Li JY, Wang SJ, Chen RS, Yang YH, Hu CJ, Tsai CH, Wang HC, Wu SL, Chang MH, **Fuh JL ***. Comparison of activities of daily living impairments in Parkinson's disease patients as defined by the Pill Questionnaire and assessments by neurologists. *J Neurol Neurosurg Psychiatry* 85(9):969-73, 2014.
7. Chen PL, Yang CW, Tseng YK, Sun WZ, Wang JL, Wang SJ, Oyang YJ, **Fuh JL ***. Increased Risk of Dementia after Anesthesia and Surgery. *British Journal of Psychiatry* 204:188-193, 2014.
8. Yang AC, Wang SJ, Lai KL, Tsai CF, Yang CH, Lo MT, Huang NE, Peng CK, **Fuh JL ***. Cognitive and neuropsychiatric correlates of EEG dynamic complexity in patients with Alzheimer's disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 47: 52-61, 2013.
9. Cheng CY, Tsai CF, Wang SJ, Hsu CY, **Fuh JL ***. Sleep Disturbance Correlates with White Matter Hyperintensity in Patients with Subcortical Ischemic Vascular Dementia. *Journal of Geriatric Psychiatry and Neurology* 26(3):158-64, 2013.
10. Tsai CF, Lee WJ, Wang SJ, Shia BC, Nasreddine Z, **Fuh JL ***. Psychometrics of the Montreal Cognitive Assessment (MoCA) and its Subscales: Validation of the Taiwanese version of the MoCA and an Item Response theory analysis. *Int Psychogeriatrics* 24 (4): 651-658, 2012.

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Plasma biomarkers on longitudinal cognitive changes in Taiwanese patients with Alzheimer disease

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia and mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia. According to the recent nationwide survey in Taiwan, the age-adjusted prevalence of dementia and MCI were 8% and 18.8% respectively among those aged 65 or more. We have enrolled 1,071 patients (809 (75.5%) AD and 262 (24.5%) MCI) from August 2012 to August 2016 in 4 teaching hospitals and followed up these patients. We will discuss the impact of plasma biomarkers on longitudinal cognitive changes in Taiwanese patients with AD.



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Academic background:

*Ph.D. Chemistry (2009), California Institute of Technology
B.S. Chemistry (2000), National Taiwan University*

Research career:

*Assistant Professor (2012.07- present), National Taiwan University.
Postdoctoral Fellow (2010.07- 2012.05), Massachusetts General Hospital and Harvard Medical School.
Adviser: Dr. Bradley T. Hyman, MassGeneral Institute for Neurodegenerative Disease and Department of Neurology. Characterization of tau protein misfolding inside neuronal synapses of Alzheimer's disease subjects.*

Expertise:

- *Protein damage and protein quality control in age-related disorders:
Synaptic pathology in Alzheimer's disease subjects and animal models
Cellular defense against oxidatively damaged proteins as an anti-aging mechanism*
- *Mass spectrometry in proteomics and metabolomics research: methodology development and clinical applications*
- *Material and acoustical properties of antique Italian violins: decoding the secrets of Stradivari violins through material analysis, historical research, and acoustic measurements*

Professional services and honors:

- *Alzheimer's Disease Research Fellowship, American Health Assistance Foundation (2010.07-2012.05)*
- *California Tobacco-Related Disease Research Program Fellowship (2004.04-2007.03)*



Recent main publications:

(A) Original research articles

1. **Tai, H. C.**; Khidekel, N.; Ficarro, S. B.; Peters, E.C.; Hsieh-Wilson, L. C.* Parallel identification of O-GlcNAc modified proteins from cell lysates. *J. Am. Chem. Soc.*, 2004, 126, 10500-10501.
2. Lin, W. Y.; Murugesh, M. G.; Sudhakar, S.; Yang, H. C.; **Tai, H. C.**; Chang, C. S.; Liu, Y. H.; Wang, Y.; Chen, I.W.; Chen, C. H.; Luh, T. Y.* On the rigidity of polynorbornenes with dipolar pendant groups. *Chem. Eur. J.*, 2005, 12, 324-330.
3. **Tai, H. C.**; Besche, H.; Goldberg, A. L.; Schuman, E. M.* Characterization of the brain 26S proteasome and its interacting proteins. *Front. Mol. Neurosci.* 2010, 3, 12.
4. Koffie, R. M.; Hashimoto, T.; **Tai, H. C.**; Serrano-Pozzo, A.; Joyner, D.; Hou, S.; Kopeikina, K. J.; Frosch, M. P.; Lee, V. M.; Holtzman, D. M.; Hyman, B. T.; Spires-Jones, T. L.* Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-beta. *Brain*, 2012, 135, 2155-68.
5. **Tai, H. C.**; Serrano-Pozo, A.; Hashimoto, T.; Frosch, M. P.; Spires-Jones, T. L.; Hyman, B. T.* The synaptic accumulation of hyperphosphorylated tau oligomers in Alzheimer disease is associated with dysfunction of the ubiquitin-proteasome system. *Am. J. Pathol.*, 2012, 181, 1426-1435.
6. Taylor, A. M.*; Wu, J.; **Tai, H. C.**; Schuman, E. M.* Axonal translation of β -catenin regulates synaptic vesicle dynamics. *J. Neurosci.*, 2013, 33, 5584-5589.
7. Kopeikina, K. J.; Polydoro, M.; **Tai, H. C.**; Yaeger, E.; Carlson, G. A.; Pitstick, R.; Hyman, B. T.; Spires-Jones, T. L.* Synaptic alteration in the rTg4510 mouse model of tauopathy. *J. Comp. Neurol.* 2013, 521, 1334-1353.
8. Perez-Nievas, B. G.; Stein, T.; **Tai, H. C.**; Dols-Icardo, O.; Scotton, T. C.; Barroeta-Espar, I.; Fernandez-Carballo, L.; de Munain, E. L.; Perez, J.; Serrano-Pozo, A.; Frosch, M. P.; Lowe, V.; Parisi, J. E.; Petersen, R. C.; Ikonomic, M. D.; Lopez, O. L.; Klunk, W.; Hyman, B. T.; Gomez-Isla, T.* Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. *Brain*, 2013, 136, 2510-2526.
9. **Tai, H. C.***; Wang, B. Y.; Serrano-Pozo, A.; Frosch, M. P.; Spires-Jones, T. L.; Hyman, B. T.* Frequent and symmetric deposition of misfolded tau oligomers within presynaptic and postsynaptic terminals in Alzheimer's disease. *Acta Neuropath. Commun.*, 2014, 2, 146.
10. Huang, C. F.; Liu, Y. H.; **Tai, H. C.*** Synthesis of peptides containing 2-oxohistidine residues and their characterization by liquid chromatography-tandem mass spectrometry. *J. Pept. Sci.*, 2015, 21, 114-119.
11. Yang, C. I.; Tsai, B. N.; Huang, S. J.; Wang, T.Y.; **Tai, H. C.**; Chan, J. C.* Aggregation of Beta-Amyloid Peptides Proximal to Zwitterionic Lipid Bilayers. *Chem. Asian J.* 2015, 10, 1967-1971.



