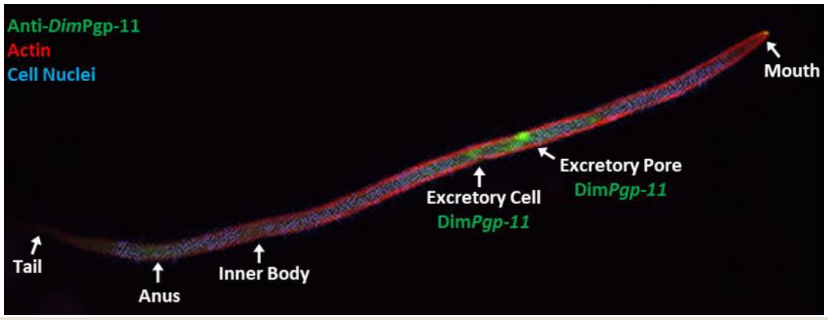

Anthelmintic resistance in *Dirofilaria immitis*: Mechanisms and molecular markers

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Abstract

Dirofilaria immitis is a parasitic filarial nematode of veterinary importance. It is the causative agent of dirofilariosis, a potentially fatal pulmonary infection of canids and felines. Dirofilariosis can be prevented with macrocyclic lactone (ML)-based chemoprophylaxis. The MLs are potent parasiticides which target the invertebrate specific glutamate gated chloride channels (GluCls). The MLs bind pseudo-irreversibly to the GluCls opening the pore leading to hyperpolarization and paralysis of the neuromuscular system, impacting alimentation, locomotion, and mediation of sensory input and response. The MLs are a class of generally safe drugs and have been used as dirofilariosis chemoprophylaxis since the mid 1980s. Unfortunately, the continuous use of ML-based chemoprophylactics over the last four decades has led to the development of drug resistance. These ML-resistant *D. immitis* isolates are phenotypically and genotypically distinct from the wildtype susceptible populations.

The aim of the thesis was to characterize potential mechanisms and molecular markers of ML resistance in *D. immitis*. For the first objective I developed of an *in vitro* colorimetric enzymatic activity assay based on the concept that MLs act on the microfilariae (mf) by paralyzing the excretory pore muscle, inhibiting the release of enzymes, metabolites, and immunomodulatory molecules. I demonstrated that the secretion of the metabolic enzyme triosephosphate isomerase (TPI) via the excretory-secretory pore (ESP) was unaffected by ivermectin (IVM) exposure in ML-resistant isolates. For the second objective I characterized *D. immitis* P-glycoprotein 11 (*Dim*Pgp-11), a gene strongly linked to the ML-resistant phenotype. I measured the level of genetic polymorphism, constitutive expression, and demonstrated, for the first time, that *Dim*Pgp-11 is strategically located surrounding the ESP in the mf lifestage. Lastly, I assessed the tryptophan catabolism enzyme, kynureninase (*Dim*KYNU-1), a gene with newly identified genetic changes associated with ML resistance. I validated the genetic polymorphism and measured its potential impact of the constitutive expression of *Dim*KYNU-1 and its downstream product 3-hydroxyanthranilic acid (3HA). The thesis provides a novel perspective on the phenotypic and genotypic consequences of the development of multigenic ML resistance in *D. immitis* for the possible future development of anti-filarial pharmaceuticals.

About the Candidate

Emily obtained her Bachelor of Science with a Double Major in Biology and English from the University of King's College in 2017. She joined the McGill University Institute of Parasitology in 2017 as a Masters student and was fast-tracked to the PhD program in 2018. She is a doctoral candidate in a cotutelle program at McGill University and Toulouse III: Université Paul Sabatier. Her research focuses on mechanisms of action of anthelmintic drugs and the genetics of drug resistance in the parasitic filarial nematode *Dirofilaria immitis*.