Unlocking the Secrets of Brain Disease

2015 International Research Symposium

November 5-7, 2015
La Jolla, California
Dear Colleagues:

2015 marks the 22nd annual CurePSP International Research Symposium, and I am pleased to have served as Scientific Director for each one. This year we introduce Alex Klein, PhD, a neuroscientist who has taken the newly created, full-time staff position of Vice President - Scientific Affairs. I am in the process of passing the torch to Alex in regards to my involvement in future symposia. However, I will continue to chair the Scientific Advisory Board for as long as CurePSP will have me.

This year is a little different. For the first dozen or so years, we held the Research Symposium in the same city as the Society for Neuroscience Annual Meeting, with the Symposium occurring the day afterwards. We eventually discovered that few of our attendees had actually attended the SFN conference. So we created a freestanding meeting in Baltimore, Maryland, CurePSP’s home city. That venue worked well, culminating in a record 75 attendees last year.

But this year, we loaded up the truck and moved to La Jolla. This location provides easier access to the many West Coast scientists working on PSP and other tauopathies, both in academia and in the private biotech sector. We also hoped that scientists from the Pacific Rim and Asia might find it easier to attend. CurePSP will soon have to decide whether to return to the West Coast, or perhaps rotate locations every other year. We would be interested in your opinion, so please contact Alex Klein (klein@curepsp.org) to share your thoughts.

This year’s agenda is also different in that only two CurePSP grantees are presenting results: Christoph Wiessner of Asceneuron, on his company’s development of a drug to encourage glycosylation of tau as a way to reduce its aggregation; and Natura Myeku of Columbia, on her work to improve proteasome function in tauopathies. The majority of the day will be devoted to keynote updates from some of the acknowledged leaders in our field: Adam Boxer, Marc Diamond, Dennis Dickson, Jeff Kelly and Ken Kosik.

Another innovation for the 2015 Research Symposium is two specialized discussion panels featuring current leaders in those areas. The panel on genetics and epigenetics will comprise Jeff Friedman, Giovanni Coppola, Günter Höglunger and Jerry Schellenberg. The panel on clinical trials will comprise Joel Braunstein, Trish Caruana, Günter Höglunger, Roger Lane and Irfan Qureshi, preceded by an overview from Adam Boxer.

During the Symposium, be free with your comments because this is the time and place to share your new ideas and to constructively disagree with the speakers, no matter how senior or established they may be. CurePSP is dedicated to being part of that open scientific process, and our partners in that endeavor are YOU. The thousands of people with PSP and CBD, present and future, are hoping that today we will each hold up our ends of the deal.

Sincerely,

Lawrence I. Golbe, MD
Chair, CurePSP Scientific Advisory Board
Schedule

Thursday, November 5
Reception, 7:00 pm - 8:30 pm, Grande Colonial, Sun Room

Friday, November 6
Registration and Breakfast: 7:00 am - 8:00 am, Scripps Seaside Forum
Symposium: 8:00 am - 5:20 pm
Cocktail reception: 5:20 pm - 7:00 pm

Saturday, November 7
Working Brunch: 9:30 am - 12:30 pm, La Valencia Hotel, 1132 Prospect Street, La Jolla, CA

Hotel/Venue Information

Grande Colonial
910 Prospect Street
La Jolla, California 92037
Phone: (855) 267-4884

Scripps Seaside Forum
8610 Kennel Way
La Jolla, California 92037
Phone: (858) 534-5604

La Valencia Hotel
1132 Prospect Street
La Jolla, California 92037
Phone: (858) 534-5604

Transportation

Shuttles from Grande Colonial hotel to Scripps Seaside Forum leave promptly at 7:00 am and 7:30 am, November 6, 2015.

Shuttle from Scripps Seaside Forum to Grande Colonial hotel leaves promptly at 7:00 pm, November 6, 2015.

PLEASE NOTE: Attendees are encouraged to take the shuttle from the Grande Colonial to the Scripps Seaside Forum as parking is limited.
CurePSP 2015 International Research Symposium

Agenda
November 6, 2015, Scripps Seaside Forum, La Jolla, California

Registration and Breakfast
7:00 am – 8:00 am

Welcome and Introductions
8:00 am – 8:15 am
William R. McFarland
Chair, Board of Directors, CurePSP
Lawrence I. Golbe, MD
Robert Wood Johnson Medical School
Jeffrey S. Friedman, MD, PhD
Friedman Bioventure

Keynote
8:15 am - 9:00 am
Marc Diamond, MD
University of Texas Southwestern Medical Center
“Tau seeding activity and strain composition in tauopathy syndromes.”

