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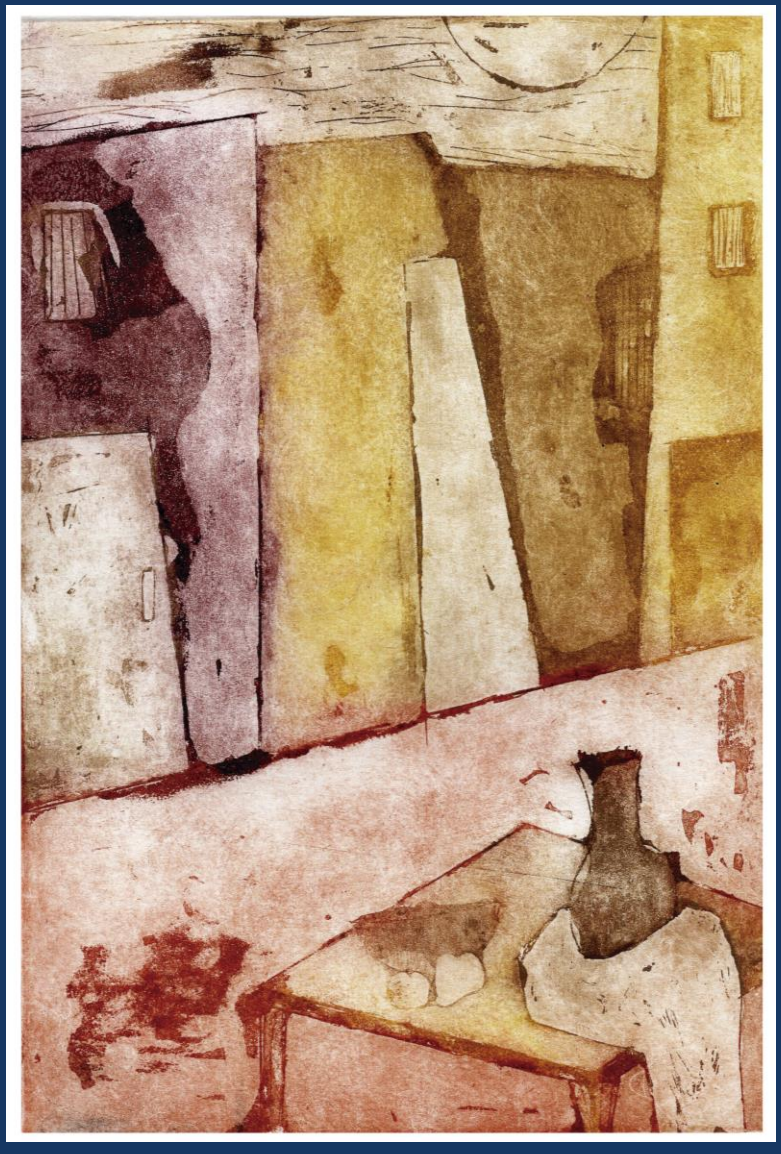

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(AACyTAL)

con la participación de
The Histochemical Society

13 - 16 de noviembre de 2019
Hotel 13 de Julio - Mar del Plata

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ANNUAL MEETING OF BIOSCIENCE SOCIETIES 2019

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(AACyTAL)

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November 13th – 16th, 2019
Hotel 13 de Julio - Mar del Plata

CHIEF EDITORS

Dra. Mónica Costas
Dra. Gabriela Marino
Dr. Pablo Azurmendi

0141 - EFFECTS OF MELIA AZEDARACH EXTRACT ON T. CRUZI EPIMASTIGOTES PROLIFERATION

Laura FRACCAROLI | María Daniela RUIZ | Pablo TORRES | Luciana LAROCCA | Carolina CARRILLO | Verónica DE PINO

