TB-001 - **Miltefosine and Amphotericin B susceptibility in reference strains and clinical isolates of Leishmania spp. responsible for tegumentary leishmaniasis**

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Tegumentary leishmaniasis (TL) is a complex of diseases caused by several species of the protozoan of the genus *Leishmania*. In Brazil, TL is caused mainly by *Leishmania (Viannia) braziliensis, L. (Leishmania) amazonensis* and *L. (V.) guyanensis*, being the first, the most prevalent species. In recent years, leishmaniasis has presented an increasing number of cases, mainly in urban regions. The treatment of TL in Brazil consists in the use of pentavalent antimonials and amphotericin B (AmB), drugs that are considered costly, toxic, and require parenteral administration. Recently, miltefosine (MF) was approved for the clinical treatment of TL in Brazil, although it is not yet available in the National Health System. In this study, we aim to evaluate the *in vitro* susceptibility to AmB and MF in all *Leishmania* species responsible for TL in Brazil and in a panel of 16 clinical isolates of *Leishmania* spp. from a reference center for treatment of TL. The *in vitro* susceptibility to AmB and MF of clinical isolates and species of *Leishmania* were determined in promastigote and intracellular amastigote forms. The results obtained indicated a moderate variation in the susceptibility to these drugs in clinical isolates and in *Leishmania* species in both forms of the parasite. In addition, an AmB resistant line of *L. (L.) amazonensis* is currently selected *in vitro*. These findings will contribute to evaluate the limitations of the use of AmB and the potential of MF as an alternative drug for the treatment of LT in Brazil. **Supported by:**FAPESP (Processo: 2020/01948-1) **Keywords:**Tegumentary leishmaniasis, amphotericin B, miltefosine

TB-002 - **Studies on paromomycin susceptibility and resistance in *Leishmania amazonensis***

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Cutaneous leishmaniasis is a disease that has presented, in recent years, an increasing number of cases in Brazil. The disease is caused mainly by *Leishmania amazonensis* and *L. braziliensis*. The treatment of the disease in Brazil is limited to the use of parenterally administered drugs that induce several side effects. Paromomycin (PM) was already approved as alternative to the treatment of visceral leishmaniasis in Southeast Asia. Although not used in the treatment of cutaneous leishmaniasis, it is important to investigate the potential of this drug against species endemic in Brazil. Here, we selected PM resistant lines of *L. amazonensis* in promastigote and intracellular amastigote forms by stepwise selection and mutagenesis followed by drug selection. To understand the molecular basis of PM susceptibility and resistance, our main goal is to identify and validate genes associated with susceptibility and resistance to PM through whole genome sequencing of these PM resistant lines and clinical isolates of *L. amazonensis* with differential *in vitro* susceptibility, previously characterized by our group (Coser et al., 2021). We are also investigating the accumulation of PM in these resistant lines and clinical isolates, using a PM fluorescent analog. Previous results indicate a direct correlation between PM susceptibility and the accumulation of the drug. This study will contribute to a better understanding of the mechanism of action and resistance of PM that are not completely understood in *Leishmania*, as well as its potential use in chemotherapy of the cutaneous leishmaniasis. **Supported by:**FAPESP (Processo 2019/22175-3) **Keywords:**Leishmania amazonensis.Paromomycin.Resistance

TB-003 - **Could the inositol pyrophosphates (PP-IPs) be involved in DNA repair pathways in the human pathogen Trypanosoma cruzi? Preliminary analyses**

