Study could lead to new drugs to treat sleeping sickness

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(PhysOrg.com) -- Knowing the structure of an enzyme essential to the protozoan parasite that causes African sleeping sickness may lead to new drugs to combat the often-fatal disease and several other related disorders that afflict millions of people around the world.

Scientists believe the discovery may also provide new, more effective treatment for Chagas disease, prevalent in Central and South America, and leishmaniasis, which has reached epidemic proportions in parts of Africa, Brazil, and Afghanistan.

All three diseases are caused by trypanosomatids, single-celled parasites transmitted by insect bites that are notoriously resistant to treatment and eradication.

"Our work may provide the basis for developing an effective treatment for such protozoan infections," says Galina Lepesheva, research associate professor of biochemistry at Vanderbilt University and lead author of the study, published last month as the cover article in the Journal of Biological Chemistry.

Lepesheva, research associate professor of biochemistry, came to Vanderbilt in 2000 as a post-doctoral fellow from Minsk, Belarus, to work with Michael Waterman, chair of biochemistry and the paper's senior author.

Both researchers are experts in a family of enzymes used throughout the

animal kingdom to make sterols, lipid molecules essential for cell membrane function and integrity. "Without the appropriate membrane structure the organisms can't reproduce and don't survive," says Waterman.

Drugs used to treat fungal infections such as athlete's foot and ringworm work by a similar mechanism, by preventing sterol biosynthesis, and they also can potentially kill trypanosomatids. But until the structure of the parasite's enzyme was solved, it was not known that these drugs bind to the enzyme like keys in a lock, or how researchers might design a better key.

The researchers tested hundreds of compounds as potential inhibitors. The best "hits" were then analyzed in cellular experiments to select those with the strongest antiparasitic activity and lowest toxicity for humans.

One of the strongest inhibitors was co-crystallized with the enzyme, and the structure of that complex was chosen by journal editors as the cover illustration.

"Based on this experience," says Lepesheva, "we can say that the inhibitor co-crystallized in the complex with the enzyme has all the features to serve as a lead compound for antitrypanosomal therapy."

Currently Lepesheva and her colleagues, including Jeffrey Johnston, professor of chemistry and co-director of the Vanderbilt Chemical Synthesis Core, are designing even more specific inhibitors that could be used in combination with current drug regimens to kill Trypanosoma brucei with few, if any, side effects.

Most drugs used to treat fungal infections are topical, applied to the skin. Now it may be possible to develop safer, more effective oral medications, not only for protozoan infections, but for systemic fungal

infections in people whose immunity is impaired by diseases like AIDS, Waterman adds.

Co-authors of the paper include Fernando Villalta and Minu Chaudhuri, trypanosomatid experts at Nashville's Meharry Medical College, as well as researchers at the University of Toronto, the Free University of Brussels, Northwestern University and Texas Tech University.

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