MEDSTAR HEALTH RESEARCH INSTITUTE INC
APPLICATION SUMMARY

Charles and Mary Latham Fund Board Meeting

Request Date:	October 30, 2020
Project Title:	Association between HIV antiretroviral treatment and central nervous system energy metabolism Principal Investigator: Amanda Blair Spence, MD
Request Amount:	$15,000.00
Program Area:	Medical Research

Organization Information	**Contact Person for Application**
Medstar Health Research Institute Inc 6525 Belcrest Road www.medstarresearch.org HYATTSVILLE, MD 20782 Tel: (301) 560-7300 Fax: 301-560-7373	Mrs. Sarah E Wright-Gaul Senior Proposal Development Specialist (281) 732-6860 research@medstar.net

Organization's annual operating budget: $3,800,000.00

Background
MedStar Health Research Institute (MHRI), founded in 1963, is the research division of MedStar Health. MHRI provides scientific, administrative, and regulatory support for clinical research throughout the MedStar Health system. Led by Dr. Neil Weissman, MHRI supports more than 1,000 associates dedicated to advancing health through research.

MHRI's core services include a biostatistics and epidemiological center, clinical research centers, a research pharmacy, two accredited pre-clinical laboratories, biochemistry and biomarker core laboratories, a core platelet center, a cardiac and vascular pathology center, a genetics/genomics/proteomics research core, a cardiovascular core imaging center, an institutional review board, and an office of research integrity. In the last year, more than 1,000 active studies, involving thousands of patients, resulted in nearly 1,000 peer-reviewed publications. MHRI is in the top 20% of U.S. institutions receiving funds from the National Institutes of Health and other federal agencies, with approximately 60% of its studies being federally funded.

Wherever you look throughout the MedStar Health system, you're likely to find the highly qualified scientists and investigators conducting leading edge clinical research.

MedStar Health Research Institute researchers cover many areas and types of research. From bench to bedside and into the community, associates across MHRI work to advance the scientific understanding of disease and point the way toward better and more effective treatments. As the research-focused entity of MedStar Health, this is our contribution to the healing work performed throughout the system and in the communities we serve.

Project/Program Budget (if applicable):

Project/Program Title: Association between HIV antiretroviral treatment and central nervous system energy metabolism
Principal Investigator: Amanda Blair Spence, MD

Project Summary (250 words or less)
Cognitive disorders affect over one-half of all persons living with HIV (PLWH) and the only known treatment and preventive strategy are effective treatment with antiretrovirals (ARVs).1,2 However, direct neurotoxicity of ARVs may contribute to the ongoing problem of cognitive impairment in treated HIV.3 Work from our group demonstrated worsening of some cognitive domains with the use of specific ARV classes of medication.(unpublished data) However, the mechanisms of this phenomenon is unknown. Changes in neurometabolism have been associated with cognitive dysfunction, acute HIV infection, and older medications used to treat HIV.4–7 How current first line therapy affects neurometabolism and correlates with cognitive outcomes is unknown. We propose to conduct a pilot study to evaluate differences in select brain metabolites using magnetic resonance spectroscopy (MRS) among individuals treated with currently recommended first line ARVs for HIV treatment or prevention and correlate with cognitive testing.

Statement of Problem
Despite the widespread use of antiretroviral therapy (ART) cognitive disorders are common among PLWH, and up to 52% of PLWH have evidence of cognitive dysfunction.1 Treatment with effective ART improves cognition, but neurologic complications remain common despite therapy.8–10 Effective HIV treatment requires sustained viral suppression through treatment with ARVs and is associated with improved health outcomes and decreased risk of viral transmission.11,12 Our group demonstrated worsening cognitive function among women living with HIV (WLWH) despite viral suppression with variability based on type of ARV exposure (FIGURE 1). Women exposed to integrase inhibitors (INSTIs), a first line ART agent for HIV therapy, exhibited worsening of executive function, memory, and cognitive processing speed.11,13 We also noted worsening of executive function with treatment using non-nucleoside reverse transcriptase inhibitors (NNRTIs), an alternative class of ART.11,13 There are no consensus recommendations on ART management strategies for cognitively impaired PLWH or persons at risk for cognitive impairment. Clinicians and researchers have attempted to implement ART treatments with greater central nervous system (CNS) penetration for patients with cognitive impairment as a treatment strategy as greater CNS penetration is correlated with decreased HIV RNA in the cerebrospinal fluid (CSF).14 However, studies yielded mixed results with improved, worsened, or equivocal cognitive

testing with use of agents with higher CNS penetration.15–18 In addition, clinical trials with non-antiviral agents have not been successful.2 Continuous ART is required for sustained viral suppression and improves other health outcomes, but has mixed effects on cognitive trajectories. Thus a better understanding of the pathogenesis of cognitive impairment among PLWH including the specific effects of ART is required to effectively develop treatment plans based on current available agents and develop new treatment strategies.

When HIV enters the CNS, virions are released that can infect surrounding microglia and astrocytes. This leads to the release of neurotoxic viral proteins and glial activation, and it is thought that this chronic inflammatory response at least partly drives the progression of cognitive impairment. Maintenance of this chronic inflammation is postulated to cause metabolism changes in glia cells with resulting lower metabolic support to neurons and consequently changes in cognition.19 Changes in metabolism in PLWH occur in acute HIV infection, correlate with virologic control, and are predictive of cognitive impairment.4,5,20 These metabolic changes are not only due to HIV infection but are also associated with older HIV antiviral treatments.6,7 This suggests potential neurotoxicity of some ARVs as these metabolites are linked to neuronal health.21 Metabolic changes related to current first line treatment strategies including the INSTIs and newer NNRTIs are unknown. This is important to understand not only for PLWH, but also for HIV-seronegative individuals who are taking ARVs for prevention of HIV in the form of pre-exposure prophylaxis (PrEP) for the prevention of HIV. These individuals do not have HIV, but receive potentially toxic medications for preventative purposes.

Specific Aims

The evolution of changes and factors that influence changes including ARVs in brain metabolism among PLWH are poorly understood. Thus, studies are needed to assess the contribution of ART to brain metabolism. Specific Aim 1: To determine differences in brain metabolites in the frontal cortex, hippocampus, and medial temporal lobes using proton magnetic resonance spectroscopy (MRS) among age matched treated HIV-seropositive persons on integrase inhibitors (INSTIs) or (NNRTIs), HIV-seronegative individuals on PrEP, and HIV-seronegative individuals. Metabolic changes related to neuroinflammation, HIV direct toxicity, and/or drug exposure contribute to neurocognitive outcomes.19 In our prior work, we identified changes in multiple cognitive domains related to INSTI or NNRTI exposure, but the underlying mechanisms driving these changes are unknown and may be related to CNS metabolism.(unpublished data) Changes in CNS metabolism are observed with older therapies used to treat HIV, but the effect current first line therapies including the INSTIs or the newer NNRTIs on CNS metabolism are unknown.6,7 We propose to use MRS to determine differences in brain metabolites (choline, n-acetylaspartate, myo-inositol, creatinine, lactate, acetate) in the frontal cortex, hippocampus, and medial temporal lobes among HIV-seropositive individuals on INSTIs, HIV-seropositive individuals on NNRTIs, HIV-seronegative individuals on PrEP, and HIV-seronegative individuals not taking any ARV medications. Specific Aim 2: To correlate the levels of brain metabolites in the frontal cortex, hippocampus, and medial temporal lobes using proton magnetic resonance spectroscopy (MRS) with HIV-serostatus, exposure to ARVs, and cognitive testing.

Changes in brain metabolism occur in early HIV-infection and in HIV associated cognitive disorders.4,22–25 However, how these changes are related to neurocognitive changes in treatment experienced individuals with HIV and HIV-seronegative individuals exposed to ARVs for prevention is unknown. All study participants will complete a validated neuropsychiatry battery of testing and a modified Lawton Independent Activities of Daily Living questionnaire to assess functional impairment.26,27 Neuropsychiatric testing outcomes will be stratified by HIV-serostatus and ARV use.

Research Strategy: Significance

Once HIV enters the CNS via infected macrophages/monocytes across the BBB virions are released that can infect surrounding microglia and astrocytes. This leads to the release of neurotoxic viral proteins and glial activation, and it is thought that this chronic inflammatory response promotes cognitive impairment among HIV-seropositive individuals. Maintenance of this chronic inflammation can cause changes in the metabolism in glia cells which lead to less metabolic support to neurons and consequently changes in neurocognition (FIGURE 2).19 Alterations in cellular metabolism, and specific metabolites in the CNS such as N-acetylaspartate, myo-inositol, glutamate, can be used as markers for neuronal health and glial activation. Other metabolites such as lactate and citrate are markers of cognitive impairment in PLWH and increased aerobic glycolysis is associated with worsening cognitive status.19,28 Even among those on effective therapy there are alterations in the level of glucose.29 Changes in brain mitochondria have been described in patients taking older HIV treatment therapies including stavudine and didanosine, and in vitro mitochondrial alterations in neuronal cell lines and primary neuron cultures have been described with efavirenz, a type of HIV treatment in the NNRTI class of ARVs.6,7 However, differential changes in energy metabolism related to current first line HIV treatment agents are unknown and have not been described in the literature. Understanding the alterations in energy metabolism related to specific ARV drug exposure will allow for further exploration of (1) ARV neurotoxicity; (2) effectiveness of specific ART in mediating ongoing inflammation; and (3) effectiveness of specific therapies in controlling the CNS viral reservoir both chronically and early in HIV infection latency induces a unique metabolic signature.30 This information can be used to develop effective treatment and management strategies for cognitively impaired PLWH.

This study is of particular relevance to the District of Columbia (DC) as there are currently 12,322 residents living with HIV. More than one-half are over the age of 50.31 In this aging population of PLWH, the recognition and management of comorbid conditions including those associated with aging such as cognitive disorders is imperative.32,33 The Centers for Disease Control's (CDC) Health Brain Initiative has declared cognitive impairment a public health priority as these disorders not only affect the quality of life of the person living with the disorder and caregivers but also place a strain on the healthcare system.34 The work outlined in this proposal may aid in understanding the pathogenesis of this public health priority and support future studies of treatment strategies.

Research Strategy: Innovation

Changes in brain metabolism among PLWH have clearly been noted in the literature.4,22–25 Changes have been described as they relate to acute HIV infection, cognitive disorders among PLWH, HIV viral load in CNS, immune status, and as a predictors of cognitive impairment.4,5,20,35 Studies related to ARVs and changes in brain metabolism are limited evaluation of changes related to initiation of ART in patients with and without cognitive impairment.21,36,37 However, how these changes relate to specific ARV class in either HIV-seropositive or HIV-seronegative individuals is unknown and has never been studied. Incorporating a population of HIV-seronegative individuals, already receiving ARVs for a medical indication will provide an HIV-seronegative control with drug exposure and allow for the examination of drug effect without the confounder of the virus.

