Towards improved antileishmanial drug screening models to capture the risk of post-treatment relapse

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Post-treatment relapse occurs with all known antileishmanial drugs and is of global medical concern. Apart from treatment failure, the scarce collection of existing drugs suffers several drawbacks including toxicity, high cost, parenteral administration requiring hospitalization and the emergence of drug resistance. Moreover, the current R&D pipeline does not capture the risk of relapse, as the ontogeny is poorly understood and currently no efficient prognostic tests exist.
The recent discovery of long-term hematopoietic stem cells (LT-HSC) as a major parasitic niche for drug survival, sheds new light on the underlying mechanisms of disease recurrence. This cellular niche located in the bone marrow serves as a sanctuary where visceral *Leishmania spp.* rapidly adopt a quiescent phenotype. Both the cellular niche and parasite quiescence confer *Leishmania* tolerance to drug exposure. Initial assay development relied on LT-HSC isolation by lineage depletion and fluorescence-activated cell sorting (FACS). This is an arduous and time-consuming process resulting in limited cell yields which restricts its use as an *ex vivo* assay in the lead optimization process. Also with regard to animal ethics, strategies have been explored to reduce the use of mice for bone marrow collection.
Here we describe the optimization of *ex vivo* LT-HSC expansion, a pivotal step towards the establishment of a medium throughput antileishmanial drug screening platform aimed at improving lead selection to reduce the risk of relapse.

Keywords: visceral leishmaniasis, relapse, long-term hematopoietic stem cells, quiescence, *ex vivo* expansion

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