2016 Hawai‘i Neuroscience Symposium

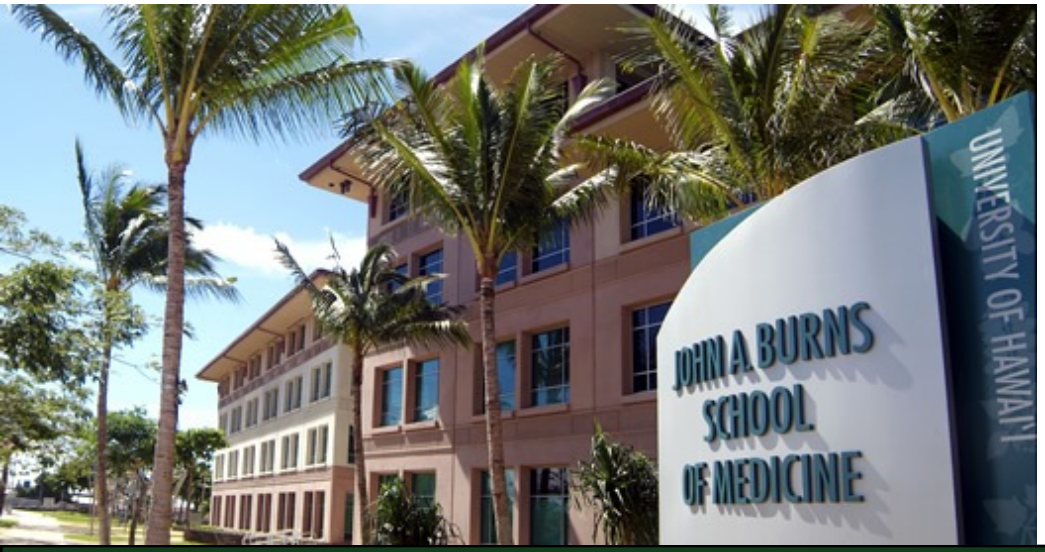
Neuroscience Talent & Innovation in Hawai‘i

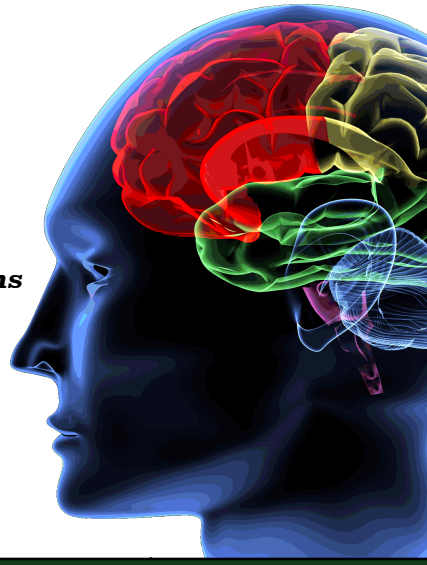
Special Mahalo to
Melia Young, Pascha Hokama, Heather Acidera,
Janet Huynh, Jaclyn Khil, Michael Sonson

Saturday, August 20th 2016

John A. Burns School of Medicine
University of Hawai‘i

651 Ilalo Street
Honolulu, HI 96813





Program Agenda

8:30 am Registration

9:00 am Opening Remarks and "Charge" to Participants
Jerris R. Hedges, MD, MS, MMM
Mariana Gerschenson, PhD

9:10 am Positioning Hawaii for the New Era of Neuroscience
Kore Kai Liow, MD, FACP, FAAN

9:30 am New Era of Neuroscience: Looking into the Future
Raman Sankar, MD, PhD

10:00 am Basic Science: N-terminal Fragment (Light Blue) of Beta Amyloid is Produced by Cleavage of APP by the Action of Beta and Alpha Secretases and its Future Implication for Alzheimer's Disease Therapy
Robert Nichols, PhD

10:30 am Imaging Studies of Brain Development and Aging
Linda Chang, MD

11:00 am Neuroscience Poster Presentations
Pupus & Drinks

11:30 am Clinical Science: Neuroimaging Correlates of Monocyte/Macrophage Infiltration in HIV-infected Individuals: A Cross-sectional Pilot Study Using IV Furomoxytol
Beau Nakamoto, MD, PhD, FAAN

12:00 pm Panel Discussion
- The new era in neuroscience and its implication for Hawaii
- How to position Hawaii in a strategic spot and leverage our unique island characteristics for advancements in neuroscience
- How community partners can work together to increase collaboration and cross-training

Thank you for joining us at the 2016 Hawai'i Neuroscience Symposium

Linda Chang, MD

Linda Chang is a Clinician-Researcher and Professor of Medicine (Neurology) at JABSOM. She received her M.S. and M.D. degrees from Georgetown University, and completed her Neurology Residency and Fellowships in neuromuscular disease and dementia disorders/neuroimaging at the University of California at Los Angeles (UCLA), where she became Faculty and received tenured in the Department of Neurology (1992-2000). She was then recruited to be Chair of the Medical Department at Brookhaven National Laboratory (2000-2004) before relocating to Hawaii. Since 2004, she co-directs the UH-QMC Neuroscience & MR Research Center, with Dr. Thomas Ernst, at the Queen's Medical Center in Honolulu. She conducts clinical-translational research in various neurological disorders, including HIV-associated neurocognitive disorders and methamphetamine or marijuana use disorders, in the settings of brain aging and brain development.

Dr. Chang currently serves on three Editorial Boards, and has been a reviewer for numerous journals, grant review committees and advisory boards. She has published more than 200 scientific papers and 30 book Chapters and conducted many clinical research studies sponsored by the NIH. She also collaborates extensively with other investigators nationally and internationally.

Beau Nakamoto, MD, PhD

Dr. Beau Nakamoto received his MD and PhD from the University of Hawaii John A. Burns School of Medicine. He completed a neurology residency at the University of Utah and returned to Hawaii as a general neurology consultant at Straub Medical Center. He is an Associate Professor at the University of Hawaii with a research focus in the pathogenesis of HIV-associated neurocognitive disorders.

