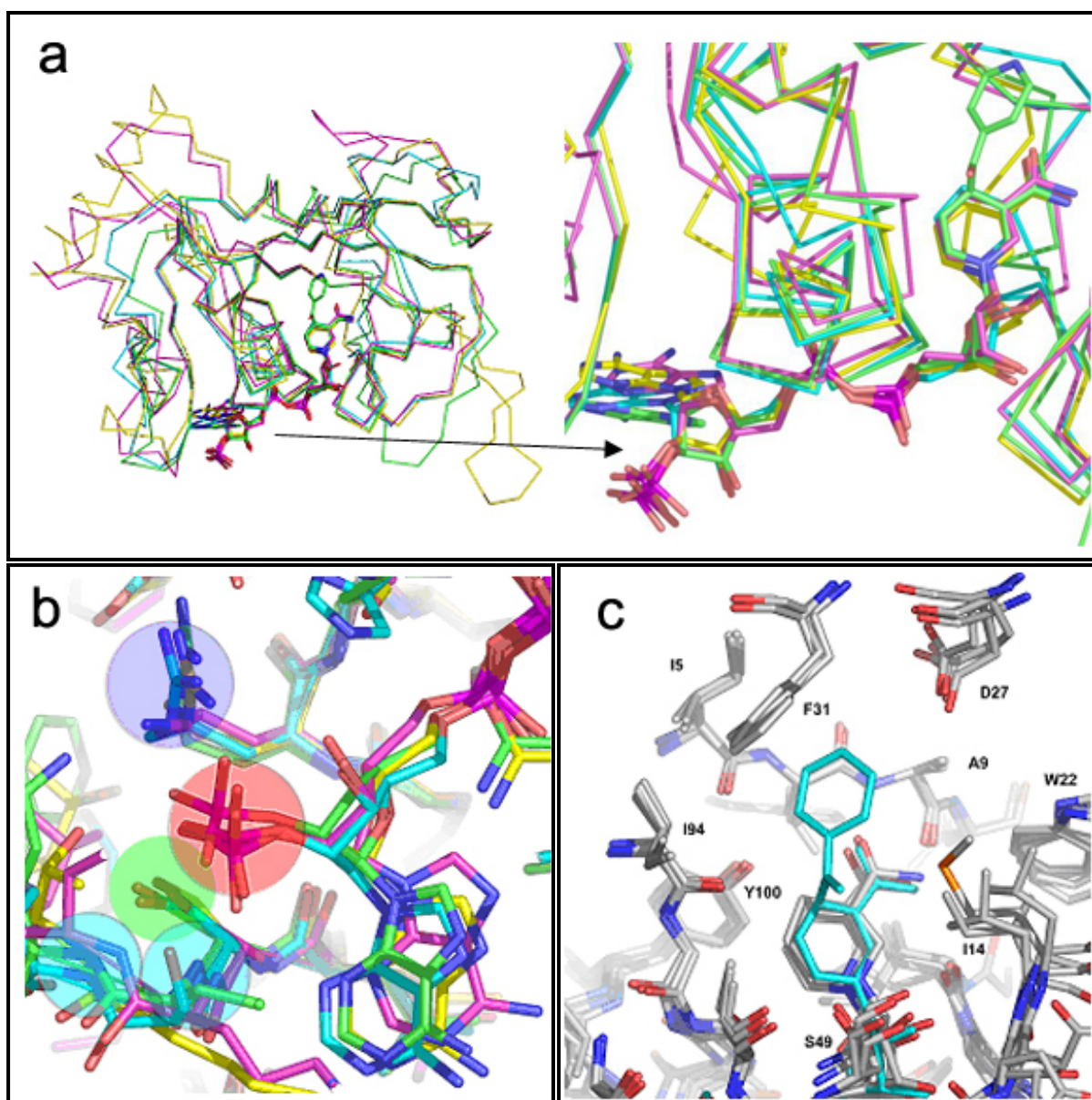


Supplementary Information

Mycobacterium tuberculosis Dihydrofolate Reductase is a Target for Isoniazid

Argyrides Argyrou, Matthew W. Vetting, Bola Aladegbami & John S. Blanchard



Supplementary Figure 1 Comparison of crystal structures of DHFRs from three organisms determined at $7.2 \leq \text{pH} \leq 8.0$ with the *Mtb*-DHFR structure determined at pH 4.6. **a**, The overall structure (left) and conformation of the bound NADPH (right) of *Mtb*-DHFR (green, this work), *Escherichia coli* DHFR (cyan, 1RX1), *Plasmodium vivax* DHFR (yellow, 2BL9), and human DHFR (maroon, 1PD8) are similar. **b**, The 2'-phosphate (red circle) of NADPH/NADP⁺

interacts with a conserved serine residue (green circle), conserved basic residue (arginine or lysine, blue circle), and two consecutive amide backbone atoms from a conserved loop (cyan circles). **c**, Residues that comprise the binding pocket for the isonicotinoyl moiety of INH-NADP (cyan), which is part of the dihydrofolate binding site, are conserved.

Organism	PDB ID	Crystallization conditions	Reference
<i>Mycobacterium tuberculosis</i>	1DG8	100 mM sodium acetate pH 4.6 1.6 M ammonium sulfate 10% glycerol	1, this work
<i>Plasmodium vivax</i>	2BL9	100 mM tris pH 7.2 30% PEG-4000 10% glycerol	2
Human	1PD8	100 mM potassium phosphate pH 8.0 61-63% ammonium sulfate	3
<i>Escherichia coli</i>	1RX1	100 mM imidazole pH 8.0 300 mM CaCl ₂ 15% PEG-6000	4

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