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REUNIÓN CONJUNTA SAIC SAI&FAIC SAFIS 2022

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

LXX REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INMUNOLOGÍA (SAI) & 3ER CONGRESO FRANCO-ARGENTINO DE INMUNOLOGÍA (FAIC)

REUNIÓN ANUAL 2022 DE LA SOCIEDAD ARGENTINA DE FISIOLOGÍA (SAFIS)

16-19 de noviembre de 2022
Hotel 13 de Julio – Mar del Plata

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and molecular dynamics simulations, suggest a cooperative binding mode to VDR of UVB1 and PTX, which in turn elicits a close regulation of the conformational behaviour of the activating factor 2 (AF-2) region of VDR. The combination of UVB1 and PTX strongly favours the AF-2 conformation that resembles the one observed for the natural substrate calcitriol. Altogether, these results suggest the potential combination of a calcitriol analogue with lower doses of conventional chemotherapeutics for aggressive BC treatment.

598. (784) **AQUEOUS EXTRACT OF THE ARGENTINEAN NATIVE PLANT *PROSOPIS CALDENIA* (CALDÉN) INDUCES CYTOTOXIC EFFECTS AGAINST TRIPLE-NEGATIVE BREAST CANCER CELLS**

María Julia Ferronato[1,2], Ana Paula Pedersoli[1], Eliana Noelia Alonso[1,2], Agustina Ibarra[1], Agustina Gutierrez[2,3], Pablo Marinangeli[3,4], Valentina Clemente[1], Georgina Pamela Coló[1,2], María Eugenia Fermento[1,2], Alejandro Carlos Curino[1,2], María Marta Facchinetti[1,2]

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Plant-originated drugs/formulations are employed as a complementary therapy for treating various human ailments including cancer. Recently, native species from Argentina belonging to genus *Prosopis* have begun to be studied for their beneficial biomedical properties. *Prosopis caldenia* (Pc) is locally known as “Caldén” and it has not been studied from a medicinal point of view. The aim of this work was to investigate the antitumor potential of Pc leaves aqueous extract (PcAE) against MDA-MB-231 and 4T1 Triple Negative Breast Cancer (TNBC) cells. To this end, cell viability was studied by colorimetric crystal violet and MTT assays in cells treated with vehicle or PcAE (10-100-1000-2500-5000 ug/ml). Cell cycle was analysed by flow cytometry in cells stained with propidium iodide. Cell migration was assessed by “wound closure” assays. The results show that PcAE reduced cell viability in a concentration-dependent manner in both cell lines at 48 and 72 hours (h) of treatment ($p<0.001$). Cell cycle analysis demonstrate that PcAE (1000 ug/ml) arrested 4T1 cells at S-phase (48 h: PcAE 49.51 ± 0.24 vs. vehicle 35.92 ± 0.67 %; $p<0.001$ - 72 h: PcAE 41.83 ± 2.55 vs. vehicle 32.75 ± 2.77 %; $p<0.05$). In MDA-MB-231 cells, PcAE (1000 ug/ml) induced S-phase arrest at 48 h (PcAE 43.62 ± 1.15 vs. vehicle 37.19 ± 0.41 %; $p<0.001$) and increased the percentage of cells in sub-G0 population at 72 h of treatment (PcAE 3.78 ± 0.25 vs. vehicle 2.16 ± 0.12 %; $p<0.01$). Regarding cell migration, PcAE decreased the migratory capacity of MDA-MB-231 cells (1000 ug/ml, 16 h, $p<0.001$). These results show, for the first time, the antitumor effects of the active principles present in an aqueous extract of Caldén leaves on TNBC cells. This study highlights the importance of the native species of our country as a potential resource of metabolites with therapeutic implications in cancer.

599. (813) **HEMOXYGENASE-1 GENETIC VARIANTS EFFECTS ON BREAST CANCER PROGRESSION**

Schweitzer Karen, Alonso Exequiel Gonzalo, Mascaró Marilina, Fernández Chávez Lucia, Coló Georgina Pamela, Alonso Eliana Noelia, Ferronato María Julia, Fermento Eugenia, Curino Alejandro Carlos and Facchinetti María Marta.