Kore Kai Liow, MD, FACP, FAAN

Kore Kai Liow, MD, FACP, FAAN is director of Hawaii Pacific Neuroscience and Clinical Professor of Neurology at University of Hawaii John Burns School of Medicine. He completed clinical research fellowship at NINDS, NIH in neurophysiology and EEG after finishing neurology training at University of Utah. He specializes in developing new and innovative therapies for some of the most challenging and complex neurological disorders and has served as Principal Investigator or Site PI for over 70 phase I-IV trials sponsored by the NIH, CDC and the industry.

Panel Members

Todd Devere, MD
Chief, Neurology Dept. Kaiser Permanente
Associate Professor, Dept. of Medicine, JABSOM

Henry Lew, MD, PhD
Professor and Chair, Dept. of Communicative Sciences and Disorders, JABSOM

Kamal Masaki, MD
Professor and Chair, Dept. of Geriatric Medicine, JABSOM
Director of Geriatric Medicine Fellowship Program, JABSOM

Jeffery Douglas Miles, MD
Associate Professor, Dept. of Medicine, JABSOM

Lee Ellen Buenconsejo-Lum, MD
Designated Institutional Official (DIO) and GME Director
Professor of Family Medicine & Community Health, JABSOM

Enrique Carrazana, MD
Director, Board of Directors, Marinus Pharmaceuticals

Vivek Nerurkar, MD
Professor and Chair, Dept. of Tropical Medicine, Medical Microbiology and Pharmacology
Director, Biocontainment Facility, JABSOM

Research Presentations

N-terminal fragment (light blue) of beta amyloid is produced by cleavage of APP by the action of beta and alpha secretases and its future implication for Alzheimer's Disease Therapy
Robert Nichols, PhD

Dr. Nichols has had an active, independent research program since 1990, as a medical school faculty member. He has been able to maintain support of this research program through various sources of funding, including R-level NIH grants. The primary focus of his research revolves around synaptic regulation, an area in which he has published consistently for over 25 years. Much of the work has involved complementary in vitro and in vivo approaches. For the last 15 years, he have connected our research on synaptic regulation to Alzheimer's disease. Recently, he have turned to investigating the neuropathological events underlying the earliest stages of Alzheimer's disease and has promising leads on possible translational applications.

Imaging Studies of Brain Development and Brain Aging
Linda Chang, MD

Over the past few decades, advances in Magnetic Resonance Imaging (MRI) techniques allow unprecedented quantitative measurements of brain structure, chemistry, physiology, and function. Therefore, MRI is a powerful tool to evaluate the living brain both in normal brain development, brain aging and in any neuropsychiatric disorders. Given the ever changing brains of humans throughout the lifetime, non-invasive repeated quantitative measurements are needed to accurately assess brain disorders and to monitor treatment effects. Examples of how we used neuroimaging techniques, in relation to other clinical measures, to evaluate and monitor treatment effects in neurological disorders will be presented.

Clinical Science: Neuroimaging Correlates of Monocyte/Macrophage Infiltration in HIV-infected Individuals: A Cross-Sectional Pilot Study Using IV Furomoxytol
Beau Nakamoto, MD, PhD

HIV continues to be a major global public health issue affecting approximately 37 million people worldwide and 1.2 million people in the U.S. Early in the HIV epidemic in the 1980s, a majority of the neurological manifestations of HIV presented as opportunistic infections. Following introduction of effective combination antiretroviral therapies (cART) in the mid-1990s, the neurological complications associated with severe immunosuppression became less common though HIV-associated neurocognitive disorders (HAND) and HIV-associated distal symmetric polyneuropathy persist and are the more common HIV-associated complications a neurologists should be familiar with.

Eradication of HIV form the brain is limited by the selective permeability of the blood-brain barrier that interferes with the bioavailability of cART in the brain. Furthermore, while current cART is extremely effective at restricting active HIV replication, it is ineffective against latently infected (i.e., ability of a pathogenic virus to lie dormant within a cell) macrophages and microglia in the brain. The presence of such HIV reservoirs in the brain leads to a dramatic increase of HIV viral loads if cART is stopped or interrupted. As a result, HIV-infected patients require lifelong cART. Efforts to find a cure for HIV and eradicate HIV reservoirs in the brain are areas of ongoing research.

Poster Presentations

Neuroprotection Action of a Hexapeptide Core Sequence within Beta Amyloid

Forest K, Lawrence JLM, Alfulaij JLM, Arora K, and Nichols RA
Department of Cell & Molecular Biology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI

OBJECTIVE: Alzheimer's disease (AD) is a progressive neurodegenerative disease, manifested as short-term memory loss as well as cognitive decline and language dysfunction. As the current treatments for the disease are minimally efficacious for a limited period of time, identifying the cellular mechanisms underlying AD may elucidate a target pathway(s) for effective treatment. One possible pathway is the neurotoxicity triggered by the accumulation of beta amyloid (Aβ), a short peptide found in the brains of individuals with Alzheimer's disease. Aβ was originally identified in dense neuritic plaques, which are one of several histopathological hallmarks in AD. However, there is now considerable evidence that in normal healthy brains, soluble oligomeric Aβ functions as a neuromodulator. Recently, our laboratory has shown that at low concentrations (pM-nM) a naturally produced N-terminal Aβ fragment (N-Aβ) is twice as effective as full-length Aβ as a neuromodulator, stimulating receptor-linked increases in Ca2+, enhancing long-term potentiation (LTP) and enhancing contextual fear conditioning. In addition, we have shown that N-Aβ reverses the inhibition of synaptic potentiation by full-length Aβ (Aβ42). Preliminarily, we have found that N-Aβ also protects against Aβ42-induced neurotoxicity. We further identified a hexapeptide core sequence within N-Aβ, YEVHHQ (Aβcore), which is found to be equally as effective as N-Aβ in Ca2+ signaling but is not toxic. We have therefore postulated that the Aβcore would have neuroprotective potential. RESULTS and CONCLUSION: Co-treatment or rescue with the Aβcore was shown to protect against Aβ42-induced oxidative stress (ROS) and apoptosis (TUNEL staining; cell survival) in the neuronal cells. In addition, we have identified residues in the Aβcore essential for functional regulation, namely the two successive histidines at positions 4 and 5. Lastly, we have shown that stabilized Aβcore (N-terminal acetylated; C-terminal amidated) and/ or D-amino acid-substituted Aβcore were also effective. SIGNIFICANCE: Through this study, we will gain an understanding of the mechanism by which the Aβcore protects again Aβ-induced toxicity.