Research Strategy: Approach

In order to evaluate our primary aims of determining differences in brain metabolites among individuals treated with first line ARVs and correlate with cognitive outcomes we will utilize MRS to determine the levels of brain metabolites as this methodology has been used to determine change in brain metabolism in HIV infection and among those with cognitive impairment with and without HIV.4,38,39 The treatment study groups consist of: HIV-seropositive persons on INSTIs or NNRTIs, HIV-seronegative individuals on PrEP, and HIV-seronegative individuals as we plan to evaluate first line treatment regimens for both HIV treatment and prevention. INSTIs including dolutegravir and bictegravir are first treatments for HIV treatment naive individuals. The NNRTIs of doravirine and rilpivirine are alternative treatment regimens.13,40 First line treatments for HIV prevention include combination tenofovir alafenamide and emtricitabine.41 We plan to recruit from HIV-seropositive persons having at least 2 years of drug exposure and are virally suppressed to remove the confounder of virus and ensure adequate exposure to the drug. A one year exposure to ARVs was chosen for HIV-seronegative individuals as tenofovir alafenamide/emtricitabine combination was only approved for PrEP in October 2019. Prior to that the only approved agent for PrEP was tenofovir disoproxil-fumarate/emtricitabine.42 Having both an HIV-seropositive group and a HIV-seronegative group both exposed to ARVs will allow for the exploration of drug effect on metabolism without the confounder of HIV. We will evaluate choline, n-acetylaspartate, myo-inositol, creatinine, lactate, acetate in the frontal cortex, hippocampus, and medial temporal lobes as these metabolites are associated with neuronal health and can be altered by HIV and initation of ART.21 As our prior work demonstrated changes in executive function, memory, learning, and cognitive processing we selected the frontal cortex, hippocampus, and medial temporal lobes for evaluation.43,44 A validated neuropsychiatric battery will be used to evaluate the following cognitive domains: verbal learning and memory, executive function, processing speed, attention, motor skills, processing speed, and language fluency.26,27

Research Design and Methods

General Strategy/Study Design Overview: We will characterize differences in the levels of specific neurometabolites among treated HIV-seropositive individuals, HIV-seronegative individuals treated with ARVs in form of PrEP, and HIV-seronegative not currently taking ARVs. We will recruit study participants from an existing cohort of

clinical patients and use a snowball chain referral sampling method where current study participants refer contacts for additional recruitment.
Study Team Members: Amanda Blair Spence, MD, the principal investigator, is a trained infectious disease specialist and has examined cognitive impairment among PLWH. John VanMeter, PhD is the Director of the Center for Functional and Molecular Imaging (CFMI) and will provide expertise in neuroimaging and facilitate the use of the CFMI for neuroimaging. Stanley Fricke, PhD is a Professor of Radiology and Director of Medical Physics and will provide expertise on neuroimaging and magnetic resonance spectroscopy. Princy Kumar, MD is the Chief of Infectious Diseases at Georgetown, she leads a division that provides care for over 1000 PLWH, and has extensive research in the development of ARVs. She will assist with recruitment and provide additional expertise on ARVs. Seble Kassaye, MD, MS is an Associate Professor of Infectious Disease, principal investigator of the MACS-WIHS-CCS and STAR-cohort studies (two large HIV-cohort studies), and epidemiologist. Dr. Kassaye will assist with recruitment, analysis, and data interpretation.
Recruitment Strategy: We will recruit participants from an existing cohort of HIV-seropositive and HIV-seronegative PrEP clinic patients at Georgetown. We will use a snowball recruitment method to recruit HIV-seronegative individuals not taking ARVs as well as additional HIV-seropositive and HIV-seronegative PrEP participants. Additional advertising may be pursued using Research Match, an established web-based recruitment strategy accessible to our site through the Georgetown-Howard Universities Center for Clinical and Translational Science (http://www.georgetownhowardctsa.org/).
Study Population: Inclusion criteria for HIV-seropositive participants include: (1) HIV viral suppression defined as HIV RNA ≤200 copies/mL for 2 years; (2) Treatment with a stable ART regimen for 2 years; (3) Treatment with an INSTI (dolutegravir or bictegravir) with a backbone of tenofovir alafenamide/emtricitabine or an NNRTI (rilpivirine or doravirine) with a backbone of tenofovir alafenamide/emtricitabine; and (4) Age 25-55. Inclusion criteria for HIV-seronegative ART treated (PrEP) participants include: (1) Treatment with PrEP for at least 1 year; (3) Negative HIV testing at enrollment; and (3) Age 25-55. Inclusion criteria for HIV-seronegative participants not on ART include (1) Negative HIV testing at enrollment and (2) Age 25-55. All participants should be able to read and communicate in English to complete the neuropsychiatric testing. Five participants will be recruited for each treatment group.
Neuropsychiatric Testing Strategy: All study participants will complete a validated neuropsychiatry battery of testing (TABLE 1) as well as a modified Lawton Independent Activities of Daily Living questionnaire to assess functional impairment with a trained study team member.26,27
Magnetic Resonance Imaging/Spectroscopy (MRI/MRS): Participants will undergo MRS at the Center for Functional and Molecular Imaging (CFMI) at Georgetown to determine levels of specific brain metabolites including choline, n-acetylaspartate, myo-inositol, creatinine, lactate, and acetate in the frontal cortex, hippocampus, and medial temporal lobes. These specific areas were chosen as prior work by our group demonstrated changes in executive function, memory, learning, and cognitive processing in chronically treated WLWH.
Additional Testing: HIV seronegative individuals will undergo rapid HIV testing on enrollment to document HIV-negative serostatus. A peripheral blood draw, urine, and

hair sample will be obtained and stored for future drug levels and inflammatory marker analysis.
Analysis Plan: We will estimate the quantification of metabolites contributing to the observed H-MRS spectra with LCModel software, version 6.3 (Provencher, Inc, Oakville, Canada). The software will fit a linear combination of canonical metabolite peaks from an empirical scanner-specific basis set to estimate concentrations and uncertainties contributing to observed data with a minimum of subjective input. Unsuppressed water suppressed spectra will be used to estimate metabolite concentrations using a scaling technique. In addition, eddy current effects and improve baseline fit, line shape, and zero-order phase corrections are applied within the model. The main outcome variables will be estimates of the following metabolite concentrations: choline, n-acetylaspartate, myo-inositol, creatinine, lactate, acetate for each participant. Cramer-Rao lower bounds will be used to ensure data quality. Descriptive statistics will be used to characterize group differences.
As an exploratory descriptive analysis, we will describe levels of specific metabolites by HIV-serostatus and neurocognitive testing. The study is designed to demonstrate feasibility and generate preliminary data for sample size calculations that will be used for future funding application. Thus, a sample size calculation was not included.

Challenges
While we do not anticipate any challenges recruiting treated HIV-seropositive individuals from our clinic population, recruitment of HIV-seronegative individuals will be more challenging. We have an established population of HIV-seronegative individuals on PrEP in our clinic which we will recruit from, but we will also use a snowball method of recruitment for HIV-seronegative individuals. Our group has successfully employed this strategy in the past to recruit for research study participants. Additional challenges include the logistics of performing neuroimaging during the COVID-19 pandemic. Our team has successfully restarted research with university approval and this includes studies utilizing neuroimaging. The CFMI where the scans are performed is open and appropriate participant screening, physical distancing, and environmental cleaning measures are in place to ensure the safety of research participants and staff. The guidelines will be followed closely during the study, and all team members will have appropriate training. Updates to the protocol will be made as needed based on current university and Centers for Disease Control guidelines.

Future Plans
The results of this study will establish feasibility and reproducibility of neuroimaging techniques to measure brain metabolites. The preliminary data will be used for sample size calculation and to support the application for larger adequately powered studies assessing differences in neurometabolites among patients exposed to specific ARVs. These studies will include (1) longitudinal and cross-sectional studies of ARV treatment experienced patients; (2) longitudinal studies at initiation of HIV treatment; and studies in HIV-seronegative individuals including those on ARVs in the form of PrEP for prevention. The data from this study can also be used to potentially develop effective treatment and management strategies for cognitively impaired PLWH.

Future Funding Opportunities: With the preliminary data obtained from this study we plan to apply for an R21 grant through the National Institutes of Health (NIH). The data obtained from this grant will also be used to support an application for a K-series NIH funded career development award.

Budget Breakdown
PERSONNEL:
Amanda Blair Spence, M.D., Principal Investigator, 0.60 calendar months; Dr. Spence is an Assistant Professor of Medicine in the Division of Infectious Diseases and Travel Medicine at Georgetown University. As the principal investigator Dr. Spence will lead and direct the studies proposed and will work directly with all members of the study team to ensure progress on this project. She will interpret results and be responsible for all manuscripts. No salary support is requested.

Stanley Fricke, Ph.D., Co-Investigator, 0.36 calendar months; Dr. Fricke is a Professor of Radiology and Director of Medical Physics at Georgetown University Medical Center. He also serves as an MRI physicist at Children's National Medical Center. He specialized in the integration of recording, registering, and processing of electromagnetic activity. He will provide expertise on neuroimaging. No salary support is requested.

Seble G. Kassaye, M.D., MS, Co-Investigator, 0.36 calendar months; Dr. Kassaye is an Associate Professor of Medicine in the Division of Infectious Diseases and Travel Medicine at Georgetown University as well as Principal Investigator of the Washington Metropolitan MACS/WIHS-CCS. She will provide expertise in epidemiology, HIV as well as assist with recruitment and collaboration with the cohort. No salary support is requested.

Raymond Scott Turner, M.D., Ph.D., Co-Investigator, 0.36 calendar months; Dr. Turner is a Professor of Neurology at Georgetown and Director of the Memory Disorders Program. He will provide expertise on dementia and cognitive disorders. No salary support is requested.

John VanMeter, M.D., Co-Investigator, 0.36 calendar months; Dr. VanMeter is an Associate Professor of Radiology at Georgetown University Medical Center. He also serves as the Director of the Center for Functional and Molecular Imaging at Georgetown. He will provide expertise in neuroimaging of those with cognitive impairment. No salary support is requested.

TBN, Phlebotomist, 0.24 calendar months; The Phlebotomist will collect samples for HIV Testing and prepare for storage.

OTHER EXPENSES:

Student Assistant: A student will be hired to administer neuropsychiatric testing and to collect patient hair samples. The student will dedicate approximately 54 hours to the study at $15 per hour. (54 hours X $15 per hour = $810)

Total: $810

Lab Cost: Neuroimaging will be performed to measure the diffusion of water across the blood brain barrier and the presence of certain metabolites in the brain. The cost of one hour of imaging is $200. I am estimating approximately 2 hours of imaging for 20 patients. ($200 per hour X 2 hours X 20 patients = $8,000)

HIV Testing will be performed on all HIV seronegative patients. I am estimating approximately 10 patients.
(Testing @ $120 X 10 patients = $1,200)

Collected samples must be stored. $281 is requested to cover the cost of storage.

Total: $9,481

Patient Cost: Participants will be reimbursed for participation in the study and also for transportation expenses.

Incentives - $130 X 20 patients = $2,600
Transportation - $20 X 20 patients = $400

Total: $3,000

Patient Recruitment: We will reimburse enrolled study patients that recruit other study participants that can be enrolled. Using this incentive, we anticipate 5 enrolled referrals. ($100 X 5 = $500)
Total: $500

Recommendation/Notes

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Spence, Amanda Blair

eRA COMMONS USER NAME (credential, e.g., agency login): SPENCEAB

POSITION TITLE: Assistant Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Kentucky	B.S.	05/2006	Biology
University of Louisville	M.D	05/2010	Medicine
University of Louisville	Residency	06/2013	Internal Medicine
Georgetown University	Fellowship	06/2017	Infectious Disease

A. Personal Statement

Both my research and clinical interests lie in the care of persons living with HIV. My vision is that my research will help to end the HIV epidemic and improve the lives of those living with the virus through effective treatment and management of the virus and virus related comorbidities. The development of strategies to predict, prevent, and treat/manage HIV-related comorbidities and therapy related toxicities are critical to these goals. I started my infectious disease fellowship in 2015 as an experienced internal medicine physician and developed clinical and research interests in the care of persons living with HIV as well as other populations with immune dysregulation. During my full-time clinical fellowship training and transition to a faculty position I designed and implemented studies examining the infectious complications of intestinal and multivisceral transplant recipients. I utilized the skills gained from these projects to transition to my work relating to HIV treatment and co-morbidities within the Women's Interagency HIV Study (WIHS) now MACS/WIHS Combined Cohort Study. This work is synergistic with my clinical practice where one is directly informative of the other. I have examined the differential classification of renal disease in women living with the virus, incidence of cancer and cancer screening rates, factors related to viral suppression and treatment success, as well as the effect of antiretroviral treatment on neurocognitive outcomes. My primary interest is in neurocognitive disorders among women living with HIV, and I received a pilot award to study longitudinal neurocognitive outcomes correlated with specific antiretroviral therapy. In this work, we noted emerging trends in the development of neurocognitive impairment in women exposed to specific drug classes. The work described in this proposal is an extension and continuation of this work where we will use neuroimaging to determine changes in neurometabolism related to antiretroviral drug exposure.

