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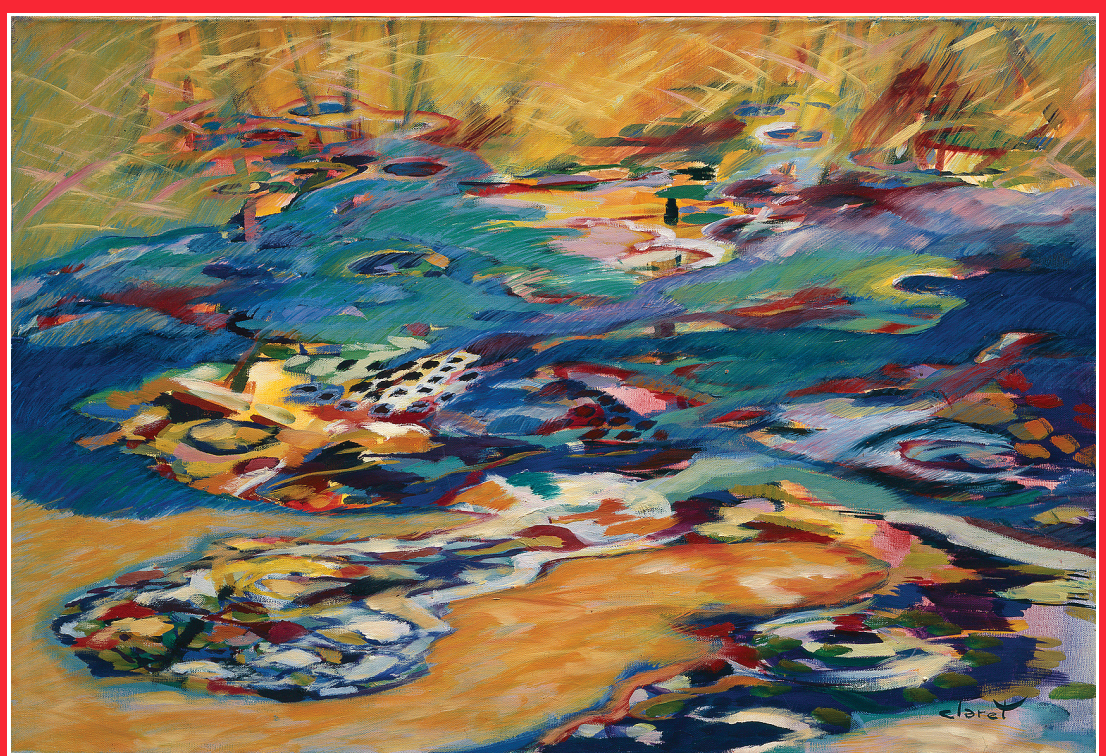

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LXI REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)

LXIV REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INMUNOLOGÍA (SAI)

XLVIII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE FARMACOLOGÍA EXPERIMENTAL (SAFE)

VII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE NANOMEDICINA (NANOMEDAR)

V CONGRESO NACIONAL DE LA ASOCIACIÓN ARGENTINA DE CIENCIA Y TECNOLOGÍA DE ANIMALES DE LABORATORIO (AACYTAL)

15-19 de noviembre de 2016
Hotel 13 de Julio – Mar del Plata

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LXI ANNUAL MEETING
ARGENTINE SOCIETY FOR CLINICAL INVESTIGATION
(SAIC)

LXIV ANNUAL MEETING
ARGENTINE SOCIETY OF IMMUNOLOGY
(SAI)

XLVIII ANNUAL MEETING
ARGENTINE SOCIETY OF EXPERIMENTAL PHARMACOLOGY
(SAFE)

VII ANNUAL MEETING
ARGENTINE SOCIETY OF NANOMEDICINE
(NANOMEDAR)

V NATIONAL CONGRESS
ARGENTINE ASSOCIATION FOR SCIENCE AND TECHNOLOGY OF LABORATORY ANIMALS
(AACYTAL)

