# Novel *Trypanosoma brucei* heterogeneity is associated to tissue invasion and adaptation

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## Abstract

Recent research across eukaryotes has demonstrated the importance of heterogeneity for a plethora of biological phenomena, ultimately related to population survival. *Trypanosomes* have very complex life cycles, which rely on the successful adaptation the parasites must display to both the insect vector and the mammalian hosts. In order to investigate parasite heterogeneity in a holistic manner, we used surgical approaches and intravital microscopy on rodent models to characterize in vivo parasite morphology, cell cycle, stumpy formation, PAD1 expression, motility type, and velocity of parasites inside the vasculature and extravascular spaces. We studied 12 organs throughout 20 days of infection. Inside the vasculature, we found that the morphology of parasites can be quite variable (14-28 μm range in length; 1.2-3.5 μm range in width) and that crossing into the extravascular space of several organs, including large reservoirs, is associated to the presence of particularly long and large forms. Characterization of the extravascular parasites first revealed a group of organs in which parasites do not undergo significant changes relative to the blood counterparts, either because they colonize the organ poorly or because they are only transiently colonized. Second, we found that in white adipose tissues, pancreas, spinal cord, yellow marrow, and brain, parasites undergo significant phenotypic changes relative to the blood counterparts but similar within this group, indicating that lipid-rich environments trigger a common phenotypic adaptation. Third, in lymphoid organs including the spleen and RBM, parasites undergo another unique adaptation, different to that observed in lipid-rich tissues. Moreover, by atomic force microscopy, we show that the viscoelastic properties of organs are heavily modified throughout infection. This study reveals a remarkable heterogeneity in the parasite population among and within organs, which probably play key roles in organ invasion and establishment of chronic infection.