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In model eukaryotes, inositol pyrophosphates (PP-IPs) are involved in a wide range of processes, such as regulation of telomere length and homologous recombination (HR). However, the action mechanism of PP-IPs in pathways related to DNA metabolism is not fully understood. The PP-IPs (IP_7 and IP_8), are synthesized by pathways involving the participation of IP6K and PP-IP5K kinases, respectively. Trypanosomatids, which encompass parasites of great medical relevance, such as *Trypanosoma cruzi* , apparently do not present homologues for PP-IP5K, which make these organisms excellent models for the study of PP-IPs. The goal of this study is to deplete the IP6K gene in *T. cruzi* , generating KO lineages ($IP6K^{-/-}$), and investigate the possible participation of IP_7 in DNA repair pathways. After the 1 st round of genome editing using CRISPR-Cas9 and clone selection, PCR analyzes revealed a single null population ($IP6K^{-/+}$). The second round of transfection is being done to achieve a possible double null population ($IP6K^{-/-}$). After clone selection and isolation, lineages will then be characterized phenotypically, and the absence of IP6K, as well as IP_7 , will be checked by qPCR and PAGE, respectively. Episomal IP6K add-back lineages will be generated to demonstrate the specificity of the assay and eliminate bias due to off targets. $IP6K^{-/-}$lineages and controls (WT and add-back) will be challenged with different genotoxic stress (IR, H_2O_2 , and UV) to induce different types of DNA damage. Growth curves and FACS analyzes will be done to check the proliferation pattern and possible cell cycle arrests. Next, we will establish and compare the recruitment kinetics for HR, BER, and NER repair pathways by IFA and western blot assays using specific antibodies. The possible participation of PP-IPs in DNA repair pathways could provide new routes for developing antiparasitic therapies for *T. cruzi* and other related infectious trypanosomatids. **Supported by:**SAGe-FAPESP, 2020/16480-5 **Keywords:**inositol pyrophosphates, pyrophosphorylation, Trypanosoma cruzi, DNA Damage, DNA Repair, CRISPR/Cas9

TB-004 - **Detecting compound target engagement in living *Leishmania* cells**

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Modern, target-based drug discovery strategies hold the promise of delivering better, safer medicines for leishmaniasis. However, progress in this area has been hampered by the lack of tools for the validation of new chemical entities effective against genetically-validated molecular targets. Here we used bioluminescence resonance energy transfer (BRET) to detect compound target engagement and determine its potency and binding kinetics within promastigotes and macrophage-residing amastigotes of *Leishmania*. Our assay is based on BRET between a donor, the target protein fused to NanoLuc (a small engineered luciferase), and an acceptor, a cell-permeable fluorescent probe that binds to the BRET donor. Displacement of the BRET probe from the target by a competing ligand disrupts energy transfer and directly proves target engagement in living cells. Here, we used the CLK1 protein kinase of *Leishmania mexicana* as a target for validation of this technique. Commercially-available BRET probes did not bind to purified NanoLuc-fused CLK1 *in vitro* or in cell-based assays using genetically-engineered *Leishmania* expressing the fusion protein. Using the purified protein, we identified novel CLK1 ligands from a human kinase ligand library. Based on available structural information, we modified one of these ligands to function as a *Leishmania*-permeable BRET probe. We used this probe in cell-based assays to identify novel compounds that can engage CLK1 in both promastigotes and intracellular amastigotes. We also confirmed that compounds that could bind our target in cells were also able to inhibit its phosphotransferase activity *in vitro*. Finally, we showed that these compounds could kill *Leishmania* promastigotes and intracellular amastigotes, and that overexpression of CLK1 led to resistance, confirming our findings. We expect this assay can be expanded to other genetically-essential targets to expedite the discovery of new anti-leishmanial compounds. **Keywords:**Leishmania.Drug discovery.Protein kinases

