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# medicina

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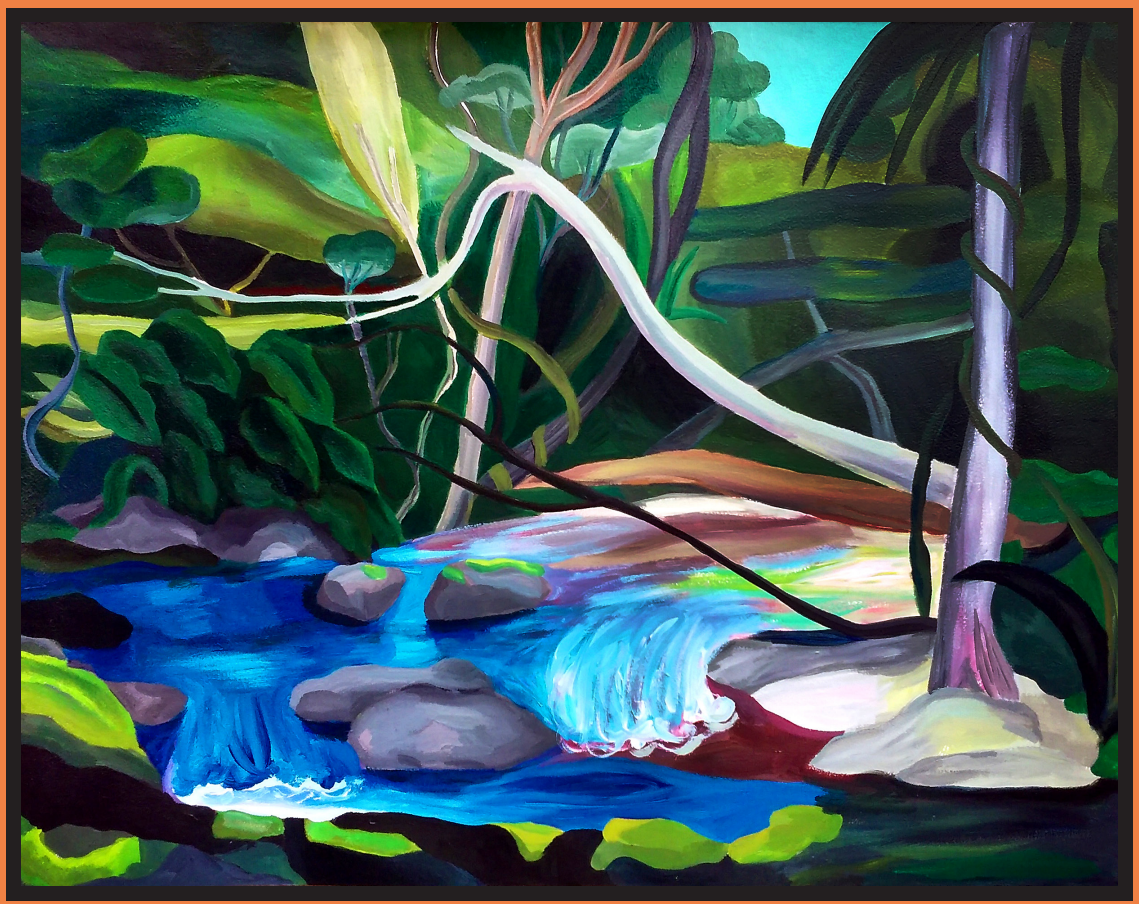

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# REUNIÓN CONJUNTA SAIC SAB AAFE AACYTAL 2023

**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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**STATIC ACTION BY A NOVEL CU(II) COMPLEX DERIVED FROM ACYLHYDRAZONE ON HUMAN OSTEOSARCOMA MODELS**

Lucía Santa Maria de la Parra[1], Adolfo I. B. Romo[2], Joaquin Rodriguez-Lopez[2], Gustavo A. Echeverría[3], Oscar E. Piro[3], Ignacio E. León[1,4].

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Osteosarcoma (OS) is a frequent bone cancer, affecting largely children and young adults. Cisplatin (CDDP) has been efficacious in the treatment of different cancer such as OS but the development of chemoresistance and important side effects leading to therapeutic failure. Novel therapies including copper compounds have shown to be potentially effective as anticancer drugs and one alternative to usually employed platinum compounds. The aim of this work is to evaluate the antitumoral activity of a novel copper(II) compound with a acylhidrazone in 2D (monolayer) and 3D (multicellular spheroids) OS models. Using MTT assay we demonstrated that the complex significantly reduced the cell viability in MG-63 $IC_{50}$: 1,09±0,06$\mu$M and in non-tumoral mouse fibroblast L929 $IC_{50}$: 2,52±0,02$\mu$M ($p<0.0001$), showing that Cu complex has selectivity index value of 2.3 compared to CDDP(SI = 0.3). In addition, we observed that interact with calf thymus DNA (CT-DNA) suggesting that the complex binds to DNA in an intercalative manner. Reactive oxygen species (ROS) generation was determined by oxidation of fluorescence dye DHR-123, evidenced that the complex caused an increment in ROS production after 3 h in a dose-manner response between 10$\mu$M and 25$\mu$M ($p<0.01$). Flow cytometry studies demonstrated that the compound inhibits cell proliferation and conveys cells to early apoptosis at 0.5$\mu$M (26.6%) and late apoptosis 1.25$\mu$M (15.1%) ($p<0.0001$). On the other hand, MG-63 spheroids were cultured by the hanging drop technique and the effect of the compound on cell viability was evaluated by resazurin reduction assay ($IC_{50}$:16.3±3.1$\mu$M) showing that $IC_{50}$ value was 4 times lower than CDDP (65±6$\mu$M) ($p<0.0001$). Finally, the compound reduced the spheroid cell migration in a dose-dependent manner from 7,5 to 20 $\mu$M suggesting a dual anticancer and antimetastatic actions. In summary, this copper complex displays a promising dual anticancer and antimetastatic action on OS 2D and 3D.

