PhD DEFENCE Friday, February 2nd, 2018

Student: Sara Saberi

Title: DYNAMICS OF TELOMERE LENGTH AND MITOCHONDRIAL DNA CONTENT IN A COHORT STUDY OF HIV-INFECTED AND HIV-UNINFECTED PREGNANT WOMEN AND CELL CULTURE MODELS

Time and location: 9:00am PST; Room 200 of the Graduate Student Centre (6371 Crescent Road), UBC Vancouver Point Grey Campus

Supervisor: Dr. Helene Cote

ABSTRACT

Globally, women constitute around 50% of HIV-infected individuals. While mother-to child transmission accounts for 90% of new HIV infections among children, combination antiretroviral therapy (cART) reduces the risk from 25% to <2%. Treatment guidelines now promote lifelong cART for all persons living with HIV. This implies that more women will be conceiving on cART and exposing their unborn child over a longer period. Nucleoside reverse transcriptase inhibitors can have off target effects. These drugs can inhibit reverse transcriptase activity of telomerase, which could lead to a shortening of leukocyte telomere length (LTL). LTL has been described as a marker of cellular aging and a predictor of age-related diseases over time. Several antiretrovirals (ARVs) can exert mitochondrial toxicity, leading to mitochondrial dysfunction. The overarching hypothesis of my research was that LTL and mitochondrial DNA (mtDNA) content would be affected by cART in clinical and cell culture samples.

I measured LTL in blood samples collected from 64 HIV-infected and 41 HIVuninfected women at three visits during pregnancy using monochromatic multiplex quantitative polymerase chain reaction. CART treatment status during pregnancy was not associated with shorter LTL. However, smoking throughout pregnancy and receiving a ritonavir-boosted protease inhibitor regimen were independently associated with shorter LTL among HIV-infected women. Whether these reflect telomere attrition or redistribution of cellular subsets is unclear.

In clinical studies, it is challenging to distinguish between the effects of HIV vs. those of cART. I used cultured placental and T-lymphoblast cells to study the changes in mtDNA content following either short term exposure to individual ARVs at increasing concentrations, or longer term exposure (21 days) to cART regimens at 1×Cmax, (maximum concentration) prior to returning the cells to cART-free medium for ten more days, to allow recovery/repair. Most ARVs and cART studied here induced increased mtDNA content, postulated to reflect mitochondria biogenesis in response to cellular stresses and/or damage, something that could promote the clonal expansion of mtDNA mutations. However, changes in mtDNA content in response to ARV exposure can be both bidirectional and cell-specific; and appear to be reversible. Mitochondria

morphological changes were suggestive of increased mitophagy to preserve mitochondrial health.