

GLOBAL BRAIN 2016 TALK ABSTRACTS:

Principal Investigator: Dr. Mustafa al'Absi, Professor
Max & Mary LaDue Pickworth Chair
Director, Duluth Medical Research Institute (DMRI)
University of Minnesota Medical School

Title: The Khat Research Program (KRP): Progress and Achievements

The international Khat Research Program (KRP) is a multidisciplinary research and training initiative focusing on khat, concurrent use of other substances, and mental health comorbidity. The program involves nine universities in five countries. Accomplishments to date include 1) six training workshops, 2) two institutional review boards (research ethical committees), 3) five human clinical/laboratory studies, 4) eight community surveys, and 5) two acute experiments in primate animal models. The program has published 34 peer-reviewed articles, conducted five research symposia, and presented 28 scientific presentations in regional and international conferences. Primary research findings so far indicate that chronic exposure to khat leads to dependency, cognitive impairments, exacerbation of psychiatric symptoms, and dysfunction in emotional regulation and the stress response. In addition, KRP's leading investigators have been keen to promote capacity building and launched the Africa and Middle East Congress on Addiction (AMECA). AMECA is an outreach initiative focusing on addiction and mental health comorbidity. AMECA has already conducted three conferences (in Ethiopia, Morocco, and Botswana) and one symposium (Morocco). The fourth AMECA conference is planned to take place in Monastir, Tunisia, in December 2016. These regional and international outreach activities should strengthen capacity for research and services to address substance use disorders and comorbid mental health problems in Africa and the Middle East.

Principal Investigator: Birbeck, Gretchen

Name of Presenter: Izukanji Sikazwe

Talk Title: Cohort of HIV-Associated Seizures and Epilepsy in Zambia

Institution Affiliation: Center for Infectious Disease Research in Zambia

Cohort of HIV-Associated Seizures and Epilepsy in Zambia (CHASE)

Background:

Acute seizures in HIV-infected individuals are often the initial presentation of serious, underlying neurological disease that may be the result of opportunistic infections (OIs), adverse reactions to antiretroviral medications, or other metabolic derangements requiring intervention. Zambia has an HIV prevalence of 13.3% and an epilepsy prevalence rate of 14.5/1000 people. The risk for recurrent seizures among HIV-infected people, who experience new onset seizure, is unknown, with little epidemiological data available to guide the clinical decision making of whether or when to start anti-epileptic treatment.

CHASE I Award #: 1R21NS073509:

Aims:

- To characterize seizure etiology and recurrent seizure risk in HIV-infected Zambian adults who experience new onset seizures and
- To obtain pilot data to determine the feasibility of a prospective cohort study to assess clinically relevant interactions between anti-retroviral therapy (ART) drugs and anti-epileptic drugs in Zambia.

Methods:

Study implementation was July 2011 – June 2014. HIV-infected adults presenting with new seizures within 2 weeks of their index seizure were screened for enrolment into the study. In addition to baseline history and physical examination, laboratory, neuroimaging, electroencephalogram and neuropsychiatric assessments were done to elucidate the seizure etiology and long-term effect during the follow-up period.

Results: Over a period of 22 months, 352 participants were screened, with 95 enrolled and followed up for a mean duration of 293 days. Their mean age was 37 years, 57% (54) were male, median CD4 111 cells/ μ l, 32% (30) on ART, with 83% had Karnofsky >50. CSF PCR studies in 61 participants identified pathogens such as EBV (28%), JCV (4%), MTB (5%), VZV (5%) and CMV (5%). Cryptococcus was identified in 14% of participants through India ink or cryptococcal antigen test. Multiple pathogens present in varying combinations were seen in 20% of participants. Seizure etiology remained unknown in 17% of participants despite extensive work up. During the follow up period, 24% had recurrent seizures, while 39% died.

Conclusions: Seizures in HIV-infected adults in Zambia are associated with significant morbidity and mortality. Multiple infectious etiologies and/or metabolic abnormalities account for the majority of cases. Seizure recurrence is common raising the need for the availability of AED that can be used in HIV-infected patients on ART.

CHASE II Award #: R01NS094037

Award Period: Sept 15 2015 – Aug 31 2020

Aims:

- a. To delineated seizure etiology, determine the risk of seizure recurrence, and identify risk factors for epilepsy development and death in HIV infected children in an urban and rural setting as well as HIV infected adults in a rural population.
- b. To conduct an exposure-control study of adults with epilepsy and HIV on EI-AEDs and ARVs vs. people on ARVs only matched on ARV regimen and duration of ARV treatment to compare the proportion of people with viral genotypes indicative of ARV resistance mutations
- c. To build capacity of Zambian professionals by supporting Masters level training Public Health as well as establish a Radiology MMed training program with a curriculum

Principal Investigator: Bielas, Stephanie

Title: “Genetic Diagnosis of Heritable Neurodevelopmental Disorders with Exome Sequencing”

Presenter: Stephanie Bielas

Talk Title: Genetic Diagnosis of Neurodevelopmental Disorders with Exome Sequencing in India

Institutional affiliation: University of Michigan School of Medicine

Grant Number: 1R21NS094047-01, Bielas & Girisha,

ABSTRACT

Anju Shukla¹, Anshika Srivastava², Arul M. Chinnaiyan³, Katta M Girisha¹, Stephanie L. Bielas²

1. Department of Medical Genetics, Kasturba Medical College, Manipal University, Manipal, India
2. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA
3. Howard Hughes Medical Institute, Michigan Center for Translational Pathology, University of Michigan, Ann Arbor, Michigan, USA

The incidence of children with inherited neurodevelopmental disorders (NDD) is high in low- and middle-income countries (LMIC) and becoming an enormous burden on health care resources. While individual inherited NDD are rare, in aggregate they affect millions of people. Whole exome sequencing (WES) has risen to the forefront of genetic testing in High and Middle Income Countries (HMIC) based on its potential to uncover genetic causes responsible for inherited NDD conditions, while circumventing bottlenecks caused by candidate gene screening approaches. An ongoing collaboration between University of Michigan Medical School, USA and Kasturba Medical College at Manipal University, India is establishing infrastructure to use WES for genetic diagnosis of NDD in the Department of Medical Genetics at Manipal University. To address common hurdles in adopting this technology we (1) have identified reliable and timely sequencing options, (2) continue to build WES bioinformatic analysis capabilities, and (3) are supplementing education of medical genetics and genetic counseling professionals. Through these efforts we have performed trio-WES on 10 families, identifying 5 novel alleles for known genetic causes of NDDs. No pathogenic variants were identified in 5 probands. The diagnostic success with this small sample size is on par with that for clinical WES in HMIC. We look forward to building on every aspect of this experience. Our newly established bioinformatics infrastructure will allow WES data to be periodically reanalyzed in light of new genetic findings, allowing us to improve the rate of genetic diagnostic over time. This data will also benefit genetic diagnosis of inherited diseases and genetic testing policy in India nationally

Principal Investigators: **Michael J. Boivin (USA) & Noeline Nakasujja (Uganda)**

Title: Computerized Cognitive Rehabilitation in Children after Severe Malaria.

Presenter: Michael J. Boivin, PhD, MPH

Grant Number: R01HD064416

Grant Title: Computerized Cognitive Rehabilitation in Children after Severe Malaria.

Presentation Title: A randomized controlled trial of the neuropsychological benefits of computerized cognitive rehabilitation training in Ugandan children surviving severe malaria.

Michael Boivin^{1,2}, Noeline Nakasujja³, Alla Sikorskii¹, Horacio Ruiseñor²-Escudero¹, Itziar Familiar-Lopez¹, Robert O. Opoka³, Bruno Giordani²

¹Michigan State University, ²University of Michigan, ³Makerere University, ⁴University of Minnesota

INTRODUCTION: The principal study aim was to evaluate the effectiveness of computerized cognitive rehabilitation training (CCRT) in improving neuropsychological performance and psychiatric outcomes in Ugandan children who survive severe malaria.