November 15-19, 2016
13 de Julio Hotel – Mar del Plata

with more aggressive forms of several types of cancer. ACSL4 is part of the mechanism responsible for increased breast cancer cell proliferation, invasion and migration. Thus, the aim of this work was to analyze the expression of a typical, MKP-3, and an atypical MKP, DUSP18, in cells with different ACSL4 expression levels. The experimental model is based on the stable transfection of MCF-7 cells with ACSL4 using the tetracycline Tet-Off system (MCF-7 Tet-Off/ACSL4), in which doxycycline down-regulates ACSL4 expression. mRNA levels of MKP-3 and DUSP18 were evaluated by semiquantitative RT-PCR. The expression of MKP-3 and DUSP18 was increased 1.5 and 1.8-fold ($P<0.05$) in ACSL4 overexpressing MCF-7 cells. Doxycycline treatment reduced the increase in mRNA levels of both phosphatases to control values (MCF-7), confirming the participation of ACSL4 in this effect. The biological significance of the variation of phosphatase expression and the increase in tumor aggressiveness mediated by ACSL4 have not been determined yet. However, these studies may contribute to molecular and functional characterization of these phosphatases, mainly DUSP18.

167 (2075) **EFFECT OF LEPTIN ON THE APOPTOSIS OF TROPHOBLAST EXPLANTS TRIGGERED BY ACIDOSIS**

Antonio Pérez-Pérez[1], Ayelen Rayen Toro[2], Teresa Vilariño-García[1], Malena Schanton[2], Julieta L Maymó[2], Cecilia L Varone[2], Víctor Sánchez-Margalet[1]

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Decrease in gas exchange at the level of the placenta is a serious complication during pregnancy. Disturbance pH of the internal environment can alter fetal, maternal and placental functions. In particular, the decrease in pH can alter the fetal tissue homeostasis causing irreparable fetal death or to damage by metabolic acidosis. In this context we decided to study the effect of lowering the pH of the process of apoptosis in placental explants and leptin action under such conditions. Based on previous results of our research group and the central role of p53 in the regulation of apoptosis, we hypothesize that pH changes in the placental cells increase apoptosis by altering the expression of p53 as well as their target genes. In this context we investigated the posible antiapoptotic effect of leptin in trophoblast cells subjected to different pHs. Explants human placenta at term were incubated in DMEM F-12 at different pH (7.4, 7 and 6.8) in the presence or absence of 10 nM leptin. They were analyzed by Western blot and qRT-PCR p53 levels and its downstream effectors p21, BAX and BCL-2, as well as the cleaved fragment of PARP-1 and the active form of caspase-3. We found an increase in phosphorylation (Ser 46) p53 and p21 expression, PARP-1 and activation of caspase-3 in the explants incubated at pH 7 and 6.8. Conversely, these effects were attenuated in the presence of 10 nM leptin both pH 7 and pH 6.8. The BCL-2 / BAX ratio decreased to pH 7 and 6.8 compared with explants incubated at pH 7.4, an effect that is counteracted by treatment with leptin. These data demonstrate an anti-apoptotic effect of leptin potential involving the regulation of p53 axis explants cultured placental acidic pHs, suggesting that placental leptin has a protective effect on trophoblast cells.

168 (150) **MODULACION DE LA EXPRESION DE CISD1 POR LA ACTIVIDAD DEL CANAL CFTR**

Consuelo Mori[1], Mariángeles Clauzure[1], María Macarena Massip Copiz[1], Ángel Gabriel Valdivieso[1], Tomás Antonio Santa Coloma[1].

