1. Understanding Drug-Resistant Epilepsy in Ethnically Diverse Patients
   Bryce Kalei Chang, Krista Chang, Xiaoting Liu, Gen Slattery, Huanli Hu, Yi Yu, William Lew, Kore Kai Liow

2. Sense of Place: A History of Neurology in Hawaii
   William Harris, Heather Miura, Nicole Anzai, Selin Kutlu, Christina Tse, and J. Douglas Miles

3. Understanding Patients With Epilepsy that Use Unconventional Treatments: Medical Marijuana Use in Hawai‘i
   Richard Ho, Jingyi Zhang, Carol Lu, Breenne Fong, Karlyn Oura, Ava Shipman, Huanli Hu, Amara Appana, Evan Minami, Georgenia Slattery, Ann-Janin Bacani, Enrique Carrazana, Kore Kai Liow

4. Geriatric Syndromes and Inflammation in Older HIV-infected Adults with Cognitive Impairment
   Kalei R.J. Hosaka, Lishomwa Ndlovu, Meredith Greene, Shireen Javandel, Thomas Premeaux, Isabel E. Allen, and Victor Valcour

5. Hypertension as a risk factor for Alzheimer's disease: A bivariate logistic regression of patient demographics in Hawai‘i
   Tamara Ohta, Geetika Patwardhan, Daniel Omura, Sheaffer Rafto, Raelynn Chu, Ann-Janin Bacani, Kore Kai Liow

6. Optimizing the MGMT Assay for Human Glioma Tissues
   Jana Wieland, John Silber
Understanding Drug-Resistant Epilepsy in Ethnically Diverse Patients

Bryce Kalei Chang, Krista Chang, Xiaoting Liu, Gen Slattery, Huanli Hu, Yi Yu, William Lew, Kore Kai Liow

INTRODUCTION: Drug-resistant epilepsy (DRE)—defined as the failure of two appropriate, well-tolerated anti-epileptic drug (AED) regimens to achieve seizure freedom for the patient—affects 20-40% of patients with epilepsy and largely contributes to the burden of $12.5 billion spent yearly on epilepsy care. Patients with DRE suffer increased seizure-related morbidity and mortality, and decreased quality of life reflected in lower academic achievement, inability to drive, unemployment, and social stigma. Currently, neurosurgery remains the only possible cure for patients with DRE. A better understanding of risk factors for DRE is required to facilitate treatment discovery.

Multiple studies in predominantly white Scottish, Finnish, and American patients have shown the most important risk factor for DRE is failure of the first AED regimen to achieve seizure freedom. Studies in white Parisian and Finnish patients demonstrated symptomatic focal epilepsy is more difficult to treat than idiopathic generalized epilepsy. Other comorbidities associated with DRE in predominantly white Scottish and American patients include recreational drug use, depression, and obstructive sleep apnea.

This study investigates risk factors for DRE in an ethnically diverse sample of epilepsy patients as a step toward developing preventive strategies and therapies serving minority patients.

METHODS: Patients with a diagnosis of epilepsy were identified at a Hawaii-based neuroscience practice from 2014 to 2018 using ICD-10 codes for epilepsy. A total of 475 patients were included in the final sample. Data were analyzed using Statistical Package for the Social Science.

RESULTS: The number of AEDs, focal epilepsy, generalized epilepsy, smoking, COPD, age, and ethnicity were significantly associated with DRE. The logistic regression model was significant $\chi^2(8)=5.361$, $p=0.718$ (Hosmer and Lemeshow Test of good fit), explained 46.6% (Nagelkerke $R^2$) of variance in DRE, and correctly classified 79.6% of cases (sensitivity: 75.9%, specificity: 81.6%, positive predictive value: 69.7%, negative predictive value: 85.9%).

