

Spotlights on new publications

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New drug targets - XII

Schistosomiasis: Although praziquantel (PZQ) is documented as a safe drug of choice in treatment of schistosomiasis, still emerging resistance was reported in some endemic countries. Recent concern targeting histone deacetylases (HDACs) and histone acetyltransferases (HATs) encouraged a group of scientists from Brazil and USA (**Jessica Lobo-Silva et al.**) to utilize *Schistosoma* histone demethylases (HDMs) as important factors in cercarial transition to schistosomula, and in sexual differentiation in adult worms. Advanced projects in *S. mansoni* transcriptomic and genomic researches allowed the scientists to identify specific gene products to be evaluated for *in silico* analysis. Therefore, the investigators hypothesized that recognition of specific epigenetic markers that potentiate *S. mansoni* life cycle transition would pave the way towards identification of potential drug targets. On the other hand, *in silico* analysis would offer potential time saving and cost benefits in the era of development of novel drugs.

Recent experimental studies utilized inhibition of HDACs, HATs and HDMs, as epigenetic markers, and claimed its usefulness as a promising approach for drug discovery against eukaryotic pathogens. Several inhibitors were evaluated in treatment of schistosomiasis such as trichostatin A, sirtuins (HDACs inhibitors), and PU139 (HATs inhibitor). As well, importance of histone demethylase (HMT) and histone methyltransferase (HDM) for gene regulation and development of schistosomal life cycle stages was also documented. In this context, two families exert demethylase activity, K-demethylases (KDMs) or lysine specific demethylase (LSD), and Jumonji C (JMJC) domain-containing demethylases, and fourteen potential HMTs were recently described in schistosome. Using molecular docking, the investigators evaluated fourteen annotated *S. mansoni* demethylase enzymes identified as orthologs of human KDMs, to select *Smp_034000* as the most suitable drug target. Transcriptomic analysis revealed that *Smp_034000* expression peaks on 1-day newly transformed schistosomula and 5-week-old adult worms. Molecular modeling studies were conducted to predict the specific site for interactions between *S. mansoni*

HMT and GSK-J4, a specific HMT inhibitor. Then, its chemotherapeutic effect was evaluated on adult worms and schistosomulae *in vitro* cultures. Ultrastructural analysis showed that GSK-J4 decreased adults' motility with marked loss of viability and reduced oviposition with a satisfactory IC50 as well as in a dose- and time-dependent manner. It is worth mentioning that GSK-J4 affects female worms more severely and rapidly than males (40% death rate vs 0%) after 72 h of treatment, with pronounced decrease in oviposition. In addition, confocal microscopy revealed loss of architecture of muscle fibers and alterations in cell-cell contact suggesting GSK-J4 effects on the integrity of cellular junctions. Regarding oviposition, the investigators hypothesized that GSK-J4 reduced egg size during egg formation before its release into the culture medium due to alteration of vitelline cells packing inside the zygote. It was concluded that *Smp_034000* inhibition should undergo further evaluation and validation as a new strategy for development of novel anti-schistosomal drug. Compiled from "**The anti-schistosomal potential of GSK-J4, an H3K27 demethylase inhibitor: insights from molecular modeling, transcriptomics and *in vitro* assays.**" *Parasit Vectors* 2020 Mar; 13(1): 140.

Malignant malaria: One of the most important stations in *Plasmodium* spp. life cycle is egress and *de novo* RBCs invasion. In the present compilation, **Madeline G. Dans** and her colleagues from Australia hypothesized that molecules and receptors contributed in that critical process may be considered as novel drug targets. Identification of potent inhibitors of egress and invasion was the main objective of their study. The investigators screened the Medicines for Malaria Venture (MMV; <http://www.mmv.org/research-development>) that includes 400 compounds against neglected tropical diseases, among them 125 compounds with antimalarial activity.

The library was screened using a bioluminescent semi-high throughput system to identify inhibitors of egress and invasion. Fifteen and twenty-four inhibitors were identified according to their effects to inhibit

parasite egress and RBC invasion by >40% and >90%, respectively. Among them, only eleven compounds were selected for further analyses after exclusion of compounds that do not inhibit parasite growth. Using cell-based assays and live cell microscopy, the investigators categorized the selected compounds into two categories; either direct or indirect inhibitors. The only direct inhibitor of egress process was MMV676881 through inhibiting the breakdown of RBCs membrane. There were two direct specific inhibitors of RBCs invasion; MMV020291 through blocking merozoite invasion, and MMV006833 through inhibiting ring development. The remaining eight compounds were found to indirectly block egress and invasion cascade; preventing late schizont maturation (two compounds), and six general growth inhibitors that do neither

specifically block egress nor invasion, but may induce growth defects that indirectly hinder the invasion process. It was concluded that the approach utilized in the present compilation allowed the investigators to identify three specific inhibitors, one for merozoite egress, and two for RBCs invasion; either blocking merozoite invasion or arresting ring development. Besides, several other general growth inhibitors that strongly act during the invasion stages were also identified. The investigators suggested that these inhibitors could complement current anti-malarial drugs. Compiled from **“Screening the medicines for malaria venture pathogen box for invasion and egress inhibitors of the blood stage of *Plasmodium falciparum* reveals several inhibitory compounds.”** *Int J Parasitol* 2020 Mar; 50(3):235-252.