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Hemoxygenase-1 (HO-1) is a microsomal enzyme that catalyzes the degradation of the heme group, and its C-terminal truncated form can translocate to the nucleus and perform functions at the transcriptional level. Our laboratory has already shown that HO-1 has antitumoral effects in breast cancer. We have additionally confirmed that the HO-1 truncated form is not enzymatically active. The aim of this work was to study the effect of genetic overexpression of HO-1 variants (full-length form (FL), full-length form without enzymatic activity (H25A) and nuclear truncated form (T-HO1)) on cellular processes related to cancer development, and also the molecular mechanisms through which HO-1 would modulate the cellular processes investigated. To accomplish this goal, we used T47D human breast cancer cell line that was stably transfected with plasmids overexpressing HO-1 variants. To analyse cell behaviour between variants, we performed viability assays and flow cytometry, and to quantify differential protein expression we used immunofluorescence and western blot. We observed significant differences in cell viability between wild-type T47D cells and T47D cells overexpressing HO-1 variants. We found that the wild-type form is more proliferative than the FL-, H25A- and T-HO1-overexpressing forms ($p<0.05$, two-way ANOVA). We also observed that in H25A-overexpressing cells this behaviour results, in part, from an increase in cell death ($p<0.05$, two-way ANOVA). Finally, by immunofluorescence, we observed differences in the number of actin filopodia. So far, these results indicate that the overexpression of HO-1 FL seems to display an anti-tumor role. The behaviour of the H25A and the T-HO1 forms would indicate that the anti-tumor behaviour is the result of HO-1 enzymatic activity and its nuclear role. Future experiments will allow us to understand the role of the different pathways involved between HO-1 variants.

600. (846) **SYNERGISTIC COMBINATION OF PACLITAXEL WITH NOVEL NON-HYPERCALCEMIC CALCITRIOL ANALOG EM1 AGAINST TRIPLE-NEGATIVE BREAST CANCER CELLS: NEW MECHANISM OF ACTION**

Josefina Alejandra Guevara[1], Agustina Ibarra[1], María Julia Ferronato[1], Eliana Noelia Alonso[1], María Eugenia Fermento[1], Georgina Pamela Coló[1], Cristian Alejandro Vitale[2], Evangelina Mascaró[2], Mario Alfredo Quevedo[3], María Marta Facchinetti[1], Alejandro Carlos Curino[1].

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3 Unidad de Investigacion y Desarrollo en Tecnologia Farmaceutica (UNITEFA-CONICET), Facultad de Ciencias Quimicas, Ciudad Universitaria, Universidad Nacional de Cordoba, Cordoba, 5000, Argentina.

Triple-negative breast cancer (TNBC) is currently treated with cytotoxic drugs such as paclitaxel (PTX) since it lacks targeted therapies, although it shows limitations in extending patient survival. The known mechanism of action of PTX is binding to β-tubulin and inducing apoptosis. The vitamin D receptor (VDR) is expressed in different tissues, including TNBC. Calcitriol, its natural ligand, shows antitumor activity, but its usefulness is limited by the hypercalcemia it causes at antitumor doses. Reports suggest that PTX shows synergism when combined with calcitriol. The aim of this work is to combine PTX and non-hypercalcemic VDR analogs synthesized by our group, to study the potential synergism of the calcitriol analog EM1 with the cytotoxic PTX. EM1 in combination with PTX (EM1+PTX), showed a synergistic effect on the viability of 4T1 and MDAMB231 TNBC cell lines ($p<0.001$), CI<1. In contrast, EM1+PTX showed an antagonistic (protective) effect on non-tumor mammary HC11 cells ($p<0.001$), CI>1 (viability assays by crystal violet staining, Chou-Talalay method). In addition, (EM1+PTX) delayed the migration of 4T1 and MDAMB231 cells ($p<0.001$, wound closure assay). Interestingly, synergistic effects were lost when the Vitamin D Receptor (VDR) was silenced in 4T1 cells. Docking and molecular dynamics studies showed a direct interaction of PTX with the VDR by binding to the region near AF-2, stabilizing the active conformation between the VDR and its natural ligands. Cell cycle analysis by flow cytometry showed that the percentage of cells in the sub G0/G1 phase induced by PTX is higher in wild-type than in VDR-silenced cells. These results suggest that combining EM1 with current chemotherapy could increase