Keynote
9:00 am - 9:45 am
Kenneth S. Kosik, MD
University of California, Santa Barbara
“Exploring novel roles for Tau.”

Mid-Morning Break
9:45 am - 10:00 am

Brain Bank Update
10:00 am - 10:30 am
Dennis W. Dickson, MD
Mayo Clinic

Keynote
10:30 am - 11:15 am
Jeffery W. Kelly, PhD
The Scripps Research Institute
“Chemical and biological adaptation of proteostasis to ameliorate degenerative diseases.”

Clinical Trials Overview
11:15 am - 12:00 pm
Adam L. Boxer, MD, PhD
University of California, San Francisco

Lunch and Posters
12:00 pm - 1:30 pm

Panel on Clinical Trials
1:30 pm - 2:45 pm
Chair: Adam Boxer, MD, PhD
University of California, San Francisco
Joel B. Braunstein, MD, MBA
C2N Diagnostics
Trish Caruana, MSW
CurePSP and Patient Engagement Program (PEP)
Günter U. Höglinger, MD
Philips University Marburg, Germany
Roger Lane, MD, MPH
Isis Pharmaceuticals
Irfan Qureshi, MD
Bristol-Myers Squibb

Research Grant Presentation
2:45 pm - 3:10 pm
Grantee: Christoph Wiessner, PhD
Asceneuron S.A.
“O-GlcNAcylation of tau: From basic mechanisms to new therapeutics for PSP.”

Break
3:10 pm - 3:25 pm

Research Grant Presentation
3:25 pm - 3:50 pm
Grantee: Natura Myeku, PhD
Columbia University, Taub Institute for Alzheimer’s Disease Research
“26S proteasome dysfunction and cognitive impairment caused by aggregated tau accumulation can be attenuated by PKA-mediated phosphorylation of proteasomes.”

Panel on Genetics and Epigenetics
3:50 pm - 5:05 pm
Chair: Jeffrey S. Friedman, MD, PhD
Friedman Bioventure
Gerard Schellenberg, PhD
Perelman School of Medicine, University of Pennsylvania
Giovanni Coppola, MD
Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles
Günter U. Höglinger, MD
Philips University Marburg, Germany

Summative Discussion
5:05 pm - 5:20 pm

Cocktail Reception
5:20 pm - 7:00 pm
William R. McFarland
Bill McFarland, Chair, CurePSP Board of Directors, has extensive experience in operations management, information technology, project management, process improvement, profitability enhancement, organizational development, and mergers and acquisitions. The effective use of technology as a strategic asset is his forte. Bill’s hands-on experience as an operations executive, coupled with the knowledge he gained as the director and chief technology officer of a large data processing organization, give him the ability to address compelling issues and provide practical solutions in today’s fast-moving banking environment.

Lawrence I. Golbe, MD
Dr. Golbe is Professor of Neurology at Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ. He graduated from Brown University and NYU School of Medicine and did residency training at NYU/Bellevue before assuming his current position in 1983. His research in the clinical genetics and epidemiology of Parkinson’s and related disorders identified the first known Mendelian mutation causing Parkinson’s disease in the gene for alpha-synuclein. His work more recently centers on the genetics, epidemiology and clinimetrics of PSP. He devised the PSP Rating Scale, which has become the standard clinical measure for PSP worldwide. He has worked closely with CurePSP, serving since 1992 as Director of Research and Clinical Affairs and chair of its Medical Advisory Board.

Jeff Friedman, MD, PhD
After receiving a BS in biology from MIT, Jeff earned a MD and PhD in Cancer Biology with Irv Weissman at Stanford University. Dr. Friedman went on to train in Pediatrics at Boston Children’s Hospital and was a fellow in Pediatric Hematology/Oncology at the Dana Farber Cancer Institute. From 2003-2012, Dr. Friedman was a Principal Investigator and Assistant Professor at the Scripps Research Institute (La Jolla, CA), studying red cell and bone marrow disorders. Currently, he oversees a mixed portfolio of private and public companies in the biotechnology and pharmaceutical space, with an emphasis on platform technologies, oncology, neurodegenerative disease and genomics. He also is Chair of the Research Committee and a board member of CurePSP.