TB-005 - **A STRUCTURE-BASED DRUG DISCOVERY PROGRAM TARGETING *LEISHMANIA* GLYCOGEN SYNTHASE KINASE 3**

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Leishmaniasis is a group of neglected tropical diseases caused by parasites from the genus *Leishmania*, which claims over 20,000 lives and affects more than 1 million people every year. Current treatments are not satisfactory – most have severe side effects and require hospitalization. Unfortunately, the development of new drugs to treat leishmaniasis has been hampered by the difficulty to identify valid therapeutic targets. Protein kinases represent promising candidates for drug development against parasitic diseases. Glycogen synthase kinase 3 (GSK3) is a multifunctional Ser/Thr kinase found in all eukaryotes. In humans, there are two isoforms, alpha (GSK3A) and beta (GSK3B), which show both distinct and redundant functions. Counterparts of human GSK3 have been described in *Leishmania*, GSK3a and GSK3b (long and short isoforms, respectively). Both kinases have been identified as genetically-essential for parasite viability, and GSK3b has also been pharmacologically validated. Here we started a target-based drug discovery program to develop potent and selective inhibitors of *Leishmania infantum* GSK3a and GSK3b. In order to identify initial hits, recombinant protein kinases were produced and screened against a set of ~1,400 compounds. Biochemical assays were employed to validate positive hits and to determine IC_{50} and Ki values. Promising compounds were further investigated by phenotypic assays to evaluate its antileishmanial activity and host cell toxicity. We are currently pursuing structural determination of protein-inhibitor complexes to elucidate ligand-binding modes and to guide lead optimization. We expect the data obtained in this work to support a structure-based drug design program to investigate the use of GSK3a and GSK3b as therapeutic targets against leishmaniasis. **Supported by:**Eurofarma, DNDi, FAPESP, Embrapii, CNPq **Keywords:**target-based drug discovery.therapeutic targets.leishmaniasis

TB-006 - **Building tamoxifen/clemastine chimera as a strategy to explore new treatments for leishmaniasis**

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The range of drugs available to treat leishmaniasis are far from ideal: they induce lethal side effects, require special infrastructure due to parenteral administration and some of them have been showing a decrease on responsiveness to treatment. Collectively, these shortcomings make the discovery of new alternative treatments an urgent matter.
Replacing an existing approved medication is an attractive strategy to accelerate drug discovery and, in this context, we have identified both tamoxifen, a known anti-breast cancer drug, and clemastine fumarate**,** an antihistamine drug, as displaying potent anti-leishmanial activity. Both molecules have been proposed to target the same enzyme, inositol phosphorylceramide synthase (IPCS), but also exhibit other pharmacologies. To explore this in greater detail and develop more effective selective compounds, we have built a library of tamoxifen/clemastine hybrids based on the common features shared by these molecules. Following initial screening against *Leishmania major* promastigotes, those with an EC_{50} < 5 μM were selected for further testing against other species of *Leishmania* and preliminary cytotoxicity evaluation against HepG2 cells. The most potent molecule to date has an EC_{50} = 0.27 ± 0.026 μM against *L. major* with a SI > 300. Current efforts are focused on turning this compound into a probe to identify the protein target. This presentation will describe the details of these studies together with the application of the probe in target identification and validation.
Supported by:GCRF-CDT, UKRI **Keywords:**Leishmania.Tamoxifen.Clemastine

TB-007 - **A SYBR GREEN-BASED REAL-TIME PCR ASSAY FOR DISCRIMINATION OF LEISHMANIA INFANTUM AND CRITHIDIA-LIKE PARASITES IN SAMPLES OF HUMAN VISCERAL LEISHMANIASIS**

