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Trypanosome Genomes May Reveal New Drug, Vaccine Targets

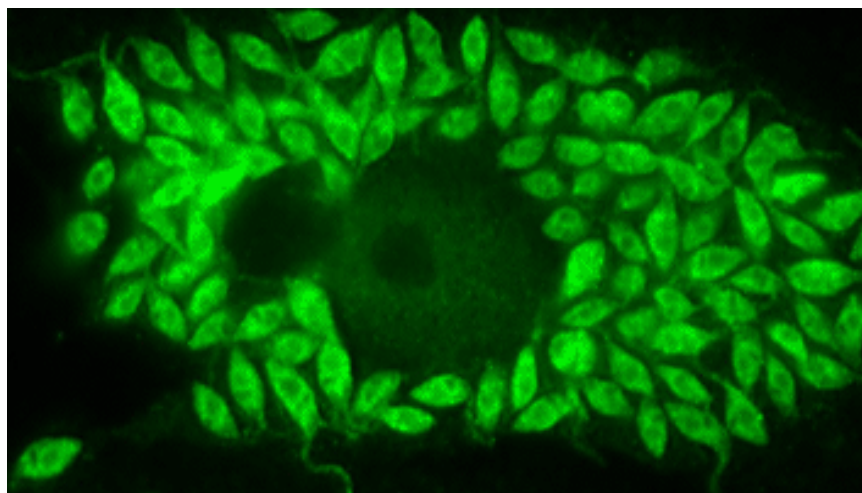


Image Title: Cells from mammals infected with *T. cruzi*. The green color results from labeling with antibodies directed to a protein on the surface of the trypanosome. - Vanina Campo

A team of international scientists has sequenced the genomes of three species of parasites responsible for causing diseases that kill or cripple millions, primarily in tropical and sub-tropical countries. Howard Hughes Medical Institute (HHMI) scientists who participated in the project say the sequencing of the genomes of the parasitic protozoa that cause Chagas disease, African sleeping sickness, and leishmaniasis, could significantly impact world health. Some of the genes discovered may prove to be good drug and vaccine targets.

The research is published in a special issue of the journal *Science* focusing on the genome sequences of *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania major* and the public health threat that these parasites represent. One of the studies' key findings is the identification of gene sequences that are involved in the host-parasite relationship and in the regulation of the parasite metabolism.

Another important finding, according to Mariano Levin, a co-author of the *T. cruzi* paper, is that scientists now know what the three trypanosomes have in

common. “We know that they share 6,000 genes, and 2,000 of those genes are found only in these three parasites,” said Levin, a HHMI international research scholar at the Institute for Research on Genetic Engineering and Molecular Biology in Buenos Aires, Argentina. “This is extremely important because among those 2,000 genes, you may be able to find targets for drugs that will only affect the parasite and not the host.”

"This study will advance tropical medicine by helping us develop new drugs against these diseases."

- Shulamit Michaeli

Shulamit Michaeli, a HHMI international research scholar at Bar-Ilan University in Israel and co-author on the *L. major* paper, also is optimistic about the impact of the work on drug development. “By providing information on virulence factors, critical enzymes in key metabolic pathways, and potential vaccine candidates, this study will advance tropical medicine by helping us develop new drugs against these diseases,” she said.

Alberto Frasch, a HHMI international scholar from Argentina, agrees. “Having a sequenced genome should aid us immeasurably in finding new drugs,” said Frasch, who is director of the Institute for Research in Biotechnology of the National University of General San Martin in Buenos Aires and an author on the *T. cruzi* and *L. major* papers. Frasch explained that the drugs currently available to treat diseases caused by trypanosomes “either have toxic side effects or lack efficiency in some stages of infection, as in chronic Chagas disease.” “Also,” he said, “drug resistance in diseases caused by trypanosomatids complicates their treatment. The information obtained from genome analysis might help us understand the resistance mechanisms to drugs now used.”

Trypanosomes are a type of single-celled microorganism that has developed elaborate schemes to evade the immune systems of their hosts. They are spread to humans through contact with infected animals. *Trypanosoma cruzi* causes Chagas disease, a devastating public health problem in Central and South America and Mexico, while *Trypanosoma brucei* causes African sleeping sickness, and *Leishmania major* causes leishmaniasis.

African sleeping sickness, which affects people living in sub-Saharan Africa, is characterized by early fever and progresses to heart and kidney dysfunction, neurological destruction, and eventual death. Fever and heart impairment are also hallmarks of Chagas disease, which infects 16 to 18 million people, causing severe chronic illness and tens of thousands of deaths per year. Heart failure is responsible for most deaths from Chagas disease, which also causes liver problems and neurological impairments that can

affect swallowing. Fever and liver disorders characterize leishmaniasis.

The sequencing of the trypanosome genomes presented significant challenges, according to Michaeli. Certain characteristics of the trypanosomes' genome made this task particularly tricky, she said. "The basic tools of cloning and sequencing were normal, but because there are lots of repetitive sequences, reassembling the genome in the right order was more complex," she explained.

"The outcome of the genome project has major impact not only from the medical point of view," Michaeli added. "The genome project confirmed that trypanosomes lack the ability to control the expression of protein-encoding genes at the level of transcription. It is the first eukaryote we have seen whose gene regulation occurs mainly post-transcription and mainly through exotic mechanisms such as trans-splicing and editing."

Another HHMI international research scholar, Santuza Teixeira of Brazil, was a co-author of the *T. cruzi* paper. HHMI's international research scholars serve as role models for scientists in developing countries, who increasingly are joining a global battle against the infectious and parasitic diseases that decimate their people.

HHMI supports the research of outstanding scientists in 38 countries, many of them developing nations.