Marc Diamond, MD
Marc Diamond, MD, founding Director of the Center for Alzheimer’s and Neurodegenerative Diseases and Professor of Neurology and Neurotherapeutics, completed an internship, residency and chief residency in neurology at the University of California, San Francisco (UCSF) in 1997. After a postdoctoral fellowship, he was a faculty member in the Neurology Department at UCSF from 2002-2009. From 2009-2014, he was the David Clayson Professor of Neurology at Washington University in St. Louis, before he was recruited to UT Southwestern. His research focuses on molecular mechanisms of neurodegeneration in Alzheimer’s disease and related disorders, with the goal of developing novel therapies and diagnostic tools.

Kenneth S. Kosik, MD
Kenneth S. Kosik, a physician scientist, completed a BA and MA in English literature from Case Western Reserve University in 1972 and an MD from the Medial College of Pennsylvania in 1976. He served as a resident in neurology at Tufts New England Medical Center and was Chief Resident in 1980. He also held a series of academic appointments at the Harvard Medical School and achieved the rank of full professor there in 1996. Dr. Kosik has held appointments at McLean Hospital, Brigham and Women’s Hospital, Massachusetts General Hospital and the Dana-Farber Cancer Institute. In 2004, Kosik became the Harriman Professor of Neuroscience Research and Co-Director of the Neuroscience Research Institute at the University of California, Santa Barbara.

Dennis Dickson, MD
Dr. Dickson’s professional career has been devoted to the neuropathology of degenerative disorders, particularly those that produce dementia and Parkinsonism. He is the neuropathologist for the Mayo Clinic Alzheimer Disease Research Center and the Center Director for the Udall Center for Excellence in Parkinson’s Disease Research. Dr. Dickson directs the brain bank for the State of Florida Alzheimer Disease Initiative and the Society for Progressive Supranuclear Palsy. He received his BS (Biochemistry) and MD degrees from the University of Iowa and is past president of the American Association of Neuropathologists.
Jeffery W. Kelly, PhD

Jeffery W. Kelly, PhD, is the Lita Annenberg Hazen Professor of Chemistry in the Department of Chemistry and the Chairman of the Department of Molecular and Experimental Medicine at the Scripps Research Institute. He also served as Vice President of Academic Affairs and Dean of Graduate Studies at Scripps for nearly a decade. His research is focused on uncovering protein folding principles, understanding the etiology of protein misfolding and/or aggregation diseases and using this information to develop novel therapeutic strategies. Kelly cofounded FoldRx Pharmaceuticals based on his discovery of Tafamidis. In 2012, Kelly cofounded Misfolding Diagnostics, Inc., a San Diego company focusing on the early diagnosis of degenerative diseases.

Adam L. Boxer, MD, PhD

Dr. Adam L. Boxer is an Associate Professor of Neurology at the University of California, San Francisco (UCSF), where he directs the Neurosciences Clinical Research Unit. He also oversees the Alzheimer’s Disease and Frontotemporal Lobar Degeneration (FTLD) Clinical Trials Program at the UCSF Memory and Aging Center. Dr. Boxer’s research is focused on developing new treatments and biomarkers for neurodegenerative diseases, particularly those involving tau and TDP-43. He is the Principal Investigator of the Advancing Research and Treatment for FTLD (ARTFL) Clinical Research Consortium, a collaborative project funded by the National Institutes of Health to create a 15-center North American research network to support the development of new therapies for FTLD, including PSP and CBD.

Giovanni Coppola, MD

Dr. Giovanni Coppola is an Associate Professor of Psychiatry and Neurology at the University of California, Los Angeles. The long-term goal of his work is to advance the understanding of the genetic architecture of neuropsychiatric disorders by adopting a combination of genetic (sequencing, genotyping), genomic (gene expression, epigenetics) and bioinformatic (integrative network analysis) approaches. As Director of the UCLA Semel Center for Informatics and Personalized Genomics, he is interested in setting up an infrastructure for large-scale genomic studies and research access to the electronic medical record system.

Trish Caruana, MSW

Ms. Caruana received her Master’s in Social Work at the University of Maryland and worked as a senior clinical manager at the Johns Hopkins Hospital in the Department of Psychiatry and Neuroscience. She has extensive experience in the field of mental health and the effects of chronic illness on patients and their families. At CurePSP, Ms. Caruana is Executive Vice President and has spearheaded new programming and broadened the reach of education and support services to patients, care partners and healthcare professionals.

