were chosen based on their solubility and availability and were tested both on infected cells and T. cruzi epimastigote. We analyzed the infection in Vero cells using trypomastigotes expressing ß-gal at 96 h PI. At 50 µM, Bromhexine and Rosuvastatine caused a marked reduction on the infection (96 and 55 % compared to DMSO infection), while Sulfazalasine and Doxycycline led to a mild reduction in the infection (20 % for both drugs). At the indicated concentration, these drugs did not affect host cell growth significantly. When tested on epimastigotes, only Doxycycline demonstrated to affect viability at concentrations ranging from µM. These results indicate that while Bromhexine, Rosuvastatine and Sulfazalasine might modulate the infection by affecting the host cell PARG, Doxycycline could possibly be affecting both the parasite and the host cell enzyme, although effects on other molecular targets can not be disregarded.

0780 - SYNTHETIC TETRAHYDRO-ß-CARBOLINES DERIVATIVES IN THE MURINE MODEL OF CHAGAS DISEASE

Agustina CASASCO (1) | Gisela C MUSCIA(2) | Patricia PETRAY(1) | Fernanda FRANK(1)

IMPAM (UBA-CONICET) (1); DEPTO QCA ORGÁNICA, FFYB, UBA (2)

Abstract/Resumen: Tetrahydro-ß-carbolines (ßC) have shown a variety of pharmacological activities including anti-trypanosomatids effects. We studied in vitro anti-T. cruzi activity of 12 ßC derivatives, selecting 4 of them by their selectivity indexes. The aim of this work was to evaluate their in vivo effect on the murine model. BALB/c mice were infected with T. cruzi RA or K98. ßC 253, 268, 269 or 274 (1 mg/kg/day) were administrated by ip route when parasitemia became detectable 10 days post infection. Controls were treated with Benznidazole (Bz) or vehicle (C). Parasitemia, clinical condition and survival were evaluated for 30 days in RA-groups and for 60 days in K98-groups. At the end of the experimental period, K98-groups were submitted to histopathological analysis and the myopathy-linked enzyme marker creatine kinase (CK) was also evaluated. ßC 253 and 269 provoked a 58.5 and 45.6 % reduction of circulating parasites respectively at the peak of parasitemia. As well, 253 elicited an increase in survival ($p<0.05$ vs. C). Surprisingly, although 274 was not effective controlling parasitemia, a significant decrease in skeletal and heart muscle infiltration (vs. C) was observed with an improved survival. Mice treated with 253 and 268 showed significant lower tissue infiltration than C and Bz. All treated mice presented lower seric CK activity compared to C ($p<0.05$) in coincidence with histopathologic findings. The nature of the various substituent groups could influence the biological activity of the compounds. ßC 268, has a strong electron donor group, while 269 and 274, are substituted with strong donor and weak attractor electron groups. ßC 253, which has only a weak electron attractor group, was able to reduce parasitemia, increase survival and promote lower tissue injury. Our studies therefore provide a good starting point since ßC 253 could be considered a promising lead compound for the development of new therapies for Chagas disease.

0806 - PROFILING THE HDAC INHIBITORS ACTIVITY AGAINST THE MODEL OF CESTODE PARASITES MESOCESTOIDES CORTI

Hugo Rolando VACA | Ana María CELENTANO | Natalia MACHIAROLLI | Federico CAMICIA | Mara ROSENZVIT

IMPAM (UBA-CONICET)

Abstract/Resumen: Echinococcosis and cysticercosis are neglected diseases (1) caused by the cestode parasites Echinococcus ssp. and Taenia solium, respectively. These diseases affect socioeconomically disadvantaged population and represent a significant problem in human and animal health. There is a scarce availability of compounds approved for chemotherapy. Thus, it is imperative to identify new drugs. In this work, we investigated histone deacetylase (HDAC) enzymes as potential drug targets to develop new therapies against neglected diseases caused by cestodes. We previously reported the presence and expression of HDACs in several cestode parasites. Furthermore, we showed that Trichostatin A (TSA), a pan-HDAC inhibitor, produces a decrease in parasite viability, alterations on the tegument and morphology and an increment of the total amount of acetylated proteins, including acetylated histone H4, on the cestode laboratory model Mesocestoides corti (2). Here, we present the activity profile of a series of HDAC-inhibitors (HDACi) against on viability of M. corti larvae, using a worm tracker device for high-throughput screening in parallel with microscopy observation. We evaluated 40 compounds, comprising HDACi against class I, II and III HDACs. The commercial compounds Entinostat (a HDACi against class I HDACs) and Mz25 (a HDACi against class III HDACs), and two structure-based novel inhibitors designed against the HDAC8 from Schistosoma mansoni (3) were the most potent HDACi. These compounds produced a decrease of 100% in the viability and alterations on the tegument and morphology of M. corti at concentrations of 20 and 50 µM ($p<0.001$). Entinostat produced a 100 % decrease on parasitic viability, even at concentrations as low as 2 µM ($p<0.001$). These results suggest that HDAC class I and III from cestodes could be considered as putative drug targets for neglected diseases caused by cestodes. References 1. WHO. Geneva World Heal Organ. 2012:15 p. 2. Vaca HR, et al. Int J Parasitol Drugs drug Resist. 2019;9: 120-32. 3. Heimburg T, et al. J Med Chem. 2016;59(6):2423-2435.
Acknowledgements: This work was supported by CONICET, UBACyT and PICT. We thanks Drs. Manfred Juang and Wolfgang Sippl for provide us the HDAC-inhibitors. Nodo Bioinformático IMPaM-UBA-CONICET (https://bioinfo.fmed.uba.ar/).

