Linking In Vitro Activity, In Vivo Response, and Tissue Distribution in Cutaneous Leishmaniasis

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Abstract

Cutaneous leishmaniasis (CL) is a parasitic skin disease caused by multiple *Leishmania* species and is characterised by a a spectrum of skin manifestations. Current treatment options are limited and associated with variable efficacy and toxicity, highlighting the need for improved therapeutic strategies.

Here, we present comparative data from preclinical evaluation of two DND*i* candidate compounds, DNDI-6174 and DNDI-0690. In vitro susceptibility was assessed using peritoneal macrophages infected with seven different *Leishmania* species, followed by 72-hour drug incubation.

Antileishmanial activity in the skin was evaluated in dose-response studies using *L. major* parasites genetically modified to express a red-shifted luciferase reporter. Parasite burden was quantified throughout treatment by bioluminescence imaging, enabling non-invasive assessment of treatment response within infected skin. Distinct *in vivo* efficacy profiles were observed between the two compounds. For DNDI-0690, MALDI-FT-ICR mass spectrometry imaging was performed to assess intralesional drug distribution, revealing heterogeneous spatial distribution within skin lesions. For DNDI-6174, washout experiments were conducted to evaluate parasite rebound following treatment cessation.

Together, these studies highlight differences in *in vitro* activity, *in vivo* dose-response behaviour, tissue distribution, and post-treatment effects between two candidate compounds for CL. These findings illustrate the importance of evaluating drug candidates across complementary experimental systems to better characterise compound-specific performance in CL.