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Cystic fibrosis (CF) is an autosomic recessive disease caused by mutations affecting the activity of CFTR chloride channel, which indirectly affect the expression of a net of genes. CDGSH iron sulfur domain 1 (CISD1; initially cloned in this laboratory as named successively CFTR-RG2, KLPX, ZCD1 and CISD1), also referred to as mitoNEET, is a protein localized on the outer membrane of mitochondria. Oriented toward the cytoplasm, the CDGSH domain of CISD1 contains a redox-active 2Fe-2S cluster, which is stabilized by pioglitazone. We have previously described that CISD1 gene expression was decreased in a CF cellular model and restored in the same cells ectopically expressing wt-CFTR (CFDE and CFDE/6RepCFTR cells). The initial results were further validated by using confocal FISH and real-time PCR, using CFDE and CFDE/6RepCFTR cells incubated or not with glibenclamide (50, 100 µM, 24h) or CFTR(inh)172 (2.5, 5 µM, 24h), another Cl- transport inhibitor (more potent and specific than glibenclamide). A similar differential expression was obtained using another CF cellular model: IB3-1(CF cells) and S9 cells (IB3-1 corrected cells), now using CFTR-stimulation (isoproterenol, db-cAMP, IBMX) instead of CFTR-inhibition. Now we used another cellular model, human colon adenocarcinoma T84 cells (known to express the CFTR), and by real-time PCR we determined that CISD1 gene expression was decreased in T84 cells treated with CFTR(inh)172 (10 µM, 24h), compared to control cells. These results confirmed that CISD1 expression is decreased in CF cells or in cells with impaired CFTR function. We are now studying the possible mechanisms involved in this regulation, which will be discussed. Acknowledgments: Grants from ANPCYT [PICT 2007-00628 and PICT 2012-1278], CONICET [PIP 11220080102551 2009-2011 and PIP 11220110100685 2012-2014] and UCA to TASC; and research fellowships from CONICET (to MMMC, CM and MC).

PRESENTACIÓN DE POSTERS SAFE I / SAFE POSTER PRESENTATION I

ENDOCRINOLOGÍA / /ENDOCRINOLOGY

169 (630) **ANTIPROLIFERATIVE EFFECTS OF OXYTOCIN AND DESMOPRESSIN ON CANINE MAMMARY CANCER CELLS**

Micaela Andrea Benavente[1], Carolina Paula Bianchi[1], Fernanda Imperiale[2], Marcelo Alfredo Aba[1].

[1]Laboratorio de Endocrinología, Centro de Investigación Veterinaria de Tandil (CIVETAN), CONICET, Facultad de Ciencias Veterinarias, U.N.C.P.B.A., Tandil, Buenos Aires, Argentina. [2]Laboratorio de Farmacología, Centro de Investigación Veterinaria de Tandil (CIVETAN), CONICET, Facultad de Ciencias Veterinarias, U.N.C.P.B.A., Tandil, Buenos Aires, Argentina.

Neoplasms of the mammary gland represent the most frequent tumor type in the female dog, and according to the histologic criteria, approximately 50% are malignant. In the most aggressive cases of mammary cancer, surgery is not enough to warrant a favorable outcome, and adjuvant therapies are needed to improve the patient's overall survival. Several *in vitro* studies performed on murine and human cancer cells have suggested that some peptide hormones can modúlate tumor growth. However, little is known about its effects on canine cancer. The aim of the present study was to evaluate the effects of Oxytocin (OT) and Desmopressin (DDAVP) on proliferation of the canine mammary cancer cell line CMT-U27. The cells were grown in 96-well plates, at two densities ($4x10^3$ and $8x10^3$ cells/well) in 200 µl of RPMI-1640 supplemented with 10% Fetal Bovine Serum. After overnight culture, the medium was removed and replaced with médium containing OT or DDAVP at five concentrations: 10, 50, 100, 500 and 1000 nM, or medium without drugs (controls). After 72 h of incubation, cell viability was determined using the MTT colorimetric dye reduction method. With $4x10^3$ cells/well, OT at 1000 nM resulted in a 25% of inhibition of cell viability($p<0.01$). Surprisingly, OT 50 nM resulted in a higher inhibitory effect (18%) than 500 nM (9%). At $8x10^3$ cells/well, OT showed a significant antiproliferative effect (almost 25%) with the highest concentration ($p<0.05$). Desmopressin at 1000 nM and $4x10^3$ cells/well reduced cell growth by 22% ($p<0.05$). At 50, 100, 500 nM the inhibitory effect was lower. With $8x10^3$cells/well, DDAVP at 100, 500 and 1000 nM exhibited a mild antiproliferative effect ($p>0.05$). In conclusion, OT and DDAVP can inhibit proliferation of CMT-U27 cells, by almost 20% at the highest concentrations.