METHODS: 150 Ugandan CNS malaria survivors (two years after illness) and 150 non-malaria children 5 to 12 years were randomly assigned to 3 treatment arms (56 Captain's Log CCRT, 55 active controls, 52 passive controls). The Kaufman Assessment Battery for Children, 2nd ed. (KABC-2), Tests of Variables of Attention (TOVA), CogState computerized cognitive tests, the Behavior Rating Inventory for Executive Function (BRIEF), and the Achenbach Child Behavior Checklist (CBCL). These tests have been administered before and after an 8-week training period of 24 computer sessions.

RESULTS: CNS malaria survivors receiving CCRT showed significant improvements (compared to passive controls) on KABC-II Learning, KABC-II Conceptual Reasoning, CogState working memory, BRIEF Behavior Regulation Inventory, and Achenbach CBCL psychiatric symptoms. They also showed marginally significant improvements on the TOVA overall performance index (ADHD score). Non-malaria children receiving CCRT (compared to control groups) showed significantly greater improvement on KABC-II Story Completion, TOVA simple Response Time (an attention measure), and CogState maze chase (visual-motor tracking/attention), and CogState maze learning. Both CCRT and active controls had similar levels of improvement across the 24 training sessions using the Captain's Log internal evaluator outcomes, indicating comparable fidelity of training for the two computer intervention groups.

CONCLUSIONS: CCRT has proven effective and sustainable in rehabilitation for severe malaria. Comparable gains were observed for both the full Captain's Log CCRT and limited Captain's Log (active control). CCRT and computerized cognitive tests are viable for evaluating and treating brain-injured children in resource-poor settings.

PI name and Country: Hélène Carabin, USA

Major foreign collaborator name and country: Athanase Millogo / Burkina Faso

Presenter name: Hélène Carabin

Grant number: R01NS064901

Grant title: EFECAB: improving pig management to prevent epilepsy in Burkina Faso

Background and objective: Neurocysticercosis (NCC) is believed to be the leading cause of late onset epilepsy in developing countries. Yet, there is no agreement as to which type of intervention is most cost-effective and sustainable to control the infection. The overall objective of EFECAB, a community-based randomized controlled trial, is to estimate the effectiveness of an educational program, developed using a PREDECE-PROCEED approach, to control human and porcine cysticercosis. The long term goal is to control NCC-associated neurological disorders.

Current research activities: Here are some of our ongoing activities:

1) Estimating the effectiveness of our intervention: We are now cleaning the final results of the human and pig serological and the questionnaire data. The human serological data is the primary outcome to determine the effectiveness of EFECAB. We are frantically working at matching participants and households where pigs are raised to all 3 visits and to make sure that their answers to the questionnaires are coded in a standard manner. We already have some preliminary data on the effectiveness of the program on modifying knowledge, attitude and practices regarding cysticercosis in our population. This will result in at least two publications.

2) Estimating the proportion of NCC among people with neurological disorders: We are finalizing determining the agreement between the three radiologists who read all 241 CT-scans and are talking with them so that they reach a consensus on the presence of NCC lesions. The classification of calcified lesions as being NCC can be very difficult but we want to be as confident as we can about our results before we publish. Planned publications include the proportion of NCC among people with epilepsy and headaches and a description of lesions linked with severe chronic headaches in this population.

3) Estimating the sensitivity and specificity of the AgELISA and EITB tests to detect cysticercosis: A sub sample of sera, already analyzed with the Ag-ELISA, were sent to the CDC for analysis with the rT24 test and the LLGP-EITB. The samples had initially been analysed only with the rT24 and the results appeared to be inconsistent with the previous findings in the literature. We are therefore retesting these samples with both test to ensure validity. The presence of antibodies will give us information on exposure of the participant/patient to parasite eggs in addition to the information that the AgELISA gives us on current infection. Ultimately, this information will help us better classify patients as possible or definitive NCC cases. This will result in at least one publication and contribute to others.

4) Estimating the prevalence of *T. hydatigena* and *T. solium* in pigs: The AgELISA which we are using to test for cysticercosis in pigs is known to interact with *T. hydatigena*. In the absence of data on the prevalence of *T. hydatigena* in pigs in Burkina Faso, we conducted an additional study in the abattoir at Koudougou to estimate the prevalence of this parasitic infection and to assess the level of reaction to the AgELISA test we are using to detect cysticercosis. These analyses will result in 1-2 publications.

5) Estimating the impact of sampling proportions on estimates of prevalence of epilepsy and severe chronic headaches. Most studies conducted in developing countries do not use a random

sampling method to select participants. We are working with Brown University to adjust for possible selection bias introduced by sampling. Data from the field is being reviewed to estimate sampling weights. This is expected to result in at least one publication and contribute to many more.

Principal Investigator: Debaun, Michael

Presenter: Brittany Covert, MPH

Title: Primary Prevention of Stroke in Children with Sickle Cell Diseases in Sub-Saharan Africa

Grant Number: 1R01NS094041-01

Strokes in sickle cell anemia (SCA), particularly in children living in Africa, are associated with significant morbidity and an increased risk of premature death. In the US, primary prevention of strokes in children with SCA involves screening for elevated transcranial Doppler ultrasound (TCD) velocity coupled with regular blood transfusion therapy for those with elevated velocities. However, regular blood transfusion therapy is not feasible in Africa due to inadequate supply of safe blood and the reluctance of parents to accept regular blood transfusion therapy for their children. Promising preliminary data from our feasibility trial in Kano, Nigeria (1R21NS080639-NCE, NCT01801423; October 2012 – August 2014) support the potential use of moderate dose hydroxyurea (HU) therapy of 20 mg/kg/day for primary prevention of stroke in children with SCA. In the feasibility trial, we screened 331 participants; 92% (25 of 27) of participants with elevated TCD measurements elected to enroll and receive HU therapy. While 75% (210 of 280) of the screened participants with non-elevated TCD measurements, agreed to be followed for a minimum of three years to assess the background rate of morbidity and mortality. Among those on HU therapy, 80% (20 of 25) of the participants who reached their third month on HU therapy dropped their elevated TCD value to below 200 cm/sec in both middle cerebral arteries. Based on the results from the recently completed Transcranial Doppler (TCD) With Transfusions Changing to Hydroxyurea trial (NCT01425307), demonstrating that children with an elevated TCD measurement can be switched to HU therapy after one year of blood transfusion, coupled with our preliminary trial results indicating a decrease in TCD velocities in 2/3rds of the participants over 3 months, we propose a two center randomized clinical trial (1R01NS094041-01; September 2015 – July 2020) to test the following hypothesis: There will be a **66% relative risk reduction of primary strokes** in children with SCA, and elevated TCD measurements (n=220), randomly allocated to **moderate dose vs. low dose HU therapy (10 vs. 20 mg/kg/day) for 3 years**. The aims of the trial are to: 1) determine the efficacy of moderate vs. low dose HU therapy for primary stroke prevention; 2) determine the efficacy of moderate dose HU therapy for decreasing the incidence of all cause-hospitalization for any cause (pain, acute chest syndrome, infection, or other) when compared to low dose HU therapy; and 3) assess long-term safety of HU therapy (mean 6.5 years) in participants from the feasibility trial with an elevated TCD measurement (n=25), when compared to children with an initial normal TCD (n= 210, followed for at least 3 years). In preparation for this application, the teams from Nigeria have received 1 month of patient-oriented research training at Vanderbilt University School of Medicine. This trial will help us to determine whether moderate dose HU therapy can prevent thousands of strokes in children at high risk in Africa, while simultaneously helping build research capacity among the next cadre of physician scientists in Nigeria.