Roger Lane, MD, MPH

Dr. Lane graduated from Bristol University Medical School, UK, in 1984, and received a Masters in Public Health from Columbia University in 1998. His career highlights include early oncology clinical development at Roche from 1989; global medical neuroscience at Pfizer from 1992; neuroscience clinical development and global medical affairs at Novartis from 2001; and neuroscience clinical development at BMS from 2010. Dr. Lane has been VP Clinical Development, Isis Pharmaceuticals, Inc. since 2014.

Irfan Qureshi, MD

Irfan Qureshi, MD, is a neurologist serving as Medical Director in the Exploratory Clinical & Translational Research group at Bristol-Myers Squibb. He focuses on clinical development of targeted therapies for rare and genetically defined diseases, including progressive supranuclear palsy. Previously, Dr. Qureshi was at the Albert Einstein College of Medicine, where he held appointments of Assistant Professor in the Departments of Neurology and Medicine and Investigator at the Institute for Brain Disorders and Neural Regeneration. At Einstein, he conducted translational research with an emphasis on epigenetics, non-coding RNAs, and stem cells and regenerative medicine. Dr. Qureshi earned his MD from Einstein (Philip Hunt Scholar), and holds a BS in Biomedical Engineering from Johns Hopkins University.
Günter U. Höglinger, MD

Dr. Höglinger is a Chair for Translational Neurodegeneration at the German Center for Neurodegenerative Diseases (DZNE) in Munich, Germany, and a senior physician at the Neurological Clinic of the Technical University of Munich. He studied medicine and physics at the Universities of Regensburg and Würzburg, with a specialty in neurology. Dr. Höglinger worked on his doctorate at the University of Munich and the University of Bern, concentrating on stem cells in Parkinson's disease. His work includes the identification of natural environmental factors as triggers of atypical Parkinson syndromes in Guadeloupe, and his current focus is uncovering the causes, the redevelopment and improvement of diagnostic and therapeutic options in neurodegenerative Parkinson syndromes.

Christoph Wiessner, PHD

Christoph Wiessner is Chief Operating Officer and a founder of Asceneuron SA, which was created in 2012. With 24 years of experience in drug discovery for neurodegenerative diseases, he was a director at Merck Serono, Geneva, Switzerland, in the Neurodegenerative Diseases department prior to Asceneuron. Earlier, he worked for 14 years at Novartis, Basel, Switzerland and eventually headed the CNS Target and Lead Discovery Unit. While at Novartis, he led the drug discovery team for CAD106, a vaccine for Alzheimer’s disease currently in Phase II. Christoph obtained his PhD in the laboratory of Nobel laureate Hartmut Michel (Max-Planck-Institute for Biophysics, Frankfurt, Germany).

Natura Myeku, PhD

Natura Myeku is an associate research scientist at Columbia University in the Taub Institute for Alzheimer’s disease. She received her PhD from the Graduate Center-CUNY in 2011. Dr. Myeku was a post-doctoral fellow in Dr. Karen Duff’s laboratory, where she studied the impact of accumulated tau species on the Ubiquitin Proteasome Pathway (UPS) and how in vivo activation of proteasome reduces tauopathy and cognitive decline. In her first years as an independent investigator, she received a grant from Cure PSP to study dysfunction of synaptic proteasomes in early stages of tau-related disorders. Dr. Myeku is also interested in translational science and, in parallel, she is investigating several drugs that can increase proteasome function as a novel therapy for tauopathy disorder.

Gerard Schellenberg, PhD

Dr. Schellenberg is a Professor in the Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania. His career has focused on applying advanced genome technology to the problem of finding the underlying causes of human diseases. For the past 12 years, Dr. Schellenberg has also been studying the genetics of autism. He participates in the large collaborative network of autism researchers called the Autism Genome Project (AGP). Currently, he leads the Alzheimer’s Disease Genetics Consortium that is bringing new genomic technology to further understand the genetics of Alzheimer's disease. He is applying advances in DNA sequence technology to both Alzheimer's disease and autism to reveal the nature of genetic changes that cause both disorders.