B. Positions and Honors

Positions and Employment

2010-2013	Resident, Department of Internal Medicine, University of Louisville, Louisville, KY
2013-2015	Attending Physician, Internal Medicine, Hospitalist, CogentHealthcare/Sound Physicians, Multiple Sites
2015-	Attending Physician, Internal Medicine, EchoLocums, Multiple Sites
2015-2017	Fellow, Division of Infectious Diseases and Travel Medicine, Georgetown University, Washington, DC

2017- Attending Physician, Division of Infectious Diseases and Travel Medicine, Georgetown University, Washington, DC

Other Experience and Professional Memberships

2010- American College of Physicians
2013- American Board of Internal Medicine, Internal Medicine, Board Certified
2013- Kentucky, Licensed Physician, License Number 45915
2013- Pennsylvania, Licensed Physician, License Number MD449519
2014- Ohio, Licensed Physician, License Number, 35.123001
2015- Maryland, Licensed Physician, License Number D80097
2015- District of Columbia, Licensed Physician, License Number MD042937
2015- Member, American Society of Microbiology
2015- Member, Antibiotic Stewardship Committee, Georgetown University Medical Center
2015- Member, Infection Control Committee, Georgetown University Medical Center
2015- Member, Infectious Diseases Society of America
2016-2017 Chief Fellow, Infectious Disease, Georgetown University Hospital
2017- American Board of Internal Medicine, Infectious Disease, Board Certified

Honors

2017 Georgetown Department of Medicine Faculty Development Award
2018 Georgetown Department of Medicine Faculty Development Award
2020 Alpha Omega Alpha

C. Contributions to Science

Neurocognition in women living with HIV

Neurologic complications of HIV remain common even in those on effective treatment, and direct neurotoxicity of antiretrovirals has been proposed as a mechanism for the continued prevalence of HAND. However, there are gaps in knowledge in epidemiology, presentation, pathogenesis, and treatment of neurocognitive disorders in women living with HIV. Our group has investigated exposures to specific antiretroviral drug classes and neurocognitive function overtime in women living with HIV (WLHW) demonstrating that a significant portion of virologically suppressed WLWH had evidence of neurocognitive dysfunction in the context of mostly long-standing HIV infection. We have also collaborated with other groups to understand these issues in WLWH.

- Dastgheyb R, Fitzgerald K, Chan C, Buchholz A, Xu Y, Williams D, Springer G, Anastos K, Gustafson D, **Spence A**, Adimora A. Neurocognitive Profiles Among Virally Suppressed Women with HIV. InJOURNAL OF NEUROVIROLOGY 2019 Oct 1 (Vol. 25, No. SUPPL 1, pp. S11-S12). 233 SPRING ST, NEW YORK, NY 10013 USA: SPRINGER.
- Williams DW, Li Y, Dastgheyb R, Fitzgerald KC, Maki PM, **Spence AB**, Gustafson DR, Milam J, Sharma A, Adimora AA, Ofotokun I. Associations between Antiretroviral Drugs on Depressive Symptomatology in Homogenous Subgroups of Women with HIV. Journal of Neuroimmune Pharmacology. 2020 Jan 13:1-4.
- Rubin LH, Li Y, Fitzgerald KC, Dastgheyb R, **Spence AB**, Maki PM, Sharma A, Gustafson DR, Milam J, Weber KM, Adimora AA. Associations between Antiretrovirals and Cognitive Function in Women with HIV. Journal of Neuroimmune Pharmacology. 2020 Mar 24:1-2.

HIV associated co-morbidities and aging

Since HIV has become a chronic illness with expected long-term survival for those receiving appropriate therapy, recognition and management of common comorbid conditions including those associated with aging have become increasingly important. I have contributed to the growing body of literature describing the effect of these comorbidities on persons living with HIV as well as preventative strategies.

- **Spence AB**, Levy ME, Monroe A, Castel A, Timpone J, Horberg M, Adams-Campbell L, Kumar P. Cancer Incidence and Cancer Screening Practices Among a Cohort of Persons Receiving HIV Care in Washington, DC. Journal of Community Health. *Accepted*. 2020
- Johnston CD, Hoover DR, Shi Q, Sharma A, Hanna DB, Anastos K, Tien PC, Fischl M, Gustafson D, **Spence A**, Karim R. White Blood Cell Counts, Lymphocyte Subsets, and Incident Diabetes

Mellitus in Women Living With and Without HIV. AIDS research and human retroviruses. 2020 Feb 1;36(2):131-3.

HIV treatment and outcomes

With the development of effective antiretroviral therapy persons living with HIV have life expectancies close to that of the HIV seronegative. However, there still remain challenges in implementation of effective strategies including treatment adherence, maintenance of viral suppression, and retention in care. I have contributed to research to understand the social, clinical, and provider interactions that drive long-term viral trajectories using a multidisciplinary team and a mixed methods approach including surveys, in-depth interviews, and focus discussions.

- **Spence AB**, Wang C, Wilson T, Anastos K, Cohen M, Greenblatt R, Fischl M, Ofotokun I, Kempf MC, Adimora A, Milam J, Ocampo JM, Kassaye, S. Viral Suppression After Intermittent Viremia: Women's Interagency HIV Study 1994-2015. Proceedings of the Conference on Retroviruses and Opportunistic Infections 2017 March 4-7; Boston, MA; 2017.
- Chandran A, Edmonds A, Benning L, Wentz E, Adedimeji A, Wilson TE, **Blair-Spence A**, Palar K, Cohen M, Adimora A. Longitudinal Associations Between Neighborhood Factors and HIV Care Outcomes in the WIHS. AIDS and Behavior. 2020 Mar 13:1-8.

Infections in transplant recipients

Data on the infectious complications of small intestinal and multivisceral transplantation is limited to small case series as this procedure is only performed in a limited number of centers world-wide. Our group conducted the largest single center study of these infections and outcomes and has added to the body of literature describing infectious complications in this population.

- **Spence, AB**, Natarajan, M., Fogleman, S., Biswas, R., Girlanda, R., & Timpone, J. (2019). Intra-abdominal infections among adult intestinal and multivisceral transplant recipients in the 2-year post-operative period. *Transplant Infectious Disease*, e13219.
- **Spence AB**, Fogleman S, Raffaele G, Matsumoto C, Kumar P, Biswas R, Fishein T, Timpone J. Intraabdominal infections (IAI) and bloodstream infections in small intestinal and multivisceral transplants (IMVTX) [abstract]. *Am J Transplant.* 2016; 17 (suppl 3)

D. Additional Information: Research Support and/or Scholastic Performance

Georgetown Department of Medicine Feasibility Award July 2020-
Novel neuroimaging techniques in women living with HIV
The purpose of this project is to establish the feasibility of novel neuroimaging techniques to measure blood brain barrier, neuroinflammation, and neurometabolites among women living with the virus.
Role: Principal Investigator

District of Columbia Center for AIDS Research Pilot Award May 2018-
Antiretrovirals and neurocognition in women living with HIV
The purpose of this project is to determine longitudinal neurocognitive outcomes among women living with HIV exposed to specific antiretrovirals, determine if serum biomarkers related to Alzheimer's disease are predictive of neurocognitive dysfunction and/or correlated with specific antiretroviral use, and determine if genetic polymorphisms associated with Alzheimer's disease are correlated with specific neurocognitive outcomes.
Role: Principal Investigator

Agency NIH/NIAID 5U01A134994-20 PI: Kassaye, Seble and Merenstein, Daniel July 2017-
Washington Women's Interagency HIV/AIDS Study (WIHS)
The goal of this project is to identify mechanisms of HIV disease progression in women living with the virus. Emphasis is placed on virological, immunological, and genetic factors as they affect interactions between HIV and the host including HIV-associated co-morbidities.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: John W. VanMeter, PhD

eRA COMMONS USER NAME (credential, e.g., agency login): jvanmeter

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Oklahoma, Norman, OK	BS	12/87	Computer Science
Dartmouth College, Hanover, NH	MS	05/91	Computer Science
Dartmouth College, Hanover, NH	PhD	09/93	Computer Science

A. Personal Statement

I have 25 years of experience in the field of neuroimaging and their application to the study of normal and abnormal brain development. My graduate work was on the development of automated methods for segmentation of structural MRI images of the brain by tissue class for input into a frameless stereotactic microscope for neurosurgery. This was followed by a 2-year position at NIH as a Staff Fellow in the Laboratory of Neuroscience in the National Institute of Aging, where I was on the leading edge of the application of fMRI and PET. In particular, I had a major role in the first study of the neurobiological basis of dyslexia using fMRI (Eden, et al. Nature, 1996) and several other studies examining sensory processing in the auditory and visual domains. Subsequently, I was Director of Research and Development at Sensor Systems, Inc for 5 years during which time I led the development of a commercial software package (MEDx) that is used by 300 research labs worldwide to analyze structural and functional MRI as well as the subsequent development of one of the first FDA-cleared fMRI clinical analysis packages. Further, I designed and developed the database and data transfer systems used for the MRI data collected in the NIH Pediatric Brain Development project (http://www.brain-child.org), a longitudinal study utilizing MRI that studied brain development in 500 children at 7 sites across the country. I have been PI of an NIH-funded STAART (Studies to Advance Autism Research and Treatment) center grant project, in which I have used a number of MRI-based techniques including fMRI, DTI, and MR spectroscopy to investigate the neurobiological basis of autism. In the STAART project, we have scanned over 140 children between the ages of 5 and 18, about half of whom are on the spectrum for Autism Disorder (ASD). My recently ended R01 (MPI) applied these techniques to prospectively identify specific deficits or features of underdevelopment in prefrontal cortex and other reward processing centers that predict alcohol initiation and act as risk factors in escalation of alcohol use in a longitudinal study of adolescents. Together, these experiences have led me to develop expertise in pediatric imaging, in longitudinal studies employing MRI, and in the integration of different kinds of MRI data, all three of which are highly relevant to the current application. In addition, I have experience in a range of technical approaches to MRI data analyses, such as connectivity of fMRI data, as outlined in more detail below.

I have been Director of Georgetown University's research-dedicated 3T MRI facility, the Center for Functional and Molecular Imaging (CFMI), since 2006. During that time, I have obtained major equipment grants: two Shared Instrumentation Grants from NIH with funding worth $1,800,000 that provided for the TIM and Prisma upgrades, and internal grant funding for the purchase of a $30,000 mock scanner. In addition, I was Core Director for Neuroimaging first on the Georgetown University/Children's National Medical Center GRC grant and subsequently the Georgetown-Howard Universities Center for Clinical and Translational Science (GHUCCTS) Clinical and Translational Science Award grant. I have also been the Georgetown site PI for the Neuroimaging Core of the Intellectual and Developmental Disabilities Research Center since 2006.