the therapeutic effect on the cancer cell and prevent cell damage on normal cells. This differential effect could decrease the adverse effects associated with chemotherapy, through a new mechanism of action never before described for PTX.

601. (879) **RELEVANCE OF NEUTROPHIL EXTRACELLULAR TRAPS IN THE CONTEXT OF HER2+ BREAST CANCER TREATMENT**

Romina Karas[1], Marianela Abrigo[1], Ivana Tapia[1], Virginia Wolos[1], Elisa Bal de Kier Joffé[1,2], Miriam Diament[1], Gabriel Fiszman[1,2].

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Trastuzumab (Tz) and Trastuzumab-emtansine (T-DM1) are therapeutic monoclonal antibodies of choice for patients with HER2-overexpressing breast cancer tumors. However, some patients acquire resistance to these therapies. Tumor-associated neutrophils represent a heterogeneous cell population and their recruitment in the tumor environment may produce and release “neutrophils extracellular traps” (NETs). Although NETs are present in various tumors, their roles in tumor biology have not been clarified yet. Previously, we demonstrated that HER2+ BT-474 human breast cancer cells growing as tumor spheroids activate neutrophils promoting NETs formation, without affecting their growth after 72 hs of coculture.
The aim of this work was to study the role of NETs on Tz and T-DM1 treatment of BT-474 cells in 3D cultures. BT-474 spheroids (500-600um diameter) were incubated with 0.5 x 10^6 neutrophils from healthy donors and were treated with Tz 50ug/mL or with T-DM1 10ug/mL during a week. At the endpoint, spheroid volume was quantified, and viability was determined by trypan blue dye exclusion.
We observed that, while anti-HER2 treatments inhibited the growth and decreased the viability of tumor spheroids, the presence of NETs partially attenuated their cytotoxic effect. Changes in spheroid volumes after treatment were: Tz -9% vs NET-Tz +46.6% ($p<0.01$), T-DM1 +15.1% vs NET-T-DM1 +67% ($p<0.01$). Cell viability shown after treatment (relative to IgG-treated control spheroids) was: Tz 89.7% vs NET-Tz 114.7 ($p<0.05$), T-DM1 26.9% vs NET-T-DM1 229.6% ($p<0.001$). In summary, NETs could be attenuating Tz and T-DM1 cytotoxic effect by inhibiting drug diffusion. Further studies may help to better understand some of the microenvironment roles behind the acquisition of drug resistance in HER2+ breast cancer.

602. (901) **MICROBIOME RELEVANCE IN TUMOR TISSUE OF EARLY BREAST CANCER PATIENTS**

Leonardo Dandeu[1*], Pablo Aguilera[2*], Sofía Sidlik[1], Alberto Penas-Steinhardt[2], Pablo Marenco[3], Martín Vázquez[4], María del Pilar Carballo[3], María Fernanda Alsina[3], Norma A Chasseing[1], Vivian Labovsky[1].

