Discovery of enzyme in the sleeping sickness parasite streamlines drug development

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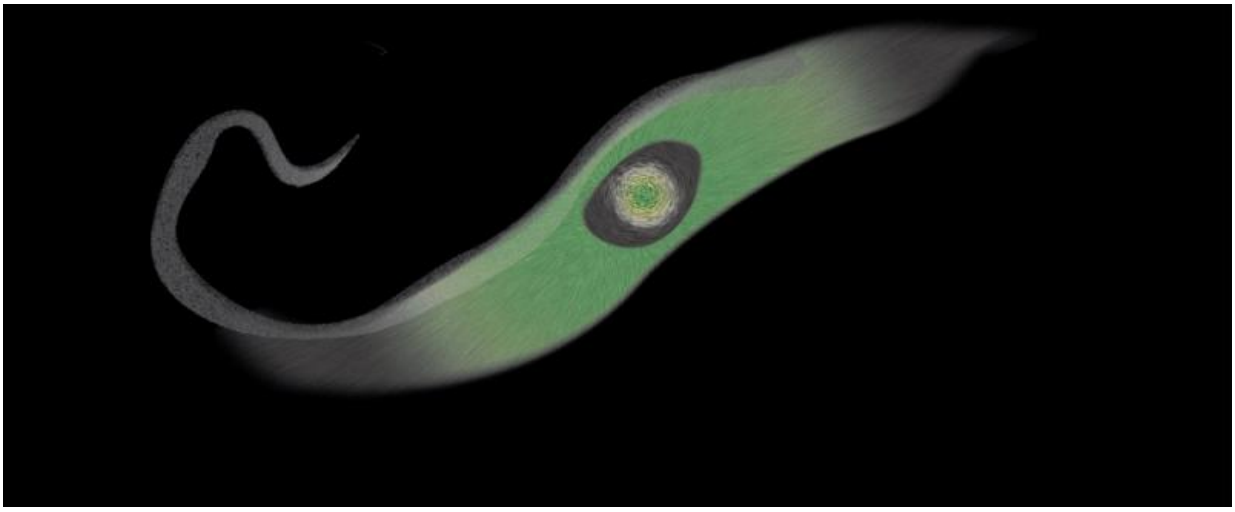

African sleeping sickness is caused by the unicellular parasite Trypanosoma brucei. Credit: Anders Hofer

Researchers from Umeå University in Sweden have discovered that the single-celled parasite causing African sleeping sickness has a defence mechanism against potential pharmaceuticals under development against the disease. The deadly parasite has an enzyme that can cleave and hence disarm adenosine analogue pharmaceuticals. This according to a study recently published in the *Journal of Biological Chemistry*.

African sleeping sickness is caused by the single-cell parasite

Trypanosoma brucei and is spread by infected tsetse flies in sub-Saharan Africa. The disease is deadly, affecting both humans and livestock. At present, no vaccine exists and the pharmaceuticals available are highly toxic, troublesome to use or can only be used on some variants or stages of the disease. The only medication that can treat all forms of the disease in humans is Melarsoprol, which in 5–10 percent of treatments leads to fatal brain damages.

The disease can erupt epidemics and the number of sleeping sickness cases in the last 20 years has varied between 20,000 and 500,000. In the last decade, the number of cases has been limited for instance thanks to discovering patients and treating them before they carry the disease on. But researchers have warned that an increased resistance against antibiotics among parasites can lead to an intensification in the number of cases again. This is why there is a great need of new pharmaceuticals. In animal models, researchers have seen promising results with so-called adenosine analogues, a drug group usually used on other diseases but yet not on African sleeping sickness.

To survive, this parasite is fully dependent on purines – nutrients absorbed from the blood and used as building blocks to produce RNA and DNA. This dependency is something is exploited in the development of pharmaceuticals. The idea is to develop adenosine analogues that are similar to natural purines and are therefore absorbed by the parasites, but subsequently damage them. These substances can be used to cure mice infected with the disease but have so far not been tested on human sleeping sickness patients.

"Up until now, researchers have been unaware of why some pharmaceuticals based on adenosine analogues work against sleeping sickness whereas others don't," says Anders Hofer, researcher at the Department of Medical Biochemistry and Biophysics and last author of the article in the *Journal of Biological Chemistry*. "We are now able to

show that the parasite has an enzyme able to cleave some of the adenosine analogues and this gives us an idea of why some drugs don't work."

The discovery enables researchers to control if the adenosine analogues that previously only had low efficiency on the parasite are cleaved by this enzyme. The pharmaceutical substances able to be cleaved by the parasite could then be made more efficient by changing their molecular construction in order for them not to be recognised by the enzyme.

"By manipulating the chemical structures of the more inefficient drugs, we are hoping to render them uncleavable and in that way bypass the parasite's protective enzyme. In doing so, it would be possible to develop many more pharmaceutical candidates to choose from, which would increase the opportunities to find a final drug with as few and harmless side effects as possible for use on humans," says Anders Hofer.Researchers from Umeå University in Sweden have discovered that the single-celled parasite causing African sleeping sickness has a defence mechanism against potential pharmaceuticals under development against the disease. The deadly parasite has an enzyme that can cleave and hence disarm adenosine analogue pharmaceuticals. This according to a study recently published in the *Journal of Biological Chemistry*.

More information: Munender Vodnala et al. Trypanosoma brucei methylthioadenosine phosphorylase protects the parasite from the antitrypanosomal effect of deoxyadenosine: implications for the pharmacology of adenosine antimetabolites, *Journal of Biological Chemistry* (2016). DOI: 10.1074/jbc.M116.715615

Provided by Umea University