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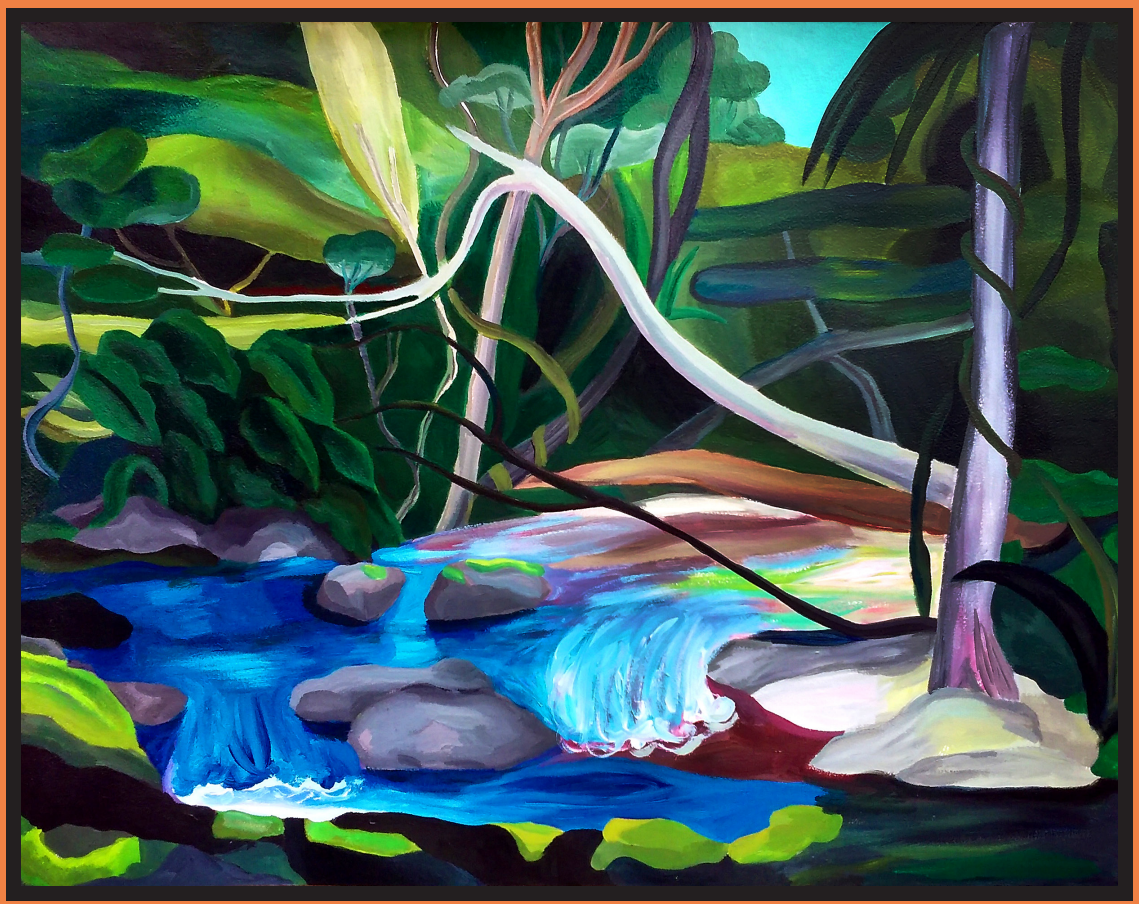

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LXVIII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)

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
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rotransmitters released by stimulated nerves. Then, synaptic vesicles were described with the electron microscope help and, in this field, a young Zieher began his career. In his first works, around 1963, he demonstrated that axonal vesicles from rat hypothalamus were the source of the observed norepinephrine high concentration. And then, together with Jaim Etcheverry, he proposed thecotransmission concept. This was contrary to the prevailing idea at that time, proposed by Henry Dale, "a neuron, a neurotransmitter". Conclusion: Seen today NT is a complex, robust and versatile concept, but it should not be forgotten that the human species development and its culture has depended, depends and will depend on the brain cells communication. We owe a small part of this knowledge to Luis María Zieher.

417. 625. **EXPLORING SEROTONIN-GATED ION CHANNELS THROUGH REPURPOSING STRATEGIES**

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A drug repurposing strategy that considers the chemical structure and molecular action on serotonergic Cys-loop receptors offers valuable guidance for the rational reuse of existing drugs, thereby reducing the time and costs associated with developing new medications. We focused on nematode and vertebrate 5-HT-gated ion channels and tested several drugs in clinical use using electrophysiological techniques. In nematodes, a unique serotonin-activated chloride channel, MOD-1, is emerging as a new target for antiparasitic drugs. In humans, 5-HT3A is involved in emesis and is an important player in the enteric nervous system. We previously demonstrated that tryptamine and its derivatives could be good candidates for anthelmintic therapy, acting on the serotonin MOD-1 receptor. We found that sumatriptan and eletriptan, from the triptan family, inhibit 5-HT-induced currents of MOD-1 receptor in a concentration-dependent manner. By using the nematode *Caenorhabditis elegans*, we revealed the anthelmintic actions of sumatriptan and eletriptan at the behavioral level. Our locomotor activity assays showed that both drugs produced a decrease in worms' activity, with eletriptan being more potent than sumatriptan. Mutants lacking MOD-1 were partially resistant to both drugs. Also, we revealed novel aspects of MOD-1 function from the molecular level to the organism level, which may contribute to provide new directions for anthelmintic drug discovery and drug repurposing. By electrophysiology techniques we revealed that the anthelmintic piperazine (PZE), which acts at nematode GABA and MOD-1 receptors, decreased human 5-HT3A macroscopic currents elicited by 5-HT. The analysis showed that PZE acts as a negative allosteric modulator; thus PZE or its derivatives may be explored as promising therapeutic tools that may replace classical orthosteric antagonists. Our drug repurposing strategy contributes to identify new targets and potential uses of drugs on a rational basis.

