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Prof. Maria Paola Costi
(UniMoRe)
Prof. Philippe Loiseau
(Université Paris-Saclay)

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Proteomic contribution to the omic path for the identification of novel drugs overcoming resistance in Leishmaniasis

Authors:

Lorenzo Tagliazucchi (a), Greta Fiorini (a), Ana Perea-Martínez (b), Raquel García-Hernández (b), José Ignacio Manzano (b), Maria Paola Costi (a)Francisco Gamarro (b),

Affiliation: Higher Education & Associated Organisations; **a)** Università di Modena e Reggio Emilia, Dipartimento di Scienze della Vita, Italy. Government/Intergovernmental Organisations except Higher Education; b) Instituto de Parasitología y Biomedicina "López-Neyra", IPBLN-CSIC, Granada, Spain.

Area of expertise needed:
Chemical sciences (medicinal Chemistry and synthesis, analytical chemistry, molecular modelling, others)
Biological sciences (molecular biology and interactions, pharmacology, others)
Health Sciences (Health Science, parasitology, others)
Other medical science (database, data mining, data curation and computational modelling, others)

As the world is now facing increasing treatment failure against leishmaniasis, deeper investigation on the molecular mechanisms responsible for drug resistance and therapeutic failure is needed. The currently few available drugs, such as Sb complexes, paromomycin and miltefosine, show severe side effects and develop different resistances, so innovative molecules should be considered [1]. The aim of our research in the frame of the Spanish Grant RTI2018-097210-B-100 (IPBLN-CSIC) is to study the modulation of infected human monocytes by *L. infantum* clinical isolates from patients with therapeutic failure, using proteomics approaches that can be further integrated with the transcriptomics studies to achieve information for novel drug discovery studies. A THP-1 cell line was infected with different

clinical isolates of *L. infantum* lines from therapeutic failure patients with leishmaniasis. The samples were divided in two groups: a drug resistant group, and a cluster of strains isolated from immunocompromised patients with therapeutic failure and without drug resistance phenotype. Samples were digested and analyzed in a UHPLC-Orbitrap Q-Ex™, then Progenesis QIP™ and Mascot Matrix™ were used for peptide quantification. A differential analysis between non-infected THP-1 cells and the human cell line infected with heat inactivated *L. infantum* promastigotes assessed a baseline reference. The comparison between samples generated a list of differentially expressed proteins (DEPs). A network enrichment analysis process was applied through different freely accessible bioinformatic tools (STRING, Panther, Reactome, others). This work led to the identification of relevant biological process associated with drug resistance/therapeutic failure mechanisms. A comparison between proteomics and transcriptomics datasets identified at the IPBLN-CSIC, among other results, evidenced two proteins/transcripts with the same expression trend: Transferrin receptor protein 1 (TRFC), involved in Fe^{2+} homeostasis, and Nucleoside diphosphate kinase (NDK3), responsible for apoptotic process. Both processes are observed in *Leishmania* infection [2,3]. The expected results are to reconcile the proteomic results with transcriptomic data achievements as founding concepts to identify new protein targets involved in *Leishmania* drug resistance and therapeutic failure mechanisms. We aim to set up drug design programs of new molecules and from repurposing studies and to offer a drug combination therapy to avoid drug resistance and therapeutic failure phenomena.

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[1] Ponte-Sucre, A. et al. 2017. *Drug resistance and treatment failure in leishmaniasis: A 21st century challenge*. PLoS Negl Trop Dis 11, e0006052. [2] Das, N.K., et al. 2009. *Leishmania donovani depletes labile iron pool to exploit iron uptake capacity of macrophage for its intracellular growth*. Cellular Microbiology 11, 83–94. [3] Moreira, D.S. et al. 2016. *Involvement of nucleoside diphosphate kinase b and elongation factor 2 in Leishmania braziliensis antimony resistance phenotype*. Parasites Vectors 9, 641.