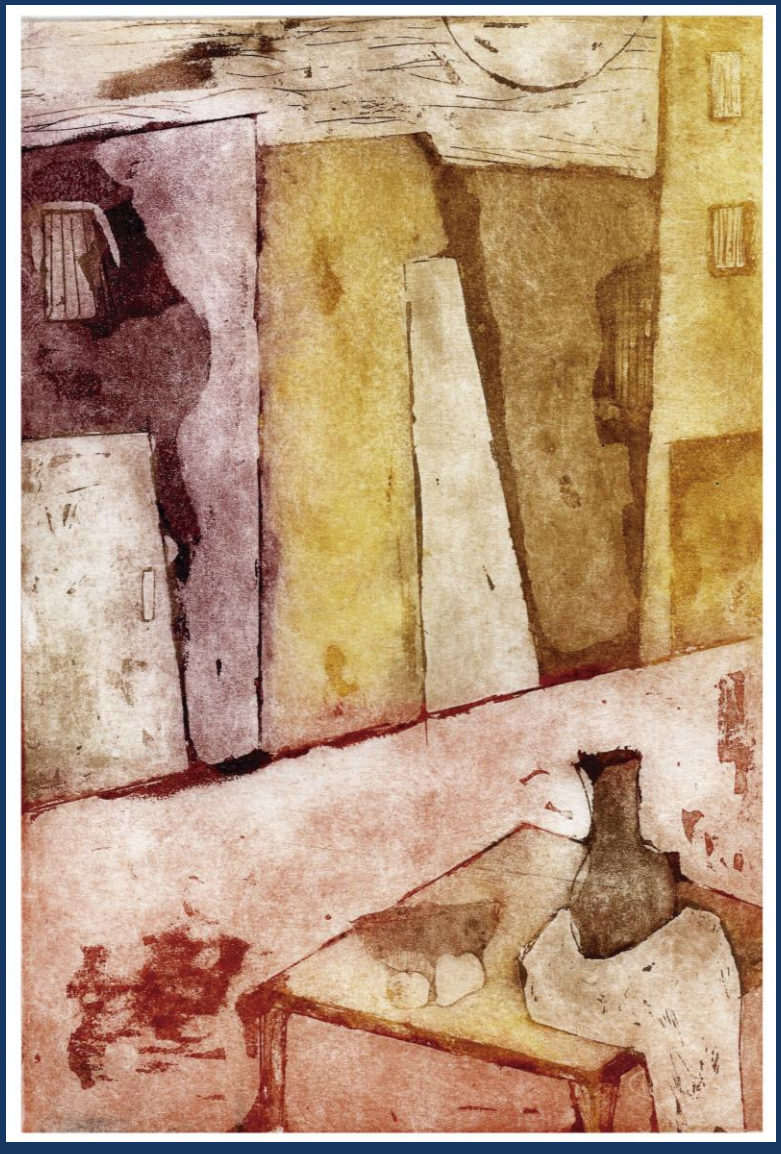
2019

medicina

BUENOS AIRES VOL. 79 Supl. IV - 2019

80° Aniversario



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La Tapa (*Ver* pág. 4)
Atardecer en la tarde
Antonella Ricagni

MEDICINA (Buenos Aires) – Revista bimestral – ISSN 0025-7680 (Impresa) – ISSN 1669-9106 (En línea)

REVISTA BIMESTRAL
Registro de la Propiedad Intelectual N° 02683675
Personería Jurídica N° C-7497
Publicación de la Fundación Revista Medicina (Buenos Aires)
Propietario de la publicación: Fundación Revista Medicina
Queda hecho el depósito que establece la Ley 11723

Publicada con el apoyo del Ministerio de Ciencia, Tecnología e Innovación Productiva.
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Vol. 79, Supl. IV, Noviembre 2019

in 71 % RL, 86 % in RS and 67 % in RL/RS treated mice. The cardiac tissue of untreated animals had multiple and extensive inflammatory foci that were reversed with drug treatments. Therapy with BNZ microparticles could be useful to efficiently treat the murine T. cruzi infection, decreasing the amount of BNZ administered to provide a promising clinical treatment.