ICT MILSTEIN - CONICET

Abstract/Resumen: Chagas disease is an endemic parasitosis caused by the protozoan Trypanosoma cruzi (T. cruzi). The current therapies are limited in efficacy and show multiple side effects. Thus, there is a need to identify new effective and specific trypanocidal strategies. Melia azedarach (MA), native of Asia but widely distributed in several countries, known as "Paraíso", has been described to have therapeutic properties such as antifungal and antihelmintic. The aim of this work was to evaluate the effect of extracts obtained from ripe fruits from MA in the proliferation of T. cruzi epimastigotes. To approach this aim we performed MA extracts using water, ethanol and DMSO as solvents. We tested the extracts in cultures of epimastigotes from the Y-GFP strain in concentrations between 0 and 6 mg/ml. We observed that only DMSO extracts dose dependently decreased the proliferation of the parasites. The IC50 calculated at day 4 of culture was 0.94 mg/ml (0.81-1.09 mg/ml). To evaluate the stability, we stored the extract at 4 and -20 ºC during 15 days. Then, we calculated the IC50 of both in Y-GFP epimastigotes observing that the storage at -20 ºC maintained the activity while the extract at 4 ºC decreased its activity by half. We tested the citotoxicity of the DMSO extract in Vero cell line with MTT assay, calculating a selectivity index of 1.2. While it is not optimal, it is proximal to those obtained for Nifurtimox or Benznidazole. We performed an HPLC separation of the extract recollecting different fractions. Preliminary results showed that the individual fractions did not decrease epimastigotes proliferation, while the pool of those fractions restored the effect. The results present herein propose that the extracts obtained from ripe fruits of MA have bioactive compounds that affect the proliferation and viability of T. cruzi epimastigotes suggesting that the citotoxic activity may be the result of the interaction of different compounds present in the extract.

0216 - MACHINE LEARNING APPLICATION TO ASSESS TARGET DRUGGABILITY. TRYPANOTHIONE SYNTHETASE AS A STUDY CASE.

Juan Ignacio ALICE | Franco CARAM | Carolina BELLERA | Alan TALEVI

FACULTAD DE CIENCIAS EXACTAS, UNIVERSIDAD NACIONAL DE LA PLATA

Abstract/Resumen: Trypanothione synthetase (TryS) has been reported as a promising drug target in trypanosomatids [1]. Metabolic control analysis has confirmed its key role in the redox metabolism of the parasites [2; 3]. Whereas some years back potential drug targets were binarily classified into druggable/non-druggable, recent work suggests that proteins could display different degrees of druggability [4; 5]. Though TryS is generally considered druggable in the sense that a (relatively small) pool of compounds capable of inhibiting the enzyme have been reported, high-throughput screens and our own experience on the target suggest that it might be indeed druggable, but "difficult to drug". Here, we have resorted to a wide range of binding pocket prediction methods to explain the low levels of success in high-throughput and in silico screen for TryS inhibitors. Tools that evaluate druggability scores, such as PockDrug [6], DoGSiteScore [7] or CavityPlus [8] as well as tools to identify ligand-binding regions or to estimate binding pocket size (e.g. FTMaps [9]) were jointly applied. Ten proteins, including TryS and nine highly druggable ones (e.g. COX-2, cruzipain, falcipain-2 and others), were studied and compared. The analysis shows that TryS, independently of the method used, is predicted as a low druggable target in comparison to the other nine, validated, highly druggable ones, which tend to display comparatively large binding pockets and better druggability scores. Therefore, we propose that, in spite of its crucial biological role in trypanosomatids, TryS might be, in fact, a challenging target to develop new therapeutic options. References: [1] Comini, MA. et al. Free Rad Biol Med 36: 1289-1302 (2004). [2] Saavedra, E. et al. Curr. Med. Chem. 25: 1-25 (2018). [3] Gonzalez-Chavez, Z. et al. Redox Biology 26: 11231 (2019). [4] Barril, X. et al. Comput Mol Sci 3: 327-338 (2013). [5] Kana, O. et al. J Comput. Alded Mol Design 33: 509-519 (2019). [6] Hussein, HA. et al. Nucleic Ac. Research 43: 436-442 (2015). [7] Volkamer, A. et al. J. Chem. Inf. Model. 50: 2041-2052 (2012). [8] Xu,Y. et al. Nucleic Acids Research. 46: 374-379 (2018) [9] Kazokov, D. et al. Nature Protocols. 10: 733-755 (2015)

