

# Scientists discover how TB 'develops invincibility' against only available treatment

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Scientists at the University of Leicester have uncovered a dramatic new twist in the battle against TB. They have identified how the killer bacterium makes itself immune to a key component of the only effective treatment against the disease.

Earlier this month, a separate team of TB researchers at Leicester announced a new advance in their fight against the resurgence of TB in Britain. They isolated the molecular 'weapons' of the bacterium and are assessing ways to make the bacterium impotent.

Now, in new research published in the *Journal of Biological Chemistry*, another team from the Departments of Biochemistry and Chemistry at the University has shown how the TB bacteria becomes resistant to one of the only available treatments for the killer disease.

Dr Peter Moody of the Biochemistry Department said: "Isoniazid is a pro-drug that an enzyme in the deadly bacteria itself makes active.

"Using the technique of protein crystallography and the incredibly bright X-ray source of the European Synchrotron at Grenoble, my team and that of Professor Emma Raven of the Chemistry Department at Leicester along with Dr Katherine Brown of Imperial College have shown how the pro-drug binds to two very similar enzymes - and from this we can see how mutations in the bacterial enzyme protect it from the treatment."

This is the first time anyone has seen the way the pro-drug binds to activating enzymes.

Dr Moody said: "Drug-resistant forms of TB are approaching 10% of the 8000 cases a year in the UK, so understanding how this works is very important."

The researchers hope that this new understanding will help drug companies devise treatments for the resistant strains.

Dr Moody added: "Unfortunately, development of the UK synchrotron source (Diamond) is under threat because of the shortfall in funding, which could limit our ability to do this sort of fundamental medical research in the future".

Citation: The Tuberculosis Prodrug Isoniazid Bound to Activating Peroxidases. Clive Metcalfe, Isabel K. Macdonald, Emma J. Murphy, Katherine A. Brown, Emma Lloyd Raven, and Peter C. E. Moody J. Biol. Chem., Vol. 283, Issue 10, 6193-6200, March, 2008

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