0816 - CHARACTERIZATION OF A NEW SEROTONERGIC G-PROTEIN COUPLED RECEPTOR FROM CESTODES: NEW POTENTIAL TARGET FOR DRUGS AGAINST NEGLECTED TROPICAL DISEASES

Federico CAMICIA (1) | Sang Kyu PARK(2) | Hugo Rolando VACA(1) | Kristen WOODHOUSE(2) | Ana María CELENTANO(1) | Agustina LOPEZ AVETRANI(1) | Mara ROSENZVIT(1) | Jonathan S. MARCHANT(2)

IMPAM (UBA-CONICET) (1); DEPARTMENT OF CELL BIOLOGY, NEUROBIOLOGY AND ANATOMY, MEDICAL COLLEGE OF WISCONSIN (2)

Abstract/Resumen: Echinococcus canadensis is a platyhelminth parasite that belongs to the class Cestoda and is the etiological agent of the Hydatid disease, a neglected disease that affects public health and the economy in Argentina and worldwide. Currently, the treatment for echinococcosis in humans relies on benzimidazoles. However, the emergence of resistant parasites, makes the discovery of new anthelmintic drugs an imperative need. To tackle this problem, we propose to characterize G-protein coupled receptors from cestodes as new pharmacological targets. In our previous work (1), we found that serotonergic GPCRs (5-HT GPCRs) are of major importance in cestode movement and showed distinctive pharmacology. The aim of this work was to study the function of a new 5-HT GPCR from Echinococcus canadensis. Similar sequences were also found in another cestode species. Bioinformatics analyses suggest the existence of genes encoding for 5-HT GPCRs and this information was used for the design of primers. New cDNA was synthesized using RNA extracted from protoscoleces of pig origin as a template for PCR reactions. The amplificated cDNA coding for the serotonergic gene was cloned, sequenced and finally used for transient transfections in HEK293 cells. Calcium levels were measured using a fluorescent imaging plate reader (FLIPR) assay (2). When the cell line was transfected with a gene encoding for the cestode receptor, the calcium levels increased only in the presence of serotonin but not with of other ligands like tryptamine, tyramine, octopamine, acetylcholine, histidine or dopamine. The dataset confirms the bioinformatics analyses

showing that the cloned gene encodes for a new 5-HT GPCR conserved in cestodes. The cloning strategy followed by sequencing and expression in HEK cells revealed a new 5-HT GPCR. The results obtained confirm bioinformatics predictions and will be tested as a target for cestocidal drugs. References 1. Camicia F, et al. PLoS Negl Trop Dis. 2018; 12(2): e0006267. 2. Harvey JH, van Rijn RM, Whistler JL. Methods Mol Biol. 2013; 995: 43-54.
Acknowledgments We especially thank to Dr. Gabriel Lichtenstein (IMPAM-UBA-CONICET) for the bioinformatical assistance.

0846 - DRUG DELIVERY SYSTEMS BASED ON POLYELECTROLYTE-DRUG-FATTY ACIDS TERNARY COMPLEXES FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS

María Laura GUZMAN | Karen ARRIGONI | Dolores CARRER | María Eugenia OLIVERA

UNITEFA Y DEPARTAMENTO DE CIENCIAS FARMACÉUTICAS, FCQ (CONICET-UNC)

Abstract/Resumen: Cutaneous Leishmaniasis is the most prevalent form of Leishmaniasis in South America. A topical treatment is attractive because of its potential to reduce side effects, increase patient compliance and its affordability. Risedronate (Ris) and Eudragit E (EE) have shown to be active against some forms of Leishmania. Previous studies showed that EuE-Ris complexes are promising candidates for topical administration. Besides they showed in vivo anti-Leishmania activity. The literature also describes the antileishmania activity for medium chain fatty acids. Our hypothesis is that the physicochemical properties of a new material EE-Ris-Capric Acid (CA) would allow to obtain nanometric compounds with enhanced antileishmania properties. The specific objectives of this work were: a) characterize physicochemically homologous series of EE-Ris-CA systems obtained and to evaluate the release properties of the loaded drug. For this, EE-Ris-CA obtaining method was tuned up and the zeta potencial, particle size and drug release profile from Franz cells towards water, NaCl, end PBS were assayed. All systems evaluated resulted in translucent, homogeneous and physically stable mixtures, which was considered an indicative aspect of the formation of a salt or complex between AC and the components of the EE-Ris complex. All pHs value were compatible with topical route (pH: 5-6). When the molar proportion EE/CA was 1/1.2, the Z potential was considerably increased and there was also an increase in the proportion of 200 nm particles (PDI>0.3). These results, could be attributed to a greater exposure of the basic groups of PE in comparison to EE-Ris system, that could indicate some change in the structures that were previously formed. When Ris kinetic release from EE-Ris-CA was evaluated, an increase in the Ris release was founded in all media tested with regard to EE-Ris, that would indicate a release mechanism dependent on ionic exchange; thus, there is also reversible interaction between the components of the material. A new material containing antileishmanial drugs and excipients was obtained which would contribute to topical therapy to treat cutaneous leishmaniasis.