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Visceral leishmaniasis (VL) affects the bone marrow, spleen, liver and can be fatal if left untreated. In Brazil, VL is caused by *Leishmania infantum* transmitted by sandfly vectors. LV patients in Middle East and India can be co-infected with monoxenous trypanosomatids. Previously, we identify a non-*Leishmania* parasite in an atypical and fatal case of VL in Sergipe, BR. Phylogenomics revealed similarity to *C. fasciculata*, (named as *Crithidia-like*). Correct parasite identification is important for diagnosis and treatment. Thus, here our aim was to standardize a SYBR Green qPCR assay targeting species-specific genes in genomes of *L. infantum* (LinJ31_X) and *Crithidia-like* (LVH60-12060) able to discriminate and determine the parasite load theses parasites in clinical isolates samples obtained from bone marrow aspirates during hospitalizations. Clinical isolates were kept in culture for genomic DNA extraction. Genomic materials from vertebrate hosts (human, dog and cat), from other *Leishmania* species and *C. fasciculata* were also used. As a reference control in the *L. infantum* detection, primers used elsewhere for conserved region in *Leishmania* repeats (REPL) (LinJ31_L42486.1) of VL-causing species were used. The standard curve to quantify the parasite load was calculated based on the genomic DNA mass considering the genome sizes of *L infantum* and/or *Crithidia-like* plus kDNA content equivalent to one parasite. *L. infantum* sample (PP75) amplified only in LinJ31_L42486.1 and Linj31_X. Likewise, *Crithidia-like* sample was only amplified with LVH60-12060F primer. The mass one *L. infantum* and Crithidia-like were 79.2fg and 85.2fg, respectively. The standard curve was built ranging from 10^1 to 10^6 parasites/µL presenting a quantification cycle (Cq) from 30 to 25, respectively in both set of primers. The validation of these primers is still ongoing. New targets for molecular diagnosis can assist in the elucidation of atypical and severe cases of VL. **Supported by:** FAPESP grant 2016/20258-0; CNPq scholarship 133661/2020-2 and CAPES Finance Code 001 **Keywords:**A SYBR green-based real-time PCR, Leishmania infantum, Crithidia-like

TB-008 - **Biology of RNA genes in trypanosomatids**

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Trypanosomatids are unicellular eukaryotes that differ from the rest of the eukaryotes in several aspects regarding RNA metabolism, gene expression regulation and gene organization. Recently, with the advent of long-read technologies (PacBio and Oxford Nanopore Technologies), several trypanosomatid genome assemblies were published using third-generation sequencing technologies which improves genome sequencing contiguity. Even though several efforts were made in order to correctly annotate coding genes and repetitive sequences, non-coding RNA annotation has not been thoroughly assessed. These RNA genes encode functional RNA products and they are often a neglected class of genes in large scale genome analysis probably due to their sequence and structure diversity that require more dedicated annotation. Since these genes do not present the features that define coding genes (e.g. long open reading frames) and instead present limited sequence conservation, classical strategies for gene annotation can not be used. The peculiar mechanisms of RNA metabolism in trypanosomatids and the improved genomes' assemblies prompted us to study how the non-coding RNA genes are organized in these genomes. We used several optimized algorithms depending on the RNA to re-annotate them providing a complete annotation, including the identification of previously undescribed non-coding RNAs as well as the correct annotation of genes that were previously incorrectly assigned. In sum, this work reports a highly curated genome annotation, and unveils the organization of non-coding RNAs in trypanosomatid genome assemblies.

Supported by: Research Council United Kingdom Grand Challenges Research Funder 'A Global Network for Neglected Tropical Diseases' grant number MR/P027989/1. **Keywords:**non-coding RNA genome annotation.genome organization.trypanosomatids

TB-009 - **High Content Screening to Evaluate the Antileishmanial Activity of Drugs against Intracellular Amastigotes**

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Leishmaniasis is caused by several species of the protozoan parasites of the genus *Leishmania*. This disease treatment remains difficult, since the available drugs have shown to be highly toxic, besides several effects has been shown. Thus, new therapeutics are urgently needed. High content screening represents an important tool in the drug discovery process, since it optimizes the chances of finding an active compound from a large number of candidates. So, the aim of this work was to evaluate the antileishmanial activity of some commercial drugs by high content screening targeting intracellular amastigotes. Bone marrow-derived macrophages (BMDMs) were plated in 96-well plates, and then infected with *L. amazonensis* expressing RFP. 3h post-infection, cells were treated with the drugs at 10 µM. Then, image acquisition was made 24h, 48h and 72h post-treatment. It was evaluated the antileishmanial activity of 2560 drugs in the initial screening. After that, were selected 80 compounds showing at least 50% of intracellular amastigotes inhibition when compared to controls (treatment with DMSO 1%). These 80 compounds were re-tested in a second screening, in which 53 compounds maintained the activity. Next, the 53 compounds were diluted in medium and tested again, but only 38 still demonstrated antileishmanial activity. Following, the 38 compounds have determined their EC_{50} and CC_{50} values, at this point 26 compounds that demonstrated EC_{50} < 10 and SI > 10 were selected. These 26 selected compounds were repurchased lyophilized and re-tested against intracellular amastigotes, in this step 18 compounds maintained the antileishmanial activity. After other selection steps based on drug approval by regulatory agencies and route of administration, we selected 9 compounds FDA-approved and orally administered to follow in our *in vivo* studies. **Supported by:**FAPESP - 2017/19040-3
Keywords: Leishmaniasis, High Content Screening, Leishmania amazonenses