I worked with Dr. Spence on her proposal to formulate the best way to measure the measure blood brain barrier (BBB) permeability and metabolites relevant to cellular function using MR spectroscopy (MRS) My role on Dr.

Spence's grant will include setting up the MR scanning protocol, developing and implementing the data analysis procedures. I will also train Dr. Spence on the data analysis software and help to integrate the results with the rest of the study outcome measures. I will also help with the interpretation and subsequent preparation of manuscripts.

1. Shattuck KF, **VanMeter JW**. Task-based changes in proton MR spectroscopy signal during configural working memory in human medial temporal lobe. J Magn Reson Imaging. 2018 Mar;47(3):682-691. PMID: 28699178.
2. Eden GF, **VanMeter JW**, Rumsey J.M., Maisog J.M., Woods R.P., Zeffiro T.A. (1996). Abnormal processing of visual motion in dyslexia. Nature, 382, 66-69.

B. Positions And Honors

Positions and Employment

1988 - 1993	Research/Teaching Assistant, Dartmouth College, Hanover, NH
1990	Research Assistant, (ONR Grant #5-36537, "Frameless Stereotactic Microscope"), Dartmouth College, Hanover, NH
1993 - 1995	Staff Fellow, National Institute on Aging, NIH, Bethesda, MD
1995 - 2000	Director of Research and Development, Sensor Systems, Inc., Sterling, VA
2000 - 2003	Director of Methods Core, Center for the Study of Learning, Georgetown University, Washington, DC
2003 - 2009	Assistant Professor, Dept of Neurology, Georgetown University, Washington, DC Manager, 3T MRI Facility, Center for the Functional and Molecular Imaging, Georgetown University, Washington, DC
2006 - 2011	Interim Director, 3T MRI Facility, Center for the Functional and Molecular Imaging, Georgetown University, Washington, DC
2009 -	Associate Professor, Dept of Neurology, Georgetown University, Washington, DC
2011 -	Director, 3T MRI Facility, Center for the Functional and Molecular Imaging, Georgetown University, Washington, DC

C. Contribution to Science

1. My early publications are a reflection of my work in the technical development and application of fMRI and other neuroimaging techniques at a time when they were novel and difficult to implement. The range of research areas in which I worked at this time is a testament to my desire to surmount technical hurdles and to explore the full range of applications of these techniques. I worked on advancing a variety of methods, including parametric analysis, intersubject analysis, and spatial mapping. These approaches were applied to data sets examining motor, visual, and auditory systems, providing a better understanding of the functional anatomy of the brain. The five years I spent working in industry allowed me to push these techniques into the realm of clinical applications. Overall, this approach has allowed me to fully understand the power of these techniques and their limitations.
   a. **VanMeter** JW, Maisog JM, Zeffiro TA, Hallett M, Herscovitch P, Rapoport SI. Parametric analysis of functional neuroimages: application to a variable-rate motor task. Neuroimage. 1995;2:273-283. PMID: 9343612.
   b. Zeffiro TA, **Eden** GF, Woods RP, **VanMeter** JW. Intersubject analysis of fMRI data using spatial normalization. Adv Exp Med Biol. 1997;413:235-40. PMID: 9238505.
   c. Furey ML, Pietrini P, Haxby JV, Alexander GE, Lee HC, **VanMeter** JW, Grady CL, Shetty U, Rapoport SI, Shapiro MB, Freo U. Cholinergic stimulation alters performance and task-specific regional cerebral blood flow during working memory. Proc Natl Acad Sci USA. 1997;94(12):6512-6. PMCID: PMC21081.
   d. Wessinger CM, **VanMeter** JW, Tian B, Van Lare J, Pekar J, Rauschecker JP. Hierarchical organization of the human auditory cortex revealed by functional magnetic resonance imaging. J Cogn Neurosci. 2001;13(1):1-7. PMID: 11224904.
2. *In vivo* H^1 magnetic resonance spectroscopy (MRS) is a specialized MR technique that allows for the identification of the chemical makeup of tissue by quantifying the concentration of various molecules based on degree to which the structure of the molecule shields the hydrogen atoms from the scanner's field and thus modify it's resonance frequency. This level of detail provides unique information about biological processes such that it is possible to examine various metabolic processes and the change in various

metabolites in relation to diseases and their progression. My contributions have focused on the application of this technique in two areas: 1) modeling changes in prostrate cancer progression, 2) examining the impact on brain chemistry of a rare disease that affects liver metabolism of protein and 3) alterations in lactate in prefrontal cortex in GWI. In the latter work, we demonstrated a subtype of GWI in which an exercise stressor led to both increased prefrontal cortex lactate levels and decreased performance on a working memory task suggestive of dysfunction in cortical energetics.

a. Gropman AL, Seltzer RR, Yudkoff M, Sawyer A, **VanMeter JW**, Fricke ST, (2008). (1)H MRS allows brain phenotype differentiation in sisters with late onset ornithine transcarbamylase deficiency (OTCD) and discordant clinical presentations. Mol Genet Metab. 94(1):52-60. PMCID: PMC2486377.
b. Gropman AL, Fricke SF, Seltzer RR, Hailu A, Adeyemo A, Sawyer A, **VanMeter JW**, Gaillard WD, McCarter R, Tuchman M, Batshaw, ML. (2008). 1H MRS identifies symptomatic and asymptomatic subjects with partial ornithine transcarbamylase deficiency. Mol Genet Metab. 95(1-2):21-30. NIHMS ID: NIHMS74462.
c. Rayhan RU, Raksit MP, Timbol CR, Adewuyi O, **VanMeter JW**, Baraniuk JN (2013). Prefrontal lactate predicts exercise-induced cognitive dysfunction in Gulf War Illness. Am J Transl Res. 5(2):212-23. PMCID: PMC3612516.
d. Shattuck KF, **VanMeter JW**. Task-based changes in proton MR spectroscopy signal during configural working memory in human medial temporal lobe. J Magn Reson Imaging. 2018 Mar;47(3):682-691. doi: 10.1002/jmri.25816. PMID: 28699178.

3. Neuroimaging has become an increasingly important tool for understanding complex disorders that involve neurologic dysfunction at the system level but whose etiology remains largely unknown. Identifying the type(s) of neurological dysfunction in these disorders requires a multitude of imaging techniques to be applied. My contribution is this area is notable for the range of MRI-based techniques to identify neurobiological differences related to different disorders including Gulf War Illness, autism, rare genetic metabolic disorders. Together this work has led to better insight into the exact nature of the neurological dysfunction in GWI.

a. Washington SD, Gordon EM, Brar J, Warburton S, Sawyer AT, Wolfe A, Mease-Ference ER, Girton LE, Hailu A, Mbwana J, Gaillard WD, Kalbfleisch ML, **VanMeter** JW. Dysmaturation of the default mode network in autism. Hum Brain Mapp. 2014 Apr;35(4):1284-96. PubMed Central PMCID: PMC3651798.
b. Lozier LM, Cardinale EM, **VanMeter JW**, Marsh AA (2014). Mediation of the Relationship Between Callous-Unemotional Traits and Proactive Aggression by Amygdala Response to Fear Among Children With Conduct Problems. JAMA Psychiatry. 71(6):627-636. doi:10.1001/jamapsychiatry.2013.4540. PMID: 24671141.
c. Rayhan RU, Stevens BW, Raksit MP, Ripple JA, Timbol CR, Adewuyi O, **VanMeter JW**, Baraniuk JN. Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function. PloS One. 2013; 8(6):e63903. PMCID: PMC3683000.
d. Walitt B, Čeko M, Khatiwada M, Gracely JL, Rayhan R, **VanMeter JW**, Gracely RH. Characterizing "fibrofog": Subjective appraisal, objective performance, and task-related brain activity during a working memory task. Neuroimage Clin. 2016 Feb 2;11:173-80. https://doi/10.1016/j.nicl.2016.01.021. PMCID: PMC4761650.

4. Traditional fMRI data analysis has largely focused on local areas of increased activity. However, connectivity within the brain, both structural and functional, is important for understanding the ongoing dynamics of the brain and their alterations in various disorders. The cerebral cortex is comprised of clusters of cortical areas that are densely and reciprocally coupled and others that are globally interconnected. Functional connectivity is the observed coherence or correlation between a network of brain regions either during a task or at rest. I have published a range of studies using a number of ways of estimating these relationships and their effect on cognitive function, neurodevelopment, and Gulf War Illness.

a. Lee PS, Yerys BE, Della Rosa A, Foss-Feig J, Barnes KA, James JD, **VanMeter** JW, Vaidya CJ, Gaillard WD, Kenworthy LE. Functional connectivity of the inferior frontal cortex changes with age in children with autism spectrum disorders: an fcMRI study of response inhibition. Cereb Cortex. 2009;19(8):1787-94. PMCID: PMC2722789.
b. Gordon EM, Lee PS, Maisog JM, Foss-Feig J, Billington ME, **VanMeter** JW, Vaidya CJ. Strength of default mode resting-state connectivity relates to white matter integrity in children. Dev Sci. 2011;14(4):738-51. PMCID: PMC3117440.

c. Rayhan RU, Stevens BW, Timbol CR, Adewuyi O, Walitt B, **VanMeter JW**, Baraniuk JN. Increased brain white matter axial diffusivity associated with fatigue, pain and hyperalgesia in Gulf War Illness. PloS One. 2013; 8(3):e58493. PMCID: PMC3603990.
d. Rayhan RU, Washington SD, Garner R, Zajur K, Martinez Addiego F, **VanMeter JW**, Baraniuk JN. Exercise challenge alters Default Mode Network dynamics in Gulf War Illness. BMC Neurosci. 2019 Feb 21;20(1):7. https://doi/10.1186/s12868-019-0488-6. PMID: 30791869.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1XgRzj-ihTXQU/bibliography/public/

D. Research Support

Ongoing Research Support

GW160118 (Holton, Kathleen) 07/01/17-08/31/20 0.60 calendar months
DOD $46,530
Glutamate Neuro-Excitotoxicity in GWI
Role: Site-PI
This study is proposed to test whether glutamate restriction reduces GWI symptoms combined with a glutamate provocation. Positive results would support the hypothesis that glutamate is dysregulated in GWI.

2P30HD040677-11 (Gallo, Vittorio) 06/30/01-05/31/21 1.20 calendar months
NIH/NICHD $71,305
IDDRC at Children's National Medical Center
Role: Site-PI
This center focuses on developmental and cellular aspects of brain development and dysfunction and on the molecular basis of genetic diseases causing intellectual and other developmental disabilities.

1743521 (Eden, Guinevere) 03/01/18-02/28/22 0.16 calendar months
NSF/DRL $997,363
Brain Bases of Reading and Math in Children with Learning Disability
Role: Co-I
This project intends to uncover the neural bases of math and reading disabilities (MD and RD) using an intervention (tutoring) approach combined with brain imaging.

5R01HD081078-04 (Eden, Guinevere) 07/01/15-05/31/20 0.80 calendar months
NIH/NICHD $598,729
An fMRI Study on the Neural Basis of Combined Math and Reading
Role: Co-I
This project will investigate the neural correlates of successful math and reading interventions in children with comorbid MD+RD are unknown and provide important insights into MD+RD and its remediation.