0305 - EXPLORING THE LINK BETWEEN ADENINE DNA METHYLATION AND 3D GENOME ORGANIZATION IN THE PARASITE TRICHOMONAS VAGINALIS

Ayelen LIZARRAGA | Pablo H. STROBL-MAZZULLA | Natalia DE MIGUEL

INSTITUTO TECNOLÓGICO DE CHASCOMÚS (INTECH)

Abstract/Resumen: Trichomonas vaginalis is a common sexually transmitted parasite that colonizes the human urogenital tract causing infections that range from asymptomatic to highly inflammatory. Chronic infections have been associated with high risk pregnancies, increased risk of acquiring HIV and higher susceptibility to developing cervical or prostate cancer. Despite their importance in other organisms, the epigenetic mechanisms involved in gene regulation in the parasite remain poorly understood. Recent works have highlighted the importance of histone modifications in the regulation of transcription and parasite pathogenesis. However, the nature of DNA methylation in the parasite remained unexplored. Using a combination of immunological techniques and UHPLC, we analyzed the abundance of DNA methylation in strains with differential pathogenicity demonstrating that N6-methyladenine (6mA), and not 5-methylcytosine (5mC), is the main DNA methylation mark in T. vaginalis. We performed an adapted methylated immunoprecipitation assay followed by high-throughput sequencing (MeDIP-seq) on a patient-derived strain to obtain genome-wide distribution of 6mA mark. Our results revealed that this mark is enriched at intergenic regions, with a preference for certain superfamilies of DNA transposable elements. We show that 6mA in T. vaginalis is associated with silencing when present on genes. Interestingly, bioinformatics analysis revealed the presence of transcriptionally active or repressive intervals flanked by 6mA-enriched regions and results from chromatin conformation capture (3C) experiments suggest these 6mA flanked regions are in close spatial proximity. These associations were disrupted when parasites were treated with the demethylation activator ascorbic acid. This finding revealed a new role for 6mA in modulating 3D chromatin structure and gene expression in this deep-branching eukaryote.

0371 - IN SILICO-GUIDED DRUG REPURPOSING: IDENTIFICATION OF NON-COMPETITIVE INHIBITORS OF TRYPANOSOMA CRUZI AND PLASMODIUM FALCIPARUM CYSTEINE PROTEASES

Emir SALAS SARDUY(1) | Lucas ALBERCA(2) | Carolina Leticia BELLERA(2) | **Alan TALEVI** (2)

INSTITUTO DE INVESTIGACIONES BIOTECNOLÓGICAS "DR. RODOLFO UGALDE", UNIVERSIDAD NACIONAL DE SAN MARTÍ (1); LABORATORIO DE INVESTIGACIÓN Y DESARROLLO DE BIOACTIVOS (LIDEB) - UNIVERSIDAD NACIONAL DE LA PLATA (2)

Abstract/Resumen: Trypanosoma cruzi and Plasmodium falciparum are the etiologic agents of Chagas disease and Malaria, respectively. Cysteine proteases play key roles in the