TB-010 - **COMPARATIVE TRANSCRIPTOMIC ANALYSIS OF BENZNIDAZOLE RESISTANT AND SUSCEPTIBLE Trypanosoma cruzi POPULATIONS**

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INTRODUCTION: Chagas disease (CD) is an important public health problem in Latin America caused by the protozoan Trypanosoma cruzi. Nifurtimox and Benznidazole (BZ) used for CD treatment, present low cure efficacy, mainly in the chronic phase of CD and several side effects. Then, there is an urgency in the discovery of new drugs for CD treatment and a better understanding of the BZ-resistance mechanisms in T. cruzi. **OBJECTIVES:** We use the RNA seq approach with the Illumina NovaSeq technology to identify and compare the differentially expressed transcripts between BZ-resistant and -susceptible T. cruzi populations from the Tehuantepec strain. **METHODS:** All the cDNA libraries were constructed from epimastigote forms of each population, sequenced and analyzed using STAR for mapping the reads against the reference genome (T. cruzi Dm28c), and EdgeR for differential expression statistical analyses. RESULTS: The analytical pipeline considering an adjusted p-value lower than 0.05 and a fold change greater than 2.0 identified 544 transcripts differentially expressed (DE) between susceptible and BZ-resistant T. cruzi populations. Out of 544 DE transcripts, 460 presented functional annotation, and 84 were assigned as hypothetical proteins. A total of 374 transcripts were upregulated and 170 were downregulated in the BZ-resistant T. cruzi populations. Using this DE dataset, the proteins were further grouped in functional classes according to the Gene Ontology database. We observed that the main transcripts identified are associated with biological processes of pathogenesis, amino acids metabolism, response to toxic substance, proteolysis machinery, cell replication, metabolic process of nitrogen and nucleic acids, cytoplasmic translation, regulation of metabolic process, among others. **CONCLUSION:** In this study, we generated a list of genes differentially expressed in T. cruzi and confirmed that the BZ-resistance phenotype of this parasite is multifactorial and complex. **Supported by:**CAPES, CNPq, FAPEMIG e INOVA FIOCRUZ **Keywords:**Trypanosoma cruzi, RNAseq, drug-resistance

TB-011 - **Assembly, annotation and gene editing of the genome of the PH8 strain of Leishmania amazonensis with focus on multigene families encoding virulence factors**