4R01NS085131-04 (Baraniuk, James) 09/15/13-10/29/19 (NCE) 0.60 calendar months
NIH/NINDS $218,750
Exertional Exhaustion in Chronic Fatigue Syndrome
Role: Co-Investigator
This study uses a number of MRI based measures to examine changes in by an exercise challenge in chronic fatigue syndrome including: a working memory fMRI task, DTI, spectroscopy, and resting state fMRI. These exercise-induced alterations are expected to reveal mechanisms of CFS neuropathology, and provide opportunities for a new diagnostic test and insights into targets for development of drugs and other treatments.

Pending Research Support

R01 (VanMeter, Marsh, Fishbein) 09/01/20-08/31/25 1.20 calendar months
NIH/NIDA $657,504 (Georgetown)
Developmental Pathophysiology of Drug Use in a Very High-Risk Subtype of CD Youth
Role: MPI
This study proposes a secondary analysis of prospective longitudinal neuroimaging data being acquired in the multi-site NIH funded ABCD initiative. Our first aim is to shed light on how Callous and Unemotional (CU) traits specifically contribute to adverse Substance Use (SU) trajectories uncontaminated by the effects of previous use. Our second aim is to delineate the exacerbating effects of eventual SU on the pathophysiology of CU traits which, in turn, escalate SU. The third aim is to determine whether latent class trajectories of combinations of

high/low CU and SU are distinguishable, incorporating neural, cognitive, and behavioral covariates. Results will have significant clinical implications for precision-based interventions.

Completed Research Support

1S10OD023561-01 (VanMeter, John) 02/01/17–09/30/19 0.00 calendar months
NIH/OD $1,313,716
Role: PI
Prisma Upgrade for a Siemens 3T MRI Scanner
This grant funded the Prisma upgrade to the 3T MRI scanner used by 35 different PI's for their research and significantly improved the quality of the data collected (e.g., higher SNR) of this major resource.

5U54HD061221-13 (Gropman, Andrea) 08/01/15-09/30/19 0.60 calendar months
NIH/NICHD $38,032
Biomarkers of Neurological Injury and Recovery in UREA Cycle Disorders
Role: Co-Investigator
The major goal of this project was to establish a rare diseases research center (RDCRC) at Children's National Medical Center to study Urea Cycle Disorder (UCD).

W81XWH-15-1-0679 (Baraniuk, James) 09/15/13-12/28/18 0.60 calendar months
NIH/NINDS
START and STOP in Gulf War Illness
Role: Co-Investigator
GWI is a currently defined by a set of symptoms and complaints. A new way of thinking about Gulf War Disease: We established new ways to define GWI based on results from exercise stress tests, heart rate responses, magnetic resonance imaging (MRI), and a measure short nucleic acid strands (miRNA) in white blood cells and cerebrospinal fluid. This study aimed to identify better targets for therapeutic intervention.

NSF-000615741 (VanMeter, John) 08/01/17-07/31/18 0.00 calendar months
NSF-MRI $0
Role: PI
MRI: Acquisition of Prisma 3T MRI Upgrade
This grant was to also fund the Prisma upgrade but due to overlap was turned down.

1R01AA019983-01 (VanMeter, John) 09/20/11–06/30/18
NIH/NIAAA
Developmental fMRI Study of Alcohol Use in Adolescence
Role: MPI
This grant was a longitudinal investigation of executive function in adolescents to determine whether there are pre-existing deficits in prefrontal cortex that leads to early initiation of alcohol use and the role of various potential moderators.

3R01AA019983-04S1 (VanMeter, John) 07/20/2014–06/30/18
NIH/NIAAA
Developmental fMRI Study of Alcohol Use in Adolescence
Role: MPI
This supplement supported the expansion of the parent study to include an examination of all classes of illicit drug use as well as assessment of genes relevant to alcohol and drug use with respect to executive function and reward processing.

John Templeton Foundation (Marsh, Abigail) 03/01/14-02/28/17
Examining the Role of Shared Neural Representations of Pain-related Affect in Empathy and Altruism
Role: Co-Investigator
This grant explored the neurobiological basis of altruism using an experience and empathic pain and fear paradigm with altruistic kidney donors and healthy controls in an effort to better understand the phenomenon of shared neural mappings during empathy for fear, that which directly fuels altruistic motivation.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Fricke, Stanley Thomas, PhD

eRA COMMONS USER NAME (credential, e.g., agency login): Fricke

POSITION TITLE: MR-Physicist, Children's National Medical Center; Professor, George Washington University & Adjunct Professor of Oncology, Lombardi Comprehensive Center, Georgetown University Medical Center

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
North Park College, Chicago, IL	B.S.	1987	Physics/Mathematics
Massachusetts Institute of Technology, Cambridge, MA	Nucl.Eng./ SM	1991/1991	Nuclear Engineering/ Radiological Science
University of Torino, Turin, Italy	PhD	1997	Physics

A. Personal Statement

I trained at MIT (1987-1991) in nuclear engineering & radiological sciences in a joint program MIT/Harvard University's Medical School "Health Sciences and Technology" (HST). In HST I studied anatomy, quantitative physiology and the science of radiology. Graduate research at MIT's Francis Bitter National Magnet Laboratory (FBNML) centered on MRI equipment development with applications in micro MRI and dMRI. There I designed and build a gradient subsystem and interfaced it with FBNML's 8.4-Tesla spectrometer and helped to convert the spectrometer to a micro-MRI. This same subsystem was modified to work with the 4.7-Tesla oxford/IBM imaging system. My graduate Thesis was on MRI of "Biological Diffusion" (of Single Cells) where temperature dependence and restricted diffusion properties of single cells was studied. From 1999-2002 I worked at Wayne State University where I setup a Bruker 11.7-Tesla vertical bore small animal imaging/HR-MAS spectrometer laboratory and developed a magnetic resonance force microscope that was patented (USPTO Moore/Fricke US 6,683,451 B1, Jan. 27, 2004). From 2002-2007, I worked at Georgetown University (GU, Washington, DC) as the MRI physicist for the "center for functional and molecular imaging" (CFMI) responsible for training, safety training on CFMI's Siemens 3-Tesla MRI. Concurrently I was the director of GU's Small Animal Imaging Laboratory (7-Tesla 20-cm bore Bruker micro-Imaging). At GU I worked on a broad spectrum of MRI applications and equipment development for small animal imaging. I am currently Professor of Radiology and the Director of the Medical Physics Porgram.

Companies that I have owed two companies American Magnetics Incorporated (AMI) S.r.l. that provided financing for start-up radiological laboratories and International Magnet Group (IMG) S.r.l that performed general contracting for the installation of Radiological Equipment. I am currently the owner of HyperMC2 LLC that is a medical physics, consulting, custom constructions and service company that specializes in equipment integration that fills the gap between cutting edge scientific products differences to make them work in tandem for high-throughput pre-clinical imaging, tissue, cell and molecular analysis as well as other applications.

I hold credentials in HIPAA and licensed to survey diagnostic imaging equipment is Maryland, Virginia and the District of Columbia. I performed initial ACR certification for 4 MRI (two 1.5T and two 3T) and provide continuous recertification for the same. I am the MR-Physicist for the department of Diagnostic Imaging and Radiology, my role is to support MRI needs at CRI where my current research directions are the development of ultra fast gradient subsystems for MRI and animal management systems for multiplatform small animal imaging.

I successfully competed for an NHLBI intramural contract that created and supports the NHLBI branch for pediatric MRI guided cardio-catheterization entitled “MRI Diagnosis and Treatment of Cardiovascular and Lung Disease in Children” now located at our institution (CNMC) and I have turned over the PI title and responsibilities to Dr. Charles Berul. I have trained over 30,000 people in MRI safety and I host (together with MR:COMP, Germany) annual international MRI implanted devices safety workshops, this workshop empowers attendees the knowledge to provide MRI safety testing for implanted medical devices. I have sat on over a dozen NIH study section for medical devices, am a standing member and co-chair on a VA merit review study section and have been invited internationally to several study sections on medical equipment and electro-magnetic devices. I have been the PI on several government grants and contracts and investigator on several more for a total of 21.

For this project I will serve as the Georgetown University’s MRI physicist. I will provide MRI safety training and oversee the MRI safety aspects of this project. Also I am an MRI Spectroscopist (see section 6 of contributions to Science) and will work together with John VanMeter and his team to analyze spectroscopic data. As my graduate thesis was on MRI diffusion I will also work with Dr. VanMeter on Diffusion MRI findings of diffusion weighted MR angiograpy. We will help Dr. Amanda Blair Spence interpret the findings and put them into context.

B. Positions and Honors

1991-2002	President of International Magnet Group S.r.l., Florence, Italy
1999-2002	Assistant Professor of Psychiatry, Wayne State University School of Medicine, Detroit, MI
2001-2002	Director, Molecular Neuroimaging Laboratory, Wayne State University School of Medicine, Detroit, MI
2002-2006	Assistant Professor, Neuroscience, Georgetown University, Washington, DC
2002- 2007	Director, Neurobiological Magnetic Resonance Imaging Laboratory, Georgetown University, Washington, DC
2003-2007	Director of Physics, Center of Functional and Molecular Imaging, Georgetown University, Washington, DC
2004-Present	Consultant, IAMS pet animal imaging clinic, Vienna, VA
2005-2007	Director Histology and Micro Imaging Core, Neuroscience Department, Georgetown University, Washington, DC
2005-2007	Director of Small Animal Imaging Core, Lombardi Comprehensive Center, Georgetown University, Washington, DC
2006-2007	Associate Professor, Georgetown University, Washington, DC
2006-Present	Adjunct Professor, George Mason University
2007-Present	Adjunct Associate Professor, Georgetown University, Washington, DC
2007- Present	MR Physicist, Children’s National Medical Center, Washington, DC
20010-2014	Associate Professor, George Washington University, Washington, DC
2014-Present	Professor, George Washington University, Washington, DC
2015	Radiation Safety Officer, Children’s National Medical Center

C. Contributions to Science

1) Gradient Design

In 1987 I started working at the Francis Bitter National Magnet Laboratory under grant 2P41RR000995-16. There I learned the basics of Gradient coil and amplifier requirements and limitations. From 2007 – 2011 I have been working on rant R42HL086294-05 under bridge funding grant 9R42NS073289-06 from 2011 – 2014 current under no cost extension pm Ultra Fast Ultra High speed gradients. These gradients have performance that approaches 128,000 times that of today’s clinical systems. With 1.8T/m, 3-microsecond to flat top rise time, some of the anticipated uses are direct electron spin resonance imaging and Oxygen monitoring in proton therapy.

1. Weinberg IN, Stepanov PY, **Fricke ST,** Probst R, Urdaneta M, Warnow D, Sanders H, Glidden SC, McMillan A, Starewicz PM, Reilly JP: Increasing the oscillation frequency of strong magnetic fields above 101 kHz significantly raises peripheral nerve excitation thresholds. Med Phys. 2012 May;39(5):2578-83.
2. Weinberg IN, **Fricke ST**: Ultra-Fast Magnetic Field for Electron Paramagnetic Resonance Imaging Used in Monitoring Dose from Proton or Hadron Therapy. US Patent 2012/0326722 A1, Dec. 27, 2012

2) Animal Handling for Longitudinal Micro Imaging

In 2004 challenges in translational neuroscience in rodent brain models led my imaging laboratory to create the worlds highest replacement factor, most reliable animal positioning systems for multi-modality imaging. These systems allow for the placement of an animal on a holder and removal of the animal and then again placing the animal on the holder whereby the animal can be imaged in each Holder session and the same cell group within 100-micrometers can be found.