(B) Reviews and commentary articles

1. **Tai, H. C.;** Schuman, E. M.* *MicroRNA: MicroRNAs reach out into dendrites. Curr. Biol., 2006, 16, R121-123.*
2. **Tai, H. C.;** Schuman, E. M.* *Ubiquitin, the proteasome and protein degradation in neuronal function and dysfunction. Nat. Rev. Neurosci., 2008, 9, 826-838.*
3. **Tai, H. C.;** Schuman, E. M.* *Angelman syndrome: Finding the lost Arc. Cell, 2010, 140, 608-610.*
4. Chen C. C.; Su, W. C.; Huang, B. Y.; Chen, Y. J.; **Tai, H. C.*;** Obena, R. P.* *Interaction modes and approaches to glycopeptide and glycoprotein enrichment. Analyst, 2014, 139, 688-704.*

(C) Violin research articles

1. **Tai, H. C.*** *Stradivari's varnish: A review of scientific findings, Part 1. Journal of the Violin Society of America: VSA Papers, 2007, 21 (1), 119-144.*
2. **Tai, H. C.*** *Stradivari's varnish: A review of scientific findings, Part 2. Journal of the Violin Society of America: VSA Papers, 2009, 22 (1) 60-90.*
3. **Tai, H. C.*;** Chung, D. T. *Stradivari violins exhibit formant frequencies resembling vowels produced by females. Savart Journal, 2012, 1 (2), online article.*
4. **Tai, H. C.*** *Role of timbre memory in evaluating Stradivari violins. Proc. Natl. Acad. Sci. USA, 2014, 111, E2777-2778.*



Synaptic pathology in Alzheimer's disease and its link to biomarker discovery

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The best neurological correlate of dementia in Alzheimer's disease (AD) is the loss of synapses, stronger than neuronal loss and the deposition of plaques and tangles. Therefore ideal biomarkers for AD should reflect pathophysiological changes at brain synapses. The neocortex and limbic system contain trillion of synapses, averaging about 500 nm in size, making them very difficult to study. We have traditionally relied on the investigation of synapses from other mammalian species to infer about the compositions and properties of our own synapses, but it is questionable whether such extrapolation is applicable to complex neurological disorders of sporadic nature such as AD. Without direct measurements of molecular properties from synapses of AD subjects, we are unlikely to correlate existing or future biomarkers with the critical aspect of AD neuropathology concerning synaptic dysfunction.

Our laboratory is developing a series of techniques to analyze brain synapses isolated from frozen human or rodent tissues. We have captured individual synapses over glass surfaces and applied immunocytochemistry to examine protein localization. We have ascertained the pre- and post-synaptic localization of normal and abnormal tau in human subjects, and begun to apply super-resolution optical techniques to visualize synaptic tau at 30 nm resolution. We have devised novel protocols to conduct high-throughput synapse analysis using flow cytometers and cell sorters, which allowed us to establish ApoE as a synaptically enriched protein. This will also allow us to collect a million highly purified synapses carrying specific marker sets, which can be further studied by ultrastructural imaging and next-generation sequencing for transcriptomics. By shotgun proteomics methods, we have established early-phase tau hyperphosphorylation sites in the synapses of APP/PS1 mice, and identified CDK5 as the critical tau kinase downstream of beta amyloid. We would also like to explore the synaptic metabolomics changes under AD, using liquid chromatography combined with fluorescence and mass spectrometry detection. Using a combination of isolation, visualization, and multi-omics approaches, we hope to understand the pathogenesis and progression of synaptic dysfunction in AD, which may be an important basis for future biomarker and therapeutic discoveries.