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Some microbes are known to be damaging to human health. Breast microbiome composition are poorly understood. In order to study the prognostic relevance of the microbiome in the evolution of early breast cancer, a study was carried out including samples of frozen breast tumor tissues from women with invasive ductal breast carcinoma, clinicopathological stages I/II with a 5-year follow-up minimum (*Hospital Roffo*, n=22). Samples were processed and DNA was extracted using the QIAamp-DNA-Mini-Kit. The bacterial profile was identified studying the region of the 16S rRNA gene using the Illumina Miseq platform. OTUs classification and Alpha and Beta diversity analysis were performed to study their possible associations with the classic parameters of breast cancer and tumoral progression. In this way, taxonomic analysis of these samples indicates that *Proteobacteria* (44.20%) and *Firmicutes* (23.22%) are the most representative phylum followed by *Actinobacteriota* (11.00%) and *Bacteroidota* (9.44%). Difference in microbial abundances (evenness index) has been found between patients with positive sentinel node and negative sentinel node ($p=0.05$) and patients with positive progesterone receptor (PR+) and (PR-) $p=0.02$. Moreover, diversity and richness metabolic pathways were found between patients PR(+) and PR(-) (Shannon index $p=0.03$) and Ki67 marker (Chao1 index=0.02).To conclude, our results provided insight into the possible relationship between difference abundance of certain bacteria, as well as difference richness and diversity of metabolic pathways with the classical prognostic parameters: sentinel node, PR, and ki67. These results open up new paths to study the relevance of the host microbiome with the progression of early breast cancer.

ONCOLOGY VIII *Saturday, November 19, 14-15:30 hr*

Chairs: Hernán Farina - Laura Todaro - Andrea Loaiza Pérez - Patricia Pennisi

603. (17) **PTHrP/MET AXIS IN THE AGGRESSIVE BEHAVIOR OF COLORECTAL CANCER CELLS**

María Belén Novoa Díaz[1], Cintia Birkenstok[2], Pedro Carriere[1], Luis Gomez[2,3,4], Graciela Gigola[1], Ariel Zwenger[5], Natalia Calvo[1], Claudia Gentili[1]

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Met receptor is involved in the progression of colorectal cancer (CRC). Parathyroid hormone-related peptide (PTHrP) is a cytokine from the tumor and its microenvironment associated with the aggressiveness of different types of cancer. Previously, we found in HCT116 cells from CRC that the binding of PTHrP to its receptor (PTHR1) favors chemoresistance to drugs employed in CRC treatment and other events associated with an aggressive phenotype. PTHrP diminished the sensitivity of these drugs through Met. In HCT116 cells xenografts, PTHrP modulates markers expression linked to tumor progression including Met. The aim of this work is to further investigate the relationship between PTHR1, PTHrP and Met in CRC models. Using SU11274, the Met specific inhibitor, and the following techniques: western blot, wound healing assay and monitoring morphological changes we observed the reversal of cell migration ($p<0.05$) and the epithelial-mesenchymal transition (EMT) program ($p<0.01$) induced by PTHrP in HCT116 cells. Also, the effects of the cytokine on the expression of E-cadherin and Snail (both EMT markers) were reverted when the cells were pre-incubated with SU11274. These findings strongly suggest that Met activated by PTHrP participates in events associated to the CRC aggressive phenotype. Interestingly, we found *in vivo* and by immunohistochemical (IHQ) analysis that PTHrP not only enhances Met expression but also its own receptor ($p<0.01$). Finally, by IHQ, we proceeded to perform an observational analysis of human samples to validate the findings obtained by *in vitro* and *in vivo* assays. No correlation was found between the expressions of both receptors (Met and PTHR1) in the tumor samples. However, we found with statistical significance that in less differentiated tumors, Met expression increased ($P = 0.035$), while PTHR1 expression was lower ($P = 0.0496$). In conclusion, we consider that PTHrP/Met axis could have a positive impact on the knowledge of CRC biology.

604. (49) **MIGRATION AND INVASION AS CAPACITATING ABILITES FOR OSTEOSARCOMA METASTATIC SUCCESS: PARENCHYMA AND STROMA INTERTWINED**

Matías Valenzuela Alvarez[1], Luciana M. Gutierrez[1], Juan Bayo[2], María José Cantero[2], Mariana Garcia[2], Marcela F. Bolontrade[1]

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