Principal Investigator: Hyder, Adnan

Title: Developing an internet-based traumatic brain injury registry in Uganda:
A review of published literature

Hoe, C.¹, Mehmood, A.¹, Zia, N.¹, Kobusingye, O.², Hyder, A.A.¹

¹ *International Injury Research Unit, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

² *Makerere University College of Health Sciences, Kampala, Uganda*

Background: Worldwide, over 10 million people suffer Traumatic Brain Injury (TBI). Data on the burden of injuries and TBI in Uganda are scarce, which has prevented the magnitude of the burden to be appreciated and has posed a barrier to defining risks, vulnerable groups, and the impact of potential interventions. The primary aim of this review was to define core variables for an internet-based data registry focused on TBI in Uganda.

Methods: A comprehensive review was conducted. Six databases including PubMed/Medline, Embase, Scopus, Cochrane Reviews, System for Information on Grey Literature and Global Health Ovid were searched for literature pertaining to TBI in the African region and TBI registries in low-and middle-income countries. A spreadsheet was used to extract core variables and definition used for TBI.

Results: Thirty-five articles were identified as relevant to the focus of inquiry. The majority of the articles were from Nigeria, followed by South Africa and Tunisia. Few included definition used to define TBI. The most commonly collected core variables were demographics, injury event, initial assessment, emergency department care, in-patient care and outcome at hospital discharge.

Conclusion: Registries are critical for quantifying injury burden and improving quality of care. This study unveils the key variables for TBI registries in LMICs. It also highlights the need for more studies to be conducted on this important public health issue.

Principal Investigator: John, Chandy

Project title: “Neurodevelopmental outcomes in severe malaria”.

Presenter: Dr. Robert Opoka co-investigator

Authors: **Opoka R**, Idro R, Bangirana P, Namazzi R, Cusick S, Georgieff M, Datta D, Postels D, Vercellotti G, John CC

Background: Children who survive cerebral malaria (CM) are at risk of developing neurodevelopmental impairments (NDI) after the CM episode. We previously showed that severe malaria anemia (SMA) was also associated with cognitive impairment similar to impairment following CM. The goal of the grant is to investigate whether survivors of the major forms of severe malaria treated with artesunate have associated risk of developing NDI. Specifically we aim to establish the functional areas, degree and immunological, metabolic and nutritional risk factors associated with NDI.

Project methods : To recruit a cohort of 720 children aged 6 to 48 who present with any of the 5 common manifestations of severe malaria (SM) or are healthy community children (CC) from the families or neighborhoods of the children with SM. Enrolled children are followed up for 12 months. During hospitalization (SMs) or at enrolment (CCs) blood samples are taken for immunological, metabolic and micronutrient testing. Cognitive and behavioral assessments are done 12 months after enrollment using a battery of tools validated for use in African settings. Immunological, metabolic and micronutrient risk factors in children with SM will be compared to neurodevelopmental outcomes, including cognition, attention and behavior.

Progress to date: The study is currently enrolling children in 2 hospitals in Uganda. As of February 22, 2016, 443 children have been enrolled. The forms of severe malaria affecting the enrolled children include CM (n=47), SMA (n=114), respiratory distress (n=62), malaria with repeated seizures (n=106), and prostration (n=36). We have also enrolled 78 CC. To date, 102 children have completed the study, and 47 are no longer active in the study due to death, withdrawal of consent, or loss to follow up.

Challenges: The biggest challenge arose from the 17% funding cut at the start of the study. The acute budget problems were compounded by the need to have a second study site due to the changing burden of inpatient malaria. Supplemental university funding has been critical to allowing the study to continue and to achieving study goals. In addition, the study has been supported through use of infrastructure developed through previous grant funding and university funding, incorporation of personnel with high levels of training from the previous grant into the current study, leverage of capacity building from our D43 training grant, and a strong study team work ethic.

Conclusions and future plans

The NDI study is enrolling and on course to be completed in time. We plan to begin initial lab testing later this year, and continue testing on samples from the prior study and analysis of data from the prior study.

Principal Investigator: Johnson, David Kevin

Title: Fitness Predicts Cognitive Performance in Urban Latin Americans

Monica Salazar-Villanea¹, Jose Moncada-Jimenez², Mauricio Garnier-Villareal³, Edward Liebmann³, Esteban Montenegro- Montenegro¹, Eric D. Vidoni⁴, and David K. Johnson^{3&4}

1. University of Costa Rica, Psychological Research Center
2. University of Costa Rica, Research Center for Human Movement Sciences
3. University of Kansas, Department of Psychology
4. University of Kansas, Alzheimer's Disease Core Center

Introduction: Our group recently conducted a randomized clinical trial in US dwelling older adults that indicated increasing cardiorespiratory fitness (measured by VO₂ peak on treadmill) resulted in better visuospatial cognition in active healthy older adults. Maximizing an individual's cardiorespiratory fitness was the most important therapeutic target for achieving cognitive benefit. The Epidemiology and Development of Alzheimer's Disease (EDAD; R21TW009665) examined the role of fitness on cognitive performance in urban dwelling Costa Rican's.

Methods: We applied standard cognitive and physical fitness assessment batteries to a large sample of urban dwelling Latino volunteers at our University of Costa Rica sponsored satellite clinic in San Jose. The battery was a comprehensive and empirically rigorous assessment of the environmental versus organismic determinants of healthy aging and dementia in Latin Americans. Cognitive outcomes reported here were latent residual scores derived from a battery of 12 common neuropsychological tests: Verbal Memory, Visuospatial Processing, and Simple Attention. Other outcome measures were the 6-minute walk, a proxy of cardiorespiratory fitness and measures of function and disability.

Results: Higher cardiorespiratory fitness was significantly correlated to Simple Attention and Visuospatial Processing abilities, replicating previous published work.

Conclusion: Low and middle income nations will experience an unprecedented growth of the elderly population and subsequent increase in age-related neurological disorders that requires effective strategies for promoting healthy brain aging and the prevention of Alzheimer's disease. Alzheimer's disease destroys the active, productive lives of its victims and devastates their families financially and emotionally. It is estimated to affect millions of older people throughout the world. Aerobic training for older Latinos was safe and effective. Cardiorespiratory fitness (VO₂peak) and visuospatial cognition are a clinically meaningful therapeutic targets for future prevention trials in Latin America.

PI(s): Karenstan, Koenen; Stein, Dan

TITLE: Maternal Traumatic Stress and Child Development: Epigenetic Links

GRANT NUMBER: 1R21HD085849-01

PRESENTER: Nastassja Koen

BACKGROUND:

Exposure to psychological trauma, such as gender-based violence, and consequent posttraumatic stress disorder (PTSD), are prevalent in low- and middle-income countries (LMIC), including South Africa. Limited data suggest that maternal trauma exposure – and particularly PTSD – may be transmitted across generations and adversely affect offspring development. DNA methylation (DNAm) may be a plausible mechanism via which the effects of maternal mental health and trauma exposure are transmitted transgenerationally. However, there remains a paucity of work in this field.

STUDY AIMS:

The aims of this study will be three-fold: first, to expand capacity of South African collaborators to investigate bio-behavioral mechanisms underlying the impact of maternal trauma and PTSD across generations; second, to identify DNAm signatures and associated biological pathways affected by maternal traumatic stress during pregnancy in infant cord blood; and third, to test whether infant cord blood DNAm signatures associated with maternal traumatic stress are correlated with delayed infant emotional development.

