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Researchers discover possible drug target to combat sleeping sickness

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Virginia Tech biochemists are trying to deliver a stern wake-up call to the parasite that causes sleeping sickness.

Scientists identified a protein, called proliferating cell nuclear antigen or PCNA, that is vital to the sleeping sickness parasite's good health. Disrupting this protein with drugs could potentially make it impossible for the parasite to reproduce and survive, reducing the health dangers to its human hosts.

The discovery, online this week in *Cell Cycle*, suggests multiple ways to disrupt PCNA's function, said Zachary Mackey, an assistant professor of biochemistry in the College of Agriculture and Life Sciences, a Fralin Life Science Institute affiliate, and an affiliated researcher in Virginia Tech's Vector-Borne Disease Research Group.

These include using drugs to either overexpress, deplete, or block the protein. The fact that PCNA can be exploited in a variety of ways to kill the parasite means that a wide range of small molecules or drugs could be used to deregulate it.

Sleeping sickness is caused by invasion of the *Trypanosoma brucei* parasite into the host's bloodstream. The native African tsetse fly transmits the parasite, and as it initially spreads through the body, it causes fever, headache, and intense aches and pains, according to the World Health Organization.

In later stages of the disease, the parasite spreads to the brain, where it causes swelling, and slurred speech, confusion, and difficulty walking, followed by coma and eventually death.

Though a few drugs exist to treat late stages of infection, they are either very expensive or have extremely powerful side effects, according to Mackey, who is also an affiliated researcher in the Virginia Tech Center for Drug Discovery.

Melarsoprol, for example, is an arsenic derived drug, meaning its side effects are equivalent to arsenic poisoning—severe fever, rash, vomiting, encephalopathy or brain dysfunction, and sometimes death.

Eflornithine, another drug used to treat sleeping sickness and the only one that researchers fully understand, costs more than one year's salary for many of those afflicted in sub-Saharan Africa, where the disease is most prevalent.

The next step for Mackey and his team is to investigate how altering the level of PCNA kills the parasite. Once they have a better understanding of how this protein regulates the life cycle of the parasite, the team can partner with chemists to synthesize small molecules that target its disruption.

More information: www.tandfonline.com/doi/suppl/ … .987611#.VOsvTGPbaLi

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