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A new weapon against TB?

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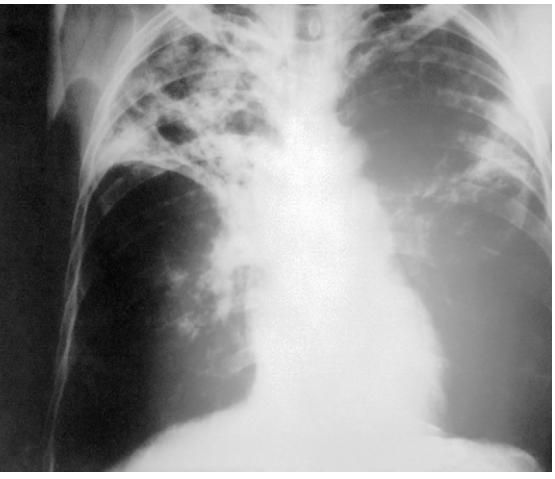
A new antibiotic treats tuberculosis (TB) much faster than the current WHO-recommended regimen, according to animal studies by European and US researchers. The drug could work against multi-drug resistant strains of TB, said the team in a recently published study [1]. Studies in healthy volunteers found the drug was safe in humans, and further human studies are underway, said lead researcher Koen Andries from drug firm Johnson & Johnson in Beerse, Belgium. TB experts and the World Health Organization (WHO) have welcomed the results but said further animal studies and full human trials were necessary before the drug was proven ready for use.

A new class of drugs

'These results are exciting are because a new class of drugs with a new mechanism of action against *Mycobacterium tuberculosis* have been identified', said Dan Hoft from the Saint Louis University Health Sciences Center, St Louis, USA. 'The drug kills *M. tuberculosis* isolates that are resistant to other TB drugs – there is no cross-resistance with existing TB drugs', he continued. 'When added to multi-drug regimens in mouse studies of TB disease, it seems to shorten the period to culture negativity compared with our currently standard regimens', said Hoft.



However, Clifton Barry (Tuberculosis Research Section, National Institute of Allergy and Infectious Diseases, Rockville, MD) welcomed the findings but urged caution. 'Mouse models should be interpreted very carefully in terms of their ability to predict clinical utility of an agent in man, especially when that agent is of a new class', he said. A Phase I study of the drug compared with placebo in 81 volunteers found the drug caused no serious side effects, said lead researcher Andries. Drug levels in volunteers' plasma were seven times higher than in successfully treated mice, found researchers. Phase II clinical trials to measure the drug's efficacy are currently underway and Phase III trials will compare it with standard treatments, said Andries.

Critical enzyme

The drug belongs to a class of compounds called diarylquinolines. The research team identified the drug class by screening for compounds that would have an effect on *Mycobacterium smegmatis* (used as a surrogate for *M. tuberculosis* because it is nonpathogenic). The most promising diarylquinoline to emerge was R207910, which 'inhibits a key ATPase enzyme which is critical for energy production in *M. tuberculosis*. This definitely is the first anti-TB drug that has been shown to do this', said Hoft.

In vitro R207910 was potent against several different mycobacteria, including drug-resistant strains of *M. tuberculosis* but did not target other bacteria, said the researchers. In murine studies a one-month regimen including R207910 reduced the bacterial load in the lungs by the same extent as the recommended regimen did after two months, they said. After two months, the mice's lungs were completely clear of bacteria. Tuberculosis therapies including R207910 could cut treatment times by 50%, said Andries.

Shortening treatment time

Shamim Qazi from the Department of Child and Adolescent Health and Development at WHO in Switzerland agreed that a shorter treatment was possible. 'Theoretically it is possible as this drug achieves higher drug concentration and has a long half life', said Qazi. 'However one would need studies first in mice and then in humans to evaluate relapse rates after a shortened course of therapy', he said.

Shortening treatment time is valuable because the current regimen is so long WHO recommends the DOTS strategy (Directly Observed Treatment, Short Course) whereby health carers monitor patients taking their drugs.

The discovery of a potential new class of drug is exciting because no new drugs have been put into first-line usage against TB since rifampin in the 1960s.

'I hope that these exciting results will energize drug development research for

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tuberculosis', said Eric Nuermberger from the Division of Infectious Diseases at Johns Hopkins University, USA. There are now several new compounds active against *M. tuberculosis* in mouse models in the drug discovery pipeline that need to be fully assessed, he said. Further animal studies 'will need to focus on the efficacy of novel combinations of these new compounds that include one or more first-line TB drugs and/or the new methoxyfluoroquinolone moxifloxacin'.

Tuberculosis causes two million deaths per year, according to the Global Alliance for TB Drug Development. Tuberculosis and HIV epidemics fuel one another and at least 11 million adults are infected with both pathogens.

Reference

1 Andries, K. *et al.* (2004) A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* doi: 10.1126/science.1106753 (E-pub. ahead of print; www.sciencexpress.org)

German stance on gene patenting at odds with the rest of Europe?

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In December, the Bundestag (lower House of Parliament) in Germany approved a biotechnology amendment to limit patent protection on human gene sequences. The limit means that a patent awarded under German law to a researcher on a human gene sequence used for a specific function would not cover a second function of the same gene, discovered later by a second researcher, according to Joseph Straus, Managing Director of the Max Planck Institute for Intellectual Property, Competition and Tax Law (Munich, Germany). This, Straus has said, contradicts the intent of the European Union (EU) Directive to give full patent protection to the discoverer of the human gene sequence.

German gene patenting law is subject to the Biotechnology Directive No. 98/44/EC, which governs all member EU states. 'This means that in principle it does allow the patenting of gene sequences but, in order to be patentable, the 'inventor' must be able to identify the protein sequence for which that gene codes and must be able to state a possible commercial use for it', explains Eike-Henner Kluge (University of Victoria, British Columbia, Canada). Legally, in Germany as well as the USA, a technologically isolated gene sequence can be patented but a 'naturally' occurring gene sequence or a naturally occurring organism cannot.

Criteria for patentability

The EU, the USA and all countries agree that there are three central requirements for patentability: novelty, non-obviousness and usefulness, Kluge continues. 'Gene sequences can be patented but only if the protein encoded can be identified,' he says. Kluge disagrees with Straus' assertion and believes that the new law passed by the Bunsdestag does not alter this specific and central aspect of EC Directive 98/44. 'What it does is limit the extent of the patent protection that Germany will recognize to only those functions of the gene that are specifically identified at the time of patent application' says Kluge.

A sign of discontent

Hans Radder (Faculty of Philosophy, Vrije Universiteit, Amsterdam, The Netherlands) observes that the extension of patent laws and regulations to the area of biotechnology during the last decades has led to a great public interest in the issue of patenting. 'The problem is that there is a gap between what has been actually invented and the scope of protection that is being claimed in the patent – the consequences of this are visible tensions in patenting practice' he says. This gap is very obvious in the case of product patents and broad patents, two types of patent that occur frequently in the area of biotechnology. 'I see the new German law as a legitimate expression of discontent with this practice of overbroad and unjustifiable patent claims,' he says.

A global law?

Looking beyond the specific German amendment, Kluge would like to see a globally binding law that deals with international patenting in general and with the patenting of genes in particular. 'At the present time, gene patenting is regulated through multilateral treaties, which lack a cogent logical as well as ethical basis, and this will need to be addressed,' he concludes.

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