METHODOLOGY

This project is a research collaboration between the Department of Psychiatry and Mental Health at the University of Cape Town (UCT) in South Africa, the Center for Molecular Medicine and Therapeutics at the University of British Columbia (UBC) in Canada, and the Department of Epidemiology at the Harvard T. H. Chan School of Public Health. It will capitalize on the Drakenstein Child Health Study (PI: H Zar, UCT), an ongoing pregnancy cohort located at UCT which follows 1000 mother-child pairs through pregnancy and for the first 2 years of life, with planned data collection through age 7. For this pilot project, we shall select 50 mother-infant dyads with exposure to PTSD during pregnancy, 50 trauma-exposed who did not develop PTSD, and 50 without trauma or PTSD during pregnancy (total N = 150). Maternal phenotype data will include sociodemographic variables, trauma exposure, PTSD, depression, psychological distress, and alcohol/substance use. Infant emotional development will be assessed using filmed maternal-infant interactions and validated neurodevelopmental measures. Child cord blood will be made available for DNA extraction, genotyping, and epigenetic analyses using the Illumina EPIC BeadChip array, an unbiased genome-wide assay.

We hypothesize (1) that infants of mothers with PTSD will show distinct DNAm profiles compared to those with no trauma, and to those with trauma exposure but no PTSD; and (2) that infant DNAm signatures associated with maternal traumatic stress will be correlated with early indicators of delayed emotional development in children. Data collection is currently ongoing.

Principal Investigator: Meya, David

Title: Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis

Cryptococcal meningitis (CM) has emerged as one of the most frequent and deadly opportunistic infections in HIV patients, with mortality between 20-30%. Early mortality from HIV-associated cryptococcal meningitis remains unacceptably high, in large part due to the high cost, toxicity, and relatively limited repertoire of effective antifungals.

Recent evidence suggests that the commonly used selective serotonin receptor inhibitor (SSRI) sertraline provides potent *in vitro* fungicidal activity against *Cryptococcus neoformans*. We hypothesize that sertraline added to standard CM induction therapy will result in increased early fungicidal activity (EFA), resulting in faster rate of fungal clearance and better clinical outcomes.

In an open-label dose-finding study, to assess safety and tolerability, we recruited HIV-infected individuals with cryptococcal meningitis who presented to Mulago Hospital in Kampala, Uganda between Aug 14, 2013, and Aug 30, 2014. The first 60 participants were given sertraline at escalating doses of 100 mg/day, 200 mg/day, 300 mg/day, or 400 mg/day as induction therapy for 2 weeks, followed by consolidation therapy with 200 mg/day for an additional 8 weeks. We also assessed 2-week cerebrospinal fluid (CSF) clearance rate of cryptococcus, termed early fungicidal activity, measured in patients with a first episode of culture-positive meningitis and two or more CSF cultures.

Participants receiving any sertraline dose averaged a CSF clearance rate of -0.37 colony forming units per mL per day (95% CI -0.41 to -0.33). Incidence of paradoxical immune reconstitution inflammatory syndrome was 5% and no cases of relapse occurred over the 12-week study period. Grade 4 or 5 adverse event risk did not differ between current US Food and Drug Administration approved dosing of 100–200 mg/day and higher doses of 300–400 mg/day.

Participants receiving sertraline had faster cryptococcal CSF clearance and a lower incidence of immune reconstitution inflammatory syndrome and relapse than that reported in the past. This inexpensive and off-patent oral medication is a promising adjunctive antifungal therapy.

Principal Investigator: Rahbar, Mohammad

Title: Epidemiological Research on Autism in Jamaica – Phase 2 (ERAJ-2)

Since 2009, our research team at the University of Texas Health Science Center at Houston (UTHealth) has collaborated with faculty at the University of the West Indies (UWI), Jamaica, to conduct a case-control study in order to investigate the interaction of three glutathione-S-transferase (GST) genes (*GSTM1*, *GSTP1* and *GSTT1*) and several environmental toxins including, lead, mercury, arsenic, cadmium, manganese, aluminum, polychlorinated biphenyls (PCBs), and organochlorine (OC) pesticides in relation to Autism Spectrum Disorder (ASD) in Jamaica. In March 2011, our collaborators at the UWI obtained funding through a grant from the Japanese Special Fund administered through the Inter-American Development Bank titled, JA Kids: The Jamaican Birth Cohort Study 2011. Dr. Samms-Vaughan serves as the PI of the JA Kids study and she offered us the unique opportunity to collect n=144 cord-blood serum/blood samples for the assessment of fetal exposure to PCBs, OC pesticides and the aforementioned six heavy metals. These samples were used to measure the levels of these toxins in the cord-blood, and compared with the levels of these toxins later at 3-4 years of age to test the hypothesis that children in Jamaica are exposed in *utero* to these chemicals and to identify factors associated with such exposures in children at 3-4 years. For the case-control component of our study, we conducted a 1:1 age- and sex-matched case-control study enrolling at least 150 pairs of ASD cases 2-8 years of age and typically developing (TD) controls. We administered a questionnaire to assess demographic and socioeconomic status, parental occupation, medical history of children, and potential exposure to the environmental toxins of interest. We used General Linear Models (GLM) to test the association of ASD status with blood lead, mercury, arsenic, cadmium, aluminum, and manganese concentrations. In addition, we used Conditional Logistic Regression (CLR) to assess associations between potential confounders and ASD case status. Based on available data, we found no additive effects of blood mercury, arsenic, cadmium, manganese, and lead concentrations in ASD. However, we found a significant interaction between the blood manganese concentrations and *GSTP1*, indicating that for children who had the Ile/Ile genotype for *GSTP1*, those with blood manganese concentrations $\geq 12\mu\text{g/L}$ had about 4-6 times higher odds of ASD than those with blood manganese concentrations $< 12\mu\text{g/L}$, ($P=0.04$).¹ Additionally, our findings indicate that TD children who had the Ile/Ile or Ile/Val genotype for *GSTP1* had a significantly higher geometric mean blood arsenic concentrations than those with genotype Val/Val (3.67 $\mu\text{g/L}$ vs. 2.69 $\mu\text{g/L}$, $P < 0.01$), but the same association for children with ASD was not statistically significant.² Furthermore, we identified a significant interaction between *GSTP1* and *GSTT1* in relation to ASD, where there was a significantly higher odds of ASD for children who were heterozygous for the *GSTP1* Ile105Val polymorphism and also had the *GSTT1* null genotype [Matched Odds Ratio (MOR) = 2.97, 95% CI (1.09, 8.01), $P = 0.03$].³ These findings are clear examples that without attention to gene-environment interaction, a lack of an additive effect of environmental toxins in ASD should not be interpreted as confirmatory of no association. However, we believe that replication of these results in other populations is warranted. To date, analysis of data from the JA Kids component of this study has revealed that the arithmetic mean (standard deviation) concentrations of cord blood lead, mercury, aluminum, and manganese were 0.83 (1.25 $\mu\text{g/dL}$), 4.38 (2.32 $\mu\text{g/L}$), 10.91 (9.10 $\mu\text{g/L}$), and 43.65 (17.65 $\mu\text{g/L}$), respectively.⁴ These results provide

levels of the aforementioned metals in cord blood that could serve as a reference for the Jamaican population.

“A randomized controlled trial of the neuropsychological benefits of computerized cognitive rehabilitation training in Ugandan children surviving severe malaria.”

Principal Investigator: Rascovsky, Katya

Project title: Young onset dementia in Latin America

Associated with R21 AG046499, **Young Onset Dementia in Colombia (TALK ABSTRACT)**

Katya Rascovsky, Ph.D.

