Synthetic molecule chokes TB growth

Compound acts by novel mechanism and is effective in mice.

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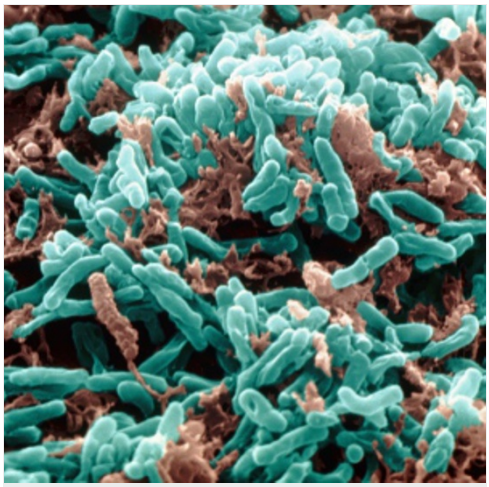
A new drug candidate has shown promising signs in treating tuberculosis. The synthetic molecule is effective in mice and bears no similarity to existing TB drugs, many of which have become inadequate as drug-resistant bacterial strains have developed. If it is shown to be safe and effective in humans, it could help to combat a disease that killed 1.4 million people in 2011.

A team led by Kevin Pethe, a microbiologist at the Pasteur Institute Korea near Seoul, investigated more than 120,000 compounds over 5 years, infecting mouse immune cells called macrophages with *Mycobacterium tuberculosis* — the bacterium that causes TB — and observing whether candidate compounds inhibited bacterial growth. “We are able to look at infection directly inside macrophage cells, allowing us to screen a large number of chemical libraries more quickly,” says Pethe.

The tests narrowed the list of candidates down to one for further synthesis and evaluation.

Reporting in *Nature Medicine*[1], the authors showed that the synthetic antibacterial compound has a novel mechanism of action: it inhibits the synthesis of ATP, the chemical that is used as a source of energy by most of the cell’s enzymes, and thereby blocks *M. tuberculosis* growth.



Coloured Scanning Electron Micrograph/EYE OF SCIENCE/SPL

Some strains of *Mycobacterium tuberculosis*, the bacterium that causes TB, have become resistant to most antibiotics — but researchers hope that a new synthetic molecule will be a more formidable weapon to fight them.

Subsequent tests showed the compound to be successful at treating TB in mice. The molecule belongs to a new class of synthetic chemicals with no similarities to existing drugs. This factor could make it tougher for the bacteria to develop resistance to it.

Valerie Mizrahi, a TB biologist at the University of Cape Town in South Africa, says the study “affirms the notion that there are new TB drug targets out there waiting to be discovered by screening diverse compound libraries. This is good news for the field and it must be celebrated”.

Next steps

Success at this stage does not guarantee that the compound will lead to an effective treatment in humans. Pethe says that the candidate drug will move on to phase I clinical trials next year to assess its safety and tolerability in a small group of healthy human volunteers. But only 5% of drugs that make it to phase I in all disease areas ultimately end up as marketed pharmaceuticals[2].

Getting the drug through the next two phases of clinical trials would also need substantial investment. Typically, state-funded institutions

such as the Pasteur Institute Korea have focused on drug discovery, with the onus for drug development placed on the pharmaceutical industry.

But the TB market does not have the financial incentives to attract large investment from big pharma, experts say. Pethe's team aims to bridge the gap with support from the Korean government and a company spun off by his institute, called Qurient. "Our goal is conflate research and the product — a model not yet established in the world," says Pethe.

"TB requires a very different approach to that of traditional pharma," says Melvin Spigelman, president and chief executive of the TB Alliance, headquartered in New York.

Christopher Dye, a senior TB specialist at the World Health Organization, says that people will sit up and take notice of the fresh research, but highlights the complications in TB drug development. If the drug eventually makes it into the clinic, another challenge will be to deploy it judiciously to prevent the bacterium from quickly evolving countermeasures. "Just to develop a drug on its own isn't the end," says Dye. "We need to make sure it's used properly and protected from resistance."

In the meantime, Pethe and his team will continue to screen new molecules to find more candidate TB drugs. Treating the disease usually requires cocktails of different drugs, and Pethe hopes his research will provide more candidates for clinicians to work with.

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References

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