pathogenesis and survival of these parasites, such as cell/tissue penetration, hydrolysis of host or parasite proteins, autophagy, and evasion or modulation of the host immune response, being considered attractive chemotherapeutic targets. Cruzipain (Cz) and Falcipain-2 (FP-2) are two essential cysteine proteases of such organisms. Previously, we have found that methacycline (a member of tetracycline family) is a non-competitive inhibitor of FP-2 (Alberca et al. 2019). In this study our objective has been the characterization of six tetracycline analogues (tetracycline, minocycline, doxycycline, oxytetracycline, chlortetracycline and methacycline) as inhibitors of these cysteine proteases by in silico and in vitro determinations. First, we used bioinformatic tools to predict possible allosteric binding pockets; subsequently, we studied their possible interactions with these proteases by molecular docking simulations. The structures of the enzymes were obtained from the Protein data bank. Finally, we proceed to inhibition studies on the purified enzymes, which confirmed that these family of antibiotics inhibit cysteine proteases in a reversible, non-competitive manner, with Ki values in the mid-micromolar order. Our results provide further evidence on the utility of computational tools as a rational basis for systematic drug repurposing.
Support: PICT 2016-2056 and 2017-0643, Incentivos UNLP and F/4081-1 and F/4081-2 International Foundation for Science grants.

0453 - EVALUATION OF A POTENTIAL ALTERNATIVE TO THE TREATMENT OF HUMAN NEUROCYSTICERCOSIS: ALBENDAZOLE-LOADED LIPID NANOCAPSULES ENHANCE THE BIOAVAILABILITY OF ALBENDAZOLE IN THE BRAIN OF HEALTHY MICE

Julia FABBRI (1) | Juan Pablo ESPINOSA(2) | Patricia Eugenia PENSEL(1) | Clara María ALBANI(1) | Sandra Karina MEDICI(2) | Gabriela ULLIO GAMBOA(3) | Jean Pierre BENOIT(4) | María Celina ELISSONDO(1)

LABORATORIO DE ZOONOSIS PARASITARIAS, IIPROSAM, FCEYN, UNMDP - CONICET (1); FARES TAIE INSTITUTO DE ANÁLISIS. (2); UNITEFA-CONICET. FCQ, UNC. (3); INSERM U1066, MINT–MICRO ET NANOMÉDECINES BIOMIMÉTIQUES, IBS-CHU ANGERS (4)

Abstract/Resumen: Neurocysticercosis (NCC) is a zoonotic disease caused by encystment of Taenia solium larvae in the central nervous system. Pharmacological treatment is performed with albendazole (ABZ). However, the slow rate of dissolution of ABZ produces a poor and erratic absorption of the drug at the gastrointestinal level. This produces wide variability in plasma and cerebrospinal fluid concentrations of the drug among patients, with variations in treatment efficacy. Lipid nanocapsules (LNCs) are drug carrier nanosystems designed to solubilize lipophilic drugs. The aim of the present work was to characterize and compare the brain pharmacokinetic behavior of a suspension of ABZ (ABZ-SUSP) or ABZ-LNCs in healthy mice. Animal procedures and management protocols were approved by the Institutional Animal Care and Use Committee (RD 148/15) of the FCEyN, UNMdP. CF-1 mice were separated into two groups (n= 44): ABZ-SUSP and ABZ-LNCs. In both cases, a single dose of 5 mg/kg of ABZ was administered orally. The brains were recovered at different post-treatment times until 16 h. The samples were analyzed by high performance liquid chromatography to quantify ABZ and its metabolites. Enhanced ABZ sulfoxide concentration profile was obtained in brains from ABZ-LNCs treated animals. Higher metabolite brain exposure was obtained after administration of ABZ-LNCs formulation to mice (area under the concentration versus time curve (AUC)= 0.82 ± 0.17 mg.h/kg and peak concentration (Cmax)= 0.14 ± 0.03 mg/kg) compared to the ABZ-SUSP (AUC= 0.29 ± 0.05 mg.h/kg and Cmax= 0.072 ± 0.01 mg/kg) ($p<0.05$). The improvement of the brain availability of ABZ observed after the administration of ABZ-LNCs to healthy mice worth to be evaluated on an animal model of NCC. This new nanocarrier as drug delivery system for ABZ could be a suitable alternative for treating NCC in humans.