418. 642. **OBTAINING AND MOLECULAR CHARACTERIZATION OF IONIC COMPLEXES WITH SODIUM PHENYLBUTYRATE AND PHENYLBUTYRIC ACID AS A STRATEGY FOR ALLEVIATING AVERSION IN THE TREATMENT OF UREA CYCLE DISORDERS**

Fiama Georgina Bolatti[1], Laura Carolina Luciani-Giacobbe[1], María Eugenia Olivera[1*]

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Sodium phenylbutyrate (SPB), employed for the treatment of urea cycle disorders, exhibits an aversive flavor that undermines treatment adherence. Eudragit EPO (EuE), a cationic polyelectrolyte, can interact with acidic drugs, typically necessitating the incorporation of inorganic counterions to enhance compatibility. The formation of EuE-SPB or EuE-PBA (phenylbutyric acid) complexes emerges as a viable strategy to ameliorate the disagreeable taste, while conferring minimal risk of perturbing the oral absorption profile due to its aptitude to limit release under salivary conditions, which dissipate at pH<5. The objective of this study involves the identification of complexation conditions and molecular characterization thereof. SPB or PBA were interposed with EuE dissolved in ethanol (1 ml/g) at EuE:SPB or PBA ratios of 1:0.5, 1:0.75, 1:1, and 1:1.25, both with and without pre-neutralization using 0.25 HCl. Subsequent to desiccation, materials were subjected to FTIR spectroscopy and thermal analyses (DSC/TGA and hot stage microscopy), utilizing precursors and physical mixtures as references. EuE-PBA spontaneously forms a semisolid material of intricate manipulability at all assessed ratios. Ionic interactions between the dimethylamino groups of EuE and the carboxylic acids of PBA, alongside hydrophobic interactions within lipophilic domains of both substances, were established. Thermal evaluation elucidated a reduction in glass transition temperature with absence of PBA fusion, coupled with no discernible weight loss, implying a loading capacity exceeding 100%. The products were anhydrous, and HCl pre-neutralization can be avoided since it did not induce differences in the evaluated properties. Characterization of EuE-SPB yielded akin outcomes, albeit yielding a manageable solid product with a loading capacity ≤ 50%. EuE-SPB or PBA complexes emerge as prospective candidates for the development of solid oral formulations possessing enhanced organoleptic attributes.

419. 669. **HEPG-2 SPHEROIDS AS A MODEL OF RESISTANT HEPATOCELLULAR CARCINOMA TO STUDY ABC TRANSPORTERS INHIBITORS FOR REVERSION OF MDR**

Andreina Quevedo[1], Natalia Poznanski[1,2], Daniel Zappia[1,3], Roxana Peroni[1,2].

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Hepatocellular carcinoma (HCC) is the most common form of liver cancer, that in turn is the third leading cause of cancer-related mortality. Chemotherapy is the first-choice treatment, but ABC transporter over-expression (MDR) in tumoral cells frequently leads to treatment failure. Since 2D culture drug screening assays had shown poor extrapolation to the clinic, it is crucial to generate MDR models with high prognostic value. Objectives: To evaluate 3D spheroids as models of MDR in hepatocellular carcinoma. Methods: HepG-2 cells were cultured in DMEM with 10% FBS, 100U/mL penicillin/streptomycin at 5%CO_2-95%O_2, 37°C. To form spheroids, cells were seeded onto agar-coated plates (3000 cells/well) for 5 days, monolayers were tested at 70/80% confluence. The induction of ABC transporters was generated by chemically induced hypoxia (100 uM $CoCl_2$ for 24/48 h) or by the presence of the cytostatic doxorubicin (0,1-10 uM; DOX). Viability was tested by the acid phosphatase assay and ABC transporters (BCRP and P-gp) expression was assayed by real-time PCR. Results: Treatment with $CoCl_2$ for 24 h reduced the viability of spheroids by 10% and the monolayer by 15%, but elevated levels of the hypoxia-inducible factor (HIF-1) messenger were selectively obtained in spheroids. DOX significantly reduced cell viability at 0.1uM in monolayer ($p<0.01$) and at 1uM in spheroids ($p<0.001$). Treatment with DOX for 24 hours induced the expression of BCRP and P-gp messengers in both conditions but it was significantly higher in spheroids ($p<0.05$). Conclusions: The spheroids showed a better ABC-related multidrug resistance phenotype compared to the monolayer culture. The present results allow us to suggest that HepG-2 spheroids are a cost-effective and simple, optimized model for the screening of ABC transporter inhibitors that could be used to reverse MDR in hepatocellular carcinoma.

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