**Mechanism Of Action Of Pyrazinamide**

**Abstract**

Tuberculosis (TB) remains the number one infectious disease killer globally. The long treatment time required to cure even drug susceptible disease presents a major hurdle to progress. Hence, the development of treatment shortening drugs is a key objective for TB drug discovery. The introduction of Pyrazinamide decades ago shortened therapy from 12 to 6 months. Over the years, many targets have been proposed based on biochemical analyses - none of them could be confirmed. In the context of the SPRINT-TB program, we employed in vitro and in vivo genetic approaches, followed by metabolomics and biophysical analyses to identify inhibition of Coenzyme A biosynthesis via binding to aspartate decarboxylase (PanD) as the mechanism of action of the drug. The identification of PanD as the target for pyrazinamide opens the way to employ rational, target-based approaches for the discovery of improved second generation pyrazinamides.

**Selected Relevant Publications for Reference**


