RESEARCH SCHOLAR PROGRAM – 2018

SUPERVISOR & PROJECT INFORMATION FORM

Please complete and return, via email only (crems.programs@utoronto.ca) by ***November 3rd 2017*** *(forms received after this date will not be posted).*

Supervisor Information

Name: Andrew Lim

Email: andrew.lim@utoronto.ca

Degree: MD, MMSc

SGS Appointment (IMS, IHPME, LMP etc..): IMS

Academic Rank: Assistant Professor

Field of Research: Sleep, Circadian Rhythms, Genetics, Epigenetics, Dementia

Research Institution Affiliation (if applicable): Sunnybrook Research Institute

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): I am available in the laboratory at least 30 hours a week. At least 2 hours per week is spent in formal group lab meetings. An addition 2-4 hours a week is available for formal face-to-face instruction of each student.

Project Information

Title: The Brain Changes in Sleep Apnea Study

Description (max 500 words):

Cerebral small vessel disease (SVD) is a key pathological correlate of dementia and other forms of neurological disability in older adults. However, an incomplete understanding of the physiological changes leading to SVD in human populations, and in particular a paucity of identifiable treatable risk factors, has impeded the development of clinical programs to prevent SVD and its neurological sequelae. Recent work in model organisms has suggested that dysfunction of the perivascular space (PVS) may play an important role in the development of SVD and in connecting it to neurological sequelae such as dementia. In these model organisms, key modulators/regulators of PVS function include slow-wave sleep, sympathetic nervous system activity, and hypoxemia. Sleep apnea, a disorder characterized by repeated obstruction of the upper airway in sleep leading to hypoxemia, high tonic and phasic sympathetic tone, and loss of slow wave sleep, may be an important modulator of PVS function, and hence risk factor for SVD and its neurological sequelae. Indeed, sleep apnea is associated with an increased burden of white matter hyperintensities – a marker of SVD cerebrovascular pathology – in community-dwelling adults, and we have shown that sleep fragmentation – a key consequence of sleep apnea – is associated with cerebral arteriolosclerosis at autopsy, and enlarged perivascular spaces on MRI. Moreover, sleep apnea is common, affecting up to 25% of middle-aged adults and 40% of older adults, and effectively treatable with continuous positive airway pressure (CPAP) leading to resolution of hypoxia, normalization of sleep architecture, and normalization of sympathetic nervous system activity. **The overall purpose of this study is to test the hypothesis that in patients with severe sleep apnea, treatment with 6 months of CPAP will result in improved small vessel, and especially perivascular, function and that these changes will mirror improvements in sleep architecture, nocturnal hypoxemia, nocturnal blood pressure, and phasic sympathetic activity.** Specifically, we hypothesize that 6 months of CPAP will result in decreased perivascular space volume, improved arterial pulsatility, improved endothelial dysfunction as measured by serum biomarkers, improved cerebrovascular reactivity, and improved white matter structure. We are studying 80 adults attending the sleep clinics at Sunnybrook Health Sciences Centre and the University of Edinburgh. Participants are undergoing home-based assessment with Health Canada approved wearable devices (24 hours of ambulatory blood pressure monitoring with a portable monitor, 7 days of actigraphy to assess sleep duration and fragmentation, and 1 night of finger-probe peripheral arterial tonometry and oximetry to assess cardiorespiratory physiology including sleep apnea), completion of a sleep and health questionnaire, banking of blood for endothelial biomarkers, cognitive evaluation, and an MRI of the brain, at 2 time points: 1) after initial polysomnographic diagnosis of sleep apnea but before the initiation of CPAP 2) after 6 months of CPAP. We anticipate that after treatment with CPAP, participants with sleep apnea will show improvements in multiple measures of cerebrovascular biology, that these differences will parallel differences in blood pressure, sympathetic nervous system activity, sleep architecture, and hypoxemia, and that they will be predictive of improvements in cognition.

This project is funded by a grant from the Leducq foundation (Co-PI Black; Co-I Lim)

If human subjects are involved, have Ethics been obtained?

☒ YES ☐ NO ☐ Application Submitted ☐ N/A

Do you expect this work will be published within the 20 months?

☒ YES ☐ NO ☐ Uncertain

Student's roles and responsibilities (please be specific)

Please indicate who will serve as the student's direct report (PI, PhD student, technician etc…)

Recruitment for this project is scheduled to begin in January 2018. The student will report directly to the PI. A full-time dedicated study coordinator will carry out the bulk of recruitment and physiological measurements, although the MD student will have an opportunity to learn the techniques and participate in this. The MD student's role will be primarily supervisory and analytic – supervising data collection, refining and implementing in-house algorithms in R and MATLAB to analyze the physiologic and psychometric data (EEG, PSG, accelerometry, peripheral arterial tonometry, ambulatory blood pressure, psytchometric testing), and then testing for an effect of CPAP on these measures. Although the bulk of the MR image analysis will be performed by the McIntosh and Black laboratories with whom we collaborate at Sunnybrook, the student will also get an opportunity to learn these techniques, and will play a key role in demonstrating the impact of CPAP on these outcomes. Anticipated manuscript(s) will demonstrate the impact of CPAP on physiologic (e.g. sympathetic nervous system measures, serum biomarkers), functional (e.g. cognition), and MR imaging measures of cerebrovascular health. As the work will involve a reasonable degree of programming and data analytics, the ideal student will have programming (especially R and MATLAB, although any language acceptable) and statistics experience, coupled with an undergraduate-level knowledge of mathematics and neurobiology.

Recent manuscripts from the laboratory related to this area include:

1. Lim AS, Yu L, Schneider JA, Bennett DA, Buchman AS. Sleep Fragmentation, Cerebral Arteriolosclerosis, and Brain Infarct Pathology in Community-Dwelling Older People. Stroke. 2016 Feb 1;47(2):516-8.