Optimal Placement of G1 Electrode in the Median Orthodromic Palmar Nerve Conduction Studies

Devine I[1] and Rubin D[2]
[1]Neuromuscular Division, EMG Lab, Hawaii Pacific Neuroscience, [2]Department of Neurology, Mayo Clinic, Jacksonville FL

INTRODUCTION: Mild carpal tunnel syndrome (CTS) is confirmed by NCSs demonstrating prolongation of the median orthodromic sensory NCS distal latency. The G1 electrode placement is not standardized. Placement at the distal wrist crease could result in a false–negative study if compression is more proximal. OBJECTIVE: To determine the effect of the G1 electrode placement during median palmar orthodromic NCSs on the distal latencies and amplitudes in control subjects and patients with mild CTS. METHODS: The median orthodromic NCS was performed on normal control subjects and subjects with mild CTS. The recording was made with the G1 electrode placed at the wrist crease and 2 cm proximal. Palmar stimulation was performed at exactly 8 cm distal to each G1 electrode site. The difference in the peak distal latencies, amplitudes, and stimulus intensities between the 2 recording sites was calculated. RESULTS: Twenty-three control subjects and 14 patients with mild CTS were studied. The mean absolute latency difference between distal and proximal sites was 0.04 ms (range: 0.9-0.3) in control subjects and 0.06 ms (range: 0.2-0.4) in patients with mild CTS. Compared to the wrist crease, the mean increase in amplitude at the proximal location was 77.8 μV (range: 0-162 μV), 146% (range: 0-471%) in control subjects, and 30.9 μV (range: 3-87 μV), 120% (range: 0-411%) in patients with CTS. SUMMARY/CONCLUSION: Distal latency is not significantly affected by the placement of G1 in the median orthodromic palmar NCS, but the recorded amplitudes are much higher when G1 is placed 2 cm proximal to the wrist crease.

Speakers

Keynote Speaker: Raman Sankar, MD, PhD

Dr. Raman Sankar is Professor of Neurology and Pediatrics and Chief of Pediatric Neurology at the David Geffen School of Medicine at the University of California, Los Angeles. He holds the Rubin Brown Distinguished Chair in Pediatric Neurology. Dr. Sankar is a graduate of the University of Bombay, India. He obtained his PhD from the University of Washington in Medicinal Chemistry and was involved in teaching and research for several years prior to entering Tulane Medical School, where he obtained his MD. He trained in pediatrics at the Children's Hospital of Los Angeles. He completed his training in neurology and pediatric neurology at UCLA. His laboratory research has addressed the mechanisms of seizure-induced injury and epileptogenicity in the developing brain, and is funded by the NINDS, NIH. Dr. Sankar has authored more than 170 research articles, reviews, and book chapters and has served on the editorial boards of Epilepsia and Epilepsy Currents. He is an elected Fellow of the American Academy of Neurology. Dr. Sankar is a member of the Professional Advisory Board of the Epilepsy Foundation. He is a member of the Commission on Neurobiology of the International League Against Epilepsy.

Jerris R. Hedges, MD, MS, MMM

Dr. Jerris R. Hedges, Dean of the John A. Burns School of Medicine (JABSOM) since March 2008, is known nationally as co-author of one of the leading texts in patient care, Roberts and Hedges' Clinical Procedures in Emergency Medicine, now in its sixth edition. Trained as an emergency physician, Dr. Hedges has spent the last three decades contributing to the medical field through his work in clinical care, university teaching, research, and administration. In Hawai'i, he is also recognized as a leader who has strengthened the medical school by building vital bridges between JABSOM's community partners and collaborators. In 2013, he was named "Physician of the Year" by the Hawai'i Medical Association (HMA).

Dean Hedges has a passion for JABSOM's missions to educate and to provide physicians for Hawai'i. He grew up in a rural community, attended a high school with few "academic achievers" and went to community college. From his modest roots, Dr. Jerris Hedges personally understands how important it is that Hawai'i's young people have opportunities to succeed, and how critical is the need to provide physicians and other health care workers in our rural, under-served communities.

Mariana Gerschenson, PhD

Dr. Mariana Gerschenson is the Director of Research and Graduate Education at the John A. Burns School of Medicine, University of Hawai'i at Mānoa. She is responsible for the strategic planning and development of research at JABSOM, research administration activities, and the five graduate (MS and PhD) programs.

Dr. Gerschenson completed her doctoral training at University of Colorado Health Sciences Center in Experimental Pathology. She pursued her postdoctoral work in the Department of Genetics and Molecular Medicine at Emory University School of Medicine in Atlanta, GA. She then worked at the NCI and NHLBI for six-years in Bethesda, Maryland and joined the University of Hawai'i in 2002. Dr. Gerschenson is a tenured Professor in the Department of Cell and Molecular Biology. She leads a federally-funded translational research program to understand the mitochondrial mechanisms of cardiovascular and metabolic disease (including lipoatrophy, insulin resistance, diabetes, and hepatic steatosis) and neurological diseases, e.g. peripheral neuropathy and dementia.

Robert A. Nichols, PhD

Dr. Robert A. Nichols is a tenured Professor in the Department of Cell and Molecular Biology at John A. Burns School of Medicine, University of Hawai'i Mānoa. He earned his PhD in Neuroscience at Stanford University, and completed his postdoctoral fellowship in Neuropharmacology at Yale University and Rockefeller University. He has had an active, independent research program since 1990, and has been able to maintain his research program through various of funding, including R-level NIH grants. His research primarily focuses around synaptic regulation, an area in which he has published consistently for over 25 years. For the last 15 years, he was able to connect his research to Alzheimer's disease and is recently investigating the neuropathological events underlying the earliest stages of Alzheimer's disease.

