Scientists hope to end sleeping sickness by making parasite that causes it self-destruct

January 15 2010

After many years of study, a team of researchers is releasing data today that it hopes will lead to new drug therapies that will kill the family of parasites that causes a deadly trio of insect-borne diseases and has afflicted inhabitants of underdeveloped and developing nations for centuries.

In an article to be published in today's issue of the Journal of Biological Chemistry, Vanderbilt University scientist Galina Lepesheva and her team are reporting their successful attempt at determining the structure of an enzyme essential to the survival of the protozoan parasites that cause sleeping sickness, Chagas disease and leishmaniasis. They say this new information provides the first up-close look at the busy enzyme and, perhaps more importantly, shows how one compound in particular prevents it from conducting business as usual.

"With human migrations, HIV co-infections and the broadening of the host reservoirs due to climate changes, sleeping sickness and other diseases caused by these protozoan pathogens are now spreading around the world, including within the United States and Europe," said Lepesheva, a research associate professor at the Vanderbilt's department of biochemistry. "It is our hope that the results of our work might be helpful for the development of an effective treatment for such protozoan infections, some of which still remain incurable."

Lepesheva and her team have set their sights on the trypanosomatidae family of parasites, which causes a trio of horrifying diseases:

• Human African Trypanosomiasis is transferred by the biting tsetse (pronounced TEE-TEE) fly in sub-Saharan Africa. Its victims suffer only flulike symptoms in the first phase of infection, but it often isn't diagnosed till after the parasite has entered the central nervous system, causing mental deterioration, mood swings, coma and death.

• Chagas disease is passed on by the the reduviid, or "kissing bug," named for its tendency to bite its victims around the lips, in South and Central America. The parasite that causes Chagas is the world's leading cause of heart disease, and the life expectancy for patients with chronic symptoms decreases by an average of nine years.

• Leishmaniasis, a disease transferred by the biting female sandfly, is prevalent in four continents and comes in four varieties, all of which either disfigure or kill its hosts. One causes skin ulcers; another causes chronic lesions resembling leprosy; the third destroys the mucus membranes in the nose, mouth and throat; the fourth causes high fever, organ swelling and, if left untreated, has a fatality rate as high as 100 percent within two years.

Screening for trypanosomal diseases is challenging, because they most often affect people in remote locations with few or no medical resources, and existing treatments lack specificity and can cause severe side effects.

Lepesheva and her team sought to damage the single-celled parasite's cellular membrane, knowing that if they could weaken that barrier, the regulation of the intercellular environment would be disrupted, and the parasite would die.

"It has been known for some time that T. brucei, the parasite that causes sleeping sickness, consumes cholesterol in its human host's blood to shore up the cellular membrane, and researchers presumed there was no

getting around that," Lepesheva said. "But we suspected the parasite, like plants and animals, still might need to make its own sterols for growth and development -- functional sterols - that could be targeted and inhibited."

The team chose to attack the parasite's enzyme known as 14DM, which is short for sterol 14α-demethylase. They picked 14DM because it has a counterpart in fungi, which cause athlete's foot and ringworm, and such fungal infections are commonly treated with drugs that prevent 14DM from making ergosterol, a sterol required for membrane synthesis.

"We tested hundreds of compounds as potential 14DM inhibitors. One of them, VNI, was one of the best in terms of killing the parasites that cause sleeping sickness, Chagas and Leishmaniasis," she said.

The team named the inhibitor VNI, short for Vienna Novartis Inhibitor, because it originally was synthesized at the Novartis Research Institute in Vienna. It binds with the worker enzyme, a lot like a piece fits snugly into a jigsaw puzzle, and blocks the enzyme's ability to make the critical sterol.

Lepesheva said having a clear picture of the structure of the enzyme and how VNI fits into it explains why VNI is effective, and it opens the door to structure-based new drug design.

Provided by American Society for Biochemistry and Molecular Biology