Research Assistant Professor

Department of Neurology and Penn Frontotemporal Degeneration Center (PFTDC)

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Abstract:

Young-onset neurodegenerative diseases such as frontotemporal degeneration (FTD) and early-onset Alzheimer's Disease (AD) affect individuals in their most productive years and represent a major source of disability. As disease-modifying clinical treatment trials emerge for specific pathologies, it will be necessary to 1) improve differential diagnosis of young-onset dementias, 2) develop sensitive and specific clinical, imaging and biofluid biomarkers that can be collected easily and reliably in developed and developing countries, 3) establish patient registries to facilitate multi-center research and recruitment in clinical trials. In collaboration with our colleagues at the Penn Frontotemporal Degeneration Center (PFTDC) and the Center for Neurodegenerative Disease Research (CNDR), we are working to establish sustainable clinical research collaborations between the University of Pennsylvania and several dementia centers in Latin America. Currently, we have ongoing projects with the following centers: 1) Memory Clinic and Institute on Aging, Pontificia Universidad Javeriana (MCIA) in Bogota, Colombia, 2) Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez" (INNN) in Mexico City, Mexico, 3) Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI) in Buenos Aires, Argentina 4) Sanatorio de los Arcos in Buenos Aires, Argentina and 5) the Peru Young-Onset Dementia Network (PYN), a consortium of researchers at the Universidad Peruana Cayetano Heredia (UPCH), Clínica Internacional and DPI Imaging Center in Lima, Peru. We are building research capacity at these sites by developing and implementing standardized methods of clinical assessment, imaging and genetics, as well as data handling, analysis and transfer. This partnership aims to create the critical infrastructure necessary for a Latin American Registry for Dementia which will facilitate collaborations between Latino dementia centers in the US and abroad. It will also help elucidate biological and cultural differences in the diagnosis and management of young-onset dementias in Latin America.

Project title: Sathiakumar, Nalini

Title: Prenatal and Early Childhood Biomass Smoke Exposure and Child Neurodevelopment
(Grant - 1R01ES023492)

Affiliation: University of Alabama at Birmingham

Presented: Dr. Nalini Sathiakumar, MD, DrPH (**Meghan Tipre, BDS, DrPH will be the presenter**)

Abstract

Household air pollution (HAP) from combustion of solid fuels used for cooking and heating is one of ten leading contributors to the global burden of disease. About 90% of rural households in developing countries use solid fuel such as wood, agricultural waste or coal for cooking and heating. One epidemiologic study suggests a relationship between HAP and child neurodevelopment, but no firm conclusions could be drawn as the result was imprecise. In Sri Lanka, a lower middle-income country, more than 78% of the population use biomass fuel in the form of unprocessed wood. We have assembled a cohort of 600 mother-infant pairs in Sri Lanka to study the effects of prenatal HAP exposure on infant neurodevelopment assessed at birth and at six months of age. In this application, we propose to extend the follow-up of the same birth cohort up to 3 years of age and evaluate effects of biomass fuel smoke exposure on child's neurodevelopment through early childhood allowing us to capture the crucial periods of brain development. It will also provide an excellent opportunity to assess effect/impact of both prenatal and postnatal exposure to HAP on child neurodevelopment with minimum exposure misclassification. We will ascertain HAP exposure from questionnaires and measure PM_{2.5}, PM_{1.0}, PM₁₀, CO and NO₂ in 300 households. Using this information and child's time activity record, quantitative exposure profiles will be developed for the 600 children in the study. Child neurodevelopment will be assessed at 18 and 36 months of age using the Bayley Scales of Infant Development. The study will then evaluate the association between prenatal and childhood HAP exposure on child neurodevelopment. This pioneer birth cohort study addresses a global research gap, and has the potential to cause a paradigm shift in addressing HAP exposure in Sri Lanka and in other countries.

Principal Investigator: Jeremy Silverman, Dept of Psychiatry, MSSM

Title: Successful Cognitive Aging and Cardiovascular Risk Factors in the Central Valley of Costa Rica

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R21TW009258

Successful Cognitive Aging and Cardiovascular Risk Factors in the Central Valley of Costa Rica

The aim of the R21 is to lay the groundwork in Costa Rica for a larger study investigating genetic characteristics associated with the lack of dementia – distinguished from dementia – in the very old. In a collaboration between the Icahn School of Medicine at Mount Sinai in New York and the University of Costa Rica in San Jose, Costa Rica, our project is advantageously performed in a middle-income country with high life expectancy and low genetic and cultural heterogeneity, facilitating genetic research, further enhanced by ascertainment of subjects within families.

In the R21, we have developed and implemented recruitment methods to ascertain Costa Rican nonagenarians, both with and without dementia, and their elderly offspring. Consented and enrolled subjects are classified first by their level of global cognitive function and then more finely characterized by their performance within individual cognitive domains – memory, executive functions, attention – and even more specific neuropsychological functions (e.g. delayed recall, sequencing) using a comprehensive neuropsychological test battery.

We have also implemented procedures for assessing cardiovascular risk factors (CVRFs) in our Costa Rican samples. Like age, many other CVRFs are also risk factors for cognitive decline, including the most definitively identified genetic risk factor for dementia and Alzheimer's disease, the apolipoprotein E (APOE)-e4 allele, and cholesterol, diabetes, high blood pressure, body mass index (BMI), C-reactive protein (CRP). To date, we have recruited over 300 elderly subjects and assessed both cognitive and CVRF protocols.

Although disease is usually investigated as an exception from non-diseased normality, resistance to disease is seldom investigated. Thus, it is commonplace to search for risk factors for disease, but not countervailing protective factors distinct from the mere absence of risk factors. Dementia research studying failure rather than success has had very limited therapeutic efficacy. Resistance is less visible than disease, since it is difficult to distinguish individuals without the disease who are actively resistant rather than lucky. However, resistance is especially likely in a group with a low disease rate despite risk factors identified in the general population. Findings from our group and others suggest that associations between cognition and some CVRFs are reversed in late old age—CVRFs that are associated with cognitive impairment in the young

elderly are associated with better cognition in the very old—with a genetic basis for this reversal.

We define resistant successful cognitive aging (rSCA) as the absence of cognitive impairment in the very old despite the presence of risk factors or even pathophysiology, due to protective factors. Our survival model for rSCA suggests such individuals are relatively likely to possess underlying protection that is not easily recognized at younger ages, such as protection against CVRF effects identified in the young elderly. Our Fogarty R21 project has initiated a response to the gap in knowledge of such protective effects by creating infrastructure in Costa Rica to evaluate CVRFs in nonagenarians and their elderly relatives. Among nonagenarians, the R21 has demonstrated a reversal of the association of cognitive impairment with APOE-e4 found in younger samples. The goal of our recently submitted Fogarty R01 utilizing this infrastructure is to identify shared genetic effects on both CVRFs and cognition, exploiting genetically-identified kinships, and investigate age-related genetic effects as explanations for reduced or reversed CVRF associations.

Principal Investigator: Tshala-Katumbay, Desire MD MPH PhD et. al.

Title: Food Cassava-Associated Neurodegeneration: Biomarkers, Cyanide and Diseases Susceptibility at the Metagenomic/Epigenetic Interface

**Department of Neurology, Oregon Health & Science University, Portland, OR, USA;
Department of Neurology, University of Kinshasa, and Institut National de Recherches Biomédicales**

(INRB) Congo-Kinshasa.

Background

Thousands of children and women of childbearing age experience a high burden of motor and cognition deficits associated with dietary reliance on cyanogenic cassava as the main source of food.

Main Objectives

A multidisciplinary team from the Oregon Health & Science University (OHSU), Michigan State University (MSU), and INRB (Congo-based National Biomedical Research Institute) conducts studies to: (1) Elucidate the clinical pattern and biomarkers of motor and cognitive deficits (MCD) in children reliant on cyanogenic cassava as the main source of food, (2) Determine whether the observed deficits were related to nutritional deficiencies, neurotoxicity, or genetic variations in the chief cyanide detoxifying enzyme TST; and (3) Build research capacity for Congolese investigators under the supervision of senior investigators from OHSU, MSU, and INRB.