1. **Fricke, S.T.**, Vink, R., Chiodo, C., Cernak, I., Ileva, L. and Faden, A.I.: Consistent and reproducible slice selection in rodent brain using a novel stereotaxic device for MRI.: J Neuroscience Methods 2004 Jun;136(1):99-102.
2. Pirko, I., **Fricke, S.T.**, Johnson, A.J., Rodriguez, M., Macura, S.I.: Magnetic Resonance Imaging, Microscopy, and Spectroscopy of the Central Nervous System in Experimental Animals.: NeuroRx 2005 Apr.; 2(2):250-264
3. Wilson E., Chiodo C., Wong K.H., **Fricke S.T.** Jung M., Cleary K.. Robotically assisted small animal MRI-guided mouse biopsy. Proc. SPIE 7625, Medical Imaging 2010: Visualization, Image-Guided Procedures, and Modeling, 762520 (February 23, 2010)
4. Heier CR, Guerron AD, Korotcov A, Lin S, Gordish-Dressman H, **Fricke ST**, Sze RW, Hoffman EP3, Wang P, Nagaraju K.: eCollection 2014. Non-invasive MRI and spectroscopy of mdx mice reveal temporal changes in dystrophic muscle imaging and in energy deficits. PLoS One. 2014 Nov 12;9(11):e112477.

3) Manganese as an MRI contrast agent.

In 1986 –as an undergraduate– I worked with Dr.s Anderson. Yamanshi, Lister and Thyvalikakath on Manganese chloride as a potential T1 and T2 shifting agent for MRI. Our work showed that MnCl2 solutions were stable and useful as MRI contrast agents. In 2009, working with Dr. Stoll and others we were issued a patent on Mn12 clusters. These Mn particles have about a 100-fold increase in contrast-ability over Mn given same molecular concentrations. We expect this to lower Mn toxicity issues.

1. Anderson, D.W., Yamanshi W.S., **Fricke, S.M**(T)**.**, Lester, P.D.: Frequency Characteristics of Relaxation Rates of Paramagnetic Solutions MnCl2 and NiCl2 From 0.15 to 6.3 T, Society of Magnetic Resonance in Medicine, New York, NY, 1987.
2. Anderson, D.W., Yamanshi W.S., **Fricke, S.M(T**)., Lester, P.D.: Frequency-Dependence of Relaxation-Times for MnCl2 and NiCl2 Solutions, Medical Physics 14 (4): 709-709, Jul.-Aug., 1987.
3. Stoll S., Mertzman J., Van Kouren E., Albanese C., **Fricke S.** Manganese-OXO Clusters as Contrast Agents for Magnetic Resonance Imaging. WO 2010/048268 A2, Apr. 12, 2010
4. Rodriguez O, Schaefer ML, Wester B, Lee YC, Boggs N, Conner HA, Merkle AC, **Fricke ST**, Albanese C, Koliatsos V.: Manganese-Enhanced MRI as a diagnostic and dispositional tool after mild-moderate blast TBI. J Neurotrauma. 2016 Apr 1;33(7):662-71

4) Magnetic Resonance Microscopy

Developed a new microscope that leveraged technology pioneered By Rugar et.al.. Whereas Rugar's instrument could be used on solid material only the microscope that Dr. Moore and I developed can be used on biological tissue. We believe this to be highest resolution microscope that uses magnetic resonance imaging technology on record. I designed the entire gradient system and several variants of the same for this microscope. I also designed the radiofrequency transmission chain, fiberoptic interferometer receiver system and specific high vacuum pass-through ports. I performed the final assembly, testing and data collection on this instrument. Our patent has been cited several hundred times and used as prior art in dozens of other patents by other researchers and inventors.

1. Moore, J.G., **Fricke, S.T.** Inventors; Wayne State University, assignee. Magnetic Resonance Force Microscope for the Study of Biological Systems. US 6,683,451 B1, Jan. 27,2004.

5) Prostate MRI/MRS

MRI imaging of the prostate requires knowledge of the prostate anatomy, as well as knowledge of normal and abnormal prostate chemistry. In mouse models it is imperative to identify tumor models that exhibit both the morphology as well as the chemistry so that when the tumor model is used for determining the effectiveness of chemical treatment is is obvious both that the tumor is reduced or eliminated and that the chemical environment returns to normal.

1. Albanese C., Rodriguez O.C., Johnson M.D., **Fricke S.T.**: Modeling of prostate cancer: basic research and preclinical applications.: Drug Discovery Today: Disease Models, 2005, 2(1):7-13.
2. **Fricke, S.T.**; Rodriguez, O.C.; VanMeter, J.W.; Dettin, L.E.; Casimiro, M.C.; Chien, C.D.; Ojeifo, J.O.; Johnson, M.D.; Albanese, C.: In Vivo Magnetic Resonance Volumetric and Spectroscopic Analysis of Mouse Prostate Cancer Models.: The Prostate 2006 May;66(7):708-17.

3. Collins S.P., **Fricke, S.T**., Rodriguez,O.C., Hailu, A., Ileva, L., Wong, K.H. Sutherland, D., McRae, D.A., Gagnon, G.J., Lynch,J.H., Dritschilo, A., Albanese, C.: High Field Magnetic Resonance Spectroscopic Imaging (MRSI) of the Prostate: Translational Research from Murine Prostate Cancer Models to Human Subjects. Implications for Safe Dose Escalation to Dominant Intraprostatic Lesions Using CyberKnife Radiosurgery. ASTRO Translational Research in Radiation Oncology, August 5-6, 2005

6) Human Spectroscopy and Metabolism

Human metabolism can be captured in-vivo, "real time" with non-invasive measurements.

1. Whitehead MT, **Fricke ST**, Gropman AL. Structural brain defects. Clin Perinatol. 2015 Jun;42(2):337-61.
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List of published work from PubMed: http://www.ncbi.nlm.nih.gov/pubmed/?term=stanley+fricke

D. Additional Information: Research Support and/or Scholastic Performance

Completed (Select 9 of 21):

NIH/National Institute of Neurological Disorders and Stroke

9R42NS073289-06 **Fricke, Stanley (PI)** 08/01/2011 - 07/31/2014 **3 calendar**
Bio-Effects if Ultra-High MRI Gradient Slew Rates
Goal: To improve MRI for neurological applications by reducing side effects of ultra-high magnetic gradient fields. The project is validating its central hypothesis in Phase II studies, sponsored by NHLBI.

HHSN268200800025C Fricke, Stanley (PI) 09/01/2009 - 08/31/2014. **6 calendar**
NIH/NHLBI Pediatric Magnetic Resonance Imaging (MRI) Diagnosis/Treatment Program
Goal: To enhance diagnosis and evaluation of pediatric and adult congenital heart disease, reduce/eliminate techniques that use ionizing radiation and reduce/eliminate sedation by creating ultra-fast imaging techniques.

NIH/National Institute of Biomedical Imaging and Bioengineering

1R43EB014626-01A1 Weinberg (PI) 01/09/2012 - 31/08/2014 **0.6 calendar**
Goals: Improve performance of MRI systems, while reducing manufacturing costs. This achieved by replacing existing wire-based gradient coil construction methods with novel proprietary 3-D additive manufacturing techniques. In Phase I, will port gradient designs to the additive manufacturing process and build and characterize a prototype gradient coil. Prepare for Phase II by offering a design of a human head-coil based on the novel manufacturing technology.
Role: Consultant 5% effort

DMRDP/Johns Hopkins 3176E

W81XWH-10-DMRDP-BRA **Cernak (PI)** 10/01/2010 – 9/30/2013 **0.6 calendar**
(DM102465) Sub Project "MR Imaging" (PI)(Fricke) Applied Physics Laboratory Contract
The Importance of Neurogenic Inflammation in Blast-Induced Neurotrauma
Goal: To study the importance of neurogenic inflammation in blast-induced neurotrauma.
Role: Sub-Project Principal Investigator 10% effort

U54HD061221 (Batshaw) 09/30/2003 - 07/31/2014 **1.2 calendar**
NIH/NCRR
Rare Diseases Clinical Research Consortia (RDRC) for the RDCR Network

Goals: To investigate the natural history, morbidity, mortality and biomarkers in children and adults with UCD, to perform a Phase II/III trial of N-carbamylglutamate to assess its efficacy in normalizing ureagenesis in patients with carbamyl phosphate 1 and ornithine transcarbamylase deficiencies, and assess neural mechanisms of injury in OTCD using structural MRI, functional MRI, and magnetic resonance spectroscopy.
Role Investigator (Magnetic Resonance Imaging Spectroscopy Physicist)

R42HL086294-05 Fricke, Stanley (PI) 12/01/2007 - 05/31/2011
NIH/NHLBI/Weinberg Medical Physics
Bio-Effects if Ultra-High MRI Gradient Slew Rates
Goal: To create MRI imaging gradients fast enough to overcome any biological effects of magnetic field switching.

1827 Fricke, Stanley (PI) 12/15/2009 – 07/14/2011
CTSI-CN
From In-Vivo Images to histology, the 'Miter Box'
Goal: Develop a new tissue sectioning “miter box” for guiding cutting blades to make cross-sectional (coronal in mouse coordinates) cuts that are indexed to in-vivo imaging “slices”.

R41-NS050141-01 Fricke, Stanley (PI) 07/15/2004 - 06/15/2005
NIH/National Institute of Neurological Disorders and Stroke
Small Animal Handling Devices for Multiplatform Imaging
Goal: Create and distribute animal handling systems that are robust, safe, easy to use and able to provide high-quality radiological images across multiple imaging platforms including MRI, CAT, PET and SPECT.

SB1341-06-Q-0573 Fricke, Stanley (PI) 08/15/2006 - 2/28/2007
National Institute of Standards and Technology (NIST)
Nano Particles and Nanoflow
Goal: To quantify the delivery of contrast agents in mouse models. To fabricate and characterize nanoparticle contrast agents in phantoms and small animals.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM 01/01/2021	THROUGH 12/31/2021

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Amanda Spence	PD/PI	0.60				0	0	0
Stanley Fricke	Co-investigator	0.36				0	0	0
Seble G. Kassaye	Co-investigator	0.36				0	0	0
Raymond Turner	Co-investigator	0.36				0	0	0
John VanMeter	Co-invetigator	0.36				0	0	0
TBN	Phlebotomist	0.24			45,000	921	288	1,209
	SUBTOTALS →					921	288	1,209

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)*	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Student Assistant - $810; Patient Neuroimaging - $8,000; HIV Testing - $1,200 Sample Storage - $281; Patient Incentives & Transportation $3,000 Recruitment Cost - $500	13,791
CONSORTIUM/CONTRACTUAL COSTS / DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*	**$** 15,000
CONSORTIUM/CONTRACTUAL COSTS / FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD	15,000

BUDGET JUSTIFICATION

PERSONNEL:

Amanda Blair Spence, M.D., Principal Investigator, 0.60 calendar months; Dr. Spence is an Assistant Professor of Medicine in the Division of Infectious Diseases and Travel Medicine at Georgetown University. As the principal investigator Dr. Spence will lead and direct the studies proposed and will work directly with all members of the study team to ensure progress on this project. She will interpret results and be responsible for all manuscripts. No salary support is requested.

Stanley Fricke, Ph.D., Co-Investigator, 0.36 calendar months; Dr. Fricke is a Professor of Radiology and Director of Medical Physics at Georgetown University Medical Center. He also serves as an MRI physicist at Children's National Medical Center. He specialized in the integration of recording, registering, and processing of electromagnetic activity. He will provide expertise on neuroimaging. No salary support is requested.

