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# medicina

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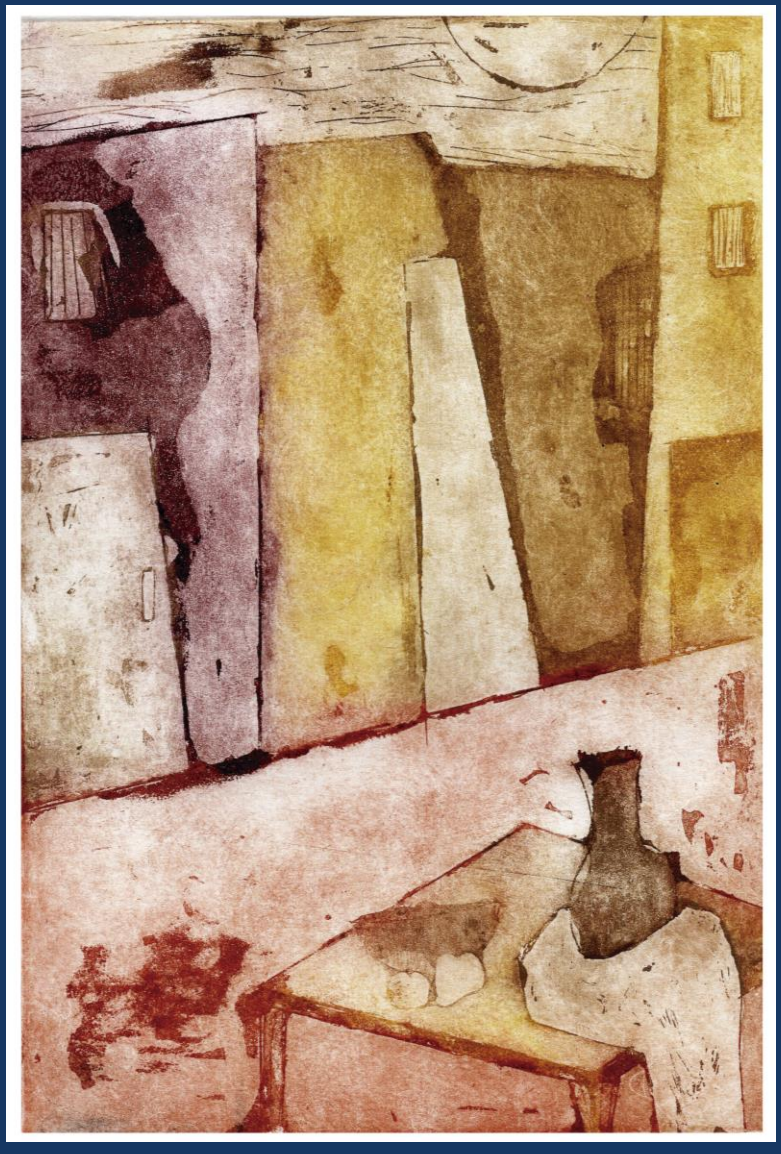

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La Tapa (*Ver* pág. 4)
***Atardecer en la tarde***
Antonella Ricagni

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# REUNIÓN ANUAL DE SOCIEDADES DE BIOCIENCIA 2019

**LXIV Reunión Anual de la**
**Sociedad Argentina de Investigación Clínica (SAIC)**

**LI Reunión Anual de la**
**Asociación Argentina de Farmacología Experimental (SAFE)**

**XXI Reunión Anual de la**
**Sociedad Argentina de Biología (SAB)**

**XXXI Reunión Anual de la**
**Sociedad Argentina de Protozoología (SAP)**

**IX Reunión Anual de la**
**Asociación Argentina de Nanomedicinas**
**(NANOMED-ar)**

**VI Reunión Científica Regional de la Asociación Argentina**
**de Ciencia y Tecnología de Animales de Laboratorio**
**(AACyTAL)**

**con la participación de**
**The Histochemical Society**

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

**EDITORES RESPONSABLES**

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

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# ANNUAL MEETING OF BIOSCIENCE SOCIETIES 2019

## LXIV Annual Meeting of
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## LI Annual Meeting of
## Asociación Argentina de Farmacología Experimental (SAFE)