Approach

Data were collected using the BOT-2 (Bruininks/Oseretsky Test, 2nd Edition) and KABC-II (Kaufman Assessment Battery for Children, 2nd edition) testing batteries for motor proficiency and cognitive performance, respectively; liquid chromatography tandem mass spectrometry (LC-MS/MS) to measure F2-isoprostanes and levels of albumin carbamoylation; and PCR-based exon sequencing to identify genetic polymorphisms in TST and other genes of interest. Graduate students were engaged in field-work and didactic training including aspects of research design and methodology in resource limited settings and responsible conduct of research.

Major Outcomes

Dietary reliance on poorly processed cassava is associated with poor neurodevelopmental trajectories in neurocognition and motor proficiency. Risk factors associated with outbreaks of cassava associated paralysis (konzo) include high exposure to cassava cyanogenic compounds as reflected in the mean (SD) levels of U-SCN of children with konzo ($520,4 \pm 355,7$) relative to those with no konzo ($382,5 \pm 226,3$) ($p < 0.05$) as well as having a child with konzo in the household (OR=1,92; $p = 0,042$). The mean (SD) level of cyanogenic content of cassava flour from select households was $92,2 (\pm 56,2)$ ppm, well above the level of 10 ppm recommended by the World Health Organization (WHO). We sequenced thiosulfate sulfur transferase (TST) and

mercapto pyruvate sulfur transferase (MPST) (the two main cyanide detoxification enzymes and key players in sulfur mediated redox mechanisms) and SOD-1 (a major player in redox regulation) and found no association between the many polymorphisms in the coding sequences and konzo. SNPs were as follows: TST (undocumented SNP, 18301275 A>G; rs1049280, 37011023 G>A; rs142340242, 37011129 C>T; rs148893857, 37011180 G>A; rs375907649, 37011290 A>G; rs61742280, 37011305 C>T; rs35156365, 37018427 A>C); FOR MPST (rs112260704, 37024123 C>G; rs60296118, 37024849 C>T; undocumented SNP, 18319900 C>T; rs59832951, 37029550 G>A); AND FOR SOD1 (rs17883296, 31659509 G>T; rs17878855, 31659614 G>C; rs7277748, 31659661 A>G; rs142752986, 31659722 T>A; rs17883998, 31666362 T>C; rs17885833, 31666429 T>C).

A sub-sample of our Kahemba konzo children (N = 40) had serum concentrations of F2-isoprostanes, well-established markers of oxidative damage, 10-100 times those reported in presumably healthy adult populations. In particular, the serum levels of 8,12-iso-iPF2 α -VI isoprostane (8,12-isop) negatively correlate with the performance scores at the KABC-II and BOT-2 testing for cognition and motor proficiency, respectively. Low motor or cognition performances significantly correlate with high serum concentrations of 8,12-iso-iPF2 α -VI isoprostane. KABC-II scores relative to serum concentration of 8,12-iso-iPF2 α -VI isoprostane in konzo children ($r = -0.78$, $p=0.00$) and non-konzo children ($r = -0.24$, $p=0.47$). BOT-2 scores relative to serum level of 8,12-iso-iPF2 α -VI isoprostane in konzo children ($r = -0.63$, $p<0.01$) and non-konzo children ($r = -0.06$, $p=0.86$). We identified two major sites in human albumin undergoing carbamoylation in vivo at lysines 214 and 428 in albumin tryptic peptides 206-219 (LDEL RDEGKASSAK, Pep 1) and 438-452(KVPQVSTPTLVEVSR, Pep 2). Once these sites of carbamoylated were detected, we developed a rapid assay for their relative quantitation using multiple reaction monitoring (MRM) to measure both carbamoylated pep 1 and 2 could be measured in individual subjects. The mean abundance of carbamoylated peptides 1 and 2 were 2.0 and 2.8 fold higher in case subjects compared to controls, respectively, with p values of 0.0035 and 0.00041, respectively.

Conclusion

The overall burden of neurotoxicity associated with cassava has been underestimated for the last several decades. The observed motor and cognition deficits may be mediated through oxidation stress and/or carbamoylation. Implementation of public health measures to mitigate the exposure and improve neurodevelopmental outcomes is of paramount importance. Ongoing studies point out to a possible metagenomic/epigenetic regulation of susceptibility to cassava cyanogens.

Funding

Grant NIEHS/FIC R01 ES0119841: Toxicodietary and genetic determinants of susceptibility to neurodegeneration (Desire Tshala-Katumbay, PI).

PI: Tshala-Katumbay, Desire

Presenter: Name: Dieudonné Mumba Ngoyi, MD, PhD

Title: A new focus of Epilepsy associated with onchocerciasis in the Democratic Republic of the Congo

Affiliation: Institut National de Recherche Biomedicale Kinshasa, DRC Congo

Onchocerciasis-associated neurodevelopmental deficits: the hit squad

[FIC Grant # 5R21TW010004, PI: Tshala-Katumbay, Desire MD MPH PhD (OHSU); Dieudonne Mumba (Speaker) and Jean-Claude Ngoyi MD PhD (INRB)]

Main Objectives

This research project brought together collaborators from the Oregon Health & Science University (OHSU), Michigan State University (MSU), and INRB (Congo-based National Biomedical Research Institute) to: (1) elucidate the degree of association between epilepsy associated neurodevelopmental deficits (ENDD) and onchocerciasis (river blindness caused by *onchocerca volvulus* (OV) in Congolese children recruited from a community subjected to mass treatment with ivermectin and known to rely on cassava as a staple food; (2) Build research capacity for Congolese investigators under the supervision of senior investigators from OHSU, MSU, and INRB.

Approach

A multidisciplinary team carried out studies using SMART (standardized monitoring and assessment of relief and transition) methodology and anthropometric measurements for nutritional assessment; the KABC-II (Kaufman assessment battery for children, 2nd edition) testing batteries for cognitive performance; electroencephalography, and funduscopy, frequency doubling technology perimetry, scanning laser polarimetry for retinal nerve fiber layer thinning during ophthalmological assessments. Snip skin biopsies were used to confirm OV-infection. Plasma cytokines were measured using the Human cytokine magnetic 30-plex (Life Technologies, CA). Graduate students were engaged in field-work, hands-on-experience, and didactic training including aspects of research design and methodology in resource-limited settings and responsible conduct of research. Studies were conducted in the OV-hyperendemic area of Kasangulu, Congo-central province, Congo-Kinshasa.

Major outcomes

Fifty-one and five percent of households were experiencing food insecurity with 59.5 % (54.3 – 64.5) of children with stunted growth. Of the 130 subjects included in a case-control study, 91 (70%) [mean age (SD): 23.2 (8.4) years] reported having epileptic seizures. Univariable logistic regression indicated that epilepsy was associated with onchocerciasis [OR: 4.42 (1.97 – 9.91), $p < 0.01$] and family history of epilepsy [OR: 5.72 (1.83 – 17.9), $p < 0.01$]. Epilepsy was also associated with poor cognition in all domains of memory, learning, and planning; and levels of growth factor EGF and IL-8. Poor memory was significantly associated with early onset of epilepsy, stunting and levels plasma growth factors and/or cytokines notably RANTES ($\rho = -0.35$, $p = 0.01$ with memory KABC-II scores) and G-CSF ($\rho = -0.42$, $p = 0.04$) in OV positive subjects. A statistically significant