Miller Fisher Syndrome: A Case Report Highlighting Heterogeneity of Clinical Features and Focused Differential Diagnosis

Yepishin I[1], Allison R[1], Kaminskas D[2,3], Zagorski N[3], and Liow K[2,3]
[1]John A. Burns School of Medicine, [2]University of Hawaii, Honolulu, HI, Hawaii Pacific Neuroscience, [3]Castle Medical Center

Miller Fisher Syndrome (MFS) is a rare variant of Guillain-Barré Syndrome (GBS) that has a geographically variable incidence. It is largely a clinical diagnosis based on the cardinal clinical features of ataxia, areflexia, and opthalmoplegia, however, other neurological signs and symptoms may also be present. Serological confirmation with the anti-GQ1b antibody is available and allows for greater diagnostic certainty in the face of confounding symptoms. A self-limiting course is typical of MFS. The following case report is that of a patient who presented with generalized weakness, somatic pain, inability to walk, and diplopia following an upper respiratory illness. The patient exhibited the classic triad of ataxia, areflexia, and opthalmoplegia characteristic of MFS, but also had less typical signs and symptoms making for a more challenging diagnostic workup. Our suspected diagnosis of MFS was serologically confirmed with positive anti-GQ1b antibody titer and the patient was successfully treated with Intravenous immune globulin (IVIG).

Utility of Neuropsychological and Neuroimaging Data in Diagnosing and Treating Veterans with Traumatic Brain Injury and Co-Morbid Post-Traumatic Stress Disorder

Roskos P[1], Gfeller J[2], Stout J[3], Luo Q[3], Malone T[3], and Bucholz R[3]
[1]Wayne State University, Department of Physical Medicine and Rehabilitation Oakwood; [2]Saint Louis University, Department of Psychology; and [3]Saint Louis University, Department of Neurosurgery

INTRODUCTION: Veterans from Operation Enduring Freedom and Operation Iraqi Freedom have a high incidence (11-23%) of traumatic brain injury (TBI), primarily due to blast exposure. Post-traumatic stress disorder (PTSD) is a common co-morbid diagnosis in this group. Clinicians have been faced with multiple challenges in diagnosing and treating Veterans with these conditions. Research using neuropsychological testing and innovative neuroimaging procedures has been conducted with the goal of improving clinical evaluation and treatment. OBJECTIVE: The aims of this presentation are to (1) provide examples of research conducted involving neuropsychological testing and neuroimaging in veterans with TBI and PTSD and (2) summarize findings from multiple projects with emphasis on clinical implications. Data were collected from a sample of 75 veterans with TBI (V-TBI), 75 civilians with TBI (C-TBI), and 75 age and gender matched healthy controls (HC). Neuropsychological testing included cognitive tests and measures of depression, anxiety, somatization, and PTSD. METHODS: Neuroimaging procedures included resting state and task-based magnetoencephalography, positron emission tomography with computed tomography, magnetic resonance imaging, diffusion tensor imaging, and resting state and task-based functional MRI. Multiple group-comparison analyses were conducted examining neuropsychological and neuroimaging data. RESULTS: Overall results of our analyses showed no differences between groups on the battery of cognitive tests, but there was evidence of greater psychological symptom severity in the V-TBI group. Veterans also showed reduced community functioning compared to their civilian counterparts. Analysis of structural, functional, and neurophysiological imaging data showed evidence for differences in veterans with TBI and co-morbid PTSD, but relationships between imaging data and measures of cognition and behavioral functioning were not consistent. These findings are supportive of other literature in this area. CONCLUSIONS: Implications for clinical practice suggest that multi-modal and multi-disciplinary methods for diagnosing and treating these patients is important. Additionally, environmental and community-based functional issues can be addressed using a rehabilitation model.

Posterior Reversible Encephalopathy Syndrome Post-Partum

Yang MS[1], Liow K[2,3], and Kaminskas D[2,3]
[1]Dept. Behavioral Health, Tripler Army Medical Center, [2]Dept. Neurology, Castle Medical Center, [3]Hawaii Pacific Neuroscience

INTRODUCTION/BACKGROUND: This is the case of a patient presenting with an acute onset of visual changes and hypertension post-partum. The brain MRI showed findings of vasogenic edema in the occipital regions indicating most consistently to a Posterior Reversible Encephalopathy Syndrome (PRES). CASE PRESENTATION: Patient is a 22 years old Caucasian female G1P1 status post spontaneous vaginal delivery at 42 weeks who experienced blurry vision and frontal headaches after her delivery. Her blood pressure ranged from 154/108 mmHg to 170/111 mmHg. Her neurological finding was significant for impaired vision. Her blood count had a hemoglobulin and hematocrit of 11.7 and 36.3, respectively. Her metabolic panel showed potassium of 3.1 mmol/L, creatinine of 0.5 mg/dL, and calcium of 8.3 mg/dL, but otherwise within normal limits else wise. The brain MRI showed patchy signal abnormalities of her occipital lobes. From these findings, she was hospitalized. Her blood pressure was controlled with labetalol and inpatient care, and her vision returned within 48 hours. She was discharged home in stable condition on labetalol 200mg PO BID and a follow up to outpatient neurology. DISCUSSION: PRES is a neurological syndrome with clinical and radiologic features. It shows headaches, visual symptoms, confusion, and seizures, and MRI findings are consistent with vasogenic edema predominantly in the posterior cerebral hemispheres. It most often occurs in the setting of preeclampsia, hypertensive crisis, or with cytotoxic immunosuppressive therapy. Best recommendations to treat this syndrome are to lower the blood pressure and to remove the offending agent if identified. For partum or postpartum, it is recommended to treat as if they have preeclampsia or eclampsia. Fortunately, most recover within weeks and are seen as follow up with neurology and a follow-up brain MRI. CONCLUSION: PRES is a syndrome consisting of clinical signs, hypertension, and radiologic findings. Most cases recover by treating the underlying cause.

Using Fluorescence Microscopy to Determine the Role of Enhanced Kinase Activity and Self-association of Mutant LRRK2 in Parkinson's Disease.

