Insights into host-target interaction from the proteome modulation analysis through untargeted LC-MS/MS Proteomics of drug resistant L infantum-THP1 infected cells

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Authors: Lorenzo Tagliazucchi [a], Giulia Malpezzi [a], Ana Perea Martinez [b], José Ignacio Manzano [b], Raquel Garcia-Hernandez [b], Diego Pinetti [c], Filippo Genovese [c], Eli Thorè [d], Bryan W. Brooks [e], Michael G. Bertram [f], Francisco Gamarro [b], Maria Paola Costi [a]

[a] Dept of Life Sciences, University of Modena and Reggio Emilia, Italy; [b] Department of Biochemistry and Molecular Pharmacology, Instituto de Parasitología y Biomedicina López-Neyra, Spanish National Research Council (IPBLN-CSIC), Spain. [c] Centro Interdipartimentale Grandi Strumenti (CIGS), University of Modena and Reggio Emilia, Italy; [d] Swedish University of Agricultural Sciences, Sweden. [e] Dept of Biology, Baylor University, Waco, Texas (US). [f] *School of Biological Sciences, Monash University, Melbourne, Australia*

Lorenzo.tagliazucchi@unimore.it

Vector borne diseases (VDBs) are the cause of more than 75% of the emerging human infections worldwide originated from animals. One of the most diffused VDB is represented by Leishmaniasis, represented by over 12M of new clinical cases every year. Depending on the endemic region of diffusion, current therapeutic options include Miltefosine, Antimonials and Paromomycin. However, the unsupervised of these few drugs in the livestock and humans has selected specific hyper-resistant strains, determining the rapid onset of concerning resistance phenomena. This led to a decrease of drugs efficacy and increase of interspecies diffusion [1,2].

With the aim to characterize drug resistance phenomena at a cellular level, we have treated THP-1 cells with clinical isolates of drug resistant *L. infantum* strain and processed the cells for a MS based proteomics analysis. The quali-quantitative differential analysis of the samples performed with Proteome Discoverer tool vs controls (non-resistant lines) revealed the presence of 15 Differentially Expressed Proteins (DEP's), 6 of which in miltefosine sample, 8 in paromomycin and 6 in Sb(V) resistant strain. Some DEPs are mutual to more than one lines, and peroxidoxin - whose role in parasitic oxidative stress neutralization is well established - resulted up-regulated (FC >2) in all the three resistant lines. We have combined these results with the outcome of the analysis of the human proteome modulated by the guest [3], which was previously investigated with STRING, Reactome, and other bioinformatic tools to define the most involved GO's.

From a guest-host cross talking analysis, we have identified the parasitic DEPs which do not share any GOs (functional and bioprocess) with the ones from THP-1. They represent a starting point of a Medicinal Chemistry programme, whose aim is to identify a druggable guest target with a low level of homology for both human and other species. This will allow the specific inhibition of the protein to obtain an antiparasitic effect, avoiding inter species off target activity. The ecotoxicological analysis, including specie-similarity analysis, will drive the whole workflow through target validation and exploitation.

References

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[3] Tagliazucchi, L et al. Label free Mass spectrometry proteomics reveals different pathways modulated in THP-1 cells infected with therapeutic failure and drug resistance Leishmania infantum clinical isolates. *ACS Inf Dis*, Jan **2023.**

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