Seble G. Kassaye, M.D., MS, Co-Investigator, 0.36 calendar months; Dr. Kassaye is an Associate Professor of Medicine in the Division of Infectious Diseases and Travel Medicine at Georgetown University as well as Principal Investigator of the Washington Metropolitan MACS/WIHS-CCS. She will provide expertise in epidemiology, HIV as well as assist with recruitment and collaboration with the cohort. No salary support is requested.

Raymond Scott Turner, M.D., Ph.D., Co-Investigator, 0.36 calendar months; Dr. Turner is a Professor of Neurology at Georgetown and Director of the Memory Disorders Program. He will provide expertise on dementia and cognitive disorders. No salary support is requested.

John VanMeter, M.D., Co-Investigator, 0.36 calendar months; Dr. VanMeter is an Associate Professor of Radiology at Georgetown University Medical Center. He also serves as the Director of the Center for Functional and Molecular Imaging at Georgetown. He will provide expertise in neuroimaging of those with cognitive impairment. No salary support is requested.

TBN, Phlebotomist, 0.24 calendar months; The Phlebotomist will collect samples for HIV Testing and prepare for storage.

OTHER EXPENSES:

Student Assistant: A student will be hired to administer neuropsychiatric testing and to collect patient hair samples. The student will dedicate approximately 54 hours to the study at $15 per hour. (54 hours X $15 per hour = $810)

Total: $810

Lab Cost: Neuroimaging will be performed to measure the diffusion of water across the blood brain barrier and the presence of certain metabolites in the brain. The cost of one hour of imaging is $200. I am estimating approximately 2 hours of imaging for 20 patients. ($200 per hour X 2 hours X 20 patients = $8,000)

HIV Testing will be performed on all HIV seronegative patients. I am estimating approximately 10 patients. (Testing @ $120 X 10 patients = $1,200)

Collected samples must be stored. $281 is requested to cover the cost of storage.

Total: $9,481

Patient Cost: Participants will be reimbursed for participation in the study and also for transportation expenses.

Incentives - $130 X 20 patients = $2,600
Transportation - $20 X 20 patients = $400

Total: $3,000

Patient Recruitment: We will reimburse enrolled study patients that recruit other study participants that can be enrolled. Using this incentive, we anticipate 5 enrolled referrals. ($100 X 5 = $500)

Total: $500

Principal Investigator: Amanda Blair Spence, MD

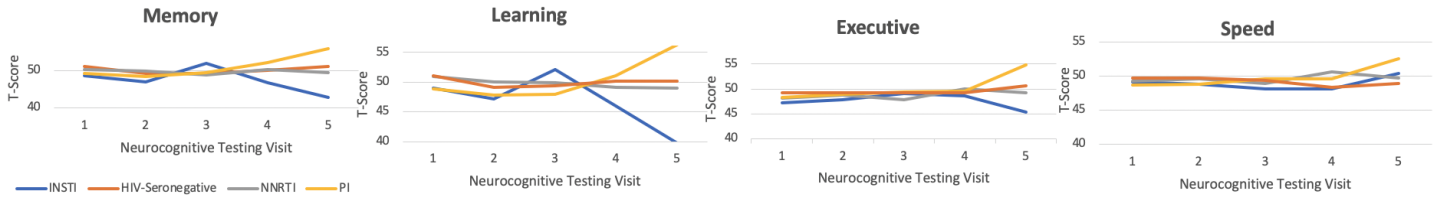
Request Amount: $15,000

Project Title: Association between HIV antiretroviral treatment and central nervous system energy metabolism

Project Summary:
Cognitive disorders affect over one-half of all persons living with HIV (PLWH) and the only known treatment and preventive strategy are effective treatment with antiretrovirals (ARVs).[1,2] However, direct neurotoxicity of ARVs may contribute to the ongoing problem of cognitive impairment in treated HIV.[3] Work from our group demonstrated worsening of some cognitive domains with the use of specific ARV classes of medication.(unpublished data) However, the mechanisms of this phenomenon is unknown. Changes in neurometabolism have been associated with cognitive dysfunction, acute HIV infection, and older medications used to treat HIV.[4–7] How current first line therapy affects neurometabolism and correlates with cognitive outcomes is unknown. We propose to conduct a pilot study to evaluate differences in select brain metabolites using magnetic resonance spectroscopy (MRS) among individuals treated with currently recommended first line ARVs for HIV treatment or prevention and correlate with cognitive testing.

Statement of Problem:
Despite the widespread use of antiretroviral therapy (ART) cognitive disorders are common among PLWH, and up to 52% of PLWH have evidence of cognitive dysfunction.[1] Treatment with effective ART improves cognition, but neurologic complications remain common despite therapy.[8–10] Effective HIV treatment requires sustained viral suppression through treatment with ARVs and is associated with improved health outcomes and decreased risk of viral transmission.[11,12] Our group demonstrated worsening cognitive function among women living with HIV (WLWH) despite viral suppression with variability based on type of ARV exposure (FIGURE 1). Women exposed to integrase inhibitors (INSTIs), a first line ART agent for HIV therapy, exhibited worsening of executive function, memory, and cognitive processing speed.[11,13] We also noted worsening of executive function with treatment using non-nucleoside reverse transcriptase inhibitors (NNRTIs), an alternative class of ART.[11,13]

Figure 1: Longitudinal changes the neurocognition of treated WLWH by drug class exposure



There are no consensus recommendations on ART management strategies for cognitively impaired PLWH or persons at risk for cognitive impairment. Clinicians and researchers have attempted to implement ART treatments with greater central nervous system (CNS) penetration for patients with cognitive impairment as a treatment strategy as greater CNS penetration is correlated with decreased HIV RNA in the cerebrospinal fluid (CSF).[14] However, studies yielded mixed results with improved, worsened, or equivocal cognitive testing with use of agents with higher CNS penetration.[15–18] In addition, clinical trials with non-antiviral agents have not been successful.[2] Continuous ART is required for sustained viral suppression and improves other health outcomes, but has mixed effects on cognitive trajectories. Thus a better understanding of the pathogenesis of cognitive impairment among PLWH including the specific effects of ART is required to effectively develop treatment plans based on current available agents and develop new treatment strategies.

When HIV enters the CNS, virions are released that can infect surrounding microglia and astrocytes. This leads to the release of neurotoxic viral proteins and glial activation, and it is thought that this chronic inflammatory response at least partly drives the progression of cognitive impairment. Maintenance of this chronic inflammation is postulated to cause metabolism changes in glia cells with resulting lower metabolic support to neurons and consequently changes in cognition.[19] Changes in metabolism in PLWH occur in acute HIV infection, correlate with virologic control, and are predictive of cognitive impairment.[4,5,20] These metabolic changes are not only due to HIV infection but are also associated with older HIV antiviral treatments.[6,7] This suggests potential neurotoxicity of some ARVs as these metabolites are linked to neuronal health.[21] Metabolic changes related to current first line treatment strategies including the INSTIs and newer NNRTIs are unknown. This is important to understand not only for PLWH, but also for HIV-seronegative individuals who are taking ARVs for prevention of HIV in the form of pre-exposure prophylaxis (PrEP) for the prevention of HIV. These individuals do not have HIV, but receive potentially toxic medications for preventative purposes.

Specific Aims:

The evolution of changes and factors that influence changes including ARVs in brain metabolism among PLWH are poorly understood. Thus, studies are needed to assess the contribution of ART to brain metabolism.

Specific Aim 1: To determine differences in brain metabolites in the frontal cortex, hippocampus, and medial temporal lobes using proton magnetic resonance spectroscopy (MRS) among age matched treated HIV-seropositive persons on integrase inhibitors (INSTIs) or (NNRTIs), HIV-seronegative individuals on PrEP, and HIV-seronegative individuals.

Metabolic changes related to neuroinflammation, HIV direct toxicity, and/or drug exposure contribute to neurocognitive outcomes.[19] In our prior work, we identified changes in multiple cognitive domains related to INSTI or NNRTI exposure, but the underlying mechanisms driving these changes are unknown and may be related to CNS metabolism.(unpublished data) Changes in CNS metabolism are observed with older therapies used to treat HIV, but the effect current first line therapies including the INSTIs or the newer NNRTIs on CNS metabolism are unknown.[6,7] We propose to use MRS to determine differences in brain metabolites (choline, n-acetylaspartate, myo-inositol, creatinine, lactate, acetate) in the frontal cortex, hippocampus, and medial temporal lobes among HIV-seropositive individuals on INSTIs, HIV-seropositive individuals on NNRTIs, HIV-seronegative individuals on PrEP, and HIV-seronegative individuals not taking any ARV medications.

Specific Aim 2: To correlate the levels of brain metabolites in the frontal cortex, hippocampus, and medial temporal lobes using proton magnetic resonance spectroscopy (MRS) with HIV-serostatus, exposure to ARVs, and cognitive testing.

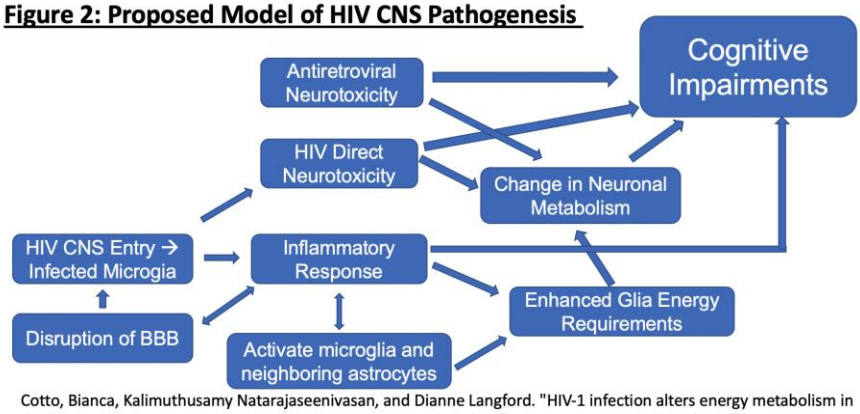
Changes in brain metabolism occur in early HIV-infection and in HIV associated cognitive disorders.[4,22–25] However, how these changes are related to neurocognitive changes in treatment experienced individuals with HIV and HIV-seronegative individuals exposed to ARVs for prevention is unknown. All study participants will complete a validated neuropsychiatry battery of testing and a modified Lawton Independent Activities of Daily Living questionnaire to assess functional impairment.[26,27] Neuropsychiatric testing outcomes will be stratified by HIV-serostatus and ARV use.

Research Strategy (Significance):

Once HIV enters the CNS via infected macrophages/monocytes across the BBB virions are released that can infect surrounding microglia and astrocytes. This leads to the release of neurotoxic viral proteins and glial activation, and it is thought that this chronic inflammatory response promotes cognitive impairment among HIV-

seropositive individuals. Maintenance of this chronic inflammation can cause changes in the metabolism in glia cells which lead to less metabolic support to neurons and consequently changes in neurocognition (FIGURE 2).[19] Alterations in cellular metabolism, and specific metabolites in the CNS such as N-acetylaspartate, myo-inositol, glutamate, can be used as markers for neuronal health and glial activation. Other metabolites such as lactate and citrate are markers of cognitive impairment in PLWH and increased aerobic glycolysis is associated with worsening cognitive status.[19,28] Even among those on effective therapy there are alterations in the level of glucose.[29]

Figure 2: Proposed Model of HIV CNS Pathogenesis



Cotto, Bianca, Kalimuthusamy Natarajaseenivasan, and Dianne Langford. "HIV-1 infection alters energy metabolism in the brain: contributions to HIV-associated neurocognitive disorders." *Progress in neurobiology* (2019): 101616.