Sanstrum B
University of Hawaii at Manoa John A. Burns School of Medicine
Department of Cell and Molecular Biology (Dr. Nicholas G. James)

Parkinson's Disease (PD) is a common neuromuscular disorder that has grown to affect nearly 2% of the population over 65, however little is known about the molecular pathways that are altered in genetic forms of the disease. One of the more commonly studied genes that have been linked to PD is LRRK2 (Leucine Rich Repeat Kinase 2). Lack of knowledge about the mutations that alter the kinase function of this protein has resulted in a lack of targeted treatment options. Our lab has performed numerous fluorescence-based models to study the protein-protein interactions of LRRK2 in live cells. We have demonstrated that the active form of LRRK2 occurs due to self-association. It was also verified that active LRRK2 dimers function to maintain proper endocytosis and vesicle transport throughout the cell. LRRK2 is also a regulator of smaller secondary proteins such as endophilin A (EndoA), and Rab7 through phosphorylation. However, the specific mechanism behind these interactions is still unknown. This study utilized Fluorescence Fluctuation Spectroscopy (FFS) and Total Internal Reflection Fluorescence (TIRF) microscopy to monitor these protein-protein interactions with LRRK2 in the cytosol and at the membrane. The combination of these assays will allowed us to monitor the dynamic interactions of LRRK2 in a novel paradigm. We found that the G2019S mutant form of LRRK2 creates significantly more higher order oligomers at the cytosol then the wild-type form suggesting that the key regulator of secondary proteins is the number of active LRRK2 dimers rather than increased kinase activity of each individual LRRK2 protein dimer. Confirming that this mechanism is the causal pathway in LRRK2 mediated neurodegeneration in PD will allow for a more precise and quick search for novel targets for advanced therapeutics.

Acute Dystonic Reaction in the Setting of Clozapine Administration

Kaplan AM, Pitts WB, and Fletes FJ
Dept of Behavioral Health, Tripler Army Medical Center

INTRODUCTION/BACKGROUND: Clozapine is an atypical antipsychotic typically administered to psychiatric patients with treatment-resistant schizoaffective disorder, treatment-resident schizophrenia, or for reduction of risk in suicidal thought processes or behavior in patients with schizophrenia or schizoaffective disorder. The incidence of extrapyramidal symptoms (EPS) are exceedingly rare in Clozapine patients, even when compared to other atypical antipsychotics. In fact, dystonic reactions are more often seen upon withdrawal from clozapine and clozapine has been used in the treatment of tardive dyskinesia. Risperidone Depot, trade name Risperdal Consta, is an intramuscular depot given every two weeks, frequently administered to schizophrenic or schizoaffective patients. CASE PRESENTATION: The presented patient is a 44 year old gentleman with long-standing history of treatment-resistant schizoaffective disorder and multiple hospitalizations to the Tripler VA Inpatient Psychiatric Unit for psychosis and suicidality. This patient had received Risperdal Consta prior to admission and consumed additional daily oral risperidone. Upon hospitalization, risperidone was discontinued and the patient was given a trial of Clozapine wherein he experienced an acute buccal dystonic reaction relieved with Benztropine administration. The only other medication that the patient received during his admission was trazodone for sleep. DISCUSSION: Given the exceedingly few reports of clozapine and acute dystonic reactions (ADRs), we examine the role that the patients only other recent medications may play in the development of an ADR in clozapine patients. CONCLUSION: This is one of the few documented episodes of acute dystonic reactions occurring in the setting of Clozapine administration. The recent administration of Risperdal Consta and/or Trazodone may have contributed to the event, leading to the consideration of long-term implications what medications should be co-administered with clozapine in psychiatric patients.

Dementia Types in Patients Evaluated for Randomized Double Blinded Study Investigating Novel Drug Targeting 5HT6 Receptor Antagonist for Alzheimer's Dementia

Young M[1], Wang L[1], Sonson M[1], Borman P[2], Piboolnurak P[2], and Liow K[1,2]
[1]John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI, [2]Center of Healthy Aging and Memory, Neuroscience Research and Clinical Trial Unit, Hawai'i Pacific Neuroscience, Honolulu, HI

INTRODUCTION: Alzheimer's Disease (AD) is currently the 6th leading cause of death in the US and the most common cause of dementia among older people. There is currently no cure for AD. For decades, the mainstays of treatment have been acetylcholinesterase inhibitors & NMDA receptor antagonists, which slows the disease progression, but offer no definite cure. Several novel drugs are being investigated, including drugs that target the 5-HT6 receptor as an antagonist. OBJECTIVE: The Center of Healthy Aging and Memory at Hawai'i Pacific Neuroscience (HPN) is involved in the investigation of the efficacy of a drug that acts as a 5-HT6 receptor antagonist in patients with AD. The principal objective was to characterize the patient population who may be eligible for this study. METHODS: A systematic retrospective review was conducted on patients with dementia at HPN. RESULTS: A total of 1035 patients were identified with dementia. Dementia-related characteristics included cognitive deficits (59.1%), memory loss (50.8%), Parkinsonism (12.5%), and Down syndrome (0.3%). Of the dementia subtypes, the frequency of Alzheimer's was the highest (44%), followed by vascular (31%), Parkinson's (8%), mixed (7%), frontotemporal (5%), and Lewy Body (5%). Majority of the patients with dementia were white (32%), followed by Asians (23%), and Native Hawaiians/Other Pacific Islanders (11%). Comorbidities represented in this cohort included neuropsychiatric disease (17.1%), CVA (7.4%), TBI (6.5%), seizures (52%), cancer (2.3%), substance abuse (2%), and NPH (0.77%). CONCLUSION: The tendency for patients with memory loss to be referred to a neuroscience center for evaluation may account for a higher incidence of TBI and seizures in our cohort population. This finding highlights the importance of neuroimaging for structural abnormalities in patients with memory loss that could be associated with TBI (n=67) or a reversible condition like NPH (n=8), and routine evaluation of memory loss with EEG in patients with probable co-existing seizure disorder (n=57).

Characteristics of Patients with Mild Cognitive Impairment (MCI) seen at the Center for Healthy Aging and Memory for the Hawaii Dementia Prevention Trial (HADEPT)

Hong D[1], Bailey D[1], Shimizu M[1], Moss K[2], Kerr N[2], Harding T[2], Blake S[2], Borman P[1,2], Piboolnurak P[1,2], and Liow K[1,2]
[1]John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, [2]Center for Healthy Aging and Memory, Hawaii Pacific Neuroscience, Honolulu, HI

