UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

TOXICOLOGY GROUP TRAINEE SEMINAR PROGRAM

Wednesday, December 17, 2014, 2:10–3:30 pm

Room 1210, 144 College Street

Title: **Prospects of Gene Therapy for Fragile X Syndrome**

Trainee: **SHERVIN GHOLIZADEH**

Supervisor: Dr. David Hampson

Advisory Committee: Dr. Derek van der Kooy and Dr. James Eubanks

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ABSTRACT:

Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by a trinucleotide repeat expansion in the FMR1 gene that codes for fragile X mental retardation protein (FMRP). As there is no pharmacological cure for FXS, the overarching goal of the present study was to determine whether restoring FMRP expression in the brains of the Fmr1 knockout mouse model of FXS could provide a comprehensive reversal of the disorder. We used a single-stranded adeno associated virus serotype 9 (AAV9) that contained a major isoform of FMRP, driven by the neuron specific synapsin promoter. The vector was delivered to the brain via a single bilateral intracerebroventricular injection into neonatal Fmr1 KO mice on postnatal day 5 (in the first phase of the study) or 0-1 (in the second phase). Western blotting and immunocytochemical analyses of AAV-FMRP-injected mice revealed neuron-specific FMRP expression in the striatum, hippocampus, retrosplenial cortex, and cingulate cortex. AAV-FMRP injections reversed the pathologically elevated repetitive behavior and the deficit in social dominance behavior seen in Fmr1 KO mice in phase 1, as well as the elevated startle response and lower anxiety in phase 2. These results provide the first proof of principle that gene therapy can correct specific behavioral abnormalities in the mouse model of FXS.

Title: **Assessing the incidence of heavy prenatal alcohol exposure among two geographically distinct populations**

Trainee: **IRA NIGHTINGALE**

Supervisor: Dr. Gideon Koren

Advisory Committee: Dr. Bhushan Kapur, Dr. Micheline Piquette-Miller

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ABSTRACT:

Objective: The focus of these studies is to measure the incidence of heavy prenatal alcohol exposure during pregnancy by meconium fatty-acid ethyl esters (FAEEs) analysis in a population-based setting. Fetal alcohol spectrum disorder (FASD) manifests a continuum of permanent birth defects and neurodevelopmental impairments that originate from maternal alcohol use during pregnancy. The number of FASD cases in parts of the sub-Saharan Africa is growing, which is a cause for concern due to the socio-economic impact. The second study conducted in Miramichi Regional Hospital is one of the only sites in Canada conducting routine toxicological screening of women in labour through urinalysis to facilitate identification of infants at risk for neonatal abstinence syndrome amongst other medical/social risk factors. Prenatal alcohol screening is not currently conducted, and carries the potential to improve infant outcomes through early interventions. The second study proposes to pilot the use of meconium FAEE analysis in order to determine the incidence of prenatal alcohol exposure in this population and divert alcohol-exposed neonates for early developmental monitoring by the Department of Paediatrics.

Method: FAEE meconium concentrations greater than 2.00 nmol/g are considered indicative of heavy prenatal alcohol exposure during the last two trimesters of pregnancy. Samples were frozen and shipped to the Motherisk Laboratory for analysis. FAEEs were analyzed by gas chromatography-mass spectrometry and quantified using deuterated internal standards. Study #1 - Meconium samples were collected from 510 newborns between September-November 2013 at Mbarara Regional Referral Hospital. Each meconium sample was accompanied with a questionnaire containing neonatal/maternal information. Study #2 - Meconium samples are being collected from consented neonates in Miramichi Regional Hospital for a one-year duration (May 2014- April 2015). Currently, there has been ~100 meconium samples collected.

Results: Study #1 - A total of 612 mothers delivered during the study period and 510 (83.3%) were successfully enrolled. 16% of mothers reported maternal alcohol consumption throughout pregnancy. Of the 504 samples, 10 samples (2%) have tested above the positive threshold concentration indicating heavy prenatal alcohol exposure during the 2^{nd}-3^{rd} trimester of pregnancy. Study #2 - Ongoing collection/sample analysis is currently being conducted for the Miramichi Regional Hospital study population.

Conclusions: The identification of specific populations in need of basic epidemiologic research on the incidence of prenatal alcohol exposure is urgently required in order to create awareness and reduce the devastation of FASD. This is the first population-wide study of an entire neonatal population examining fetal alcohol exposure conducted in Uganda. The information determined through the second study can inform the degree of regional need for programs dealing with alcohol abuse prevention during pregnancy and intervention services. This study is the first of its kind; evaluating the feasibility of universal meconium FAEE screening in an entire regional birth cohort.