Cryo-EM meets parasitic diseases: validating a novel approach to target thioredoxin-like enzymes

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Thioredoxin glutathione reductase (TGR), a selenium-containing TrxR-like enzyme, is a validated drug target against schistosomiasis, a human parasi6c infec6on affec6ng more than 200 million people. To date, only praziquantel is available for the treatment of schistosomiasis and, due to massive drug administra6on, less sensi6ve parasite strains are emerging, making the iden6fica6on of new therapies urgent. TGR, in its chimeric fusion of a glutaredoxin domain with a thioredoxin reductase domain, bridges two detoxifica6on pathways crucial for the parasite survival in the host's organism by suppling electrons to both GSH and Trx systems. However, selec6ve drug development for this class of enzyme is challenging, mainly due to the reliance on irreversible and/or covalent inhibi6on strategies, which are associated with unacceptable off-targets effects. Recently, a breakthrough by means of an X-ray crystallography fragment screening allowed the iden6fica6on of the so-called "doorstop pocket", a novel regulatory and druggable site of TGR.(1) The ini6al molecular fragments iden6fied were ligated and par6ally op6mized as first-in-class non- covalent inhibitors of TGR with efficacy against schistosome infec6ons in mice, mee6ng the criteria for lead progression outlined by WHO. Further a1empts to determine the binding mode of these inhibitors by X-ray crystallography were unsuccessful. Finally, switching to Cryo-EM technique allowed us to obtain the first structure of TGR-inhibitor complex solved at 3.6 Å resolu6on, demonstra6ng the compound bound in the doorstop pocket. Since the doorstop pocket is present in the protein family, this breakthrough offers opportuni6es for selec6vely inhibi6ng other pyridine nucleo6de-disulfide oxidoreductases essen6al for various pathogens and holds implica6ons for comba6ng cancer.