INTRODUCTION: Mild cognitive impairment (MCI) represents an intermediate state between normal cognition and dementia. This condition may have important prognostic value in identifying patients who may be at an increased risk for developing Alzheimer disease (AD). There is currently no effective treatment for MCI or AD. The Hawaii Dementia Prevention Trial (HADEPT) is looking into the role of diet and supplementation in attenuating the progression of MCI to AD. OBJECTIVE: The Center on Healthy Aging and Memory at Hawaii Pacific Neuroscience (HPN) is conducting a trial investigating the role of nutritional interventions in preventing cognitive decline in patients diagnosed with MCI. The project described here characterizes the patient population diagnosed with MCI who may be eligible for this study. METHODS: A systematic chart review was performed on patients referred from Jan. 2009 and Nov. 2011 for memory loss selected with ICD-10 code F06.7. RESULTS: 145 patients with MCI without a diagnosis of dementia were identified from a database (n = 1700). Among those who have received a diagnosis of MCI, 77.9% had neuropsychological testing on file and 60.7% had an MRI performed as part of their neuropsychological testing. Of these, cerebral atrophy was noted by MRI in 51.1% of the reports. Risk factor frequencies observed in this population included hypertension (56.6%) and hyperlipidemia (53.8%) among others (Figure 1). Current exercise was reported by 37.9% of patients; exercise was unreported in 40.7% of patient progress notes. CONCLUSION: The following aimed to characterize a population of patients with MCI who may be at risk for the development of AD. More than half of the patient population was diagnosed with hypertension and/or hyperlipidemia, which are important risk factors of MCI. Rates of other modifiable risk factors, including tobacco use and lack of exercise were also noted and may serve as possible areas of intervention in delaying the progression of MCI.

Characteristics of Patients with Parkinsonism Being Evaluated for Randomized Study Investigating a Novel Method of Administering Levodopa in Patients with Parkinson's Disease

Khil J[1], Carvalho L[1], Sonson M[2], Borman P[2,3], and Liow K[2,3]
[1]John A. Burns School of Medicine, University of Hawaii, [2]Hawaii Pacific Neuroscience, [3]The Parkinson's Disease, Movement Disorder & Neurodegenerative Diseases Center, Hawaii Pacific Neuroscience

INTRODUCTION: Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder that characteristically causes rigidity, tremor, postural instability and bradykinesia. The prevalence of PD increases with age and is as high as 1% in those that are 65 years and older. Other primary neurodegenerative disorders share many of the features of idiopathic PD and are therefore known as Parkinson-plus syndromes—however, PD remains the most common cause of parkinsonism. OBJECTIVE: The Parkinson's Disease, Movement Disorders & Neurodegenerative Diseases Center at Hawaii Pacific Neuroscience is conducting patient chart reviews for an IRB approved research project testing an innovative new delivery method for a drug used to treat Parkinson's disease patients. METHODS: Retrospective chart review conducted at The Parkinson's Disease, Movement Disorders & Neurodegenerative Diseases Center at Hawaii Pacific Neuroscience between September 2009 and November 2015. Patient chart review included extraction of patient demographics such as age and sex and primary diagnosis. Patient selection was conducted using electronic medical records via eClinicalWorks registry based on ICD-9 codes. RESULTS: Of the 326 diagnosis for parkinsonism, 243 (75%) of them were parkinson-plus syndromes and 83 (25%) of them were parkinson's disease. Of those diagnosed with parkinson-plus syndromes, 162 (67%) of the diagnoses were vascular dementia. CONCLUSIONS: Differentiating Parkinson's plus with idiopathic Parkinson's disease is important as they are treated differently. The long term prognosis, treatment focus and strategy would also differ greatly, thereby early referral to movement disorder neurologist may be important. Given a high proportion of vascular dementia and parkinsonism in the community, this has given us a great opportunity to reduce the prevalence of this cause of parkinsonism in the future. Unlike Parkinson's disease and Parkinson-plus syndromes, vascular parkinsonism is preventable by controlling vascular risk factors. Further research is needed.

Classification and Risk Factors of Post Stroke Patients with Walking Deficits in Double Blind Placebo Controlled Studies with a Selective Blocker of KCNA Voltage-Activated Potassium Blocker

Bailey D[1], Hong D[1], Piboolnurak P[1,2], Kaminskas D[1,2], Adanpo P[2], and Liow K[1,2]
[1]John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, [2]Stroke and Neurologic Restoration Center, Research & Clinical Trial Unit, Hawaii Pacific Neuroscience, Honolulu, HI

INTRODUCTION: Stroke is the 5th leading cause of death in the US, and it is the leading cause of serious long-term disability. Furthermore, walking deficits are a major cause of disability impairing the quality of life of post stroke patients. Physical and occupational therapy are the mainstay of treatment for post stroke walking deficits. Stroke can be classified as either ischemic or hemorrhagic in etiology. In the U.S., the incidence of stroke due to ischemia is 87%, while globally, the incidence of ischemic strokes is 68%. The risk of stroke greatly varies by race-ethnicity, age, and geography. Many studies have characterized risk factors associated with the types of stroke; however, there are limited studies that have examined the association of risk factors in Hawaii's unique patient population. OBJECTIVE: The Hawaii Center for Stroke and Neurologic Restoration at Hawaii Pacific Neuroscience is currently conducting a double blinded placebo controlled study with a KCNA selective potassium channel blocker. The primary objective of this project was to characterize this unique patient population of stroke patients who may be eligible for this study. METHODS: A systematic retrospective chart review was done on stroke patients with walking deficits selected using the following ICD9/ ICD10 codes: 438.2, I69.31 to I69.36. RESULTS: The majority of patients with stroke and walking deficits had ischemic infarcts (81.2%) with a subtype of ischemic strokes being a lacunar infarct (26.3%). Risk factors of hypertension (83.5%) and hyperlipidemia (66.2%) appears to be significantly higher than the general population. Modifiable lifestyle risk factor of current or former smoking (39.1%) is increased, presenting a potential area of preventive interventional strategy. CONCLUSION: Compared to national stroke racial data, patients referred to the Hawaii Center for Stroke and Neurological Restoration at Hawaii Pacific Neuroscience showed a higher population of Native Hawaiian/Other Pacific Islanders (18.8%) due to the unique racial make up of Hawaii's population. Asian patients were found to have a higher frequency of hemorrhagic infarcts as compared to ischemic infarcts, which is consistent with other national stroke data.

