

Spotlights on new publications

Sherif M Abaza

Medical Parasitology Department, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

Corresponding Author: Tel.: 00201005243428, E-mail: smabaza@hotmail.com

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New drug targets - XI

Malignant malaria: Active site inhibitors are confronted by high drug pressure, and more susceptibility to parasite gene mutations commonly linked with resistance of anti-malarial drugs. On the other hand, allosteric inhibition (previously described; New drug targets IX, PUJ 2019; 12(1):68-71) is an alternative strategy to design an efficient inhibitor. Briefly, allosteric control means function regulation of a protein by binding an effector molecule at a site other than its active site. Allosteric site allows the effector molecules to activate or inhibit protein functional dynamics. Therefore, allosteric inhibitors are not associated with parasite gene mutation because they don't alter the active site. A group of scientists (**Arnold Amusengeri et al.**) from South Africa and USA succeeded to identify allosteric modulators (SANC190 and SANC651) against *P. falciparum* HSP70-1 and HSP70-x. Transcriptomic analysis of *P. falciparum* revealed six essential HSP70 isoforms; x-z and 1-3. The investigators selected HSP70-1 and HSP70-x because both are maximally expressed during the asexual erythrocytic stages of *P. falciparum*. Besides, PfHSP70-1 was reported as survival factor, while PfHSP70-x was essential as an efficient exporter of a key virulence factor; erythrocyte membrane protein-1. Studies that utilized atom molecular dynamic simulations to identify allosteric dynamic hotspots for human HSPs 70 and 90 encouraged the investigators to develop promising modulators for PfHSP70-1 and PfHSP70-x.

To achieve this, the investigators first conducted homology modeling studies to predict the 3D-structure of PfHSP70-1 and PfHSP70-x. This was followed by molecular docking studies using high-throughput virtual screening against natural compounds for potential parasite-specific inhibitory activity. Third, the investigators utilized one hundred nanosecond molecular dynamic simulations to select two molecules; SANC190 and SANC651, that strongly modulated functional dynamics of PfHSP70-1 and PfHSP70-x. In addition, the investigators presented two videos showing binding of SANC190 and SANC651 to PfHSP70-x which triggered its structural rearrangement inducing its increased transition kinetics. Therefore, it was concluded that SANC190 and SANC651 were

strong allosteric activators, not inhibitors, but changed PfHSP70-x conformation that failed the response to innate ATP binding events. It is worth mentioning that innate ATP binding events are essential for protein (enzyme or antigen) expression. Compiled from **"Establishing computational approaches towards identifying malarial allosteric modulators: A case study of *Plasmodium falciparum* HSP70s."** *Int J Mol Sci* 2019 Nov 8; 20(22). DOI: 10.3390/ijms20225574.

Schistosomiasis mansoni: Although praziquantel (PZQ) is not effective against all the developmental stages of *Schistosoma* spp., it remains the sole chemotherapeutic agent since ~ thirty years ago. Cases of PZQ resistance reported in Africa necessitated development of new drugs to be used in combination with/or in replacement of PZQ. To identify putative anti-schistosome candidate proteins, British scientists (**Kezia CL Whitley et al.**) utilized Structural Genomics Consortium (SGC), an academic library for previous reports concerning identification of new leads against schistosomiasis, to select thirty four epigenetic probes (EPs) and three epigenetic inhibitors (EIs). The investigators defined EPs as having three properties not found in EIs; *in vitro* potency >100 nM; higher selectivity > 30-fold vs other compounds, and on-target cell activity >1 μM. The investigators selected molecules targeting histone, because schistosome histone methylation/demethylation processes are essential for egg production, miracidium to sporocyst transformation, and adults motility. The selected molecules were initially screened against *S. mansoni* schistosomula, and the results revealed thirteen EPs and one EI affecting both schistosomula phenotype and motility at 10 μM. Microscopic examination demonstrated a range of abnormal schistosomula phenotypes including granulation, swelling, elongation and irregular shape modifications. With subsequent dose-response titrations, the hit molecules were screened against schistosomula and adults. Two issues were observed; cytotoxicity against *HepG2* cells *in vitro*, and variable or contradictory EC50 scores against adults and schistosomula. However, the best hits that gained much attention for further investigations were EPs, namely LLY-507/BAY-598 and GSK-J4. Schistosome

targets for both molecules were identified; SMYD histone methyltransferase (*Smp_000700*) and JMJD histone demethylase (*Smp_034000*), respectively. Both targets are essential for schistosomes development and egg production. Gene knockout (RNA interference) of both genes encoding *Smp_000700* and *Smp_034000* revealed their essentiality for adults motility and egg production for the first, and oviposition and vitelline package of the laid eggs for the latter. Finally, the investigators predicted 3D structure of *Smp_000700* to conduct structural activity relationships (SARs) studies. It was shown that the indole group of LLY-507 stacked into its accessory pocket, whereas two *Smp_000700* aromatic amino acid residues (histidine 554 and tyrosine 642) were essential for BAY-598 binding. It is worth mentioning that no SAR studies were performed for *Smp_034000*. It was concluded that modulators of schistosome histone methylation homeostasis offered promising new generation for anti-schistosomal control. Compiled from **"The repositioning of epigenetic probes/inhibitors identifies new anti-schistosomal lead compounds and chemotherapeutic targets."** *PLoS Negl Trop Dis* 2019 Nov 15; 13(11):e0007693.

Visceral leishmaniasis (VL) is a zoonotic disease and one of the important neglected tropical diseases (NTDs). Among the reasons for considering it as a NTD is the great discrepancy between the urgent need for safe and efficient drug and the number of both infected patients and individuals at risk. Besides, there are several complicated sequelae associated with improperly treated patients. It was reported that DNA topoisomerases emerged as drug targets against diseases caused by kinetoplastids. It is worth mentioning that DNA topoisomerase IB (TopIB) cleaves

one of the DNA strands, establishing a reversible phosphodiester bond to the 3'-end and releasing a 5'-OH at the free end. Stabilization of TopIB by topoisomerase poisons produced single-strand DNA breaks, and this explains using topoisomerase poisons in oncology. Recent reports demonstrated efficient potency of topoisomerase poisons in treatment of VL both *in vitro* and *in vivo*. It is known that indenoisoquinolines (IIQs) are potent topoisomerase poisons, and moreover, they possess higher chemical stability with higher ability to overcome multidrug resistance systems. Four years ago, three IIQs; LMP400, LMP776 and LMP744 were in clinical trials. In addition, exposure to IIQs initiates phosphorylation of threonine in histone H2A to generate γ H2A prior to the onset of DNA repair mechanisms. To elucidate the inhibitory mechanism(s) of synthetic IIQs, **Camino Gutiérrez-Corbo et al.** from Spain and USA conducted the present compilation. A series of twenty compounds with IIQ scaffold were synthesized and tested *in vitro* against amastigotes and promastigotes obtained from *L. infantum*-infected mice. Inhibition of TopIB, phosphorylation of histone H2A at the putative site (threonine128) as well as stabilization of TopIB complex were also investigated. Most of these compounds gave efficient anti-leishmanial potency, with the highest potency and selectivity on introduction of an N atom in IIQ ring. Complete arrest of cell cycle progression with phosphorylation of H2A was observed mainly in S-phase. It was concluded that synthetic IIQs inhibited TopIB and initiated H2A phosphorylation, and hence could be considered as a novel drug in treatment of VL. Compiled from **"Topoisomerase IB poisons induce histone H2A phosphorylation as a response to DNA damage in *Leishmania infantum*."** *Int J Parasitol Drugs Drug Resist* 2019 Dec; 11: 39-48.