Further studies are required to evaluate its potential as antitumor agents, alone or combined with conventional cytotoxic drugs, for the treatment of dogs with advanced mammary cancer.

170 (2042) **GROWTH HORMONE INDUCED EPIGENETIC CHANGES IN LIVER SEXUALLY DIMORPHIC GENE EXPRESSION**

Belen Brie[1], María Cecilia Ramirez[1], Catalina De Winne[1], Ana María Ornstein[1], Damasia Becu-Villalobos[1].[1]*Instituto de Biología y Medicina Experimental.*

Growth hormone (GH) secretion is sexually dimorphic in many species, such as rodents and humans. In the liver GH regulates gene expression in a sexual dimorphic manner. Previous results from our laboratory showed that central disruption of the Dopamine D2 Receptor (D2R) altered the growth axis, we thus inferred and searched for alterations of sexually dependent liver gene expression. To this end, we used transgenic mice with the D2R depleted from the nervous system (*neuroDrd2KO*). Furthermore, because neonatal sexual steroids are known to imprint the growth axis, we tested the effects of the neonatal administration of testosterone in females on genetic and epigenetic regulation of the liver.

We sustained that liver sexual dimorphism is mediated by epigenetic mechanisms, induced by the GH secretion pattern. Hypermethylation of promoter regions of genes generally results in their silencing. We measured promoter methylation levels using a methylation sensitive restriction enzyme, followed by specific qPCR.

We found that the mRNA expression of female predominant genes Alcohol Dehydrogenase 1 (Adh1) and Hepatocyte Nuclear Factor 6 (Hnf-6) are masculinized in the *neuroDrd2KO* mice, and so was the Adh1 protein. On the other hand, mRNA expression of the male predominant gene*Cyp7b1* was feminized (decreased) in both our mice models. Increased methylation of the promoter region of *Hnf-6* correlated with its decreased expression in neuroDrd2KO females, while increased expression of *Adh1* in neuroDrd2KO males did not correlate with methylation status of its promoter. Furthermore, methylation could not explain the changes in *Cyp7b1* in neuroDrd2KO mice. Lastly *Adh1 and Hnf6* mRNA in the testosterone treated females was masculinized and altered methylation of the promoter correlated only with *Hnf6* expression.

Our results demonstrate that the growth axis modulates the sexual dimorphic expression of several genes in the liver, in part through DNA methylation.

FARMACOLOGÍA / PHARMACOLOGY

171 (140) **TIME COURSE OF RENAL EXPRESSION AND URINARY EXCRETION OF CAVEOLIN-2 (CAV2) IN RATS WITH CISPLATIN INDUCED ACUTE KIDNEY INJURY**.

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Caveolins (Cav), main component of caveolae, are a family of integral membrane proteins that are involved in cell surface signaling, endocytosis and in repair processes. The role of Caveolin 2 (Cav2) in kidney disease is unclear. Cisplatin (Cis) is a chemotherapeutic agent that might cause acute kidney injury (AKI). The aim of this study was to evaluate the time course of Cav2 renal expression and urinary excretion in a Cis induced AKI model. Adult male Wistar rats were injected with 5 mg/kg i.p. of Cis and the studies were performed 2 (T2, n=4), 4 (T4, n=6), 7 (T7, n=6) and 14 days (T14, n=5) after treatment. Control rats (C, n=16) received the vehicle. Plasma samples and renal tissue were collected. Urea plasma levels (Ur_p) were determined spectrophotometrically. Cav2 in renal homogenate ($Cav2_H$), in renal apical membranes ($Cav2_{ap}$) and in urine samples ($Cav2_U$) were evaluated by immunoblotting. ANOVA/Newman-Keuls test, P<0,05: a vs C; b vs T2; c vs T4; d vs T7; e vs T14. Results: Ur_p(g/L): C=0.28±0.01, T2=0.49±0.08^{c,d}, T4=2.94±0.24^{a,b,e}, T7=3.82±0.91^{a,b,e}, T14=1.03±0.23^{c,d}; $Cav2_H$(%): C=100±4, T2=102±11, T4=102±6, T7=81±6, T14=85±5; $Cav2_{ap}$(%):C=100±2, T2=28±2^{a,d,e}, T4=23±1^{a,d,e}, T7=42±4^{a,b,c,e}, T14=76±6^{a,b,c,d}; $Cav2_U$(%): C=100±3, T2=96±10^{e}, T4=114±8^{e}, T7=86±13^{e}, T14=159±21^{a,b,c,d}. Ur_p was significantly altered on days 4 and 7 of treatment and on the day 14 tended to return to its basal value.$Cav2_H$ did not change through the experiments, but $Cav2_{ap}$ was found significantly decreased in all the times evaluated. $Cav2_U$ was only increased on the 14th day. The decrease in $Cav2_{ap}$ expression could be due to Cav2 internalization, probably together with different signalling molecules. So, Cav2 might have a role in the regulation of signal transduction after AKI. The increase observed in $Cav2_U$ only in the recovery phase of AKI (day14), let us to propose it as a urinary biomarker useful to monitor reversibility of renal injury after Cis induced AKI.

