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YOU ARE INVITED TO ATTEND THE

DEFENSE OF THE DOCTORAL

DISSERTATION

"Drug discovery in Brugia malayi – Identification of an adult selective filaricidal target"

by

Tamara L. Kreiss

Molecular Biology, Genetics, & Cancer Track

B.S., 2012, Montclair State University
M.S., 2014, Montclair State University

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Biochemistry & Molecular Biology

Friday, October 8th, 2021
10:30 A.M.

Zoom Meeting

https://zoom.us/j/93827737543?pwd=T21SOHhHZGVnbjE1ckJTVHZDTmpwdz09

Meeting ID: 938 2773 7543

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ABSTRACT

Parasitic diseases are responsible for tremendous suffering and morbidity throughout the world. Novel treatment approaches depend upon an understanding of the critical functions required for parasite survival. Filarial diseases such as onchocerciasis (River blindness), lymphatic filariasis (elephantiasis) and loiasis (*Loa loa* infection) are caused by a group of parasitic nematodes transmitted to humans through the bite of infected black flies, mosquitos, and mango flies, respectively. These diseases result in significant morbidity along with economic and psychosocial impacts in endemic areas, disfiguring and incapacitating millions of individuals. Current mass drug administration (MDA) includes ivermectin, albendazole and/or diethylcarbamazine which effectively eliminate microfilariae, the larval forms which are taken up by insect vectors, but not adult parasites. There is an unmet medical need for new drugs which effectively target the adult parasites and limit responses to microfilariae killing, especially in areas with co-endemic *L. loa* infection. In addition, drugs targeting adult parasites may help in elimination programs by shortening the MDA. We have identified a novel series of compounds which selectively affect adult viability. Furthermore, these compounds appear to affect filarial parasite epigenetic regulatory mechanisms compromising parasite survival. These compounds provide both a pharmacological probe for the study of filarial parasite epigenetic mechanisms important for survival as well as providing a potential opportunity for anti-filarial drug development. Our screening program and medicinal chemistry efforts have led to the identification and development of a novel series of compounds with potent killing activity against adult filarial parasites. A structural comparison search of our compounds demonstrated structural similarity to a recently described histone demethylase inhibitor, GSKJ1/4 which also exhibits selective adult parasite killing. We have demonstrated modification of histone methylation in Brugia malayi parasites treated with our compounds indicating that the mode of drug action is at the level of histone methylation. Our results indicate that targeting *B. malayi* and other filarial parasite demethylases may offer a novel approach for the development of a new class of macrofilaricidal therapeutics. In addition to the main theme presented in this thesis, an evaluation of the mechanisms involved in drug uptake in parasitic nematodes was conducted along with a direct assessment of time-dependent bioaccumulation of a distinct class of anti-filarial agents (provided by Celgene Global Health). Finally, a brief description of unique phenotypic changes, other than motility and viability, observed upon dihydropyridine treatment of parasitic nematodes will be presented.