Dr. Wasundara Fernando *was born in Ginigathena, which is a very small town in Sri Lanka. She completed her high school education at Devi Balika Vidyalaya, Colombo, and obtained her BSc (special degree in Pharmacy) from University of Colombo in 2008. She moved to Canada in 2012 for her graduate studies and obtained her MSc and PhD degrees from Dalhousie University. Dr. Fernando's doctoral research focused on investigating the potential of food biomolecules to fight breast cancer. In recognition of the quality of her doctoral thesis, she was awarded the 2019 Dalhousie University Graduate Studies in Pathology Prize. Currently, Dr. Fernando works as a postdoctoral scholar at Dalhousie University as a Dr. David H. Hubel postdoctoral fellowship awardee. Her current research is aimed at targeting the metabolic profiles of breast cancer stem cells to improve the efficacy of immunotherapy. Outside her research, she enjoys music, poetry, painting and astronomy.*

Theme Seminar

A Journey: from a Chemist to a Cancer Biologist

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Cells in an organism are under constant exposure to extrinsic and intrinsic stressors. Molecular mechanisms are in place to dampen the detrimental effects on the cell at the level of cellular pathways and also at the level of gene expression. Ribonucleic Acid (RNA) Polymerase II is the enzyme that synthesizes messenger Ribonucleic Acid (mRNA) in eukaryotes, as the first step of gene expression. Pausing of RNA Polymerase II is widely implicated in regulating gene expression during development. An orchestration by a wide variety of transcription factors determines the output of transcription. Using both molecular and genome-wide approaches, I have shown that Polymerase II pausing is a signature that can be acquired during gene activation. My work further showed that gene activation can occur through pause release in a signal-specific manner.

To explore molecular mechanisms in dysregulation in transcription, my work continued in a laboratory focused on hematologic malignancies, focusing on *RUNX1*, an essential transcription factor in blood development. *RUNX1* mutations are a frequent occurrence in Myelodysplastic Syndrome (MDS) and leukemia. Germline loss-of-function mutations in *RUNX1* leads to Familial Platelet Disorder with propensity to develop Acute Myeloid Leukemia (FPD/AML). These heterozygous mutations lead to low platelet numbers, improper platelet structure and function and increased risk of developing leukemia later in life. Previous work by others have shown that introducing wild type *RUNX1* into patient derived iPSCs can alleviate the disease phenotype in FPD/AML models. Our efforts are focused towards identifying means to enhance the function of the wild type protein.

Src family kinases (SFK) reduce the activity of *RUNX1* by phosphorylation. Known SFK inhibitors (SFKi) such as PP2 and Dasatinib have been previously shown to increase activity of *RUNX1*. I have shown that these SFKis can drive the expression of many *RUNX1* downstream target genes. Using patient derived iPSC models, we show that the treatment with PP2 and Dassatinib can rescue some of the FPD/AML disease phenotypes including hematopoietic progenitor cell numbers. To identify additional compounds that can enhance *RUNX1* activity, we have performed a high-throughput small molecule screen of libraries of compounds using a luciferase-based model. Based on the data that I have generated, currently a clinical trial is being formulated together with NIH. I anticipate that these small molecule inhibitors can alleviate platelet dysfunction and dampen leukemic predisposition in patients that carry *RUNX1* heterozygous germline mutations.