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Leishmania amazonensis is one of the etiological agents of cutaneous leishmaniasis. Parasite virulence factors have already been studied, as they play a crucial role in the establishment of infection and disease development in the mammalian host. We report the sequencing and assembly of the PH8 strain of *L. amazonenis* combining long PacBio reads, short Illumina reads and synteny data with the *Leishmania mexicana* genome. The final assembly, composed of 34 chromosomes and 44 scaffolds not incorporated, represents a genome of ~ 32 Mb. The annotation of the *L. amazonensis* genome was transferred from the annotation of 8225 genes present in the genome of *L. mexicana*. Multigene families, such as amastins, metalloproteins GP63, A2 protein, cysteine proteases, fatty acid synthases, phosphatase and kinases, were identified using an automated pipeline, in which proteins from others Leishmania species and trypanosomatids interrogated. In addition, amastins and GP63 were characterized. In total, 25 genes encoding amastins were predicted in *L. amazonensis*. The alignment of this genes, using M-Coffee and phylogeny analyzes, using the maximum-likelihood estimation resulted in groupings corresponding to the four sub-classes of amastins (α, β, γ and δ). Analysis of the 11 sequences encoding GP63 showed the conservation of important domains, such as HExxH and SRYD, which are important for protein structure and binding to macrophage surface receptors, respectively. Finally, we tested a CRISPR-Cas9 protocol to generate knockout cell lines of the Miltefosine Transporter (TM) gene of *L. amazonensis* as a proof of concept. Expression of *Streptococcus pyogenes* Cas9 in promastigotes was achieved after transfection with pLDCN, an episomal vector. Alternatively, promastigotes were transfected with recombinant *Staphylococcus aureus* Cas9 ribonucleoprotein complex and an sgRNA. Both strategies were able to disrupt the TM gene in transfected parasites, originating knockout parasite cell lines. **Supported by:**CAPES
Keywords: Leishmania amazonensis.annotation.multigene families

TB-012 - **Novel Benznidazole Derivatives and Functionalized Graphene Oxide Matrix and its interaction with Trypanosoma cruzi parasites**

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Since the discovery of Benznidazole and Nifurtimox in the 60s and 70s and their applications in the combat against Chagas Disease, there have been few advances in the field of developing new molecules that can be used to fight the parasite, both in the acute and chronic phase of the disease. Despite a series of molecules that are currently used in addition to the reference drugs Benznidazole and Nifurtimox, we can cite Posoconazole, Ravuconazole, Itraconazole, Fexinidazole and the Benzofurans Amiodarone/Dronedarone. However, none of these new molecule have been developed or even allowed their singular use as alternative to chemotherapy.
Here, we synthesized seven new Benzinidazole derivatives keeping the nitroimidazole part of molecule, with the intention to evaluate the antichagasic activity of these prodrugs. The nitroimidazolic derivatives were submitted to *in vitro* test against epimastigote form of *Trypanosoma cruzi* and two compounds showed activity very close to Benznidazole at concentration of 5 µM.
A matrix based on Graphene Oxide was also developed and now we are envisioning their use in combination with the synthesized prototypes, in order to verify the activity and cytotoxicity of this therapeutic combination in different T. cruzi life forms. **Supported by:**FAPESP - Processo 00770-4
Keywords: Benznidazole derivatives, Antichagasic activity, Graphene oxide Matrix

TB-013 - **Use of computational approaches in a rational strategy for discovery of a new chemistry entity and repurposing FDA-approved drugs for leishmaniasis treatment by structure-based virtual screening**

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The treatment for leishmaniasis still presents a serious public health problem and its necessary to search compounds that are less toxic, more effective, and able to oral administration. Thus, the aim of this work was to select natural compounds (NAT) for a new chemistry entity (NEC), and trial FDA-approved drugs (F-drugs) to repositioning using the trypanothione reductase from *Leishmania infantum* (TrLi) in a structure-based virtual screening (SBVS) approach. Libraries with 65 NAT and 2104 F-drugs were obtained from ZINC database and computational approaches were used to select the most promising compounds and study their molecular mechanisms of action (MMA). After ADMET analyzes, 6 NAT were selected to SBVS using TRLi as target (PDB: 2JK6 and 4ADW). All of them showed conformations in the active site of enzyme. Next, the most promising compounds (NC2 and NC4) were select to study their MMA in the enzyme-inhibitor complex. Both demonstrated important interactions in the active site, and an estimated Ki of 3.4µM and 1.7µM for NC2 and NC4, respectively, in 2JK6. Corroborating, in 4ADW the Ki estimated was 4.3µM for NC2 and a Ki of 805nM for NC4. In F- drugs, a total of 100 compounds with less binding energy from 2JK6 and 4ADW were selected by SBVS. Thus, in each list, was analyzed the ADMET proprieties, compounds licensed by ANVISA and available on SUS. Finally, 3 compounds were selected for MMA study. Selected compounds demonstrated an estimated Ki of 97.5nM and 461.6nM, 9.0nM and 30.1nM, and 20.9nM and 43.7nM for SUS1, SUS2 and SUS3 in 2JK6 and 4ADW, respectively, and made important interactions with residues of catalytic triad of TRLi. Together, our data demonstrated that SBVS could be an excellent alternative to select promising compounds able to be a competitive inhibitor of TRLi, encourage us continue to investigate theirs effects in *L. infantum* and suggest that these compounds are a potential candidate for leishmaniasis treatment by oral route. **Supported by:**CAPES; CNPq; FAPERJ; IOC/FIOCRUZ **Keywords:**Drug Discovery, Structure-based virtual screening, Trypanothione reductase

