

# medicina

BUENOS AIRES, VOL. 83 Supl. V - 2023



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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

**EDITORES RESPONSABLES**

Dra. Isabel Luthy  
Dra. Silvina Pérez Martínez  
Dr. Ventura Simonovich  
Dr. Gabriel Pinto

# **JOINT MEETING SAIC SAB AAFE AACYTAL 2023**

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ASOCIACIÓN ARGENTINA DE CIENCIA Y  
TECNOLOGÍA DE ANIMALES DE LABORATORIO  
(AACyTAL)**

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

**RESPONSIBLE EDITORS**  
Dra. Isabel Luthy  
Dra. Silvina Pérez Martínez  
Dr. Ventura Simonovich  
Dr. Gabriel Pinto

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FRIDAY 17TH NOVEMBER 9:00 - 10:30

CHAIRS: PINTO, GABRIEL BERNARDO

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GINEVRO, PAULA

**1. 156. COMPARATIVE EFFECTS OF KETAMINE/XYLAZINE AND KETAMINE/MEDETOMIDINE ANESTHESIA FOR OVARIECTOMY IN WISTAR RATS**Alejandro Maruri<sup>1</sup>, Florencia Santonja<sup>2</sup>, Ivana Villa<sup>2</sup>, Sandra Zárate<sup>2</sup>, Ernesto Gulín<sup>2</sup><sup>1</sup> ITECA, ECyT\_UNSAM, CONICET, San Martín, Buenos Aires, Argentina.<sup>2</sup> Instituto de Investigaciones Biomédicas (INBIOMED), Universidad de Buenos Aires (UBA), Facultad de Medicina – CONICET. Buenos Aires, Argentina.

Refinement involves modifications of husbandry or experimental procedures that minimize or eliminate animals' pain and distress and improve their welfare. Balanced anesthesia and analgesia promote refinement in surgical procedures. This study aims to compare ketamine 75 mg/kg + xylazine 10 mg/kg (KX) combination with ketamine 60 mg/kg + medetomidine 0.25 mg/kg (KM) in clinical monitoring and time-related anesthesia parameters for ovariectomy in Wistar rats. Protocol was approved by the Faculty of Medicine IACUC (RESCD-2022-3545). Twenty-four three-month-old female Wistar rats were submitted to ovariectomy by dorsal approach. The anesthetic combination was assigned randomly, and treatment was blinded for the anesthesiologists up to data analysis. The complete protocol included pre-surgical meloxicam (1 mg/kg; sc) and yohimbine (2.1 mg/kg; ip) when procedure finished. Thermal support and ophthalmic ointment were provided during surgery and recovery. After anesthesia administration, the animal was observed up to the loss-of-righting reflex (LRR) and the loss-of-pedal withdrawal reflex (PWR-). The PWR was tested until returned positive. Time points for consciousness and exploratory behavior recovery was also recorded. Intra-surgical rectal temperature, respiratory rate and cardiac frequency were recorded. The time to achieve LRR was not significantly different between anesthetic combinations, but PWR was significantly faster for KM than KX combination ( $p=0.0173$ ). Time to recover PWR, consciousness and exploratory behavior was significantly longer in rats receiving KM than those who received KX ( $p<0.05$ ). Clinical parameters did not significantly differ between treatments. One rat from each anesthesia protocol did not recover from the procedure. KM combination resulted in a safe anesthesia surgical plane at lower doses than classical KX protocol. Still, considering the prolonged recovery times, other dosage schemes should be explored until it becomes a superior anesthetic option for ovariectomy by dorsal approach in rats.

**2. 230. NUTRITIONAL IMPACT ANALYSIS: COMPARISON OF TWO NATIONAL DIETS IN WISTAR RATS TO REFINE NUTRITION AND OPTIMIZE THE NUMBER OF ANIMALS USED IN PRODUCTION STOCKS.**Mercedes Olivera<sup>1</sup>, Marianela Ceol Retamal<sup>1</sup>, Lourdes Lloret<sup>1</sup>, Andrea Pecile<sup>1</sup>, Solana Pesca Alba<sup>2</sup><sup>1</sup> Instituto de Biología Celular y Neurociencias Prof. E de Robertis. (UBA-CONICET)<sup>2</sup> FeedVax-Oral Vaccines

Objectives: Evaluate the impact of feeding on the variables weight, consumption and excreta, during growth in Wistar rats, with two

open formula diets and a mixture of both. To evaluate physical development, reproductive performance, digestibility and preference. Materials and methods: Male and female Wistar rats (outbred) were used, divided into three groups of 9 animals in each (5 males and 4 females).

