Poster Presentation

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Enzyme lysyl-tRNA synthetase presents a new target for drug development

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Helminth parasites are an assemblage of two major phyla of nematodes (also known as roundworms) and platyhelminths (also called flatworms). These parasites are a major human health burden, and infections caused by helminths are considered under neglected tropical diseases (NTDs). These infections are typified by limited clinical treatment options and threat of drug resistance. Aminoacyl-tRNA synthetases (aaRSs) are vital enzymes that decode genetic information and enable protein translation. The specific inhibition of pathogen aaRSs bores well for development of next generation anti-parasitics. Here, we have identified and annotated aaRSs and accessory proteins from Loa loa (nematode) and Schistosoma mansoni (flatworm) to provide a glimpse of these protein translation enzymes within these parasites. Using purified parasitic lysyl-tRNA synthetases (KRSs), we developed series of assays that address KRS enzymatic activity, oligomeric states, crystal structure and inhibition profiles. We show that L. loa and S. mansoni KRSs are potently inhibited by the fungal metabolite cladosporin. Our co-crystal structure of Loa loa KRS-cladosporin complex reveals key interacting residues and provides a platform for structure-based drug development. This work hence provides a new direction for both novel target discovery and inhibitor development against eukaryotic pathogens that include L. loa and S. mansoni.

[1] Hotez ,PJ. Brindley, PJ. Bethony, JM. King, CH. Pearce, EJ. & Jacobson, J. (2008). Journal of Clinical Investigation,118(4), 1311–21.
[2] Khan, S. (2016).Malaria journa,; 15(1), 203.
[3] Khan,S. Sharma, A. Belrhali, H. Yogavel, M. & Sharma, A. (2014). J Struct Funct Genomics,15(2), 63–71

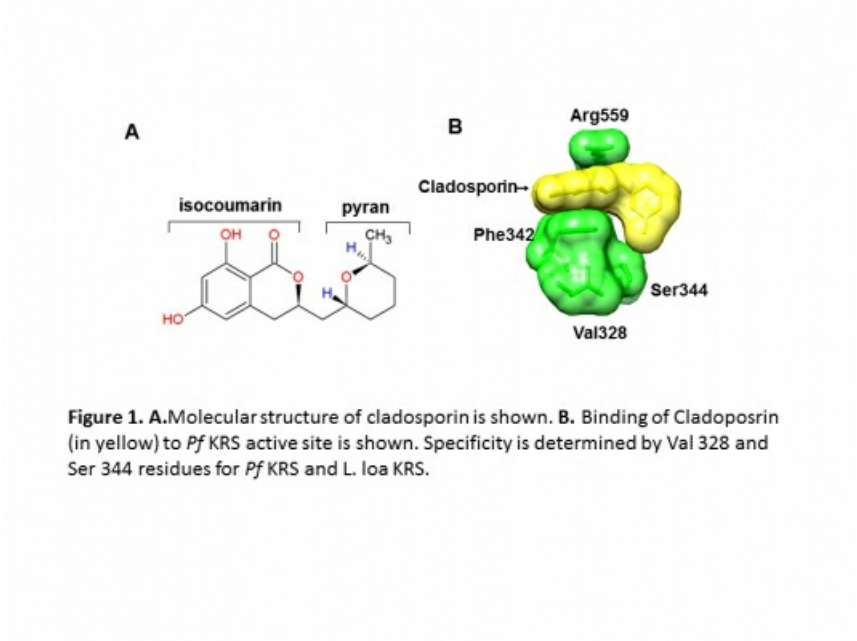

Figure 1. A. Molecular structure of cladosporin is shown. **B.** Binding of Cladoposrin (in yellow) to *Pf* KRS active site is shown. Specificity is determined by Val 328 and Ser 344 residues for *Pf* KRS and L. loa KRS.

Keywords: Aminoacyl-tRNA synthetases, cladosporin, Neglected tropical diseases