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TRYPANOSOMATIDS PARASITES ACHILLE'S HEEL: TARGETING GLYCOSOME BIOGENESIS

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Trypanosomatid infections are the cause of African sleeping sickness, leishmaniasis, and Chagas disease. The parasites use glycosomes, organelles similar to peroxisomes to compartmentalize glucose metabolism. The malfunction of this compartmentalization releases glucose processing enzymes to the cytoplasm causing runaway glucose phosphorylation, ATP depletion and subsequent cell death. The proteins Pex14 and Pex5 are essential components of the glycosomal import machinery. They bind each other by a direct protein-protein interface. It has been shown that in the absence of Pex14 glucose is toxic to the parasite. We have determined the structure of the

Pex14-Pex5 complex to develop a line of small molecule inhibitors able to disrupt the Pex14-Pex5 interaction in a competitive way. The compounds identified proved active against *Trypanosoma brucei in vivo* and in cell-based assays. We have confirmed their disruptive function on parasites glycosomes. Simultaneously, the compounds appear to be of limited toxicity to the human cell lines. Our results confirm that targeting the Pex14-Pex5 interface is a viable therapeutic strategy to treat both human and animal trypanosomiasis.

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