Joel B. Braunstein, MD, MBA

Dr. Braunstein is a cardiologist and internist, and has been CEO of C2N Diagnostics since its inception. He is a Founder and Managing Director of LifeTech Research (LTR) since 2004. Dr. Braunstein also serves as a corporate director at Tivorsan Pharmaceuticals, Centegen, Correx, NexGen Medical Systems and 3PrimeDx. He received his MD with highest distinction from Northwestern University Medical School in 1996. Subsequently, he trained in internal medicine at the Brigham and Women’s Hospital, Harvard Medical School until 1999, and as a Fellow in Cardiovascular Medicine and Robert Wood Johnson National Clinical Scholar at the Johns Hopkins Medical Institutions. Additionally, he completed an MBA with management focus in 2004 and maintained an Assistant Professor cardiology faculty position at Johns Hopkins University.
Falls in progressive supranuclear palsy occur early in the course of the disease and increase in frequency and severity over time, causing significant morbidity and mortality. Few studies have evaluated the factors contributing to these falls, or ways to predict or help prevent them.

This study analyzed comprehensive clinical data of 339 progressive supranuclear palsy patients to evaluate which factors are associated with increasing falls, unrelated to freezing. Patients were divided into two groups – Infrequent Fallers (n = 118) with no or rare falls, and Frequent Fallers (n = 221) who fell occasionally to multiple times a day. 38 clinical parameters were analyzed to determine their relationship with an increasing risk of falls. Of these, 25 were significantly correlated with Frequent Fallers. Disease duration and clinical measures of disease severity (Modified Hoehn & Yahr Stage, Total and Motor Unified Parkinson's Disease Rating Scale scores, progressive supranuclear palsy Rating Scale scores) were correlated with Frequent Fallers, while cognitive parameters (Total Mini-Mental Status Exam score, Total and Subtype Frontal Assessment Battery scores, and Dementia Rating Scale subtype scores) were not. Motoric clinical parameters such as postural stability and arising from a chair were correlated with Frequent Fallers. Modified turning, a novel clinical parameter, was highly correlated with Frequent Fallers as well. Oculomotor parameters including horizontal saccades and eyelid apraxia/dystonia were associated with Frequent Fallers, while vertical saccades were not. Two predictive models to identify Frequent or Infrequent Fallers were developed and compared. Both models were reduced to include only clinical parameters amenable to intervention, to develop a treatment plan to reduce the risk of future falls. The best multivariate logistic regression model was able to predict 92% of Frequent Fallers but only identified 26% of Infrequent Fallers. However, the Neural Network model predicted Frequent Fallers and Infrequent Fallers with 100% accuracy, after validation. Our findings indicate clinical parameters seen in the initial stages of progressive supranuclear palsy (i.e. vertical saccades) have a ‘ceiling effect’, and may not be as valuable as signs of later stages of disease (i.e. horizontal saccades) in identifying patients at risk for increasing falls. A clinically useful neural network predictive model could identify symptoms amenable to treatment to reduce the risk of future falls. This model will need to be validated prospectively.
A Geographical Cluster of Progressive Supranuclear Palsy in Northern France

D. Caparros-Lefebvre¹, MD, PhD, L. I. Golbe², MD, V. Deramecourt³, MD, PhD, C. A. Maurage⁵, MD, PhD, V. Huin,⁵ MD, V. Buée-Scherrer,⁵ PhD, H. Obriot,⁵ MS, F. Caparros,⁵ MS, B. Sablonnière,⁵ MD, PhD, L. Buée⁵, PhD, A. J. Lees⁴ MD

¹ Unit of Neurology, Centre Hospitalier de Wattrelos, France
² Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
³ University of Lille Nord de France, INSERM UMR 1172, Batiment JPARC, France
⁴ Reta Lila Weston Institute for Neurological Studies, London, UK

Objective: To describe the first cluster of pure progressive supranuclear palsy (PSP) in northern France.

Background: PSP is a rare disorder with no report of geographical, temporal or occupational clusters and very rare family occurrence. We have observed an unusual prevalence of PSP in Wattrelos and Leers (combined population 51,551) and nearby towns in northern France. For most of the 20th century, the area was a center for chromate and phosphate ore processing, textile dyeing and tanning. Significant industrial waste persists near residential areas there.

Methods: From January 2005 to July 2014, we ascertained 92 patients with PSP seeking care at the Centre Hospitalier de Wattrelos (CHW), which principally serves Wattrelos and Leers. We calculated the observed/expected (O/E) ratio using census data and four previous prevalence studies of sporadic PSP. Eighty cases received brain MRI and 13 came to autopsy.