Changes in brain mitochondria have been described in patients taking older HIV treatment therapies including stavudine and didanosine, and *in vitro* mitochondrial alterations in neuronal cell lines and primary neuron cultures have been described with efavirenz, a type of HIV treatment in the NNRTI class of ARVs.[6,7] However, differential changes in energy metabolism related to current first line HIV treatment agents are unknown and have not been described in the literature. Understanding the alterations in energy metabolism related to specific ARV drug exposure will allow for further exploration of (1) ARV neurotoxicity; (2) effectiveness of specific ART in mediating ongoing inflammation; and (3) effectiveness of specific therapies in controlling the CNS viral reservoir both chronically and early in HIV infection latency induces a unique metabolic signature.[30] This information can be used to develop effective treatment and management strategies for cognitively impaired PLWH.

This study is of particular relevance to the District of Columbia (DC) as there are currently 12,322 residents living with HIV. More than one-half are over the age of 50.[31] In this aging population of PLWH, the recognition and management of comorbid conditions including those associated with aging such as cognitive disorders is imperative.[32,33] The Centers for Disease Control's (CDC) Health Brain Initiative has declared cognitive impairment a public health priority as these disorders not only affect the quality of life of the person living with the disorder and caregivers but also place a strain on the healthcare system.[34] The work outlined in this proposal may aid in understanding the pathogenesis of this public health priority and support future studies of treatment strategies.

Research Strategy (Innovation):

Changes in brain metabolism among PLWH have clearly been noted in the literature.[4,22–25] Changes have been described as they relate to acute HIV infection, cognitive disorders among PLWH, HIV viral load in CNS, immune status, and as a predictors of cognitive impairment.[4,5,20,35] Studies related to ARVs and changes in brain metabolism are limited evaluation of changes related to initiation of ART in patients with and without cognitive impairment.[21,36,37] ***However, how these changes relate to specific ARV class in either HIV-seropositive or HIV-seronegative individuals is unknown and has never been studied. Incorporating a population of HIV-seronegative individuals, already receiving ARVs for a medical indication will provide an HIV-seronegative control with drug exposure and allow for the examination of drug effect without the confounder of the virus.***

Research Strategy (Approach):

In order to evaluate our primary aims of determining differences in brain metabolites among individuals treated with first line ARVs and correlate with cognitive outcomes we will utilize MRS to determine the levels of brain

metabolites as this methodology has been used to determine change in brain metabolism in HIV infection and among those with cognitive impairment with and without HIV.[4,38,39] The treatment study groups consist of: HIV-seropositive persons on INSTIs or NNRTIs, HIV-seronegative individuals on PrEP, and HIV-seronegative individuals as we plan to evaluate first line treatment regimens for both HIV treatment and prevention. INSTIs including dolutegravir and bictegravir are first treatments for HIV treatment naive individuals. The NNRTIs of doravirine and rilpivirine are alternative treatment regimens.[13,40] First line treatments for HIV prevention include combination tenofovir alafenamide and emtricitabine.[41] We plan to recruit from HIV-seropositive persons having at least 2 years of drug exposure and are virally suppressed to remove the confounder of virus and ensure adequate exposure to the drug. A one year exposure to ARVs was chosen for HIV-seronegative individuals as tenofovir alafenamide/emtricitabine combination was only approved for PrEP in October 2019. Prior to that the only approved agent for PrEP was tenofovir disoproxil-fumarate/emtricitabine.[42] Having both an HIV-seropositive group and a HIV-seronegative group both exposed to ARVs will allow for the exploration of drug effect on metabolism without the confounder of HIV. We will evaluate choline, n-acetylaspartate, myo-inositol, creatinine, lactate, acetate in the frontal cortex, hippocampus, and medial temporal lobes as these metabolites are associated with neuronal health and can be altered by HIV and initation of ART.[21] As our prior work demonstrated changes in executive function, memory, learning, and cognitive processing we selected the frontal cortex, hippocampus, and medial temporal lobes for evaluation.[43,44] A validated neuropsychiatric battery will be used to evaluate the following cognitive domains: verbal learning and memory, executive function, processing speed, attention, motor skills, processing speed, and language fluency.[26,27]

Statement on any animal testing: No non-human animal experimentation will be performed as part of this research proposal.

Research Design and Methods:

General Strategy/Study Design Overview: We will characterize differences in the levels of specific neurometabolites among treated HIV-seropositive individuals, HIV-seronegative individuals treated with ARVs in form of PrEP, and HIV-seronegative not currently taking ARVs. We will recruit study participants from an existing cohort of clinical patients and use a snowball chain referral sampling method where current study participants refer contacts for additional recruitment.

Study Team Members: Amanda Blair Spence, MD, the principal investigator, is a trained infectious disease specialist and has examined cognitive impairment among PLWH. John VanMeter, PhD is the Director of the Center for Functional and Molecular Imaging (CFMI) and will provide expertise in neuroimaging and facilitate the use of the CFMI for neuroimaging. Stanley Fricke, PhD is a Professor of Radiology and Director of Medical Physics and will provide expertise on neuroimaging and magnetic resonance spectroscopy. Princy Kumar, MD is the Chief of Infectious Diseases at Georgetown, she leads a division that provides care for over 1000 PLWH, and has extensive research in the development of ARVs. She will assist with recruitment and provide additional expertise on ARVs. Seble Kassaye, MD, MS is an Associate Professor of Infectious Disease, principal investigator of the MACS-WIHS-CCS and STAR-cohort studies (two large HIV-cohort studies), and epidemiologist. Dr. Kassaye will assist with recruitment, analysis, and data interpretation.

Recruitment Strategy: We will recruit participants from an existing cohort of HIV-seropositive and HIV-seronegative PrEP clinic patients at Georgetown. We will use a snowball recruitment method to recruit HIV-seronegative individuals not taking ARVs as well as additional HIV-seropositive and HIV-seronegative PrEP participants. Additional advertising may be pursued using Research Match, an established web-based recruitment strategy accessible to our site through the Georgetown-Howard Universities Center for Clinical and Translational Science (http://www.georgetownhowardctsa.org/).

Study Population: Inclusion criteria for HIV-seropositive participants include: (1) HIV viral suppression defined as HIV RNA ≤200 copies/mL for 2 years; (2) Treatment with a stable ART regimen for 2 years; (3) Treatment with an INSTI (dolutegravir or bictegravir) with a backbone of tenofovir alafenamide/emtricitabine or an NNRTI (rilpivirine or doravirine) with a backbone of tenofovir alafenamide/emtricitabine; and (4) Age 25-55. Inclusion criteria for HIV-seronegative ART treated (PrEP) participants include: (1) Treatment with PrEP for at least 1 year; (3) Negative HIV testing at enrollment; and (3) Age 25-55. Inclusion criteria for HIV-seronegative participants not on ART include (1) Negative HIV testing at enrollment and (2) Age 25-55. All participants should be able to read and communicate in English to complete the neuropsychiatric testing. Five participants will be recruited for each treatment group.

Neuropsychiatric Testing Strategy: All study participants will complete a validated neuropsychiatry battery of testing (TABLE 1) as well as a modified Lawton Independent Activities of Daily Living questionnaire to assess functional impairment with a trained study team member.[26,27]

Table 1: Neurocognitive Testing Strategy

TEST	COGNITIVE DOMAIN
Hopkins Verbal Learning Test	Verbal Learning and Memory
Stroop Test	Executive Functioning
Trail Making Test Part B	Executive Functioning
Symbol Digit Modalities Test	Processing Speed
Letter Number Span	Attention and working memory
Grooved Pegboard	Motor
Stroop Color Naming	Processing Speed
Verbal Fluency	Language Fluency
Lawson's Activities of Daily Living	N/A

Magnetic Resonance Imaging/Spectroscopy (MRI/MRS): Participants will undergo MRS at the Center for Functional and Molecular Imaging (CFMI) at Georgetown to determine levels of specific brain metabolites including choline, n-acetylaspartate, myo-inositol, creatinine, lactate, and acetate in the frontal cortex, hippocampus, and medial temporal lobes. These specific areas were chosen as prior work by our group demonstrated changes in executive function, memory, learning, and cognitive processing in chronically treated WLWH.

Additional Testing: HIV seronegative individuals will undergo rapid HIV testing on enrollment to document HIV-negative serostatus. A peripheral blood draw, urine, and hair sample will be obtained and stored for future drug levels and inflammatory marker analysis.

Analysis Plan: We will estimate the quantification of metabolites contributing to the observed H-MRS spectra with LCModel software, version 6.3 (Provencher, Inc, Oakville, Canada). The software will fit a linear combination of canonical metabolite peaks from an empirical scanner-specific basis set to estimate concentrations and uncertainties contributing to observed data with a minimum of subjective input. Unsuppressed water suppressed spectra will be used to estimate metabolite concentrations using a scaling technique. In addition, eddy current effects and improve baseline fit, line shape, and zero-order phase corrections are applied within the model. The main outcome variables will be estimates of the following metabolite concentrations: choline, n-acetylaspartate, myo-inositol, creatinine, lactate, acetate for each participant. Cramer-Rao lower bounds will be used to ensure data quality. Descriptive statistics will be used to characterize group differences.

As an exploratory descriptive analysis, we will describe levels of specific metabolites by HIV-serostatus and neurocognitive testing. The study is designed to demonstrate feasibility and generate preliminary data for sample size calculations that will be used for future funding application. Thus, a sample size calculation was not included.

Anticipated Challenges: While we do not anticipate any challenges recruiting treated HIV-seropositive individuals from our clinic population, recruitment of HIV-seronegative individuals will be more challenging. We have an established population of HIV-seronegative individuals on PrEP in our clinic which we will recruit from, but we will also use a snowball method of recruitment for HIV-seronegative individuals. Our group has

successfully employed this strategy in the past to recruit for research study participants. Additional challenges include the logistics of performing neuroimaging during the COVID-19 pandemic. Our team has successfully restarted research with university approval and this includes studies utilizing neuroimaging. The CFMI where the scans are performed is open and appropriate participant screening, physical distancing, and environmental cleaning measures are in place to ensure the safety of research participants and staff. The guidelines will be followed closely during the study, and all team members will have appropriate training. Updates to the protocol will be made as needed based on current university and Centers for Disease Control guidelines.

Future Plans: The results of this study will establish feasibility and reproducibility of neuroimaging techniques to measure brain metabolites. The preliminary data will be used for sample size calculation and to support the application for larger adequately powered studies assessing differences in neurometabolites among patients exposed to specific ARVs. These studies will include (1) longitudinal and cross-sectional studies of ARV treatment experienced patients; (2) longitudinal studies at initiation of HIV treatment; and studies in HIV-seronegative individuals including those on ARVs in the form of PrEP for prevention. The data from this study can also be used to potentially develop effective treatment and management strategies for cognitively impaired PLWH.

Future Funding Opportunities: With the preliminary data obtained from this study we plan to apply for an R21 grant through the National Institutes of Health (NIH). The data obtained from this grant will also be used to support an application for a K-series NIH funded career development award.

Program Area: Medical Research

References:

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8. Robertson, K. R. *et al.* Highly active antiretroviral therapy improves neurocognitive functioning. *J. Acquir. Immune Defic. Syndr.* **36**, 562–566 (2004).
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11. Saag, M. S. *et al.* Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2018 Recommendations of the International Antiviral Society-USA Panel. *JAMA* **320**, 379–396 (2018).
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