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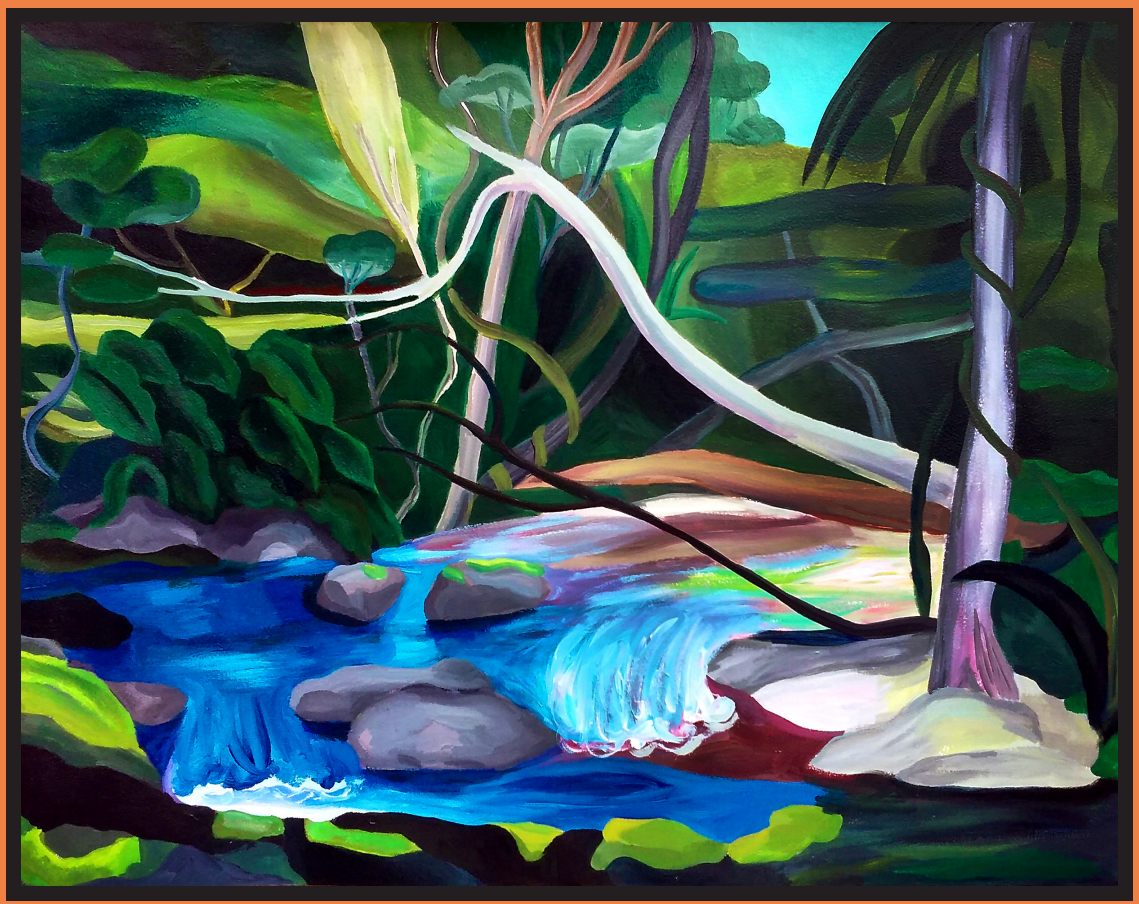

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# REUNIÓN CONJUNTA SAIC SAB AAFE AACYTAL 2023

**LXVIII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)**

**XXV JORNADAS ANUALES DE LA SOCIEDAD ARGENTINA DE BIOLOGÍA (SAB)**

**LV REUNIÓN ANUAL DE LA ASOCIACIÓN ARGENTINA DE FARMACOLOGÍA EXPERIMENTAL (AAFE)**

**VIII REUNIÓN CIENTÍFICA REGIONAL DE LA ASOCIACIÓN ARGENTINA DE CIENCIA Y TECNOLOGÍA DE ANIMALES DE LABORATORIO (AACYTAL)**

