Histone modifying enzyme (HME) inhibitors demonstrate anthelmintic activity against *Fasciola hepatica.*

Fascioliasis remains a foodborne disease of considerable global impact. In addition to primary production and economic losses in the livestock sector, the World Health Organisation estimates over 2.39 million people are also affected globally, which justifies its inclusion on the list of communicable diseases prioritised under the Elimination Initiative of 2030. A key goal of research into the sustainable control of fascioliasis is the identification of novel anthelmintics as treatment in both humans and animals is primarily reliant on a single chemotherapeutic: triclabendazole (TCBZ). Here, we present evidence that compounds affecting histone modifying enzymes (HMEs) are flukicidal as identified during *ex vivo* - screening of the Structural Genomics Consortium's epigenetic compound library. In brief, a 61-compound collection containing methyltransferase (n = 20), demethylase (n = 3), acetyltransferase (n = 6), bromodomain (n = 20) and other histone modification (n = 12) inhibitors was screened against newly excysted juvenile *F. hepatica* at an initial concentration of 10 μM (primary screen). Treated parasites were categorically scored for phenotype and motility at 24, 48 and 72 hours, with hit compounds identified as those inducing a significant degradation of parasite viability in comparison to DMSO treated controls. Hit compounds were then titrated from 10 to 0.3125 μM in a six-point serial dilution to calculate EC_{50} values (secondary screen). Putative targets of each hit compound were also identified via bioinformatic characterisation of their respective protein families. Of the 61 compounds screened, three (GSK-J4, LLY507 and NVS-CECR2-1) were found to induce significant negative phenotypes at all timepoints during primary screens. Each compound performed comparatively to TCBZ, with earliest observable affects at 1 hour post compound treatment. Titrations of each of the compounds revealed EC_{50} values of 4.17, 2.32 and 2.88 μM for GSK-J4, LLY507 and NVS-CECR2-1, respectively. Orthologues of the human protein targets were also identified for GSK-J4 (lysine demethylase 6A, *Fh*KDM6A) and LLY507 (SET and MYND domain containing protein 2/3-like, *Fh*SMYD2/3), but only distant homologues were identified for the target of NVS-CECR2-1. Each proposed *F. hepatica* target protein was found to possess the expected domains and motifs upon analysis with InterPro and direct alignment to *Homo sapiens*- and *Schistosoma mansoni*- sequences. Complementary characterisation of *F. hepatica* HMEs involved in acetylation and methylation also uncovered 63 previously uncharacterised family members, including an expansion of the sirtuin deacetylases in the liver flukes (*Fasciola gigantica, Fasciolopsis buski, Opisthorchis felineus* and *Clonorchis sinensis*) and homologous drug targets prioritised in the blood flukes (e.g., *S. mansoni* CREB-binding protein (CBP) and bromodomain-containing protein-3 (BRD3) orthologues). We believe that the compounds identified by *ex vivo* screening, in addition to the characterisation of a large complement of potential future epigenetic targets, represents an exciting opportunity for the future of *F. hepatica* drug discovery.