Glycosylflavone as Glycogen Synthase Kinase-3β Inhibitor Alleviates Tau Hyperphosphorylation and Amyloid Neurotoxicity

Liang Z[1], Zhang B[1], Su WW[1], Williams PG[2], and Li QX[1]
[1]Department of Molecular Biosciences and Bioengineering, [2]Department of Chemistry, University of Hawaii at Manoa, Honolulu, HI

Alzheimer's disease (AD) is the most common brain disorder that cannot be prevented, cured or even slowed. Hyperphosphorylation of tau proteins in neurons plays a pivotal role in AD pathology. Glycogen synthase kinase-3β (GSK3β) is a key enzyme catalyzing tau hyperphosphorylation. Selective inhibition of GSK3β is a promising therapeutic strategy for AD treatment. As part of our effort screening phytochemicals against a broad panel of kinases relevant to AD, we found a glycosylflavone, isoorientin, from corn silk selectively inhibits GSK3β. Enzyme kinetic studies and molecular modeling demonstrated that isoorientin specifically inhibits GSK3β via a substrate competitive mode, rather than the common ATP competitve mode. Cellular studies further demonstrated that isoorientin effectively attenuates GSK3β-catalyzed tau phosphorylation and is neuroprotective against amyloid-induced tau hyperphosphorylation and neurotoxicity in human SH-SY5Y cells. Isoorientin is a promising lead candidate with a novel mechanism of action for the development of AD pharmaceuticals.

Patient Profiles Referred to the Comprehensive Epilepsy Center to Investigate a Novel Epilepsy Drug with Unknown Mechanism of Action for Partial Onset Seizures

Teng J[1], Beckwith N[2], Acidera H[3], Hokama P[4], Huynh J[5], and Liow K[2,6]
[1]The University of Adelaide, Australia, [2]John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI, [3]University of California, Los Angeles, CA, [4]Swarthmore College, Swarthmore, PA, [5]Creighton University, Omaha, NE, [6]Comprehensive Epilepsy Center, Hawaii Pacific Neuroscience, Honolulu, HI

INTRODUCTION: Epilepsy is the 3rd most common neurological disorder characterized by an abnormal electrical discharge in the brain. Treatment can be classified into three generations of antiepileptic drugs (AEDs) and by their mechanism of action (MOA). These AEDs are prescribed as monotherapy or as polytherapy when the use of a single AED remains ineffective. Because approximately 50% of patients remain seizure free on a single AED, rational polytherapy, the concept of prescribing adjunct AEDs based on their different MOA, is an important consideration in the treatment of epilepsy. OBJECTIVE: The objective was to characterize patients referred to a tertiary referral center being screened for a clinical trial to investigate a novel epilepsy drug with an unknown MOA for partial onset seizures. METHODS: A retrospective chart review was conducted on new patients referred between January and May 2016 using ICD-10 codes for epilepsy. RESULTS: 95 patients were identified. <10% were on first generation AEDs while >60% were on second generation AEDs. 49.5% of patients received monotherapy, 35.8% received polytherapy, and 14.7% were not receiving treatment. 117 drugs were prescribed amongst the observed population. 47.4% of patients took levetiracetam, which acts on synaptic vesicle protein 2A (SV2A). 36.8% were on Na+ channel blockade AEDs, 6.3% on Ca2+ channel blockade AEDs, 11.6% on glutamate blockade AEDs, and 21.1% on GABA enhancing AEDs. 10% of these patients are eligible for the study and will be referred for enrollment into clinical trial. CONCLUSION: Those on polytherapy were prescribed AEDs with different MOAs, with a more widespread use of second generation AEDs. A rational approach to epilepsy treatment, especially for those needing polytherapy, is recommended to avoid inappropriate AED use. A significant proportion of patients (14.7%) were not prescribed or have tapered off AEDs after being diagnosed with nonepileptic conditions. This emphasizes the importance of making correct initial diagnoses with video electroencephalogram (VEEG) for epilepsy patients.

Does Video-EEG use in Hawaii Reduce Healthcare Utilization? A Patient Self-Reported Study

Garcia I[1], Ancheta A[2], Yang MS[3], Kaplan AM[3], Hong D[1], Goo BM[1], Hokama P[4], Taylor E[1], and Liow K[1,5]

[1] University of Hawaii, [2]Maryknoll High School [3]Department of Behavioral Health, Tripler Army Medical Center, [4]Swarthmore College [5]Video-EEG Epilepsy Monitoring Unit (EMU), Hawaii Pacific Neuroscience, Honolulu.

INTRODUCTION: Video EEG in Epilepsy Monitoring Unit (EMU) is often used to diagnose conditions such as Psychogenic Non-epileptic seizures (PNES) from epileptic seizures, iatrogenic causes or an underlying medical condition leading to changes in treatment course and options. It is not known how the change in diagnosis often leads to the utilization of healthcare resources. METHODS: This clinical survey reached out to 94 patients who received an overnight video EEG at the Hawaii Pacific Neuroscience Center in Honolulu, HI. They were asked three questions via phone call about any changes in treatment and medication, reduction in hospital and emergency room (ER) visits, and overall improvement of their care. RESULTS: 44 patients responded, amongst which 15 (34.1%) reported changes to their treatment and medications as a result of the overnight Video-EEG especially for patients with PNES who will no longer need to be on seizure medications. 29 (65.9%) did not report any changes either because the test confirmed the diagnosis with no treatment necessary to be started for suspected PNES or test confirmed the need to continue treatments for epileptic disorders. 14 (31.8%) responded yes to reduction to the hospital and emergency room visits. 29 (65.9%) reported an overall improvement in their care as a result of the overnight Video-EEG EMU. DISCUSSION: Overnight Video-EEG Epilepsy Monitoring can be useful in confirming a diagnosis of suspected PNES or classifying seizure disorder when routine EEG cannot conclusively do so. 1 out of 3 patients, who received an overnight video EEG at the EMU, self-reported that there were changes to their treatment, medications while 2 out of 3 did not result in changes in treatment but had their diagnosis confirmed with the test. 1 in 3 reported a reduction in their health care utilization including hospitalization and ER visits. Majority over 60% noted that there was an improvement in their overall care.

