Focus on Faculty #54
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I am an Assistant Professor in the Department of Medicine, Division of Experimental Medicine and an Associate Member of the Gerald Bronfman Department of Oncology at McGill. I completed a Bachelor's degree at the University of Toronto, a Master's degree at the University of Florida and a PhD at McGill.

For Greeks, Easter is the most important holiday and at the end of the Lenten fasting period there is a celebration where the family gathers to partake in the roasting of and feasting on the Paschal lamb. In my family, close to thirty of us would gather at my uncle's home where we would sit in his living-dining room and enjoy everything the holiday had to offer! As I was very busy with my studies and research the holiday gave me the opportunity to re-connect with my extended family. However, for my family, my studies were as foreign to them as the English language was when they first arrived to Canada. Trying to explain in lay terms the mechanisms of triple repeat expansion in Myotonic Dystrophy or polyA tail length changes in transcripts regulating the developmental patterning of Drosophila embryos was not an easy task. Inevitably they would ask the question "why are you doing all this?"

The transformative experience that led me to answer this question was a course I took on gene regulation in my graduating year at the University of Toronto. It was something about gene regulation, from transcription initiation, splicing, 3'-end cleavage and polyadenylation, and transport, that captured my interest and led me to pursue graduate studies and postdoctoral fellowships in this field and eventually to start my own research program. Within the complicated understanding of the processes of gene regulation the driving factor for me was and has always been – Discovery. Discovery provides an incredible euphoric feeling, especially when your eyes are the first to see the results on a gel, blot, embryo, or sequencing/mass spec. It provides scientists a link to the chain of knowledge of their predecessors and allows for the creation of new links for future scientists. Discovery is inexhaustible as there will always be questions to ask.

Efforts of the Human Genome Project and database consortia like TCGA and other "omics" approaches including transcriptomics, proteomics, and *in silico* network analysis, combined with a multitude of traditional molecular and biochemistry techniques, have significantly advanced our understanding of the genetic landscape of cancers beyond what we would fathom a decade ago. However, within this context, we must also keep in mind, how this wealth of knowledge (data) can lead to better outcomes, either through diagnostics or therapeutics, for different malignancies.

It is this "whole" understanding that I am endeavoring to apply to my research and teaching. My research into androgen receptor (AR) function has focused on the multi-faceted role for AR in prostate cancer (PCa) progression. It was clear that the AR played a pivotal role in PCa progression, but gene expression profiles could not solely account for the observable disease outcomes. Moreover, androgen directed therapeutics was proving more detrimental to patients, resulting in drug resistance and more aggressive forms of the disease. Gain-of-function properties of mutated proteins found in cancer play a profound role in cancer etiology and progression; mutated AR is critical in PCa progression and gives cancer cells powerful new ways to proliferate. My work has made it possible to link new gain-of-function properties to enhancing genetic alterations pushing tumoral heterogeneity and subsequent selection processes to further cell proliferation. To address this, I undertook a mass spectrometry approach, using clinically relevant AR mutations, to study the proteomic profile of AR. Through this process, we have redefined the functionality of AR beyond its known classical transcriptional properties. By using a sophisticated network analysis approach applied for the first time to proteomic data, AR had direct effects on RNA metabolism (splicing and translation); it mediates DNA methylation, interacts with proteasomes, and regulates cell metabolism. This work resulted in what I believe is a seminal contribution to our understanding of AR function, but more importantly it provided insight into the dynamic molecular changes that undergo during disease progression. Moreover, it set up a research program for the training of several undergraduate and graduate students, to now begin to dissect these individual pathways.

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