CONCLUSION: This study showed that a patient’s number of AEDs, type of epilepsy, age, and ethnicity affect the likelihood of having DRE in ethnically diverse patients. Patients on multiple AEDs were twice as likely to have DRE. Patients with focal epilepsy were 13 times more likely to have DRE, and patients with generalized epilepsy were 5 times more likely to have DRE. Vascular lesions, vascular malformation, and multiple temporal sclerosis in localization-related epilepsy is thought to contribute to DRE. Older age, Asian ethnicity, and black ethnicity were all significantly associated with increased likelihood of DRE. Combinations of these factors may help identify patients who are not likely to benefit from current medical treatment.

The results of this study have important care implications for the 20-40% of epilepsy patients who experience DRE, especially ethnic minorities associated with higher likelihood of DRE.
Sense of Place: A History of Neurology in Hawaii

William Harris, Heather Miura, Nicole Anzai, Selin Kutlu, Christina Tse, J. Douglas Miles

John A. Burns School of Medicine, University of Hawai’i at Mānoa, Honolulu, HI

Little is known about the birth and early development of neurology in Hawai’i. What has taken place in the last century that has ultimately converged on the 45 practicing neurologists in our state today? With an aging population, Hawai’i’s demand for neurologists, like any other specialty, is expected to increase. However, the supply of practicing neurologists in Hawai’i is declining. The low number of neurologists may be due to unique demands such as rural setting, limited funding, and fewer support services. Another possible factor that may influence the supply of neurologists in Hawai’i is that JABSOM does not currently have a third-year rotation or residency program in neurology. We seek to better understand the benefits and limitations of practicing neurology in Hawai’i, and to identify possible barriers that may contribute to the physician shortage specific to neurology in this state. This survey will assess specific strengths, challenges, and disparities within the field of neurology as a means of identifying ways to improve the practice environment in Hawai’i to the benefit of current and future neurologists. This investigation represents a collaboration between faculty and students, in consultation with alumni and neurologists in the community, working together to identify the past, present, and future state of neurology in Hawai’i.
Understanding Patients With Epilepsy that Use Unconventional Treatments: Medical Marijuana Use in Hawai'i

Richard Ho1,2, Jingyi Zhang1,2, Carol Lu1,3, Breanne Fong1,4, Karlyn Oura1,5, Ava Shipman1,6, Huanli Hu1,2, Amara Appana1, Evan Minami1,7, Georgenia Slattery1,10, Ann-Janin Bacani1,8, Enrique Carrazana1, Kore Kai Liow1,9

1Clinical Research Center, Hawaii Pacific Neuroscience, Honolulu HI, 2University of Hawaii at Manoa, Honolulu, HI, 3Johns Hopkins University, Baltimore, MD, 4University of Rochester, Rochester, NY, 5Iolani School, Honolulu, HI, 6Wellesley College, Wellesley, MA, 7University of Southern California, Los Angeles, CA, 8Chaminade University, Honolulu, HI, 9John A. Burns School of Medicine, University of Hawaii Honolulu, HI, 10State University of New York at Geneseo