association (1-sided Fischer's Exact Test at the significance level of 0.1) was found between abnormal scanning laser polarimetry and positive skin biopsy for Onchocercal volvulus ($p = 0.029$). There also a tendency toward significant association between scanning laser polarimetry and both epilepsy ($p = 0.06$) and treatment with ivermectin ($p = 0.08$). It was interesting to note a significant correlation (Spearman's correlation) between RNFL thickness and the following pro-inflammatory cytokines (IL-12: $\rho = 0.25$, $p = 0.032$; RANTES: $\rho = 0.29$, $p = 0.013$; MIP-1a: $\rho = 0.26$, $p = 0.026$; IFN- γ : $\rho = -0.209$, $p = 0.014$; TNF- α : $\rho = 0.25$, $p = 0.031$; IL-7: $\rho = 0.30$, $p = 0.01$). This finding may suggest the inflammatory nature of the optic neuropathy observed in subjects with ENDD. RNFL thickness also correlated with some anti-inflammatory cytokines (G-CSF: $\rho = 0.24$, $p = 0.031$; IL-13: $\rho = -0.24$, $p = 0.042$; INF- α : $\rho = 0.26$, $p = 0.025$; IL-1RA: $\rho = -0.25$, $p = 0.036$), which may indicate the host response to the inflammation. In a logistic regression that included scanning laser polarimetry as dependent variable and age, nutritional status, onchocercal infection parameters (treatment with ivermectin, skin nodules, positive skin biopsy for Onchocerca volvulus) as independent variables, subjects who received ivermectin were 8.9 times more likely to exhibit an abnormal scanning laser polarimetry ($p = 0.036$), meaning a thinning of the RNFL or loss of retinal ganglion cell axons. Subjects with positive scarification for onchocerciasis also tended to exhibit thinning of the RNFL, but the association only reached a borderline significance level ($p = 0.055$). A ROC analysis performed with probabilities from logistic regression indicated a good ability of the model to discriminate between people with and those without optic neuropathy, with an area under the curve of 0.83 (95% CI: 0.74-0.92), $p < 0.0001$.

Conclusion

Our findings suggest that the pathogenesis of ENDD including optic neuropathy in OV-area is multifactorial. Both neurocognitive deficits and optic neuropathy may be mediated by inflammation in the context of onchocerciasis and/or chronic malnutrition. The association between treatment with ivermectin and optic neuropathy is scientifically interesting and calls for further investigations. Further studies will determine the exact links between ENDD, optic neuropathy, inflammation (cytokines), growth factors, and axonal and/or neuronal pathology. The later will require measurement of the retinal ganglion cell-inner plexiform layer (GCIPL), which is made of the bodies of the retinal ganglion cells and the dendrites, and RNFL thicknesses using spectral domain optical coherence tomography (OCT) in combination with automated visual field.

Neuro-ophthalmologic part of the talk- Brain R21

Project Title: Determinants of Optic Neuropathy in a Community Hyperendemic for Onchocerciasis and Epilepsy

Presenter, Mwanza, JC

Mwanza JC,^{1,3} Kashama JM,² Nsambayi DL,³ Lufundusu AM,³ Okitundu D,² Mumba DN,^{4,5} Tshala-Katumbay D.^{2,4,6}

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Purpose: To determine the risk factors for optic neuropathy in a community endemic for onchocerciasis, with a high prevalence of epilepsy and that has been subjected to a mass distribution of ivermectin.

Methods: Case-control population-based study in the southwestern part of the Democratic Republic of Congo. Cases were subjects with a history of epilepsy whereas controls were those without such a history. Study participants were selected in four villages located along one road, via a door-to-door census that preceded the clinical investigation. Participants underwent a standard ophthalmological assessment with emphasis on the posterior segment of the eye, a scanning laser polarimetry (SLP) around the optic nerve head, and a skin biopsy for *Onchocerca volvulus* detection. SLP is a non-invasive technique for measuring the thickness of the retinal nerve fiber (RNFL), which is made of retinal ganglion cell axons that merge to form the optic nerve. The diagnosis of optic neuropathy was based on clinical grounds and SLP. Fischer's exact test and logistic regression were used to determine the factors associated with abnormal SLP in the study participants.

Results: A total of 66 cases and 23 controls completed all the testing and were included in the analysis. The diagnosis of optic neuropathy, based on clinical grounds and confirmed through SLP, was made in 16 subjects (18%). Univariable association analysis showed a statistically significant association (1-sided Fischer's exact test) between abnormal scanning laser polarimetry and positive skin biopsy for *Onchocerca volvulus* ($p = 0.03$), epilepsy ($p = 0.06$) and treatment with ivermectin ($p = 0.08$). There was a significant correlation (Spearman's correlation) between RNFL thickness and both pro-inflammatory (IL-12: $\rho = 0.25$, $p = 0.032$; RANTES: $\rho = 0.29$, $p = 0.013$; MIP-1a: $\rho = 0.26$, $p = 0.026$; IFN- γ : $\rho = -0.209$, $p = 0.014$; TNF- α : $\rho = 0.25$, $p = 0.031$; IL-7: $\rho = 0.30$, $p = 0.01$) and some anti-inflammatory cytokines (G-CSF: $\rho = 0.24$, $p = 0.031$; IL-13: $\rho = -0.24$, $p = 0.042$; INF- α : $\rho = 0.26$, $p = 0.025$; IL-1RA: $\rho = -0.25$, $p = 0.036$). A logistic regression that included SLP (normal or abnormal) as dependent variable and age, nutritional status, onchocercal infection parameters (treatment with ivermectin, skin nodules, result of skin biopsy for *Onchocerca volvulus*) as explanatory variables revealed that subjects who received ivermectin were 8.9 times more likely to exhibit an abnormal SLP ($p =$

0.036), meaning a thinning of the RNFL or loss of retinal ganglion cell axons. Subjects with a positive skin biopsy for the parasite also tended to exhibit thinning of the RNFL ($p = 0.055$).

Conclusions – Comments – Future Perspectives: Our findings indicated an association between optic neuropathy and positive skin biopsy for *Onchocerca volvulus*, treatment with ivermectin, and epilepsy. Subjects infected with the parasite and those with a history of ivermectin in the past were more likely to have an abnormal SLP, indicative of RNFL thinning or retinal ganglion cell axonal loss. The association between treatment with ivermectin and optic neuropathy is scientifically interesting and calls for further investigations. This is particularly true considering the scarcity of information on the possible effect of ivermectin on neurodegeneration. Previous studies have reported conflicting findings with regards to the link between ivermectin and optic neuropathy. Even assuming that there exists an association between the two, a number of questions have remained unaddressed. For example, the rate of neuronal (i.e. retinal ganglion cell) and axonal (retinal ganglion cell axon) loss and the structure-function relationship in this optic neuropathy are important aspects that merit in-depth investigations. Those investigations will require measurement of the retinal ganglion cell-inner plexiform layer (GCIPL) which is made of the bodies of the retinal ganglion cells and the dendrites, and RNFL thicknesses using spectral domain optical coherence tomography (SDOCT) in combination with automated visual field. We have described recently the method for measuring the GCIPL thickness with SDOCT. This method is currently available and used worldwide and we hope to capitalize of this to further our investigations.

PI: Vaisberg/Gallo

Title: Drug Discovery for Mental Disorders: Preclinical Studies of Peruvian Botanicals

Presenter: Carla Gallo, Laboratorios de Investigación y Desarrollo, Universidad Peruana Cayetano Heredia

Grant Number: 1R21MH095644--01A1

PI Name / PI Country Abraham Vaisberg/Peru

Major foreign collaborating country USA

Presenter Name Carla Gallo

Grant Number: 1R21MH095644--01A1

Grant Title: Drug Discovery for Mental Disorders: Preclinical Studies of Peruvian Botanicals

Mental disorders are multidimensional and severely disabling diseases, with a strong need for pharmacotherapies with better adherence, long-term outcome and patient functionality. Unfortunately, the scientific advancements in the field have not yet led to the introduction of truly novel pharmacological approaches to treatment. One of the possible avenues to achieve this goal is to take advantage of world's ancient knowledge of healing practices to direct search of new lead compounds, with expectedly novel action mechanisms that would produce better treatment outcomes.