Results: Of the 92 cases, 62 experienced symptom onset while living in Wattrelos or Leers, an O/E ratio there of 12.3. Mean onset age was older (74.3 vs 67 y) than in sporadic PSP despite the absence of old-age population over-representation. The Richardson’s syndrome/PSP-parkinsonism ratio was 32%/52%. Four other phenotypes each occurred in 2-5%. Onset was gait/balance difficulty in 52%. No occupation seemed over-represented. None of the affected patients were relatives and only 13 reported a family history of dementia or parkinsonism. Seven of the 92 were of North African ancestry. MRI was compatible with PSP, with moderate to severe midbrain atrophy in all. All autopsies revealed typical PSP pathology. Western blots detected with antibody AD2 a doublet of hyperphosphorylated tau at 64 and 69 kDa in all 12 cases that is characteristic of PSP.

Conclusions: We have identified a unique cluster of PSP likely caused by industrial metals, which can cause tau misfolding and mitochondrial dysfunction. Detailed analytical epidemiology awaits our case-control survey of environmental and genetic factors and may shed light on PSP and other tauopathies.
Many studies on PSP focus solely on the brain with few to date examining peripheral organs. Further examining the extent and type of peripheral tau in humans and its relation to PSP may provide insights into patterns of tau aggregation and further understanding of selective vulnerability. In this study we examined 5µm formalin fixed paraffin embedded sections of abdominal skin and submandibular glands of 38 clinico-neuropathologically defined cases (18 normal controls (NC), 20 PSP, and 8 PSP cases with concomitant Alzheimer’s disease (PSP/AD)). These tissues were subject to immunohistochemistry for certain tau species: AT8 (recognizing tau phosphorylated at serine residues 202 and 205), T231 (recognizing tau phosphorylated at threonine residue 231) and HT7 (recognizing human tau between residues 159 and 163). HT7 staining of abdominal skin revealed 2 cases (a PSP, and an AD/PSP case) to contain punctate staining near ducts and diffuse staining within epithelial cells lining ducts within the dermal layer; this was not present in any NC cases. No AT8 or T231 staining was present on any abdominal skin section. For the submandibular gland, all cases examined contained diffuse HT7 staining within ductal simple cuboidal epithelial cells as well as threadlike neuronal elements. A subset of cases contained HT7 staining in ganglion cells (8% NC, 13% PSP, and 25% of PSP/AD). Submandibular gland AT8 staining revealed very sparse threadlike elements in select cases (42% NC, 50% PSP, and 83% of PSP/AD) and T231 revealed ganglion cells as well as stromal nerve fascicles and threadlike elements. Only two PSP cases did not contain any submandibular gland T231 staining. These potential differences between central and peripheral nervous system tau staining may provide additional insights into selective vulnerability.
A Longitudinal Observational Study of a Cohort of Patients With PSP/CBD: The JALPAC Project

Takeshi Ikeuchi\textsuperscript{1}, Hiroshi Takigawa\textsuperscript{2}, Ikuo Aiba\textsuperscript{3}, Takayoshi Shimohata\textsuperscript{4}, Takahiko Tokuda\textsuperscript{5}, Mitsuya Morita\textsuperscript{6}, Osamu Onodera\textsuperscript{7}, Shigeo Murayama\textsuperscript{8}, Kenji Nakashima\textsuperscript{2}

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\textsuperscript{2} Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan
\textsuperscript{3} Department of Neurology, National Hospital Organization, Higashi Nagoya National Hospital, Nagoya, Japan
\textsuperscript{4} Department of Molecular Pathobiology of Brain Diseases, Kyoto Prefectural University of Medicine, Kyoto, Japan
\textsuperscript{5} Division of Neurology, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan
\textsuperscript{6} Department of Neuropathology (Brain Bank for Aging Research), Tokyo Metropolitan Geriatric Hospital & Institute of Gerontology, Tokyo, Japan

