Targeting Thioredoxin Reductases through Allosteric Control

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High-molecular-weight thioredoxin reductases (TrxRs) and glutathione reductases (GRs) belong to the pyridine nucleotide-disulfide oxidoreductase family and are central regulators of vertebrate redox pathways, orchestrating essential cellular functions. TrxRs, in particular, have emerged as critical drug targets for a range of human diseases, including parasitic infections and cancer. However, despite over 25 years of research, no selective TrxR inhibitors have successfully progressed through the drug development pipeline. This challenge stems primarily from two key factors: the field's heavy reliance on electrophilic and redox-active compounds, which frequently trigger off-target effects in vivo, and the limited structural data on protein-inhibitor complexes, which hampers rational compound optimization [1]. Using an integrated structural biology approach, we identified a previously unrecognized allosteric site on TrxRs and GR-like enzymes, which we have termed the "doorstop pocket" [2,3]. This site, located distal to the nucleophilic active site, plays a crucial role in enzyme turnover by modulating the entry of NADPH and the exit of $NADP^+$. Targeting this pocket represents a novel and promising strategy for achieving selective inhibition. Our approach has yielded particularly promising results in Schistosoma mansoni Thioredoxin Glutathione Reductase (TGR), where some of the initial compounds identified demonstrate superior efficacy compared to current treatments of schistosomiasis in animal models. Moreover, preliminary findings indicate that this strategy may also extend to human TrxR, thereby opening a potential avenue for novel cancer therapeutics [4].

[1] Ardini M. et al., The "Doorstop Pocket" In Thioredoxin Reductases - An Unexpected Druggable Regulator of the Catalytic Machinery. *J Med Chem*. **2024**, 67,15947-15967.
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[3] Petukhova VZ, Aboagye SY, Ardini M et al., Non-covalent inhibitors of thioredoxin glutathione reductase with schistosomicidal activity in vivo. *Nat Commun*. **2023**, 14, 3737.
[4] Flowers et al., Pleiotropic anti-cancer activities of novel non-covalent thioredoxin reductase inhibitors against triple negative breast cancer. *Free Radic Biol Med*. **2025**, 227, 201-209.