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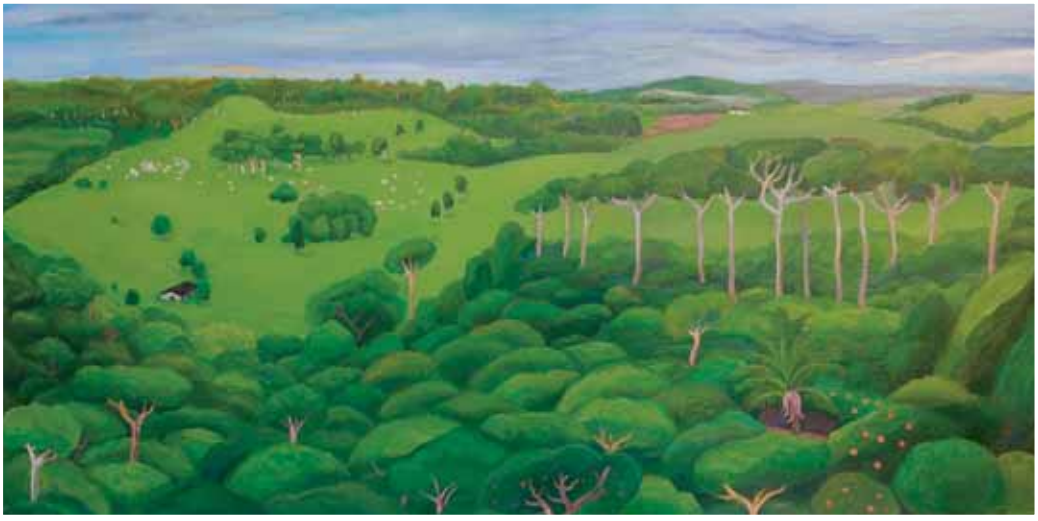

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Volumen 78, Supl. III, págs. 1-273

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MEDICINA (Buenos Aires) – Revista bimestral – ISSN 0025-7680 (Impresa) – ISSN 1669-9106 (En línea)

REVISTA BIMESTRAL
Registro de la Propiedad Intelectual N° 5350968
Personería Jurídica N° C-7497
Publicación de la Fundación Revista Medicina (Buenos Aires)
Propietario de la publicación: Fundación Revista Medicina
Queda hecho el depósito que establece la Ley 11723

Publicada con el apoyo del Ministerio de Ciencia, Tecnología e Innovación Productiva.
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e-mail: revmedbuenosaires@gmail.com – http//: www.medicinabuenosaires.com

Vol. 78, Supl.III, Noviembre 2018

Edición realizada por
Diseño y Diagramación: Andrés Esteban Zapata - aez.sgi@gmail.com - 11 5509 2767
Impreso en PQC - Berón de Astrada 2064 - C.A.B.A. - 4919 1702

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BUENOS AIRES, VOL 78 Supl. III - 2018

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32. (220) **ANTITUMOR EFFECTS OF THE VITAMIN D ANALOGUES UVB1 AND EM1 ON BREAST CANCER PATIENT DERIVED XENOGRAFTS**

María Julia Ferronato[1], Mercedes Nadal Serrano[2], Joaquín Arribas[2], Cristina Bernadó Morales[2], Enrique Javier Arenas Lahuerta[2], Yagamare Fall[3], Evangelina Mascaró[4], Cristian Vitale[4], Josefina Guevara[1], Agustina Ibarra[1], Alejandro Carlos Curino[1], María Marta Facchinetti[1]

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Despite advances in the treatment of HER2 positive and Triple Negative (TN) Breast Cancer (BC), mortality remains high due to intrinsic or acquired resistance to therapy. Therefore, new candidates to treat these subtypes of tumors are needed. Patient-Derived Xenografts (PDX) generated from recent tumor samples recapitulate the diversity of breast cancer being a powerful preclinical tool for testing new drugs. Previously, the Vitamin D analogues UVB1 and EM1 have demonstrated antitumoral effects in preclinical studies employing cell lines and animal models. Hence, the aim of the present study was to evaluate the antineoplastic effects of UVB1 and EM1 on cells derived from HER2-positive and TNBC- PDXs. The results showed that the analogue UVB1 reduced cell viability of the skin metastatic HER2-positive BC PDX118 and its Trastuzumab-emtansine PDX118 resistant cells (crystal violet assays, $p<0.001$). Also, both analogues decreased the viability of the brain metastatic HER2-positive BC PDX554 (UVB1: $p<0.001$, EM1: $p<0.01$). The cell cycle analysis of PDX118 cells treated with UVB1 and stained with propidium iodide showed an induction of cell cycle arrest in GO/G1 phase ($p<0.001$). In accordance with this result, UVB1 decreased Cyclin D1 expression in these cells by western blot. Regarding TNBC-PDXs, UVB1 and EM1 reduced the viability of cells derived from the primary tumors PDX410, PDX575 and PDX549. And, UVB1 also decreased the viability of TNBC-PDXs: PDX570 ($p<0.05$), PDX347 ($p<0.001$) and PDX454 ($p<0.01$). Finally, the combination of UVB1 and an Antibody Drug Conjugate (ADC) displayed a better effect than ADC treatment alone in PDX410, PDX570 and PDX575 ($p<0.001$). Altogether, these results suggest the potential use of these vitamin D analogues as antitumor agents to treat HER2 positive and TNBC.