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are progressive neurodegenerative disorders that are neuropathologically characterized by accumulation of phosphorylated 4-repeat tau in brain. Early diagnosis of PSP and CBD remains challenging, and the definite diagnosis is frequently deferred. The biomarkers for PSP and CBD have not been established. To identify PSP/CBD progression biomarkers both to improve understanding of disease etiology and course, and to provide crucial tools to enhance the likelihood of success of the disease-modifying therapeutic trials, we have launched a longitudinal observational study for PSP and CBD. The project was designated as JALPAC: Japanese Longitudinal Biomarker Study in PSP and CBD (UMIN18468). The JALPAC cohort will comprise patients clinically diagnosed as having PSP or CBD followed longitudinally and comprehensively for biomarker assessment using standardized data acquisition protocols at 35 clinical sites with expertise in Japan. Clinical assessment and MRI study are performed. Biological samples including blood (plasma and serum), CSF, genomic DNA, and lymphoblastoid cell lines are stored at the JALPAC biorepository. To date, 61 participants have been registered in JALPAC; the most frequent clinical phenotype is PSP-Richardson’s syndrome (n=23) followed by CBD/CBS (n=13) PSP-parkinsonism (n=9), PSP-cerebellar ataxia (n=5), and PSP-pure akinesia with gait freezing (n=5). The JALPAC project is expected to provide progress in developing biomarkers and understanding the natural history of PSP and CBD.
[18F]MK-8553: A Selective O-GlcNAcase (OGA) PET Tracer to Support the Development of MK-8719

Cristian Salinas¹, Wenping Li¹, Kerry Riffel¹, Patricia Miller¹, Zhizhen Zeng¹, Mona Purcell¹, Marie Holahan¹, Hyking Haley¹, Liza Gantert¹, Dinko Gonzalez Trotter¹, Daniel Jonathan², Ruben DeClerq³, Arie Struyk⁴, Sean Smith⁵, Jeff Evelhoch¹, and Eric Hostetler¹

¹ Translational Biomarkers, Imaging Group, Merck & Co., Inc.
² Clinical Research, ESD Operations, Merck & Co., Inc.
³ Clinical Research, Translational Pharmacology-IDL, Merck & Co., Inc.
⁴ Clinical Research, Translational Pharmacology-Neuro, Merck & Co., Inc.
⁵ Pharmacology, Psychiatry and Opportunistic, Merck & Co., Inc.

[18F]MK-8553 is a PET (positron emission tomography) radiolabeled tracer with suitable characteristics (brain penetrant, strong signal to background ratio, subnanomolar affinity, fast tissue kinetics, etc.) that allows the study of target engagement of therapeutic drugs targeting the OGA enzyme. In vivo studies in the rhesus monkey demonstrated that the [18F]MK-8553 PET signal can be modulated in a dose dependent fashion by MK-8719, a potent and selective OGA enzyme antagonist currently under development for the treatment of progressive supranuclear palsy (PSP).

In the clinic [18F]MK-8553 reported an effective dose of 17 mSv/MBq and a test-restest variability of the main quantitative PET outcome of 4% which makes it an ideal tracer to evaluate OGA enzyme target engagement. Currently [18F]MK-8553 is being utilized in humans to characterize the PK-PD relationship of MK-8719 via assessing in vivo target engagement PET tracer ensuring proper testing of the OGA mechanism and increasing the probability of a successful clinical trial by defining the right dosage and administration regime required to achieve the sustained level of enzyme occupancy needed to elicit the desired pharmacological effect.
MK-8719 is a selective and potent small molecule inhibitor of the O-GlcNAcase (OGA) enzyme that is being developed for the treatment for progressive supranuclear palsy (PSP). O-GlcNAcylation is a common post-translational modification at serine or threonine residues of intracellular proteins, mediated by the ubiquitously expressed enzymes O-GlcNAc transferase and OGA. Preclinical findings from several groups demonstrate that selective OGA inhibitors increase brain protein O-GlcNAcylation and significantly decrease tau pathology in transgenic mouse models of tauopathy. In this presentation we review the preclinical profile of MK-8719 and summarize early clinical development findings in healthy subjects.

In vitro studies demonstrated that MK-8719 is a competitive reversible inhibitor of the human OGA enzyme with comparable activity in rat, dog, and mouse. Functional studies revealed that OGA inhibition significantly increased the proportion of proteins bearing O-GlcNAc moieties (O-protein). In vivo, MK-8719 was tested in the Tg4510 transgenic mouse model overexpressing a mutated form of tau protein associated with human frontotemporal dementia. MK-8719 administration significantly increased O-protein levels in peripheral blood mononuclear cells (PBMCs) and brain tissue, and reduced tau aggregation in mouse brain. Reduction in tau aggregation in Tg4510 mice was accompanied by reductions in neurodegeneration, including reduced inflammatory marker expression, attenuation of brain weight loss, and attenuation of forebrain volume loss. These animal data support the hypothesis that sustained OGA inhibition may significantly alter the progression of disease related to neuronal tau aggregation. Finally, data from a neuronal cell line derived from human induced pluripotent stem cells shows reduced tau aggregation supporting clinical testing for therapeutic utility in humans.