172 (307) **ROLE OF ALLOPREGNANOLONE IN THE MORPHOPHYSIOLOGY OF THE RAT OVARY**.

Antonella Rosario Ramona Cáceres Gimenez[1, 2, 3], Laura Tatiana Pelegrina[1, 2], Joana Antonela Asensio[1], Fernanda Parborell[4], Myriam Raquel Laconi[1, 2].
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Allopregnanolone (ALLO), a progesterone metabolite, is a neurosteroid synthesized *de novo* in the nervous system. ALLO icv reduces LH secretion, increases progesterone and prolactin serum levels,inhibits corpora lutea apoptosis, alters follicular steroidogenesis and impairs ovulation. It also modifies ovarian angiogenesis, which takes place cyclically in the ovary and is essential for follicular and luteal development. The aim of this study was to evaluate the effect of a pharmacological dose of ALLO, using a new administration model (intrabursa), on ovarian morphophysiology, vascular development and stability.

A dose/response curve of 5 points was performed. The results presented correspond to the pharmacological dose of 6 µM. Adult Sprague-Dawley rats were used. On the morning of proestrus, vehicle and ALLO were administered at 5 µl intrabursa. The animals were sacrificed during the morning of estrus, 24 h after treatment. To assess vascular density and stability, immunohistochemistry for the von Willebrand factor (present in endothelial cells) and α-actin (present in smooth muscle cells of blood vessels) was performed. For the ovarian structures morphometric analysis, histological sections were made. Oocyte count was performed by puncturing the ovarian ampulla. ALLO caused a significant increase of angiogenesis, measured as an elevation in the detection of the W factor ($p < 0.001$) and of the α-actin protein ($p < 0.05$). It also induced a significant increase in the number of atretic follicles ($p < 0.001$) and the formation of cystic follicular entities. In this model, the treatment did not alter ovulation unlike previous findings with the model icv. Also, asignificant increase in the diameter of the corpora lutea ($p < 0.05$) of treated animals was found. We can conclude that ALLO, at this concentration, alters follicular and luteal development as well as ovarian angiogenesis. ALLO is a molecule candidate to be used as a new therapeutic alternative for ovarian disease.

173 (532) **BISPHOSPHONATES REGULATE DIFFERENTIAL CA2+ INTAKE DEPENDING OF CELL TYPE AND ORIGIN: VERO, HT29 OR EGPE, CELL LINE FROM ECHINOCOCCUS GRANULOSUS.**

Mariana Ferrulli[1], Andrea Granada[1], Emilio Roldán[1], Alicia Graciela Fuchs[1].
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The Ca^{2+} constitutes one of the most relevant cations to cell metabolism. Different channels are responsible for Ca^{2+} intake. We study antiparasitic effects of bisphosphonates (BPHs). Previously we described the antiproliferative effect of Ibandronate (IB) and Etidronate (EHDP) on EGPE cellline (Fuchs et al, 2014). Ca^{2+} accumulation and alkaline phosphatase inhibition was observed in cells treated with EHDP. Moreover, calcium entry in EGPE is