33. (221) **PRECLINICAL STUDIES OF THE COMBINATION OF EM1 CALCITRIOL ANALOGUE WITH PACLITAXEL IN TNBC**

Josefina Guevara, Agustina Ibarra, María Julia Ferronato, Eliana Alonso, Norberto Ariel Gandini, María Eugenia Fermento, Georgina Pamela Coló, Marilina Mascaró, Silvina Grioli, María Marta Facchinetti, Alejandro Carlos Curino

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Triple negative breast cancer (TNBC) does not respond to current targeted therapies as it lacks the expression of hormone receptors and epidermal growth factor receptor HER2. Therefore, current treatment options include cytotoxic drugs such as taxanes, which are limited in terms of extending patient survival or improving patient's quality of life. The vitamin D receptor is a nuclear transcription factor whose natural ligand, calcitriol, has antitumor activity. Unfortunately, calcitriol anticancer utility is limited by its hypercalcemic effects and thus, vitamin D analogues are being developed to try to solve this problem. We hypothesize that the analogue of calcitriol, EM1, has synergistic effect with Paclitaxel in TNBC without exerting additional toxicity. This would allow to use lower doses of cytotoxic chemotherapy, with the consequent reduction of adverse effects. Also, this combination could minimize or slow the development of resistance to chemotherapeutic agents. We first studied the activity of EM1 on cell count and observed that EM1 strongly decreases the viability of the 4T1 TNBC murine cell line ($p<0.001$), while not affecting significantly that of MDA-MB-231 cells. In addition, EM1 was able to retard 4T1 cell migration in the wound healing assay ($p<0.001$) and to inhibit the invasion through Matrigel ($p<0.001$). The subsequent combination assays showed that EM1 and Paclitaxel did not display antagonistic effects in the cell count of the MDA-MB-231 cells. In addition, a pilot experiment of syngeneic transplantation of 4T1 cells in Balb/C mice showed that mice did not develop hypercalcemia or other signs of toxicity, following 30 days of EM1 treatment. Importantly, although no reduction in the growth of the primary tumor was observed, a significant decrease in the number of lung metastases ($p<0.0024$) was obtained. Altogether, these results suggest that EM1 could be an effective agent in combination with Paclitaxel in TNBC, by targeting the metastatic process.

34. (266) **ANTICANCER MECHANISMS OF CALCITRIOL AND MENADIONE ON BREAST CANCER CELLS**

Solange Guizzardi, Gabriela Picotto, Valeria Rodriguez, Luciana Paola Bohl, Nori Tolosa de Talamoni

Biochemistry and Molecular Biology, INICSA (CONICET-UNC), Argentina, *CIT (VILLA MARIA- CONICET)*

Calcitriol (D), the active form derived from vitamin D3, presents antineoplastic properties in several types of cancer. However, its use as an antitumoral agent may promote secondary effects. We have demonstrated that menadione (MEN) potentiates the antiproliferative effect of D on breast cancer MCF-7 cells, at least in part, by cell cycle alteration and increasing intracellular calcium and ROS and NOS production, although the mechanisms are still under study. Our working hypothesis was that the combined treatment of D and MEN could increase the antitumoral effect of D, mainly via activation of autophagy and reduction of the migration of the MCF-7 cells. The aim of the present study was to investigate further the mechanisms involved in the antiproliferative action of the combined treatment. MCF-7 cells were treated with 100 nM D, 10 μM MEN, both or vehicle (96 h). Gene and protein expression of PMCA1b were measured by qRT-PCR and western blot, respectively. Induction of autophagy was evaluated through detection of acidic vesicular organelles (AVOs) by fluorescence microscopy and the protein expression of LC3II by western blot. Cell migration was estimated by the wound healing assay. Statistical analyses were performed by ANOVA/Bonferroni. Differences were considered significant at $p<0.05$. Both D and combined treatments diminished the gene expression of PMCA1b. However, its protein expression was increased with MEN+D. Drug combination enhanced the formation of AVOs and modified LC3II protein expression. In addition, MEN plus D treatment decreased wound closing. In conclusion, MEN increases the anticancer effect of D on MCF-7 cells partly due to changes in the expression of PMCA1b, a molecule closely related to calcium regulation and thus modifying its intracellular concentration, as we previously reported. Increased AVOs formation and LC3II expression changes suggest the activation of autophagy. The combined treatment also decreased the capacity of the cells to migrate.

35. (105) **MUSCARINIC RECEPTORS AS THERAPEUTIC TARGETS IN TRIPLE NEGATIVE BREAST CANCER TREATMENT. PACLITAXEL PLUS CARBACHOL ADMINISTERED IN A METRONOMIC SCHEDULE.**

Yamila Sanchez, Agustina Salem, María Elena Sales, Alejandro Español

CEFYBO-CONICET-UBA

We have demonstrated that the long term activation of muscarinic receptors (MR) decreases tumor cell viability pointing to MR as possible therapeutic targets in breast cancer. Metronomic therapy consists in the administration of low doses of cytotoxic drugs, alone or combined with repositioning drugs with short intervals inter-doses.