INTRODUCTION: Epilepsy is a neurological condition in which a patient has unprovoked and recurrent seizures. 1 in 26 people in America will develop epilepsy throughout their lifetime. Although, currently there is no cure for epilepsy, there are medications and surgical procedures that alleviate seizure manifestations. In the recent decade, there has been a surge in the use of cannabis-related products as potential treatments for epilepsy, particularly in children. Currently, the most common forms of cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD). Both forms of compounds are found to have anticonvulsant effects that can benefit epileptic patients. However, due to the undesired psychoactive effects and risk of abuse found in THC, researchers have shifted to focus on developing treatments of epilepsy from CBD. CBD has a better defined and superior anticonvulsant profile devoid of psychoactive and abuse liabilities. The difference in these two chemicals separates recreational and medical marijuana. Recreational marijuana contains 10-20% THC and traces of CBD. Meanwhile, medical marijuana contains highly concentrated CBD in the form of an oil that can be ingested orally or inhaled through vapor. Currently, limited data is available to support medical marijuana as an alternative solution to AEDs. Researchers are still in search of the most beneficial ratio of CBD: THC to maximize treatment benefit and minimize adverse effects. OBJECTIVES: The object of this study is to analyze a sample of patients with epilepsy using cannabis/marijuana-related products and determine factors that drove these patients into their usage of marijuana, by comparing between patients with epilepsy using recreational marijuana and medical marijuana in Hawaii. METHODS: Data was extracted from patient charts using ICD-10 codes for epilepsy. Patients were grouped by ethno-culture and clinical history was reviewed. The following were analyzed: type of epilepsy, type of marijuana product, seizure frequency, substance use, depression, anxiety, quality of life, and use of AEDs. RESULTS: Of the patients included in this study (n=1131), 57 patients with epilepsy (PWE) were found to use marijuana/cannabis related products. Severity of patient’s epilepsy is compared between recreational and medical marijuana PWE through seizure frequency and types of epilepsy. Depression, anxiety, and number of AED’s used were compared between recreational marijuana and medical marijuana PWE. CONCLUSIONS: This study shows that PWE using medical marijuana were found to have more severe cases of epilepsy. In most cases, these patients have higher frequencies of seizure and intractable epilepsy. Patients are shown to have severe risks of alcohol abuse, higher numbers of AED’s use, and depression or anxiety. There is a paucity of scientific facts that are known about medical marijuana as a form of treatment in epilepsy. The findings of this study not only provide new knowledge in this area of research but also provide information for physicians to understand PWE that use unconventional methods and provide better care and treatment for future patients.
Geriatric Syndromes and Inflammation in Older HIV-infected Adults with Cognitive Impairment

Kalei R.J. Hosaka¹, Lishomwa Ndhlovu¹, Meredith Greene², Shireen Javandel³, Thomas Premeaux¹, Isabel E. Allen³, and Victor Valcour², ³

¹University of Hawaii John A. Burns School of Medicine, ²University of California, San Francisco, Division of Geriatrics, ³Memory and Aging Center, Department of Neurology

Background: Nearly half of the HIV-infected population in the US is now older than fifty years of age with at least 6% over the age of 65. Between 35-50% live with mild to moderate cognitive impairment. Older HIV-infected adults also have a substantial burden of non-AIDS medical conditions (HANA) and are at risk for frailty, geriatric syndromes, and early mortality compared to HIV-uninfected peers. We sought to define the magnitude of geriatric conditions and multimorbidity in HIV-infected adults over age 60 who are living with symptomatic cognitive impairment. In a subset of participants, we examine associations between these geriatric conditions and inflammation.

Methods: We recruited 141 participants from the HIV Elders Study at UCSF between 2013 and 2017 who were HIV-infected, virally suppressed, 60 years or older, and clinically diagnosed with Mild Neurocognitive Disorder (MND). We conducted standardized assessment of geriatric conditions and everyday function and investigated multimorbidity burden using the Veterans Aging Cohort Study (VACS) index.

Results: Among HIV-infected older adults with MND 58% report incontinence, 55% meet criteria for pre-frailty, and a substantial proportion report dependence on iADLs (52%) or ADLs (41%). The mean (SD) VACS Index score is 33 (14), suggesting a 13.8% 5-year all-cause mortality risk. Among geriatric conditions examined, the VACS index associates with neopterin, a marker of monocyte activation (p<0.010). No associations were found between neopterin or soluble (s) CD163 and other geriatric conditions.

