THE MODE OF BINDING OF ISONIAZID, AN ANTI-TUBERCULAR DRUG, TO ARYLAMINE N-ACETYLTRANSFERASE FROM *MYCOBACTERIUM SMEGMATIS*.

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Keywords: Arylamine N-acetyltransferase; Isoniazid; Tuberculosis

Isoniazid is a frontline drug used in the treatment of tuberculosis (TB). Isoniazid is a prodrug, requiring activation in the mycobacterial cell by the catalase/peroxidase activity of the *katG* gene product. Tuberculosis kills 2 million people every year and the situation is getting worse due to the increase in prevalence of HIV/AIDS and the emergence of multidrug-resistant strains of TB.

Arylamine N-acetyltransferase (NAT) is a drug-metabolising enzyme (E.C. 2.1.3.5). The NAT enzyme is capable of acetylating and inactivating isoniazid, transferring an acetyl group from acetyl coenzyme A (AcCoA) onto the terminal nitrogen of the drug, which in its N-acetylated form is therapeutically inactive. The bacterium responsible for TB, *Mycobacterium tuberculosis*, contains and expresses the gene encoding the NAT protein [1]. It has been shown that isoniazid binds to the NAT protein from *Salmonella typhimurium* [2] and we report here the mode of binding of isoniazid in the NAT enzyme from *Mycobacterium smegmatis*, a close relative of the *M. tuberculosis* and *S. typhimurium* NAT enzymes.

The mode of binding of isoniazid to *M. smegmatis* NAT has been determined using data collected from two distinct crystal structures. This allows us to say with confidence that the mode of binding of isoniazid that we observe is not an artifact of the crystallization conditions used. We know that the NAT enzyme is active in mycobacterial cells and we propose that isoniazid binds to the NAT enzyme in these cells. NAT activity in *M. tuberculosis* is likely therefore to modulate the degree of activation of isoniazid by other enzymes within the mycobacterial cell. Determining the structure of NAT with isoniazid bound is likely to be useful in rational drug design for anti-tubercular therapy since NAT is a good drug target.

1. Upton *et al*. (2001) Molecular Microbiology Vol. 42, No. 2 : 309-317
2. Delgoda *et al*. (2003) BBA – General Subjects Vol. 1620 : 8-14