## XXI Annual Meeting of
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## XXXI Annual Meeting of
## Sociedad Argentina de Protozoología (SAP)

## IX Annual Meeting of
## Asociación Argentina de Nanomedicinas
## (NANOMED-ar)

## VI Regional Scientific Meeting of Asociación Argentina
## de Ciencia y Tecnología de Animales de Laboratorio
## (AACyTAL)

## with the participation of
## The Histochemical Society

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

**CHIEF EDITORS**

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

## 0171 - PHARMACOLOGICAL STRATEGIES TO OVERCOME MELPHALAN RESISTANCE IN VITRO

**María Belén CANCELA** (1) | Ursula WINTER(1) | Santiago ZUGBI(1) | Maria Del Rosario ASCHERO(2) | Mariana SGROI(3) | Claudia SAMPOR(4) | Adriana FANDIÑO(3) | Fabiana LUBIENIECKI(2) | Guillermo CHANTADA(5) | Angel CARCABOSO M.(6) | Paula SCHAIQUEVICH(1)

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Retinoblastoma (Rb) is the most common intraocular tumor in children. Over the last decade, innovations in Rb treatment lead to an improvement in the rate of ocular survival. However, some eyes experience a relapse after initial response that may be related to acquired drug resistance. If resistance is established, the patient may need higher doses of chemotherapy or to switch to other drugs so as to respond. Thus, our aim was to establish a melphalan-resistant (ML-RE) cell subtype as a preclinical model to characterize the resistance to this drug, cross-resistance to other agents commonly used in Rb, and to evaluate alternative treatments that may allow to overcome this phenomenon including metronomic (MT) treatment with melphalan (MLF) and the cytotoxicity to digoxin (DX) as a repositioning drug. A primary cell culture was established from the tumor biopsy of an upfront enucleated patient with intraocular Rb. The parental cell line (HSJD-RB-7) was exposed to 3 weekly doses of MLF at the IC50. Then, MLF, topotecan (TP) and carboplatin (CP) IC50 was determined in the resistant cell subtype (HSJD-RB-7-MLF) to verify resistance and to test for possible cross-resistance using the MTT assay. Also, MT-MLF (7 days) and DX IC50 was determined in HSJD-RBT-7-MLF cells. Mean (range) MLF IC50 in HSJD-RB-7-ML was 1.3 µM (0.8-1.4), 4-fold higher than in HSJD-RB-7 ($p<0.05$). TP and CP IC50 in HSJD-RB-7-MLF was 2-fold and 3-fold higher than that in HSJD-RB-7, respectively ($p<0.05$). MLF IC50 significantly decreased after metronomic treatment of HSJD-RB-7-ML cells ($p<0.05$). Both parental and resistant cells showed similar DX IC50s ($p>0.05$). We were able to establish a primary cell culture of retinoblastoma with acquired resistance to melphalan. These cells showed cross-resistance to TP and CP but were sensitive to DX and metronomic treatment with MLF.

## 0348 - DISCOVERY OF NOVEL BOVINE VIRAL DIARRHEA ENTRY INHIBITORS

**Emilse LEAL** (1) | Natalia ADLER(1) | María José PASCUAL(2) | Manuela MARTINEFSKI(1) | María Eugenia MONGE(1) | Diego ÁLVAREZ(2) | Mariela BOLLINI(1)

**CENTRO DE INVESTIGACIONES EN BIONANOCIENCIAS (CIBION), CONSEJO NACIONAL DE INVESTIGACIONES (1); INSTITUTO DE INVESTIGACIONES BIOTECNOLÓGICAS (IIB-UNSAM-CONICET) (2)**

