Targeting the histone methylation machinery in *Schistosoma mansoni*

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Dis-regulation of **epigenetic** processes is responsible for many human diseases (including cancer, diabetes and obesity). This realization had led to increasing numbers of drug discovery projects targeting the responsible epigenetic components, which has contributed to a substantial increase in the number of approved epi-drugs available. Epigenetic pathways have also been recently identified as crucial components in the developmental progression of parasitic **helminths**, in particular *Schistosoma mansoni*, the causative agent of schistosomiasis. We, therefore, hypothesised that schistosome proteins involved in epigenetic processes could be suitable **targets** for the development of next-generation anthelmintics.

This study investigated the histone post-translational methylation machinery in schistosome and it was conducted in two parts. Firstly, the schistosome components involved in protein methylation (**histone/protein methyltransferases**, HMTs) and demethylation (**histone/protein demethyltransferases**, HDMs) pathways were identified and structurally characterized. This led to the classification of 26 HMTs and 13 HDMs, which included all the previously identified members as well as 4 new proteins (2 HMTs and 2HDMs). Interestingly, some of these proteins included parasite-specific features (such as extended loops), which could be explored in detail for the development of selective anti-schistosomals. Secondly, these epigenetic components were further studied using an integrated biological–chemical approach to identify new chemical identities with anthelmintic activity. Here, *in vitro* screens against larval schistosomula and adult schistosomes confirmed interesting **anti-parasitic activity** (phenotype, motility and egg laying defects) of some compounds selected by the *in silico* approach. RNAi-based functional genomics experiments and post-translational histone modification analyses confirmed the mechanism of action of some of these **compounds** and the suitability of their targets for progression. For a particular HMT (Smp_138030), this led to the further identification of structural analogues with increased anti-schistosomal potency. Collectively, these results reveal how complementary biological, chemical, structural and functional genomic approaches can be used to identify promising starting points for further **chemical optimization** of novel anthelmintics targeting schistosome epigenetic components.

Further exploitation of such approaches may identify an efficient alternative to the current treatment for schistosomiasis and a description of our ongoing work in such a direction will be provided.