**337.** 406. **PALBOCICLIB RESPONSIVENESS OF THE MPA-INDUCED MURINE BREAST CANCER MODEL WITH DIFFERENT SENSITIVITY TO ENDOCRINE TREATMENTS**

Gabriela Pataccini[1], Andrés Elia[1], Martin Abba[3], Claudia Lanari[1], Sebastián Giulianelli[2]

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Luminal breast carcinomas represent more than 70% of all breast cancer (BC) patients. Palbociclib (PALBO), an oral CDK 4/6 inhibitor, is currently used in combination with endocrine therapy to treat advanced hormone receptor-positive, HER2-negative BC. However, about 25-35% of patients do not respond, and almost all patients, eventually, become resistant to this treatment. We have demonstrated that two tumor families from the MPA-induced BC murine model have a differential response to PALBO, regardless their response to an antiprogestin treatment (mifepristone, MFP), being the 59 family sensitive and the C4 family resistant to PALBO. The aim of the study was to evaluate the basal pRB expression, its regulation upon PALBO treatment and the transcriptome difference in both families that may shed light to understand their differential response to PALBO. RB phosphorylation levels were evaluated by IHC in 59-2-HI, 59-HI, C4-HI and C4-2-HI tumors after approximately 15 days of vehicle or PALBO treatment. RNA-Seq studies were carried out using RNA from untreated tumors. The differential expression and enrichment analysis were conducted with R/Bioconducter packages. As expected, pRB expression in the 59 tumors decreased after PALBO treatment ($p<0.001$). Contrarily, pRB levels increased after treatment in the PALBO-resistant tumors ($p<0.05$). In the latter, the basal pRB levels were lower than in the PALBO sensitive tumors. MFP was able to diminish pRB in C4-HI tumor, showing that the pRB axis is feasible of modulation. Preliminary analysis of RNA-Seq data highlights a down regulation of p18 (Cdkn2c; $p<0.05$) and an increase in Notch1 ($p<0.01$), in the PALBO resistant variants. Sensitive tumors show increases in pathways related with cell proliferation, such as S phase. We conclude that this model provides an excellent tool to dissect mechanisms related to PALBO resistance and to further investigate the link between p18, Notch 1 and RB phosphorylation mediating this effect.

**338.** 431. **HO-1 GENETIC VARIANTS AND ITS EFFECTS IN THYROID CANCER BIOLOGY**

Exequiel G. Alonso[1], Marilina Mascaró [1], Karen Schweitzer [1], Lucía Fernández Chávez[1], Georgina P. Coló[1], Eliana N. Alonso[1], María J. Ferronato[1], María E. Fermento[1], Cinthia Rosemblit[2], Alejandro C. Curino[1], María Marta Facchinetti[1].

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In previous studies on human thyroid cancer (TC), we observed elevated levels of hemeoxygenase-1 (HO-1) protein in both cytoplasmic and nuclear compartments. Additionally, increased HO-1 mRNA expression correlated with tumor progression. Activation of HO-1 through hemin treatment in the TPC-1 cell line promoted cell viability, proliferation, migration, and cell cycle progression, while inhibition via ZnPP had opposite effects. This study aimed to investigate the impact of genetically overexpressed HO-1 variants (full-length - FL, enzymatically inactive - H25A, and nuclear truncated - t-HO1) on cancer-related processes. Using stable transfections of these variants into TPC-1 cells, we observed that FL and H25A forms were predominantly overexpressed in the cytoplasm, while t-HO-1 accumulated in the nucleus. Overexpression of FL and t-HO-1 significantly enhanced cell viability ($p<0.0001$) and migration ($p<0.0001$) compared to controls. In contrast, H25A overexpression hindered these processes ($p<0.0001$) compared to FL. In primary cultures of human thyroid tumors and normal tissues, we identified HO-1 expression in the nuclei of normal cells and in nuclei/cytoplasm in tumor cells. Hemin treatment increased viability ($p<0.0001$) in tumor cells but decreased it in normal cells ($p<0.0001$). These findings correlate with prior evidence, demonstrating that hemin activation of HO-1 in tumor cells, through its enzymatic activity, exerts a protumor role. The current study revealed that FL and t-HO-1 variants independently promoted tumor-related processes, irrespective of subcellular localization. Notably, FL- impact on viability and migration seems tied to its enzymatic activity, as the H25A mutation impairs these effects. Intriguingly, nuclear HO-1 expression might differentially affect normal and tumor thyroid cells. Subsequent experiments will shed light on the relationship between HO-1's subcellular localization, enzymatic activity, and thyroid cancer progression.

**339.** 573. **NUCLEAR HO-1 INTERACTORS MIGHT DEFINE A NEUROENDOCRINE SIGNATURE IN PROSTATE CANCER**

Rocio Seniuk[1,2], Pablo Sanchis[1,2], Juan Bizzotto[1,2], Estefania Labanca[5], Nicolas Anslemino[5], Sofia Lage-Vickers[1,2], Gastón Pascual[1,2], Agustina Sabater[1,2,3], María Laura Lacreu[1,2], Julia Lechuga[1], Nora Navone[5], Elba Vazquez[1 2], Javier Cotignola[1,2], Pia Valacco[1,2,4], Ayelén Toro[1,2], Geraldine Gueron[1,2]