15-17 de noviembre de 2023
Hotel 13 de Julio – Mar del Plata

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**NEUROENDOCRINE MODEL**

Víctor A. Valdez Samaniego, Rocío Rodriguez, María Florencia Gottardo, Juan Garona, Daniel F. Alonso, Noelia P. Di Giorgio, Giselle V. Ripoll.
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Neuroendocrine tumors (NET) are a heterogenous neoplasms with a wide range of morphological and functional characteristics that can arise from any organ. In particular, small bowel tumors represent 45% of gastrointestinal neuroendocrine tumors (GI-NETs). Although they are rare tumors, their incidence has been increasing in recent years. For several years, we have studied the antitumor properties of desmopressin (dDAVP), a V2 receptor (AVPR2) agonist. dDAVP displays antiproliferative, antimetastatic, and antiangiogenic effects in numerous models such as colorectal cancer, breast cancer, and NE tumors such as small cell lung, among others. Considering that treatment and therapeutic resources are limited for the most aggressive GI-NETs and added to the lack of clinically relevant models for the study of NETs, this work aims to evaluate the effect of AVP analogs on key processes related to cancer progression on the intestinal neuroendocrine cell line, STC-1, as a model of GI-NET. In this study, AVPR2 expression in the STC-1 line was detected by immunofluorescence and confirmed by flow cytometry. Incubation of exponentially growing STC-1 cells with dDAVP (100 nM to 1,5 µM) resulted in a significant dose-dependent inhibition of proliferation with an IC50 of 0.95 µM (p< 0,0001). On the other hand, incubation with dDAVP for 7 days significantly inhibited the clonogenic growth of STC-1 showing an IC50 for dDAVP of 0.1µM. Sensitivity to chemotherapeutic agents as oxaliplatin and doxorubicin was measured by MTS assays. Also, we confirmed by flow cytometry that STC-1 express low levels of PDL-1. These results show the first evidence of the activity of the antitumor activity of dDAVP in a murine model of neuroendocrine-type invasive small intestine carcinoma. This research lays the groundwork for future explorations and approaches in the therapy of highly aggressive GI-NETs.

**353.** 613. **HEME OXYGENASE-1 IMPAIRS HORMONE-DEPENDENT BREAST CANCER CELL SURVIVAL THROUGH ITS ENZYME ACTIVITY**

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We have previously reported that induction of Heme Oxygenase-1 (HO-1), an enzyme that catalyzes heme degradation and releases iron, impairs breast cancer (BC) cell survival in both murine hormone-independent (LM3) and human triple-negative (MDA-MB-231) BC cell lines, most likely through ferroptosis induction. In this study, we aimed to evaluate the HO-1 modulation on hormone-dependent BC cell survival and to assess the involvement of HO-1 enzyme activity. To this end, we modulated HO-1 in T47D cell line by pharmacological induction (hemin, 36h) and by stable overexpression of wild-type HO1 (WT-HO1) or enzymatically inactive-H25AHO-1 (H25A). We studied cell viability (crystal violet), iron storage (Prussian blue), ROS levels (DFCA), lipid peroxidation (MDA accumulation) and the expression of ZIP14 iron importer (immunocytochemistry). We also carried out correlation studies between HO-1 mRNA levels and L-ferritin in BC subtypes (bioinformatics analysis). We found that hemin treatment and WT-HO1 overexpression decreased T47D cell viability ($p<0.01$ and $p<0.05$ respectively) and increased iron storage ($p<0.05$ in both), ROS levels ($p<0.01$ and $p<0.05$ respectively), MDA accumulation ($p<0.01$ in both) and ZIP14 expression. The treatment with an antioxidant (N-Acetylcysteine) and an iron chelator (deferoxamine) reversed the reduction of BC cell viability induced by hemin and by WT-HO-1 overexpression ($p<0.001$ and $p<0.05$ respectively). On the contrary, H25A cell viability was higher and the ROS levels and MDA accumulation were lower than in WT-HO1 cells ($p<0.05$). Bioinformatics studies confirmed a positive correlation between HO-1 mRNA and L-ferritin in BC subtypes (ER+, ER-, Basal-like, Normal-like, Luminal and HER2 enriched). In conclusion, HO-1 induction impairs cell viability in a hormone-dependent BC subtype through an increase in free iron accumulation, ROS production and lipid peroxidation, being the enzymatic activity of HO-1 necessary for its effect on cell viability.

