Topical Treatment for Cutaneous Leishmaniasis—Drug Discovery
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Purpose
Cutaneous leishmaniasis (CL), a widespread parasitic disease, affects 0.7-1.2 million people every year. Current treatments for CL are unsatisfactory. Topical treatment could reduce adverse effects through local exposure, increase patient compliance and require less stringent follow up. Benzoxaboroles, a relatively new class of compounds showed promising activity when tested against a panel of five Leishmania species. A subset of these active compounds were submitted to an array of in vitro ADME studies and the three most favoured compounds were tested in vivo in a CL mouse model.

Methods
Benzoxaborole compounds were screened against intracellular amastigotes. Physicochemical properties that influence dermal exposure such as log P_{oct/water} and solubility were determined and compared to literature values. Stability in and binding to mouse skin homogenate was also determined. Permeation of test compounds through reconstructed human epidermis (RHE) (Mattek) was measured. The disposition of promising compounds were further examined using BALB/c mouse skin in Franz Diffusion Cells (FDC). Sample analysis was performed using LC-MS/MS. The three compounds with the best overall skin disposition profile were then tested in BALB/c mice infected with L. major JISH118.

Results
The physicochemical properties of most compounds are indicative of good dermal exposure. Testing showed no remarkable instability, and most compounds were more stable than the controls (known substrates for skin esterases). Skin binding was variable, with a range of unbound fractions observed. Four compounds showed a better permeation profile than the model penetrant, testosterone when applied to the RHE. These results were confirmed in the FDC experiment. In the in vivo study, one compound showed good activity when administered topically, and a second compound exhibited good activity when administered orally.

Conclusion
The drug discovery approach applied to this project consisted of activity testing followed by limited in vitro ADME testing to identify lead compounds with a good dermal exposure and disposition. Initial in vitro results are very promising and suggest that (1) this approach will be useful in discovery of new CL drug candidates, and (2) the benzoxaboroles may provide good starting points for discovery of both topical and oral treatments for CL.