Clinical development of MK-8719 was initiated with a single ascending dose Phase I study in 16 healthy adult subjects. The objectives of this study were to evaluate safety, tolerability, and plasma pharmacokinetics of MK-8719. Single doses of up to 1200 mg were administered and were generally well tolerated. Preliminary findings from this study include dose-proportional plasma drug concentrations, and half-life estimates supporting twice-daily administration. In an exploratory assay, MK-8719 administration elicited O-protein increases in extracts from PBMCs, consistent with preclinical observations. These early Phase 1 clinical findings suggest that MK-8719 is a potential therapeutic to test the hypothesis that OGA inhibition is a viable therapy for PSP, as supported by evidence in preclinical disease models.
Using TRiC and TRiC-inspired Reagents to Prevent and/or Reverse the Pathogenesis of Tauopathies

Xuqiao Chen, Xiaobei Zhao, Xuqiao Chen, William C Mobley, and Chengbiao Wu
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Proteostasis maintains the proteome through folding of newly synthesized proteins, refolding of misfolded proteins, and clearance of damaged proteins. Dysregulation of the proteostasis network is believed to contribute to the pathogenesis of many neurodegenerative disorders such as Tauopathies, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease etc.

TRiC (TCP-1 ring complex), a cellular chaperonin, is known to be important for the folding of ~10% of newly synthesized proteins, including actin and tubulin. TRiC substrates are frequently found to be large, hydrophobic proteins with regions of β-sheet propensity that are aggregation prone, such as aggregated Tau or mutant Huntingtin (mHTT; i.e. expanded repeat HTT). As such, the normal function of TRiC is to protect against excessive accumulation of cross β-sheet containing structures in normal neurons and in those undergoing degeneration, as in the case of Tauopathies. In preliminary studies, we tested the hypothesis that increasing the levels of TRiC or TRiC-derived polypeptides would reduce the levels of mHTT and reverse defects in axonal trafficking in the BACHD mouse model of Huntington’s disease. We expressed individual subunits of TRiC using lentiviral infection and examined axonal trafficking of lysosomes and BDNF-containing signaling endosomes. The results were a highly significant reduction in the levels of mHTT, rescue of trafficking defects and neuronal atrophy. Remarkably, the same results were obtained using a soluble form of ApiCCT1, the N-terminal portion of the CCT1 subunit, applied to neurons in culture. This finding is in accord with a recent report showing that extracellular ApiCCT1 enters the cell, possibly through the presence of a TAT like sequence in this polypeptide. These exciting findings suggest that TRiC-derived reagents may serve as novel therapeutics to rescue tau-based defects in degenerating neurons. Indeed, our preliminary results providing supporting evidence for such an approach.
Objectives: PSP arises from a combination of genetic and environmental factors which lead to intermediate pathological changes in the brain, eventually causing cell death and disease. We hypothesize that there are genetic variants associated with the PSP disease process that can be identified using neuropathologic features as phenotypes in a genome-wide association study.

Methods: Tau pathology scores were assessed in 970 pathologically-confirmed PSP cases for four tau lesion types: 1) neurofibrillary tangles 2) coiled bodies 3) tufted astrocytes, and 4) tau threads by one neuropathologist from 1998 – 2013. Tau lesions were scored (0, 1, 2, or 3) in 18 brain regions. This dataset was converted into latent traits using the ltm R Package, which effectively reduces the dimensionality into a single, continuous variable for regression analyses. Linear regression was employed to test for association between latent traits using genome-wide genotyping in Stage 1 (498 PSP cases), and using age and sex as covariates.

Preliminary Results: Stage 1 identified genome-wide significant associations located at chr3q21.3 (CHCHD6), chr7q36.1 (CNTNAP2), and chr11p14.1 (MPPED2).

Conclusions: We have identified genetic variants which associate with clinicopathologic heterogeneity of PSP, having the potential to reveal novel molecular pathways involved in the PSP disease process. Additionally, these newly identified genes associated with PSP pathologic heterogeneity will provide additional information to be included in pathway analyses.
Bristol-Myers Squibb joins CurePSP in the fight against neurodegeneration

CurePSP thanks Bristol-Myers Squibb for its sponsorship of the 2015 International Research Symposium.

We look forward to being a partner in upcoming clinical trials through our Patient Engagement Program (PEP).

Please join us in congratulating Bristol-Myers Squibb for its commitment to leadership in neurodegeneration research.