**354.** 655. **IRRADIATED MDA-MB-231 BREAST TUMORS IN NUDE MICE. CAN HISTAMINE TREATMENT CONTROL GROWTH AND METASTASIS?**

Tamara Galarza[1], Nora Mohamad[1], Lara Dahir[3], Gabriela Martín[1,2]
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Ionizing radiation can promote epithelial-mesenchymal transition (EMT) activation and acquisition of cancer stem cell-like (CSC-like) properties in tumor cells that survive radiotherapy and thus facilitate metastasis. Previously we demonstrated in breast tumor cells the dual role of histamine on radio-induced EMT (favoring it at ≤ 1µM and hindering it at ≥10µM). Herein, we evaluated the *in vitro* histamine (Ha) effect on CSC-like enrichment and the link between CSC-like and EMT in MDA-MB-231 (MDA) breast cancer cells. Cells were treated with 1 or 20$\mu$M Ha and then γ-irradiated with a 2Gy dose (2Gy). After 5 days we assessed clonogenicity, mammosphere formation, and co-expression of CD44 (CSC-like marker) and Slug (EMT-associated transcription factor). In both non-irradiated and 2Gy cells, 1$\mu$M Ha did not modify clonogenicity vs controls, while 20$\mu$M Ha decreased it ($p<0.05$). 2Gy, 1$\mu$M Ha or their combination increased mammosphere formation, while 20$\mu$M Ha blocked the radio-induced rise ($p<0.001$). By indirect immunofluorescence we observed that 2Gy increased nuclear Slug and its co-localization with membrane CD44+ cells ($p<0.05$); 20$\mu$M Ha prevented radio-induced increments ($p<0.01$). *In vivo*, female nude mice were xenotransplanted with irradiated or non-irradiated MDA tumors and received or not histamine 5 mg/kg/day s.c. (HA) for 20 days. Tumor growth rate was similar in control and 2Gy tumors but lower in HA and 2Gy+HA ($p<0.05$), which also hindered vascularization. PCNA expression and mitosis paralleled these results. Intracellular TGFβ-1 (EMT promoter) was raised in HA, 2Gy and 2Gy+HA, but high vimentin expression (EMT marker) didn´t vary. Lung cellularity and metastatic foci were higher in 2Gy and 2Gy+HA mice ($p<0.05$). PCNA and vimentin-positive tumor cells in lungs were more numerous in HA, 2Gy and 2Gy+HA ($p<0.05$). Altogether, results show that even if HA may hinder control and 2Gy tumor growth it cannot prevent lung metastasis possibly due to a furthering effect on EMT.

**355.** 662. **HISTAMINE $H_3$ RECEPTOR ANTAGONISM, A POTENTIAL OPTION FOR LUNG CANCER TREATMENT?**

Paolo Laureta[1], Ignacio Ospital[1], Mónica A. Táquez Delgado[1], Melisa B. Nicoud[1], Michelle F. Corrêa[2], Gustavo A. Borges Fernandes[2], João P. S. Fernandes[2], Vanina A. Medina[1].
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Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for the highest mortality rates among both men and women. The most common type of lung cancer is non-small cell car-