This R21 is part of a long range effort directed to the discovery of new pharmaceuticals from Peruvian flora traditionally used for the treatment of mental disorders. Our main hypothesis is that plants ancestrally used by Peruvian traditional healers for treating mental illnesses are a source of novel therapeutics for these disorders. We specifically hypothesize that: 1) it is possible to isolate bioactive principles from these plants; 2) rodent behavioral models are a good start point tool for screening/validation and for further prioritization of research on those activities; 3) the isolated lead compounds will be superior to those obtained from chemical libraries in terms of better bioavailability and less secondary effects; 4) the pharmacological information obtained will help to further understand the traditional medicine conceptualization of mental disorders in Peru. Previous studies have led us to collect information on the traditional use of plants for the treatment of mental disorders in several Peruvian localities and geographical regions. We currently have extracts from 477 plant collections corresponding to 265 species from 87 different plant families. These plants are traditionally used for one or more of the following activities: antipsychotic, antidepressant, anxiolytic and sedative. Importantly, about 60% of those species have never been described in the scientific literature for their potential effects on the modulation of behavior. Half of our plant extracts have been screened so far (partly with the support of this R21) to validate their traditional medical use with behavioral tests in mice. To date we have identified 157 plant extracts having one or more potential psychotropic activity (123 antipsychotic/antimanic, 84 anxiolytic and 38 antidepressant). Additionally, with this R21, our 477 extracts have been tested for 56 receptor targets in the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill (UNC), showing they are potentially active towards several targets of interest (e.g. serotonin 5-HT₆ and 5-HT_{7A})

antagonists, nociceptin/orphanin agonists, GPR68 antagonists, among others). This screening needs to be replicated for confirmation at the PDSP before proceeding further towards the isolation and identification of the active compounds. The availability of the whole set of PDSP activities for each extract is unique and opens up a cascade of opportunities for approaching drug discovery. A multidisciplinary network of US experts has been established and consolidated during this R21, and we expect they will also collaborate with us in future R01 applications. Our new ongoing proposals are based on the following hypotheses: 1) it is possible to isolate bioactive principles from these plants; 2) animal behavioral models, molecular targets and reported use in traditional medicine are valid tools for screening/validation and for further prioritization of research; 3) analyzing the latter 3 tools in combination can potentiate the efficiency for identifying potential leads; 4) molecular target information will help to further understand the traditional medicine conceptualization of mental disorders in Peru as well as the construct validity of the animal behavioral models; 5) the isolated lead compounds –since they come from extracts of plants that are currently being used by humans- will be superior to those obtained from chemical libraries in terms of better bioavailability and less secondary effects. We are aiming to devise an experimental pipeline with a strategic planning/decision-making approach that will allow discovery with the best cost/benefit ratio. Within this aim we expect to confirm the activity of the extracts screened previously at the PDSP; to prioritize the bioassay-guided fractionation of the most appealing extracts; to develop or test new methods for the screening and bioassay-guided fractionation in order to identify novel psychotropic agents and avoid toxicity; to dereplicate and determine the molecular structure of the isolated active principle(s).

Principal Investigator: Verghese, Joe

Project title: Kerala-Einstein Study: Healthy lifestyle, vascular disease, and cognitive decline

Type: R01 AG039330

ABSTRACT

The goal of the Kerala Einstein study is to foster collaborative research to study risk factors for cognitive decline among older adults living in the southern Indian state of Kerala. Our research sites are the cities of Kozhikode, Thiruvananthapuram and Thrissur in Kerala state. The proposal will be directed by Dr Verghese, a neurologist at the Albert Einstein College of Medicine and a native of Kerala in collaboration with Dr. Mathuranath, Director, Division of Behavioral Neurology at the Sri Chitra Tirunal Institute, Thiruvananthapuram, one of India's premier postgraduate medical institutes. We now propose a more extensive RO1 grant propose leveraging the resources and collaborations successfully developed in our two-year R21 planning grant (R21 AGO29799) to study specific causes of cognitive decline in Kerala identified through our pilot research and to continue to provide training opportunities and build research capacity. Sociodemographic changes in Kerala in recent decades have created major lifestyle changes that have resulted in a cardiovascular disease epidemic as well as increased risk for dementia. We propose to examine the role of potentially modifiable healthy lifestyle variables (diet, physical activity, and social networks) of high relevance to India that may prevent cognitive decline via their effects on cardiovascular, stress, inflammation, and other pathways in 1700 older adults participating in our longitudinal cohort study in Thiruvananthapuram over a two-year follow-up period (Aim 1). Cardiovascular disease causes both macrovascular (strokes) and microvascular brain damage that may contribute to cognitive decline. However, the role of microvascular disease (microbleeds, lacunar infarctions and leukoariaosis) in dementia is not well defined. Hence, we also propose to conduct a neuroimaging substudy to identify the behavioral correlates of microvascular disease in 75 subjects with amnesic Mid Cognitive Impairment syndrome and 150 healthy controls (Aim 2). Our studies have the potential to have a major impact in building sustainable research capacity in India, ultimately leading to the development of treatment and prevention strategies that are applicable worldwide. Defining role of healthy lifestyle factors and microvascular disease in Kerala may also help in understanding the parallel epidemic of cardiovascular disease and dementia in immigrant and minority populations who comprise a third of the US population. Our collaborators and their institutions are actively involved in formulating treatment and prevention policies locally and nationally, which will help take our findings from research settings to the community in India.

Principal Investigator: Jasmin Vassileva, Ph.D., University of Illinois at Chicago, USA
Foreign Collaborator: Georgi Vasilev, MD MPH, Bulgarian Addictions Institute, Sofia, Bulgaria

Presenter name: Jasmin Vassileva

Grant number: R01DA021421

Grant title: Varieties of Impulsivity in Opiate and Stimulant Users

Utility of machine-learning approaches to identify substance-specific behavioral markers for opiate and stimulant dependence

Recent animal and human studies reveal distinct cognitive and neurobiological differences between opiate and stimulant addictions; however, our understanding of the common and specific effects of these two classes of drugs remains limited due to the high rates of polysubstance-dependence among drug users.

The goal of the current study was to identify multivariate substance-specific markers classifying heroin dependence (HD) and amphetamine dependence (AD), by using machine-learning approaches. Participants included 39 amphetamine mono-dependent, 44 heroin mono-dependent, 58 polysubstance dependent, and 81 non-substance dependent individuals. The majority of substance dependent participants were in protracted abstinence. We used demographic, personality (trait impulsivity, trait psychopathy, aggression, sensation seeking), psychiatric (attention deficit hyperactivity disorder, conduct disorder, antisocial personality disorder, psychopathy, anxiety, depression), and neurocognitive impulsivity measures (Delay Discounting, Go/No-Go, Stop Signal, Immediate Memory, Balloon Analogue Risk, Cambridge Gambling, and Iowa Gambling tasks) as predictors in a machine-learning algorithm.

The machine-learning approach revealed substance-specific multivariate profiles that classified HD and AD in new samples with high degree of accuracy. Out of 54 predictors, psychopathy was the only classifier common to both types of addiction. Important dissociations emerged between factors classifying HD and AD, which often showed opposite patterns among individuals with HD and AD.

These results suggest that different mechanisms may underlie HD and AD, challenging the unitary account of drug addiction. This line of work may shed light on the development of standardized and cost-efficient clinical diagnostic tests and facilitate the development of individualized prevention and intervention programs for HD and AD.