Bovine viral diarrhea virus (BVDV) is a pathogen of cattle that causes both acute and persistent infections, leading to substantial financial losses to the livestock industry each year. The global prevalence of persistent BVDV infection and the lack of an antiviral therapy have spurred efforts to discover and develop novel therapies in the pharmaceutical industry. Antiviral targeting of virus envelope proteins is an effective strategy for therapeutic intervention. We performed structure based virtual screening (SBVS) to identify molecules that likely bind to the region delimited by domains I and II of the envelope protein E2 of BVDV. Nineteen structurally different compounds were synthesized and evaluated in a reporter-based assay for antiviral activity. Compound PTC12 was the most active antiviral displaying an IC50 of 0.30 ± 0.13 µM against BVDV and selectivity index= 294. Also, PTC12 blocked virus entry at the stage of internalization. In order to validate the target, we performed selection and sequence analysis of drug-resistant mutants and identified R154Q as a candidate substitution associated to resistance. The mutation is located nearby the proposed binding pocket and MD simulations suggested a stable cation-π interaction between the N+ and the aromatic ring of PTC12. MM/PBSA calculations for the wild type and R154Q mutant indicate that PTC12 complexed with wt-BVDV had the most favorable binding energy (ΔGbind= -29.12 kcal/mol) whereas the complex with R154Q mutant caused a significant energetic change (ΔGbind= -21.6 kcal/mol). The physicochemical properties of PTC12 were evaluated in vitro: solubility was tested at three different pH values, and stability studies in media such as PBS, SIF, SGF, mouse or bovine plasma are currently ongoing. Altogether, we uncovered a novel druggable pocket in BVDV E2 that can be effectively targeted to block virus entry. SBVS against this target led to the identification of PTC12 as a potent BVDV inhibitor.

## 0370 - INTEGRATED PHARMACOLOGICAL EVALUATION OF THE COMBINATION OF SYNTHETIC ANTHELMINTICS AND BIOACTIVE PHYTOCHEMICALS: IN-VITRO AND IN VIVO STUDIES

**María Victoria MIRÓ** (1) | Sonia LUQUE(2) | Mercedes LLOBERAS(2) | Livio COSTA-JUNIOR(3) | Carlos LANUSSE(1) | Guillermo VIRKEL(1) | Adrián LIFSCHITZ(1)

**CIVETAN (CONICET-CICPBA-UNCPBA), FACULTAD DE CIENCIAS VETERINARIAS, UNCPBA, TANDIL (1); LABORATORIO DE PARASITOLOGÍA, INTA, ESTACIÓN EXPERIMENTAL BALCARCE (2); CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE, UNIVERSIDADE FEDERAL DO MARANHÃO (3)**

In a context of increasing anthelmintic resistance, combination of synthetic anthelmintics with bioactive phytochemicals may be a pharmacological tool for improving the nematode control in livestock. The coadministration of natural compounds and anthelmintics may lead to kinetic/dynamic interactions. This work evaluated the drug-drug interactions between synthetic anthelmintics and bioactive phytochemicals at the metabolism and drug transport level. The impact of these interactions on drug efficacy was also studied. Trial 1 include in vitro and in vivo the combination of thymol (TML) and albendazole (ABZ). The stability of TML (800 µg/ml) in sheep ruminal content and its effects (5 mM) on the metabolism of ABZ in sheep liver microsomes were evaluated. The in vivo plasma concentrations and efficacy of the combination were studied in lambs naturally infected with resistant nematodes. TML was stable in sheep ruminal content and inhibited ($p<0.05$) the ruminal sulphoreduction of ABZ sulphoxide. Besides, TML markedly inhibited the hepatic FMO-dependent S-oxygenation of ABZ (54.1 ± 11.6 %, $p<0.05$) and the sulphonation of ABZ sulphoxide ($p<0.05$). However, the in vivo pharmacokinetic changes did not improve the efficacy of ABZ after the combined treatment with TML. In trial 2 the combination of carvone (CVN) and abamectin (ABM) was studied. The modulation of CVN on the P-glycoprotein-mediated transport of Rhodamine 123 (Rho-123) was assessed using the intestinal explants model. The in vivo effect of CVN on ABM kinetic disposition and efficacy was evaluated in lambs infected with resistant nematodes. The presence of CVN increased the Rho-123 accumulation in intestinal explants (60 %, $p<0.05$). In vivo, the coadministration of CVN prolong the absorption half-life of ABM (57 %, $p<0.05$) and increased the efficacy from 94.9 to 99.8 %. In-vitro-in vivo trials are necessary to corroborate the clinical relevance of the combinations of bioactive phytochemicals and anthelmintics.

## 0605 - GA-RXODE METHOD IN BIOEQUIVALENCE STUDIES

**Eduardo NUSKE** | Mikhail MOROZOV | Héctor Alejandro SERRA