"Targeting histone modifying enzymes in *Leishmania*: a new venue for chemotherapy?"

Conservation of all classes of histone modifying enzymes (HME) in the parasite *Leishmania* suggests epigenetic regulation as an interesting target for chemotherapy. We screened 480 epigenetic inhibitors against extracellular *L. amazonensis* using a viability assay, and intracellular amastigotes using a high content phenotypic assay. We identified 25 hits that kill extra- or intracellular parasites at 10 μM or 1 μM targeting all major classes of HMEs, suggesting a potential essential role of epigenetic regulation in *Leishmania*. Interestingly, 10 hits exclusively killed intracellular parasites, revealing a host cell-dependent mechanism of action likely through modulation of macrophage epigenetic regulation. Current studies are focusing on hits potentially targeting histone methylation enzymes. Applying antibodies against epigenetic marks of histone H3 showed (i) nuclear localization for H3K4me3, H3K9me3, and H3K27me3 marks using immunofluorescence analysis in *Leishmania*, and (ii) a decrease of H3K4me3 (activation mark) and an increase of H3K27me3 (repression mark) in infected macrophages by Western blot analysis. Our data reveal a surprising complexity of epigenetic host/parasite interactions that opens interesting new venues for anti-leishmanial intervention.