PhD DEFENCE Thursday, April 25th, 2019
Student: Abhinav Ajaykumar
Title: DYNAMICS OF TELOMERE LENGTH AND MITOCHONDRIAL HEALTH IN RELATION TO COMBINATION ANTIRETROVIRAL THERAPY (CART) EXPOSURE: A COHORT STUDY OF HIV/CART-EXPOSED UNINFECTED CHILDREN AND CELL CULTURE INVESTIGATION
Time and location: 2:00 PM; Room 3402 B+C, Djavad Mowafaghian Centre for Brain Health, 2215 Wesbrook Mall, UBC Point Grey Campus, Vancouver, BC
Supervisor: Dr. Hélène Côté

ABSTRACT

Combination antiretroviral therapy (cART) during pregnancy has considerably reduced the risk of mother-to-child HIV transmission and the number of cART-exposed HIV-exposed uninfected (HEU) children is increasing. With current treatment guidelines recommending the initiation of immediate, lifelong cART at HIV diagnosis, women conceive on therapy and HEU *in utero* cART exposure spans the entire gestation period. Many antiretrovirals (ARV) cross the placenta and could exert long-term effects on HEUs. Some ARVs inhibit human telomerase reverse transcriptase (hTERT). As hTERT elongates telomeres and protects mitochondrial DNA (mtDNA) from oxidative damage, its inhibition could lead to shorter telomeres and/or increased mitochondrial dysfunction. Leukocyte telomere length (LTL) and mtDNA alterations are biomarkers of cellular aging, and have been implicated in aging and age-related diseases.

The objective of my research was to compare HEU and HIV-unexposed uninfected (HUU) children at birth and in early life, with respect to their LTL and blood mtDNA content, and investigate relationships with *in utero* cART exposure.

I measured LTL and blood mtDNA content in 324 HEU and 306 HUU children between 0-3y of age. I found that exposure to maternal cART did not affect LTL at birth, as it was similar in both groups. However, mtDNA content was higher among HEU children, particularly those exposed to boosted-protease inhibitor (PI/r) cART. This increase in mtDNA persisted at least up to age three. Additionally, maternal smoking during pregnancy affected both LTL and mtDNA content at birth.

Given these effects of cART on children's mtDNA, I aimed to further characterize how various cART regimens affect mitochondrial health using an *in vitro* human cell culture model. I also investigated the potential mitochondrial protection conferred by hTERT. I found that dolutegravir (DTG)-containing regimens negatively affected mitochondria, decreased cell proliferation and increased apoptosis. PI/r-containing regimens also affected certain mitochondrial parameters, but this effect was mitigated by mitochondrial hTERT while that of DTG was not.

DTG is increasingly used worldwide, including in pregnancy. These novel findings merit further investigation to evaluate the long-term safety of newer ARV exposure, and the predictive value of these biomarkers on HEU health outcomes. Together, this knowledge could inform treatment guidelines.