Assessing anti-T.ăcruzi candidates in vitro for sterile cidality

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Total clearance of the T.ăcruzi infection - referred to herein as ”sterile cure” - seems to be a critical prerequisite for new drug candidates for Chagas disease, ensuring long-term beneficial effects for patients in the chronic indeterminate stage. This requirement is notably supported by the recent findings of clinical studies involving posaconazole and fosravuconazole, where the majority of patients treated eventually relapsed after an apparent clearance of parasitaemia at the end of treatment. We have adapted an inăvitro system to predict the ability of a compound to deliver sterile cure. It relies on mouse peritoneal macrophages as host cells for Trypanosoma cruzi amastigotes. The macrophages do not proliferate, allowing for long-term testing and wash-out experiments. Giemsa staining followed by microscopy provides a highly sensitive and specific tool to quantify the numbers of infected host cells. Combining macrophages as host cells and Giemsa staining as the read-out, we demonstrate that posaconazole and other CYP51 inhibitors are unable to achieve complete clearance of an established T.ăcruzi infection inăvitro in spite of the fact that these compounds are active at significantly lower concentrations than the reference drugs benznidazole and nifurtimox. Indeed, a few macrophages remained infected after 96ăh of drug incubation in the presence of CYP51 inhibitors-albeit at a very low parasite load. These residual T.ăcruzi amastigotes were shown to be viable and infective, as demonstrated by wash-out experiments. We advocate characterizing any new anti-T.ăcruzi early stage candidates for sterile cidality early in the discovery cascade, as a surrogate for delivery of sterile cure inăvivo.

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