0472 - ADVANCES IN THE STUDY OF ANTHRACYCLINES EFFECT ON TRYPANOSOMA CRUZI

María Daniela RUIZ(1) | **Laura FRACCAROLI** (1) | Darío BALCAZAR(1) | Cristina VANRELL(2) | Luciana LAROCCA(1) | Patricia ROMANO(2) | Carolina CARRILLO(1)

ICT MILSTEIN - CONICET (1); IHEM-UNCUYO (2)

Abstract/Resumen: Trypanosoma cruzi (T. cruzi) is the etiological agent of Chagas disease. As current therapies are limited in efficacy, there is a need to identify new specific trypanocidal compounds. Our previous work showed that anthracyclines (antitumor agents) decreased survival and proliferation of T. cruzi epimastigotes and interfered with its putrescine uptake. The aim of this work was to deepen the study about anthracyclines effect on polyamine metabolism in epimastigotes and to analyze their effect on different T. cruzi life cycle stages. Daunorubicin (Dnr) and Doxorubicin (Dxr) were the anthracyclines selected to evaluate their effect on T. cruzi (strain Y-GFP). We performed growth curves, and measured intracellular content of polyamines, by HPLC analysis, on epimastigotes cultured in putrescine depleted medium for 1 to 15 days. Under these conditions, intracellular putrescine diminished and T. cruzi epimastigotes became significatively more sensitive to Dnr and Dxr (IC50 of 0.1 µM for Dnr and 2 µM for Dxr), not depending on the nutritional stress length. On the other hand, although Dxr and Dnr interfere with polyamine uptake, sub-IC50 doses of these did not change the intracellular concentration of putrescine during 15 days of culture. Anthracyclines effect was tested in in vitro metacyclogenesis, infectivity and amastigotes proliferation assays. Differentiation from epimastigotes to metacyclic trypomastigotes diminished by Dnr treatment (from 14.8 % in control condition to 8.9 % with Dnr). Dnr did not affect the number of infected H9C2 cells nor total number of these cells but reduced by half the number of amastigotes per cell. The findings presented herein showed that Dnr and Dxr affect T. cruzi epimastigotes survival and proliferation, metacyclogenesis and replicative capacity of amastigotes. This effect could be related to the decrease of polyamine uptake by anthracyclines and their intracellular toxic effects.

0478 - IVERMECTIN IMPROVES THE EFFECT OF ETIDRONATE AS ANTI-HELMINTHIC AGENT

María Laura GERSTISER (1) | Alejandra JUÁREZ VALDEZ(2) | Oscar JENSEN(3) | Emilio Aj ROLDÁN(2) | Alicia Graciela FUCHS(2)

CENTRO DE ZOONOSIS/ BECA "ABRAAM SONIS" (1); UNIVERSIDAD ABIERTA INTERAMERICANA (2); CENTRO DE ZOONOSIS (3)

Abstract/Resumen: MLG and AJV equally contributed. In the world, ~$2x10^{12}$ people are infected by helminths and 61% of the human`s diseases are zoonotic. Hydatidosis produced by Echinococcus granulosus (Eg) has a complex life cycle, the dog is the definitive host releases fertile proglottids (pg) in the environment and intermediate infected host's developed the hydatid cyst. Prevention is performed deworming the dog, but alive eggs are released with feces. Bisphosphonates (BP) have an antiproliferative effect on EGPE, a cell line from Eg protoscoleces G1 (Echeverria et al., 2010; Fuchs et al., 2014 and Ferrulli et al., 2019) and they decreased viability on Taenia hydatigena (Th) eggs treated ex vivo. In this study was searched the effect of etidronate (EHDP) in combination with ivermectin (I) on EGPE colonies and on Th eggs incubated ex vivo with feces. Microscopic examination of treated and untreated samples was performed in parallel. EGPE cell colonies were treated with 30 µM EHDP (GADOR, SA) and/or 20 µM I (SIGMA) and controls with excipient (E), during 5 days, 30 microscopic fields of each were analyzed. Gravida's pg, obtained after dog diagnostic deworming, were incubated with feces and treated with 0.6 mL KCl containing 1.5 % HEDP and/or 0.48 % I during 3 days, control