TB-014 - **Bone marrow response of dogs naturally infected with *Leishmania infantum* presenting different clinical outcomes**

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Canine visceral leishmaniasis (CVL) can be presented as a severe debilitating or subclinical form of the disease that progression depends on several factors, including the host immunological status triggered by the infection. Our main objective is to characterize the response of bone marrow (BM) cells in dogs naturally infected with *L. infantum* with different clinical outcomes. Initially, the longitudinal analysis of the hematological profile of resistant and susceptible dogs was monitored in a cohort study performed using random-effects models for longitudinal data. Subsequently, 8 resistant and 8 susceptible dogs were selected from the cohort study for reassessment and characterization of the BM cellular immune profile, using a myelogram, and identifying the expression of genes in BM cells using RNASeq. Also, we included in the analysis 8 control uninfected dogs. In the longitudinal analysis of the hematological profile and the blood count of the reassessed dogs, red blood cell counts, hemoglobin, and hematocrit values showed a significant decrease in susceptible dogs. Myelogram evaluation revealed that only susceptible animals showed erythroid cell hypoplasia. In the transcriptome analysis, 425 differentially expressed genes (DEGs) were identified in the samples of resistant dogs and 327 DEGs in the samples of susceptible dogs. The enrichment analyzes revealed that pathways related to DNA repair were negatively regulated in the BM cells of susceptible dogs, while pathways related to cell migration were modulated in susceptible and in resistant dogs. An algorithm based on machine learning identified a set of 4 genes (*EGR2*, *FOS*, *TINAGL1* and *ADCY9*), which exhibited the highest classification power to describe resistant and susceptible dogs. In conclusion, identified alterations in peripheral blood and BM in dogs that develop CVL shown to be associated with the susceptibility profile. DEGs will be validated by qPCR and using functional studies.
Supported by:FAPESB (Universal - Nº 05/2015), CAPES (001) e CNPq (Bolsa de doutorado - 154049/2016-6) **Keywords:**Canine leishmaniasis.spinal response.RNA-Seq

TB-015 - **Drug Discovery and Development against leishmaniasis and Chagas' disease**

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Leishmaniasis and Chagas' disease are infectious diseases caused by parasites from the genus *Leishmania* sp. and species *Trypanosoma cruzi,* respectively. The diseases are manifested in very different ways but do share common facts, including vectorial transmission and affecting mainly underserved communities in developing countries, mostly in tropical areas of the globe. Hence, they are included in the group of diseases collectively called Neglected Tropical Diseases. Unfortunately, the drugs available to treat these diseases are not effective, toxic, and/or expensive, and there is a consensus that new and better therapies are a clear unmet medical need. At UC San Diego, we have developed a drug discovery pipeline that enables the screen of libraries of compounds to identify molecules with antiparasitic activity in cell-based assays targeting the relevant forms associated with human disease. We have currently molecules in different stages of development. Our goal is to develop pre-clinical candidates. **Keywords:** Drug Discovery, Drug Development, leishmaniasis, chagas disease