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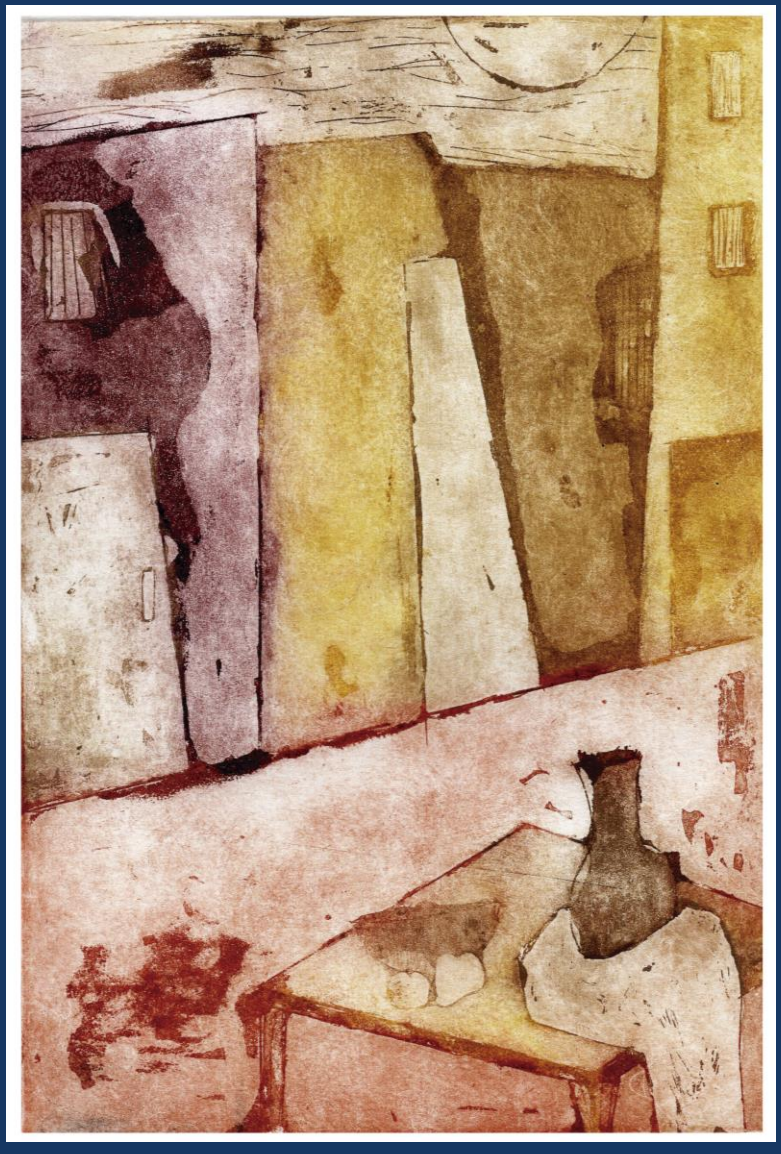

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antigens in these patients and search for epitope markers that could correlate with disease progression. Next, using a subset of ~400,000 peptides, we assayed serum samples from a 42 year old patient that showed progression of CCD. At age 39 the heart ejection fraction (EF) was 52 % accompanied by electrocardiogram with sinus rhythm, right bundle block and left anterior hemiblock (Sample1). One year later EF worsened to 39 % accompanied by complex ventricular arrhythmia (Sample2), maintaining similar values until today. Analysis of these two serum samples showed ~320 T. cruzi antigens with significant serological changes between both stages (threshold= 50 % signal change). Similar fractions of antigens increased or decreased measured antibody levels. To our knowledge, this is the first and largest collection of Chagas Disease antigens and epitopes correlated with pathology, providing a rich source of serological biomarkers.

0664 - CHAGAS DISEASE: PHARMACEUTICAL NANOVEHICLES ENCAPSULATING BENZNIDAZOLE.

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Chagas disease is an endemic parasitosis in Latin America whose etiologic agent is Trypanosoma cruzi. Benznidazole, the first-line therapy, eliminates trypanosomes in the circulatory system but seemingly does not fully eliminate parasites in tissue reservoirs, presenting a low cure rate in the chronic stage of the disease. An interesting approach to be considered is antichagasic drug delivery in novel nanotechnological vehicles. In other pathologies, nano systems are known to modify drug pharmacokinetics, improve delivery to target cells, increase drug concentration in tissues and protect circulating drug from elimination mechanisms, enhancing the drug safety profile and promoting adherence to the treatment. Our project aimed to obtain and evaluate pharmaceutical nanovehicles encapsulating benznidazole, taking advantage of the previously mentioned advantages. Here, nanoparticles were synthesized by the homogenization/ultrasonication method using two distinct matrixes: one lipidic (fatty esters) and one polymeric (ethyl acrylate, methyl methacrylate). This were evaluated in terms of drug loading and other physicochemical characteristics, with interest on developing future hybrid particles. Both types of nanoparticles presented spherical shape and encapsulation efficiencies of approximately 60 %. Mean diameter size was measured by DLS and TEM. Polymeric and lipidic particles sizes were 156.5 and 153.8 nm, respectively. Polydispersity index was around 0.2 which indicates an adequate size distribution to perform biological assays. In vitro drug release assays showed controlled release profiles in different dissolution mediums (phosphate buffer, hydroalcoholic solution and lauryl sulfate solution), with and average release of around 80 % of the drug load at 24 hours. As the next step in our research, thermal and spectroscopical methods will be included, as well as cell permeability/toxicity assays, and evaluation of trypanocidal effects in cell models.

0774 - EFFECT OF PUTATIVE PARG INHIBITORS IDENTIFIED BY AN IN SILICO APPROACH ON TRYPANOSOMA CRUZI INFECTION

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Poly-ADP-ribose polymer signaling is common to various nuclear processes related to DNA metabolism. As a reversible modification, it is regulated by a delicate balance of synthesis and degradation, being poly(ADP-ribose)glycohydrolase (PARG) the major hydrolase. We have demonstrated in mammalian cells that PARG inhibition or silencing is essential for the successful infection by the T. cruzi, making them an interesting target for the search of new treatments for Chagas disease. T. cruzi PARG inhibition also causes a delay in cell cycle. We have compiled a database of molecules tested against human PARG from which, we have inferred 1,000 ligand-based classificatory models capable of recognizing hPARG inhibitors using a semicorrelation approach and a random subspace approximation. We have generated a ligand-based model ensemble capable of recognizing human PARG inhibitors, with excellent behavior in the in silico validation step. The ensemble was applied in VS campaign, finding 26 drugs that could potentially behave as PARG inhibitors. Six drugs 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

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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.