Cancer drug target is promising lead for new TB treatments

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A key enzyme in *Mycobacterium tuberculosis* that enables the microbe to reproduce rapidly could be a golden target for new drugs against tuberculosis (TB), according to a study published in *Microbiology* on 17 November.

The human equivalent of this enzyme has been targeted in some cancer treatments as well as in immunosuppressive chemotherapies. Scientists at the University of Birmingham have now shown that inhibiting the same enzyme in *M. tuberculosis* effectively kills the bacterial cells.

The enzyme called IMPDH is crucial for the survival of both human and bacterial cells. It is involved in the first stage of producing guanine nucleotides –the raw materials needed for DNA synthesis - as well as many other housekeeping processes that keep the cell alive and functioning.

The researchers identified the three genes in *M. tuberculosis* that encode IMPDH and then screened a library of 16 compounds that were likely to impede its function to some extent. Of the 16 diphenyl urea (DPU) compounds, 3 were able to inhibit IMPDH by more than 90%, killing *M. tuberculosis* cells.

Project leader Professor Gurdyal Besra explained why IMPDH is a promising target to tackle TB. "IMPDH is essential for cells to proliferate rapidly, which is one of the characteristics of microbial infection as well as human cancers. IMPDH has been used as a target in

some anti-cancer drugs, as blocking the enzyme can prevent proliferation of the cell and induce cell death. Our findings show that inhibiting the bacterial version of IMPDH is a strategy that could be exploited for anti-TB drugs," he said. "The DPU compounds we tested have selective activity against Mycobacterium species, meaning that any future drugs based on these would be specific and would not affect human cells."

9 million people are newly diagnosed with TB each year with increasing incidences of multi-drug resistant (MDR)-TB and extensively drug resistant (XDR)-TB. "In the face of growing resistance to current therapies, we desperately need new treatments for TB that are safe and effective," stressed Professor Besra. "We are tapping the potential of a so far unexploited target which could lead to the synthesis of a novel anti-tubercular drug and our findings, so far are extremely encouraging," he said.

Provided by Society for General Microbiology