Characteristics of Patients Being Evaluated for a Randomized, Double-Blind, Double-Dummy, Parallel Group Study Assessing the Safety and Efficacy of a Novel B Cell Immunotherapy in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS)

Hong D[1,2], Goo B[2], Lau J[2], Ocol J[2], Oyama D[2], Taylor E[2], and Liow K[1,2]

[1]John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, [2]Hawaii Pacific Neuroscience, Honolulu, HI

INTRODUCTION: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by immune-mediated destruction of myelin with subsequent gliosis. Myelin plays an important role in both insulating axons and facilitating neuronal transmission, and individuals with MS present with several characteristic signs and symptoms, including muscle weakness, impaired coordination and balance, and sensory disturbances. Multiple sclerosis affects an estimated 400,000 people in the United States and 2.5 million people worldwide, with an age of onset between 20 and 40 years. This condition affects nearly twice as many females than it does males. Individuals of northern European ancestry are particularly susceptible. OBJECTIVE: Hawaii Pacific Neuroscience (HPN) if participating in a randomized, double-blind, double-dummy, parallel group study assessing the safety and efficacy of a novel B cell immunotherapy compared to a proven approved therapy in patients with relapsing-remitting multiple sclerosis (RRMS). This project represented a subset of this clinical trial, with the goal of identifying patients who may be eligible for this study. METHODS: A systematic chart review was performed on patients with MS at HPN using ICD-10 G35. Descriptive statistics were performed on this cohort in Microsoft Excel. IRB approval was obtained prior to chart review. RESULTS: The demographic of the identified patients aligns with previously reported epidemiological data for MS for age of onset, female to male ratio and ethnicity. The average age of onset for HPN MS patients was 34.9 ± 12.5 years, falling into the average twenty to forty-year old age range. There are almost twice as many females (31) as males (15) that have MS and the majority of MS patients are Caucasian, which agrees with the high risk groups for MS. CONCLUSIONS: Due to the limited patient population however, we are not able to make statistical conclusions to compare the sample to national averages.

Characteristics of Patients Being Screened for a Clinical Trial to Investigate the Synthetic Amino Acid Precursor, Prodrug to Neurotransmitter Norepinephrine Capable of Crossing the Protective Blood–Brain Barrier in Treatment of Orthostatic Hypotension in Patients with Neurodegenerative Disease

Khil J[1], Acidera H[2], Hokama P[2], Huynh J[2], Ota M[2], Borman P[1,2], Piboolnurak P[1,2], and Liow K[1,2]

[1]John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, [2]Hawaii Pacific Neuroscience, Honolulu, HI

INTRODUCTION: Orthostatic hypotension (OH) is a fall in systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing. The prevalence of OH increases with age and affects approximately 20% of patients above the age of 65 years. OH results from both neurogenic (NOH) and nonneurogenic causes. This study focused on patients with OH due to neurodegenerative disease like Parkinson's disease, multiple system atrophy, and Lewy Body Dementia. OBJECTIVE: The primary objective of this study was to determine the prevalence of OH in Hawaii Pacific Neuroscience patients screened for a clinical trial investigating a prodrug used to treat NOH patients at the Center for Healthy Aging, Memory and Brain Health and the Center for Parkinson's Disease, Movement Disorders and Neurodegenerative Diseases. All OH patients enrolled in the clinical trial have to meet the inclusion criteria. METHODS: The screening procedure required blood pressure measurements after the patient was supine for 5 minutes, immediately after the patient stands and after the patient has been standing for 3 minutes. RESULTS: Of the 108 screened patients, 7 patients tested positive for OH. Only 2 cases were previously diagnosed indicating the remaining cases were undiagnosed. 3 cases could have been attributed to autonomic failure associated with Parkinson's disease. CONCLUSION: OH is common in patients with neurodegenerative diseases, especially those on medications related to their primary neurological diagnosis such as PD. Therefore, it is important to ask patients about symptoms of OH and conduct appropriate blood pressure measurements. Proper medication management at neuroscience centers should also be conducted to prevent missing the diagnosis of OH. Results of the clinical trial will be made available at a later time.

Treatment Modalities and Demographics of Epilepsy Cases Referred for Study Investigating Voltage Gated Sodium Channel Blocker as Adjunctive Treatment of Partial Onset Pediatric Seizures

Carvalho L[1], Khil J[1], Knight T[2], Sonson M[2], Devine I[2], and Liow K[1,2]

[1]John A. Burns School of Medicine, University of Hawaii, [2] Hawaii Pacific Neuroscience

INTRODUCTION: Epilepsy in the pediatric population can be treated with antiepileptic drugs, however, it is estimated that 20-30% of patients will remain refractory to medication. OBJECTIVES: To characterize the pediatric and adolescent patients diagnosed with partial onset epilepsy in Hawaii who may benefit from an ongoing clinical trial of a voltage-gated sodium channel blocker. METHODS: Retrospective chart review was performed on 1450 patients evaluated at Hawaii Comprehensive Epilepsy Center and Pediatric Neurology Division, both at Hawaii Pacific Neuroscience, between September 2009-November 2015 via eClinicalWorks registry. Demographic information was extracted and patient information was used to identify those who met the inclusion criteria for the trial. Inclusion criteria was defined as: age 2 - 17 years, currently taking 1-3 antiepileptic drugs, simple partial seizure or complex partial seizures with or without secondary generalization, confirmed diagnosis of partial onset epilepsy as defined in the classification of seizures of ILAE (International League Against Epilepsy) with documented EEG performed at the Neurophysiology Laboratory of Hawaii Comprehensive Epilepsy Center, documented EEG recording with focal abnormalities and without generalized epileptiform activities, and documented seizure frequency of > 4 seizures in a month. RESULTS: Of the 1450 epilepsy patients evaluated at the Comprehensive Epilepsy center at Hawaii Pacific Neuroscience, 34 patients were between 2-17 years of age. Of the 34 patients, 35.5% (n=12) were not currently taking antiepileptic medication. Partial onset seizures (including simple partial, complex partial, and secondarily generalized seizures) comprised 61.8% (n=21) of the number of total diagnoses of epilepsy. Of these, 8.8% (n=3) were refractory, and 0% had a documented seizure frequency of >4 seizures per month. CONCLUSIONS: Of the 34 patients who met criteria by age, none fulfilled inclusion criteria based on a required seizure frequency of >4 seizures per month, a medication regimen of 1-3 antiepileptic drugs, and a confirmed diagnosis of partial onset epilepsy. 35.3% of patients are not taking any medications due to the nature of pediatric seizures, as some may not need long term treatments for conditions such as Rolandic Epilepsy. In order to find patients who meet the criteria for the ongoing clinical trial, further investigation is required.