**UNIVERSITY GRADUATE SCHOOL BULLETIN**

**ANNOUNCEMENT**

Florida International University  
University Graduate School

Doctoral Dissertation Defense  
“Regulatory mechanisms of *Leishmania* aquaglyceroporin AQP1”

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**Abstract**

Pentavalent antimonials [Sb(V)] are the primary drug of choice against all forms of leishmaniasis. Emergence of antimony unresponsiveness is a major issue. There is a dire need of understanding antimony resistance mechanisms in *Leishmania*. One important mechanism is the down regulation of the trivalent antimony [Sb(III)] (the active form of Sb(V)) uptake system. To date, *Leishmania* aquaglyceroporin AQP1 is the only reported facilitator of Sb(III). *Leishmania* do not have promoters. They primarily regulate their genes at post-transcriptional and/or post-translational levels. We reported that mitogen activated protein kinase 2 (MPK2) positively regulated AQP1 stability through the phosphorylation of the threonine 197 (T197) residue of AQP1. The goal of this study was to elucidate the regulatory mechanism(s) of AQP1 in *Leishmania* in order to advance our understanding about the physiological role(s) of AQP1 in *Leishmania* biology. When *Leishmania* promastigotes were treated with the proteasome inhibitor MG132, SbIII accumulation was increased due to upregulation of AQP1. Alteration of lysine 12 of AQP1 to either alanine or arginine improved protein stability. Cells co-expressing a dominant-negative MPK2 mutant exhibited severely reduced AQP1 expression, which was reversed upon addition of MG132. Interestingly, the dominant-negative MPK2 mutant could not destabilize either AQP1\textsubscript{K12A}/AQP1\textsubscript{K12R}. Stabilization of AQP1 by MPK2 led to its relocalization from the flagellum to the entire surface of the parasite. Both altered AQP1\textsubscript{K12A} and AQP1\textsubscript{K12R} were restricted to the flagellum only. The data demonstrated that lysine12 was targeted for AQP1 proteasomal degradation playing an integral role in subcellular localization of AQP1 as well as its interaction with MPK2. This study also demonstrated that the stability of *AQP1* mRNA in different *Leishmania* species was regulated by their respective 3’-untranslated regions. Cutaneous leishmaniasis causing species accumulated more antimonite and therefore, exhibited higher sensitivity to antimonials than species responsible for visceral leishmaniasis. This species-specific differential sensitivity to antimonite was found to be directly proportional to the expression levels of *AQP1* mRNA. The differential regulation of *AQP1* mRNA explained the distinct antimonial sensitivity of each species. This study will help us to identify new drugs for treatment in the future and also lead to a novel understanding of parasite biology aspects such as integral membrane protein trafficking and regulation.

**Date:** November 6, 2015  
**Time:** 10:00AM  
**Department:** Biological Sciences  
**Major Professor:** Dr. Rita Mukhopadhyay  
**Venue:** WC 130, Modesto A. Maidique Campus