# Birmingham pushes ahead on global scourge of TB

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Scientists at the University of Birmingham have taken a crucial first step towards deciphering the atomic make-up of a key drug target in tuberculosis (TB).

They hope the breakthrough will be instrumental in helping to lead to the development of new therapies to tackle this ancient disease.

In the online journal PLoS Pathogens, microbiologists Professor Gurdyal (Del) Besra, Dr Klaus Fütterer and Dr Luke Alderwick, from the School of Biosciences, report the structure of the enzyme EmbC, that plays a vital role in assembling the cell envelope of the tubercle bacillus Mycobacterium tuberculosis.

Once rampant in Europe and North America, TB has largely vanished from public view in the developed world. However, the disease remains a problem of global proportions in spite of World Health Organisation-led efforts to contain its spread.

Rising drug resistance is hampering the WHO's global efforts to tackle tuberculosis, threatening modern treatment options.

When Robert Koch first isolated Mycobacterium tuberculosis in the late-19th century, he immediately noted the unusual waxy consistency of its cell envelope, the structure surrounding the bacillus. Modern analysis has shown it contains unusually large fatty acids known as mycolic acids. In addition, the cell envelope includes so-called glycolipids, which help subvert the host's immune system. Assembly of these glycolipids involves arabinosyltransferase enzymes, among them EmbC, that are embedded in the membrane of the bacillus, building up the glycolipid one sugar at a time.

Around 15 years ago, while working in a laboratory at Colorado State University, Professor Besra demonstrated that the bactericidal effect of the frontline TB drug ethambutol is caused by inhibiting EmbC and the closely related arabinosyltransferases EmbA and EmbB . Yet how ethambutol interferes with enzyme activity has remained obscure.

Using X-ray crystallography, Dr Alderwick and colleagues have identified the precise structure of the extracellular carbohydrate-binding domain of EmbC.

Professor Besra commented: 'This information will be invaluable in working out how EmbC catalyses sugar transfer and will provide a critical cornerstone to develop a novel inhibitor.'

## Note to Newsdesks

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