COST Action CM1307

1rst Annual Meeting

Targeted chemotherapy towards diseases caused by endoparasites

BOOK OF ABSTRACTS

OCTOBER 27-29, 2014

Hotel Regina

Calvi – Corsica

France

www.costcm1307.org/CM1307_2/1st_Meeting.html

This first COST Action CM1307 conference has been organized by two French universities: Paris-Sud and Strasbourg as a joint meeting with the French consortium of antiparasitic chemotherapy (CaPF). The conference and the Working Group meetings will be held in Hotel Regina, Avenue Santa Maria 20260 Calvi, Corsica – Tel : +33-4 95 65 24 23 – Fax : 33-4 95 61 00 09 Email : infos@reginahotelcalvi.com

Advances in the chemotherapy against human and animal parasitic diseases remain limited largely because drug candidates have low specificity and show poor in vivo bioavailability. This meeting aims at uniting scientists with different backgrounds to create synergistic interactions paving the way for antiparasitic drug discovery for diseases caused by protozoa and helminths.
The scientific aim is to bundle together the identification and validation of parasite drug targets based on the established genomes, medicinal chemistry including structure-based drug design, natural products, crystallography, bioinformatics, and drug targeting using chemical and nanotechnological approaches to improve drug performance.

The meeting is focused on eight topics :

1- Medicinal chemistry
2- Strategies for drug discovery
3- Mechanisms of action of antiparasitic drugs
4- Drug development
5- Biological targets
6- Progress in screening systems
7- Drug targeting
8- Mechanisms of drug resistance/failure

This first COST CM1307 conference is followed by the meetings of two chemistry Working Groups :
WG2 dedicated to Medicinal Chemistry and WG3 dedicated to Natural Products.

Organizing Committee:

Didier Belorgey (CNRS-University of Strasbourg, FR)
Agn□s Berton (University Paris-Sud-CNRS, FR)
Elisabeth Davioud-Charvet (CNRS-University of Strasbourg, FR)
Patrice Le Pape (University of Nantes, FR)
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Scientific committee:

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Thomas Schmidt (University of Münster, GE)
Ana Tomas (University of Porto, PT)

Understanding MIL treatment failure

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Oral miltefosine (MIL) has been introduced as first-line therapy for visceral leishmaniasis in endemic areas with antimonial resistance. Although increased post-treatment relapse rates were recently reported, MIL-resistant Leishmania donovani strains have yet not been isolated. To study MIL-resistance mechanisms and dynamics, we recently developed an in vitro procedure to experimentally induce resistance in intracellular amastigotes (Parasitol Res. 2014, 113:1875-81). Adopting in vitro selection on several L. donovani and L. infantum isolates, only L. infantum LEM3323 developed resistance. While the amastigote IC_{50}-values of the other strains did not increase, promastigote back-transformation nevertheless became positive at increasing MIL concentrations. These results trigger three research questions: 1/ What relevance does the promastigote back-transformation have to assess drug susceptibility? 2/ What parasitological characteristics form the basis for LEM3323 resistance development? 3/ Is there a difference between induced resistance of LEM3323 compared to L. infantum LEM5159 that acquired resistance in the field?

Isolates from cured and relapse patients were subjected to IC_{50} evaluation and promastigote back-transformation. All isolates proved to be susceptible to MIL, while back-transformations were positive at high MIL-concentrations, hence suggesting reduced susceptibility. In depth evaluation of the assay revealed that a few susceptible parasites may remain viable after MIL treatment giving rise to positive back-transformations. Since treatment failure cannot be linked to in vitro resistance, other parasitological, host and/or drug factors should be taken into consideration. For example, in comparison to strains that did not develop MIL-resistance in vitro, LEM3323 showed a significantly higher intracellular replication. The infectious and virulent potential of this strain is currently being further investigated. To unravel mechanisms underlying the resistant phenotype, LEM3323 and LEM5159 were subjected to genomic and functional analysis. For the LdMT gene, LEM3323 carries a deletion while LEM5159 shows a non-synonymous SNP. DsRed-transfected LEM3323 and LEM5159 did not accumulate BODIPY-labelled MIL while the susceptible LEM3323 counterpart showed MIL-uptake, endorsing the functional role of LdMT.