Drug breakthrough in fight against neglected diseases

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Scientists from the Drug Discovery Unit (DDU) at the University of Dundee - working together with partners at the University of York and the Structural Genomics Consortium in Toronto - have made a major breakthrough in identifying new treatments for a fatal disease which infects tens of thousands of Africans each year.

Their findings, published in the latest edition of the world's leading scientific journal *Nature*, describe a new approach to tackling the fatal parasitic disease human African trypanosomiasis (HAT), commonly known as sleeping sickness due to disturbance of the sleep cycle caused by parasites infecting the brain.

The breakthrough made at Dundee shows promise for the development of effective, orally administered, low toxicity drugs to treat sleeping sickness.

"This is one of the most significant findings made in recent years in terms of drug discovery and development for neglected diseases," said Professor Paul Wyatt, Director of the Drug Discovery for Tropical Diseases programme at Dundee.

"We now have a valid drug target for HAT and have found leads for drugs which can be dosed orally. These two findings represent significant strides in the development of a full blown drug against sleeping sickness suitable for clinical trials.

"HAT comes in two stages - we know the drug leads we have identified in this paper can treat the first stage and we are very optimistic that we can now further develop them to treat the second, more serious stage."

It is estimated that drugs may be ready for human clinical trials in around 18 months.

Dr. Shing Chang, R&D Director of the Drugs for Neglected Diseases Initiative, said, "This is a significant discovery. It is a good example of applying state of the art scientific knowledge and tools in a collaborative effort to address the unmet needs of neglected patients."

The World Health Organisation estimates around 50,000-70,000 people in sub-Saharan Africa are infected with the disease, which is spread by the bite of a tsetse fly.

The disease has two stages, the second of which is particularly difficult to treat in poverty-stricken rural areas, where many victims live. Of the two drugs currently available, one - an arsenic-based drug - has fatal side effects in around one in 20 patients, and the other, eflornithine, is costly, requires prolonged hospital treatment and is not effective against all forms of the disease. Increasing reports of treatment failures with these drugs is causing concern that soon there may be no effective treatment for this fatal disease.

In response to the need for new and safe treatments, the DDU has already made good progress in developing compounds that have proved effective at killing the parasites, and that work well in the first stage of the disease. The compounds disrupt the enzyme N-myristoyl transferase, or NMT for short, which is essential for survival and growth of the parasites.

"The process of developing drugs consists of a number of hurdles which

have to be passed," said Professor Wyatt. "The first is identifying an Achilles heel of the parasite, such as an enzyme which is essential for the survival of the parasites, known as a drug target.

"The second is to confirm that molecules can disrupt these targets and so kill the parasite, a process called "target validation". The next is "lead optimization" to develop these early molecules into candidate drugs for clinical trials. That is where we are now. The final hurdle is to show safety and efficacy of the new drug in patients."

The Dundee team worked with partners from the University of York and the Structural Genomics Consortium during the course of the research. Professor Debbie Smith's group in York's Centre for Immunology and Infection (CII) originally identified NMT as a drug target with great promise for HAT. Together with colleagues in the York Structural Biology Lab, Professor Smith and her team also developed the assay and materials for screening in Dundee.

Professor Smith said, "We are excited that our research has contributed to development of a novel compound that kills parasites, an important step in developing new therapeutics against this neglected tropical disease. Our early proof-of-principle studies together with recent definitive experiments confirming the specificity of the new compounds confirm the importance of working collaboratively in the quest for new drugs in this area".

Dr Ray Hui's group within the SGC produced a three-dimensional representation of how the new molecules interact with NMT. This information greatly aids the design of better compounds and can accelerate the discovery of new drug candidates.

The initial aim of the Dundee research team was to target the first stage of HAT but fears over the decreasing efficacy of the current stage two

drugs led the World Health Organization to shift their priorities towards a treatment for the second stage. The Dundee scientists are actively working towards this new goal.

"Our initial aim was to develop a safe oral treatment for the first stage of the disease that would avoid the use of needles and be simple to use for control purposes," explained Professor Alan Fairlamb of the DDU.

"However, we are optimistic that we can address the new WHO priorities for a new treatment for the second stage of the disease."

Professor Mike Ferguson, who established the DDU along with Professor Fairlamb, said that although there was some way to go before a new drug can be developed, this represented a major breakthrough and that he was very proud of the team's achievements.

He also praised Professor Debbie Smith and colleagues at the University of York and members of the SGC for their contribution to the project.

Tragically for sufferers, African sleeping sickness is a neglected disease, one which has simply not been on the radar of large pharmaceutical companies. The shareholder value driven model of big drug companies, which works so effectively in the developed world, is not relevant to areas such as sub-Saharan Africa, where patients cannot afford to pay for their medicines.

The Drug Discovery Unit at Dundee was formed in 2005 specifically to fill the void of research and development of drug targets for diseases of poverty like African sleeping sickness, leishmaniasis, and Chagas' disease that afflict the developing world.

"There is little economic incentive for big pharmaceutical companies to engage in diseases from sub-Saharan Africa," added Professor Fairlamb.

"We've seen that these companies are now looking to Asia and Latin America as emerging markets, but one doesn't exist in Africa yet.

"We welcome the positive change in attitude of major pharmaceutical companies towards some of the big neglected diseases in recent years. We hope to go into partnership with a pharmaceutical company, once we have a candidate drug that has passed all the necessary preclinical safety and efficacy tests."

Provided by University of Dundee