0486 - POLY(ADP-RIBOSE)GLYCOHYDROLASE ACTIVITY IS IMPORTANT FOR LYSOSOME FORMATION DURING T. CRUZI INVASION

Maria Clara CHIATELLINO | Silvia FERNANDEZ VILLAMIL | Salomé VILCHEZ LARREA

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Chagas´ disease stands as one of the main public health problems in Latin America. Trypanosoma cruzi, protozoan parasite responsible for this disease, has a complex life cycle comprising several stages that allow it to multiply and disseminate. During the cell invasion step, the parasite modulates several metabolic pathways in the host cell; therefore, drugs that operate on these pathways could be used with therapeutic aims. Signaling though PI3k/Akt elicited in the host cell during T. cruzi infection. Activation of this pathway is important since it has anti-apoptotic effects that operate in favor of the infection and is also crucial for the regulation of the lysosome dependent and independent invasion mechanisms. Recently, it has been reported that Poly(ADP-ribose)Glycohydrolase (PARG) participates in the regulation of the PI3k/Akt route by downregulating Akt phosphorylation in cancer cells. In our infection model, PARG inhibition by DEA 1 µM or silencing by iRNA (shPARG) in Vero cells, the % of phosphorylated Akt is not altered when compared to wild type infected cells, but the upregulation of Akt levels on wild type (35 % at 15 min and 80 % at 6 h PI) cells could not be observed in cells where PARG activity is absent. Lysosome formation in response to parasitic infection is also altered when Vero cell PARG is inhibited or silenced: at 1 h PI, LAMP-1 (lysosome marker) signaling diminishes in DEA 1 µM-treated or shPARG cells in comparison to wild type cells. The reduction in lysosome density can also been observed in the absence of infection, indicating that lysosome formation regulation by PARG might be operating also in physiological conditions. Previous results obtained by our group showed that PARG inhibition led to a marked decrease in T. cruzi infection in vitro. These new findings could indicate that the downregulation of the lysosome invasion pathway could partially account for the reduction in T. cruzi infection when PARG activity is absent.

0490 - COMPUTATIONAL REPOSITIONING OF BIOACTIVE COMPOUNDS FROM LARGE CHEMOGENOMIC SCREENS: IDENTIFICATION OF CONSERVED DRUGGABLE MODULES BETWEEN YEASTS AND TRYPANOSOMES

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Detailed characterization of the cellular response to chemicals is fundamental to understand the mechanism of action of drugs. One strategy to do this is to analyze the growth capacity (fitness) of gene mutants exposed to different drugs. Recently, a number of genome-wide fitness profiling assays were performed on Saccharomyces cerevisiae. These chemical-genomics screens were based on whole-genome collections of heterozygous and homozygous deletions and quantified the growth fitness of each strain in the presence of different chemicals. Now, several such chemogenomic datasets are available, providing a rich source of pharmacogenomic associations between drugs and genes ("druggable modules"). In contrast, in trypanosomes pharmacogenomic associations are scarce, hence these yeast chemogenomic screens may serve as good starting points to guide repurposing opportunities. The aim of this project is the curation and standardization of yeast-based chemogenomic assays from published studies, and the development of an orthology mapping pipeline. Using this pipeline to find conserved druggable modules between yeasts and T. cruzi, we obtained 93,758 gene-drug interactions, with a set of 3,005 unique genes and 2,430 unique drugs. Further filters were applied to each set. For drugs, filters were applied to retain compounds that are drug-like, novel, commercially available, and with low potential promiscuity; with a final iteration to maximize chemical diversity within the set. For genes, we selected those that have T. brucei orthologs with significant fitness phenotypes when knocked down (through an orthology mapping between T. cruzi genes and T. brucei whole-genome RNAi essentiality assays described in Alsford et al., 2011). After standardization and filtering we obtained a library of 50 compounds, associated with 78 candidate protein targets in T. cruzi.

References: Alsford S (2011) Genome Research 21: 915-24. DOI:10.1101/gr.115089.110

0492 - TDR TARGETS: DRIVING DRUG DISCOVERY FOR HUMAN PATHOGENS THROUGH INTENSIVE CHEMOGENOMIC DATA INTEGRATION

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The volume of biological, chemical and functional data deposited in the public domain is growing rapidly, thanks to highly-automated sequencing and screening technologies. However, there is still a large data imbalance between well-funded model organisms and pathogens causing neglected diseases. We developed a chemogenomics resource, (TDR Targets, tdrtargets.org), that aims to organize and integrate heterogeneous large datasets with a focus on drug discovery for human pathogens. The database also hosts chemical and genomic data from other organisms to leverage data for comparative and inference-based queries. One of the major impacts of TDR Targets is to facilitate target and chemical prioritizations by allowing users to formulate complex queries across diverse data spaces. In this communication we will highlight new data and functionality updates in TDR Targets. In this release, the database has been updated to integrate data on >2 million bioactive compounds; 20 pathogen genomes; and 30 complete genomes from model organisms and other related pathogens. Furthermore, the data was also used to populate a recently developed network model (Berenstein et al., 2016) to produce i) a novel druggability metric for targets based on the connectivity in the network to bioactive compounds, ii) guide new prioritization strategies for both targets and compounds, and iii) visually aid in the navigation across target/compound spaces in the web interface. This network model connects protein (target) nodes to compounds, based on curated bioactivity annotations. It also connects proteins to other proteins based on shared annotations, and compounds to other compounds based on chemical similarity and substructure metrics. This chemogenomic network facilitates a number of inferences, such as inferring plausible targets for orphan drugs or candidate compounds for orphan targets.

References: Berenstein AJ et al (2016) PLOS Negl Trop Dis 10: e0004300. DOI: 10.1371/journal.pntd.0004300

0538 - ANTI-TRYPANOSOMA ACTIVITY OF HYBRIDS OF BILE ACIDS AND NATURAL ALKALOIDS