Conclusions: HIV-infected older adults with symptomatic cognitive impairment carry a substantial burden of other geriatric conditions. Our work supports the need for comprehensive geriatric systems of care for cognitively impaired individuals aging with HIV.
Hypertension as a risk factor for Alzheimer’s disease: A bivariate logistic regression of patient demographics in Hawai’i

Tamara Ohta¹, Geetika Patwardhan², Daniel Omura³, Sheaffer Rafto⁴, Raelynn Chu⁴, Ann-Janin Bacani⁵, Kore Kai Liow⁶,⁷

¹University of Portland, Portland, OR, ²University of Hawaii, Manoa, Honolulu, HI, ³Wheaton College, Wheaton, IL, ⁴Boston University, Boston, MA, ⁵Chaminade University of Honolulu, Honolulu, HI, ⁶Memory Disorders Center, Hawaii Pacific Neuroscience, Honolulu, HI, ⁷Clinical Research Center, Hawaii Pacific Neuroscience, Honolulu, HI

INTRODUCTION: Alzheimer’s disease (AD) is the most common neurodegenerative disorder, affecting over 12 million individuals worldwide. AD is thought to result from the accumulation of amyloid beta protein plaques and Tau neurofibrillary tangles, which contribute to its characteristic progressive dementia. Treatments have been focused on the prevention of possible indicators and comorbidities associated with AD, such as hypertension, but the literature has been mixed with regard to the relationship that exists between blood pressure and AD.

OBJECTIVE: To determine whether hypertension and dementia of the Alzheimer’s type are comorbid with one another.

METHODS: A retrospective chart review was conducted at the Memory Disorders Center at Hawaii Pacific Neuroscience between January 2011 and August 2018. Patients diagnosed with dementia were filtered through eClinicalWorks using the trial’s inclusion and exclusion criteria. A bivariate logistic regression was used to determine which combination of variables is correlated with having AD.

RESULTS: Asians (30.8%) and Whites (20.2%) contributed the greatest percentage of individuals with AD and hypertension. Hypertension and hypothyroidism were the top two comorbidities found in patients with AD. The bivariate logistic regression showed that older individuals are more likely to have both hypertension and AD, so age is a significant (p<0.001) confounding variable to age and hypertension.

CONCLUSION: The results of the bivariate logistic regression showed that when age was factored in, all other variables were no longer significant because age increases the likelihood of having both AD and hypertension, confounding any previous associations.
Optimizing the MGMT Assay for Human Glioma Tissues

Jana Wieland¹,², John Silber PhD²

¹John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; ²University of Washington, Seattle, WA

The DNA repair protein O⁶-methylguanine-DNA methyltransferase (MGMT) is a known mechanism of resistance to alkylating agent-based treatments for human malignant gliomas, including current radiotherapy with temozolomide, the contemporary standard of care. The usual clinical methods for determining tumor MGMT content (e.g., immunohistochemistry) are limited by insensitivity and the association of surrogate measures of MGMT gene expression (e.g., CpG methylation status of MGMT promoter) with MGMT activity is not quantitative. The biochemical assay of MGMT has the advantages of being conceptually simple and relatively easy to perform. The assay exploits the fact that MGMT acts by transferring a methyl group from the O⁶ position of guanine and covalently binding it to a cysteine in the protein’s active site. This mechanism produces native guanine in DNA and an inactive methyl modified protein. By using exogenous DNA containing ³H-labelled O⁶-methylguanine, it is possible to estimate the number of MGMT molecules in a volume of tumor homogenate. While biochemical assays circumvent the problems associated with other methods of determining MGMT content, it is seldom employed, even in laboratory settings, primarily because of the absence of a standard, optimized assay. The goal the project is to establish a standardized assay that is optimal for determining activity in homogenates of glioma tissue. To meet this objective we will;

1. Establish basic biochemical parameters by determining
   i. linearity with amount of extract assayed and incubation time
   ii. lower limits of detection
   iii. reproducibility between assays
   iv. effect of repeated freeze-thawing on extract activity.

2. Examine possible confounding factors found in tissue homogenates by determining the effect on activity of
   i. iron from blood on the re-dox state of cysteine
   ii. salt concentration
   iii. tumor DNA.

Suppression of the glioma DNA repair capacity has the potential to lead to the development of new therapies that can dramatically improve the prognosis for individuals with malignant gliomas.