TT4CL

TARGETED TREATMENT FOR CUTANEOUS LEISHMANIASIS

Preclinical research demonstrates D121 outcompetes miltefosine

Experiments for a new drug often begin with in vitro assays. When promising results are obtained, researchers may progress to animal models, (including rodents) to further assess the molecule's effects in a more complex biological system.

***Katrien Van Bocxlaer**, a trained pharmacist, has dedicated her professional career to research focused on drug delivery to the skin in the context of parasitic diseases, and more specifically on leishmaniasis. She started her reserach at the London School of Hygiene & Tropical Medicine and is now continuing at the Skin Research Centre, University of York, in the United Kingdom.*

***Dr Vanessa Yardley** is a member of the Drug Discovery Group (DDG) at London School of Hygiene and Tropical Medicine (LSHTM), established 125 years ago to address global health challenges related to tropical diseases.*

Vanessa is an Assistant Professor in the Faculty of Infectious & Tropical Disease where she works on drug discovery and drug development projects. For many years she has worked with kinetoplastid infections, especially Leishmaniasis. She was one of the first researchers performing in vitro studies on D121 in 2012.

See https://doi.org/10.1093/jac/dks273

As part of the TT4CL project under Horizon 2020, Katrien and Vanessa successfully conducted a comparative study to assess the efficacy of D121 in an innovative mouse model designed specifically to investigate cutaneous leishmaniasis.

Ambition TT4CL: Revolutionizing Treatment for 12 Million People

The ambition of the TT4CL project is to establish a new standard treatment for cutaneous leishmaniasis, a parasitic disease affecting approximately 12 million individuals across 98 countries, predominantly among the most socioeconomically disadvantaged populations. Each year, there are an estimated 700,000 to 1.2 million reported cases, though this figure likely represents an underestimation of the true prevalence.

Transmitted by the sandfly, the parasite infiltrates the skin, resulting in persistent ulcers, nodules, or lesions that often heal slowly and spontaneously, yet leave behind severe and disfiguring scars. While not typically fatal, cutaneous leishmaniasis profoundly impacts individuals' quality of life, leading to stigmatization, discrimination, and psychological distress, particularly among children.

Through the development of an effective oral drug, the TT4CL project aims to alleviate the burden of this debilitating disease and improve the well-being of millions worldwide.

TT4CL

TARGETED TREATMENT FOR CUTANEOUS LEISHMANIASIS

Diverse Strains, Singular Solution

Cutaneous leishmaniasis is caused by a variety of strains, each with distinct geographical distributions. In the Old World, strains such as *L. major, L. tropica,* and *L. aethiopica* prevail, while the New World harbours strains like *L. braziliensis, L. mexicana, L. panamensis,* and *L. guyanensis,* among others.

Katrien and Vanessa **assessed the efficacy of D121 in vitro in an intramacrophage model using seven different Leishmania strains originating from both the Old and New World**.

The potent in vitro antileishmanial activity of D121 merited further investigation in an experimental CL model *(L. major)* where it demonstrated superior activity to miltefosine.

This investigation corroborates earlier findings from studies conducted in dogs and hamsters, **demonstrating the superior performance of D121 against Leishmania parasites found in both visceral organs and the skin**, when compared to the sole oral treatment available on the market, miltefosine. Notably, the study revealed a marked reduction in the size of skin lesions with D121 administration, whereas miltefosine, administered at the same dosage and regimen, merely arrested lesion progression without inducing substantial reduction.

Innovative Strategic Development

The TT4CL consortium has embraced an **innovative strategic approach** to D121 development. Avivia's comprehensive efforts yielded distinct formulations of D121, employing varied excipients and release profiles, including two fast-release and two slow-release formulations. Katrien and Vanessa conducted a thorough comparison of these different formulations alongside the drug substance itself, utilizing a mouse model infected with *L. major*.

This comprehensive evaluation **allowed for simultaneous optimization of treatment efficacy and formulation refinement.**

D121 has emerged as a promising oral drug candidate for the treatment of cutaneous leishmaniasis, aligning effectively with the ambitious goals of the TT4CL project. Notably, there is a **strong indication that D121 may require a shorter treatment duration compared to the 28-day regimen of miltefosine**, the current standard oral treatment. Moreover, emerging evidence suggests a broader safety margin for D121, potentially enabling administration of higher dosages.

These favourable attributes of D121 - its potential for a shorter treatment duration and an expanded safety profile - could significantly enhance patient compliance. With a reduced treatment period and a wider safety window, D121 holds promise for improving patient adherence to treatment protocols, ultimately contributing to better outcomes for individuals affected by cutaneous leishmaniasis.

For those interested in a deeper dive into this research, comprehensive information can be accessed in the publication titled:

J Antimicrob Chemother publication-Journal-Antimicrobial-Chemotherapy.pdf

DOI: 10.1039/d0md00343c

Katrien Van Bocxlaer has also presented these research results at numerous prestigious events, underscoring the significance and impact of her findings. Some of these presentations include:

The British Society for Parasitology,
York, UK, August 2022

World Leishmaniasis Conference,
Carthagena, Colombia, August 2022

The International Congress of Parasitology (ICOPA),
Copenhagen, Denmark, August 2022

This project received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 815622.

St George's University of London

Avivia

Eberhard Karls Universität Tübingen

London School of Hygiene & Tropical Medicine

Oblita Therapeutics

Tehran University of Medical Sciences