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## Surprise Finding Identifies Ways to Fight African Sleeping Sickness

A drug currently used to help transplant patients may unexpectedly lead to new cures for African sleeping sickness, according to a new study by a Howard Hughes Medical Institute international researcher.

While studying how the disease-causing parasite *Trypanosoma brucei* evades the human immune system, HHMI international research scholar Miguel Navarro unexpectedly discovered that rapamycin, an immunosuppressant, kills the parasite in cell cultures. The finding points to several novel targets for drugs that may kill the *T. brucei* parasite. Navarro and his colleagues will publish their article during the week of September 8, 2008, in the online early edition of the *Proceedings of the National Academy of Sciences*.

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African sleeping sickness, also called African human trypanosomiasis, occurs in sub-Saharan Africa. The infection is caused by the parasite *Trypanosoma brucei*, which is transmitted by tsetse flies. After a person is bitten by an infected fly and the parasite crosses into the brain, its presence triggers confusion, disrupted sleep, and other neurological symptoms. The disease is fatal if untreated. The most recent series of African sleeping sickness outbreaks occurred in 2005 and infected 50,000 to 70,000 people in Angola, the Democratic Republic of the Congo, and Sudan, according to the World Health Organization. However, poor surveillance continues to make it difficult to calculate the true toll of the disease.

Current therapies for sleeping sickness have been used since the 1920s and can cause severe side effects, including changes to the brain's structure and function. In many cases, the parasite can develop resistance to the drugs used to treat the infection.

Navarro, a cellular and molecular biologist, has been searching for clues that might aid the development of better therapies. Part of what makes sleeping sickness difficult to treat is that the parasite constantly shifts its surface

coating to hide from immune system antibodies.

While studying how the parasite does this, Navarro realized that four genes in the TOR family might play a key role in this avoidance mechanism. TOR is so named because it is the target of rapamycin, a drug that causes cells to stop dividing and shrink. It is also a potent immune suppressant and is often prescribed to stifle rejection of transplanted tissues and organs. Navarro wanted to inhibit the TOR proteins to assess their effect on the parasite's immune-avoidance system.

Before Navarro's experiments, the drug had never been tested against trypanosomes, the class of parasites that includes *T. brucei*. Scientists had previously found that rapamycin was ineffective against the parasite that causes malaria. We thought, 'There's a very small chance it's going to work against trypanosomes, but let's give it a try,' said Navarro, a researcher at the Institute of Parasitology and Biomedicine at the Spanish National Research Council in Granada, Spain. And then we got a surprise.

The infectious trypanosomes treated with rapamycin sprouted multiple nuclei and grew into odd shapes. The cells don't divide properly, Navarro said. They look so weird and grotesque we call them monsters. These malformed cells died in their culture dishes, suggesting that a rapamycin-related drug might be able to halt the infection in people. Rapamycin itself couldn't be used to regularly treat patients because of its immune suppressing properties, but some derivatives that do not affect the immune system are currently being tested as anticancer drugs.

In other organisms, like yeast, rapamycin halts growth and disrupts the cell cycle by squelching protein production. But those organisms don't display the weird shapes that Navarro saw in *T. brucei*. He decided rapamycin might be acting in a different way in the sleeping-sickness organism.

Further investigation confirmed Navarro's suspicion. In other organisms, rapamycin inhibits TOR1, but in *T. brucei*, the drug instead blocked TOR2. This made sense, because TOR1 controls the rate of cell growth, while TOR2 directs the spatial growth of the parasite—its shape. Rapamycin looks like it might be effective in stopping trypanosome infection, but it works in a completely different way than it does in other single-celled organisms, Navarro said.

A scan of the parasite's genome yielded another surprise: it contained two additional *TOR* genes. This discovery indicates that *T. brucei* has four *TOR* genes, the highest number recorded in any organism. Most single-celled organisms have only one or two *TOR* genes, Navarro said. Because the trypanosomes are ancient, having split from other eukaryotes early in evolution, they apparently have additional *TOR* genes.

These newly-found *TOR* genes, which also appear to be involved in cell growth, present promising targets for future drug development, Navarro said. He's also begun testing rapamycin derivatives against *T. brucei*. We're hoping we can find a rapamycin-like drug that blocks TOR's control of cell

proliferation without also inhibiting the human immune system, he said. That would be a really good finding.