0858 - SCREENING AND IDENTIFICATION OF METACASPASE INHIBITORS, EVALUATION OF INHIBITION MECHANISM AND TRYPANOCIDAL ACTIVITY

Brian Daniel PÉREZ LÓPEZ | Emir SALAS-SARDUY | Vanina Eder ALVAREZ

IIBIO-UNSAM

Abstract/Resumen: Targeting proteases is a common strategy to identify new antiparasitic agents due to their essential contribution to parasite growth and development. Metacaspases (MCAs) are cysteine proteases (Clan CD) present in fungi, protozoa and plants. These enzymes, which are associated with crucial events in protozoa parasites (i.e. cell death and cell cycle progression), are absent in the human host, thus arising as attractive drug targets. To find new MCAs inhibitors bearing trypanocidal activity, we adapted a continuous fluorescent enzymatic assay to a medium-throughput format and carried out the screening of different compounds collections, followed by the construction of dose-response curves for the most promising hits. We used MCA5 from T. brucei (TbMCA5) as a model for the identification of inhibitors from the GlaxoSmithKline HAT and CHAGAS chemical boxes; two collections grouping 404 non-cytotoxic compounds with high antiparasitic potency, drug-likeness, structural diversity and scientific novelty. We also assessed a third collection of 9 compounds from Maybridge database identified by virtual screening as potential inhibitors of the cysteine peptidase falcipain-2 (Clan CA) from Plasmodium falciparum. As a result, 4 hits from the HAT and CHAGAS boxes showed modest IC50 values in the range 79-142 μM. Remarkable, HTS01959 (Maybridge collection) resulted the most potent inhibitor with IC50 of 14.39 μM; also inhibiting other MCAs from T. brucei and T. cruzi (TbMCA2= 4.14 μM, TbMCA3= 5.04 μM and TcMCA5= 151 μM). HTS01959 behaves as a reversible, slow binding and noncompetitive inhibitor of TbMCA2, where the mechanism of action includes RedOx components. Importantly, HTS01959 displays trypanocidal activity against bloodstream forms of T. brucei and trypomastigotes forms of T. cruzi, with non-cytotoxic effect on VERO cells. Thus, HTS01959 seems to be a promissory starting point to develop more specific and potent chemical structures to target MCAs from trypanosomatids parasites.

0860 - PROTEINS INVOLVED IN DNA HOMOLOGOUS RECOMBINATION REPAIR IN TOXOPLASMA GONDII: BRCA2 AND RAD51 CHARACTERIZATION

Constanza CRISTALDI | Ana María SALDARRIAGA CARTAGENA | Agustina GANUZA | Sergio ANGEL | Laura VANAGAS

INSTITUTO DE INVESTIGACIONES BIOTECNOLÓGICAS "DR. RODOLFO UGALDE", UNIVERSIDAD NACIONAL DE SAN MARTÍN

Abstract/Resumen: Toxoplasma gondii is an obligate intracellular parasite, belonging to the phylum Apicomplexa and is responsible of toxoplasmosis infection. Although there are treatments against toxoplasmosis, due to the toxicity of the drugs used there is an intensive search for new treatments against the parasite and innocuous to the host cell. There are conserved components of the homologous recombination DNA repair (HRR) pathway in T.gondii that could present unique characteristics which make them attractive therapeutic targets. Among them, a putative T. gondii BRCA2 was identified in silico because of the presence of conserved domains with the human homologous. In higher eukaryotes BRCA2 interacts with the recombinase RAD51, which is also present in T. gondii, generating an essential complex for the HRR. T. gondii BRCA2 and RAD51 genes were cloned and expressed in bacteria to obtain recombinant proteins used to produce specific mouse polyclonal antibodies. RAD51 was expressed as an entire recombinant protein, but for BRCA2 only the OB1 domain was expressed due to its high mass, near 480 kDa. The antibodies were titrated by ELISA, and used to detect their presence in T.gondii by Western blot (WB) and their subcellular localization by indirect immunoflourescence (IFA) either in normal conditions or using DNA damaging agents such as phleomycin and metylmethanesulfonate (MMS). The results showed no differences in the protein expression by WB in a DNA damage context, compared to non-treated parasites, for both proteins. When parasites were analyzed by IFA TgBRCA2 showed a spotted distribution along the whole parasite (nucleus included) in normal and DNA damage conditions. The antibodies obtained against these two important proteins will allow us to make progress in the understanding of the complex BRCA2-RAD51, which is fundamental to study the DNA repair by HRR observed in other eucaryotes.