Promising compound selected as drug candidate for tuberculosis

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(Medical Xpress)—A New Zealand-designed compound that shows promise against treatment-resistance tuberculosis (TB) has been selected as a drug candidate by international non-profit drug developer the Global Alliance for TB Drug Development (TB Alliance).

The compound, TBA-354, was designed by scientists at the Auckland Cancer Society Research Centre (ACSRC) and Maurice Wilkins Centre for Molecular Biodiscovery in partnership with the TB Alliance and the University of Illinois at Chicago.

TBA-354 has been more potent in preclinical studies than another compound in its class, PA-824, which has already shown promise in clinical trials. This is the first new class of drugs to be developed for TB in nearly 50 years, and the first designed to work against the persistent form of the disease.

Clinical results reported earlier this year suggest that PA-824, in combination with an existing TB drug, could treat some drug resistant forms of TB in just four months in contrast to the 18-24 months required for current regimens. TBA-354, the follow-on compound, may prove to be even more effective.

"TBA-354 is an improved, second-generation version of PA-824," says Professor Bill Denny, Co-Director of the ACSRC and a Maurice Wilkins Centre principal investigator. "It is much more potent than PA-824, longer lasting, and has greater activity against resistant strains

of the disease. Recent trials by the TB Alliance show that PA-824 can shorten the treatment period for TB and it's encouraging that in TBA-354 we have a compound that is clearly superior to PA-824."

"This has been an excellent and productive collaboration, across groups with different skills, where we have learned much from each other that we can apply in future," says Associate Professor Brian Palmer of the ACSRC and Maurice Wilkins Centre, who led the project's chemistry team of Drs Adrian Blaser, Iveta Kmentova, Hamish Sutherland and Andrew Thompson.

The TB Alliance expects to complete preclinical studies of TBA-354 by early 2013 and will then seek permission from the US Food and Drug Administration to begin trials in humans.

Professor Denny says that when PA-824 was discovered it clearly showed promise but had limitations and little was known about the nitroimidazole class to which it belongs. The New Zealand scientists discovered how to optimise each part of the drug, designing and synthesising nearly a thousand "second generation" molecules and sending the best of them to colleagues at the University of Illinois at Chicago for testing. In the process they also developed a new method for synthesising the drugs, which will simplify and reduce the cost of production.

TBA-354 emerged as the most promising candidate, with the greatest potency against TB. At the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Francisco this week the TB Alliance announced that TBA-354 had been selected for further development.

"New Zealand has an outstanding reputation in drug discovery and it's exciting to see the ACSRC's expertise in cancer drug development being

used in the fight against one of the most devastating infectious diseases in the world," says Professor Rod Dunbar, Director of the Maurice Wilkins Centre. "Skills honed over decades at the ACSRC with a focus on cancer have been very elegantly applied to a completely different kind of disease, showing how broadly our clever scientists can apply their expertise."

TB is second only to HIV/AIDS as the greatest infectious killer worldwide, and while with most cases and deaths occur in low and middle-income countries, it is a major health concern in the Asia-Pacific region. Treatment regimens are complex, lengthy and challenging to follow and the disease is developing resistance to current antibiotics, especially in its persistent form. If a potent new drug like TBA-354 proves more effective against TB than current treatments it has the potential to reduce the duration, cost and side-effects of treatment.

Provided by University of Auckland