Group 1 fed with diet C, 2 with diet G and 3 with the mixture of both diets 50/50. The composition of each diet was identified with the information provided by the supplier. A weight curve, the comparison of the consumption and amount of excreta was made from the 17th day of age, also a macroscopic analysis of feces morphology in animals 60 days onwards. The productive and reproductive characteristics of the females of each group from the 9th week of age were analyzed, and finally the food preference.

Conclusions: It was observed that composition is similar in both formulations, but with differences in the origin of the proteins: C uses cereals as the main protein source, while G uses animal protein. When analyzing the feces, it was observed that those belonging to diet C contained pieces of whole ingredients, indicating that it was not digested completely with a size of 0.5-0.8 mm. In the feces of diet G, a homogeneous consistency and color was observed, measuring 0.9-1.3 mm. There was 15% more excreta with diet C and 11% more with mixed diet over diet G. There was 25% more intake with diet c and 11% more with the mixture over diet G. Reproductive outcomes: Pregnancy - C: 66.6%, mixed: 78%, G: 88%. Productivity (pups/month/female) - C: 8, mixed: 10, G: 11. Litter size at birth - C: 12, mixed: 15, G: 17. Last pup rate - C: 8/9, mixed: 11/13, G: 13/14 months. Mortality rate at birth and weaning: C: 35%, G/mixed: 10%. The weight curves elaborated for each group showed differences among themselves. It was verified that the animals prefer diet G, over diet C and the mixture.

**3. 267. 3 RS APPROACHES FOR THE STUDY OF SIGNALING EVENTS TRIGGERED BY PESTICIDE INDUCED NEUROTOXICITY.**Melisa Conde<sup>1,2</sup>, Athina Maniscalchi<sup>1</sup>, Leticia Nicasio<sup>1</sup>, Oriana Benzi Juncos<sup>1,2</sup>, Melania Funk<sup>1</sup>, Natalia Alza<sup>1,3</sup>, Gabriela Salvador<sup>1,2</sup>.<sup>1</sup> Instituto de Investigaciones Bioquímicas de Bahía Blanca, Universidad Nacional del Sur (UNS), Consejo Nacional de Investigaciones Científicas y Técnicas. <sup>2</sup> Departamento de Biología, Bioquímica y Farmacia, UNS. <sup>3</sup> Departamento de Química, UNS

Maneb (MB), a dithiocarbamate pesticide, can cross the blood-brain barrier and is considered an environmental risk factor associated with Parkinsonism. Our aim was to characterize redox signaling during MB-induced neurotoxicity in different experimental models according to the 3Rs principle.

Taking into account full Replacement we firstly exposed neuronal cell line cultures to MB and we detected increased expression levels of the redox sensitive transcription factor Nrf2 and its regulator Sirt1. Neuronal MB exposure also triggered the increase of lipid peroxidation, GSH depletion, Gpx4 downregulation and mitochondrial alterations, indicating that ferroptosis is involved in the mechanism of cell death. We confirmed these results in a model of relative Replacement by using glial mixed primary cultures. We also demonstrate that Nrf2/Sirt1 signaling is a protective strategy against neurotoxicity. Based on these results and with the aim of evaluating phenotypical aspects for establishing a preclinical model, we design an experimental paradigm with C57BL/6 mice. Following Refinement criteria, treatments were performed with the supervision of a veterinarian who care the animal welfare during the entire procedure. C57BL/6 mice (18-20g) were intraperitoneally injected with MB (100 mg/kg) for 6 weeks. Behavioral tests (Open Field and Rotarod) were performed on week 3 and 6 of treatment. One day after the last administration, animals were sacrificed by cervical dislocation. Forebrain,

midbrain and hindbrain were separated for molecular determinations. To apply the Reduction criteria all other animal organs were used for related investigations. MB-treated animals showed a decrease in total distance travelled, supported and unsupported rears and in falling latency. These results indicate that MB neurotoxicity triggers a parkinsonian phenotype in C57BL/6. The results presented here constitute a platform for toxicological and preclinical studies according to 3Rs principles.

**4. 271. DEVELOPMENT OF THREE-DIMENSIONAL (3D) ENGINEERED TISSUE MODEL FOR IN VITRO STUDY OF HUMAN ENDOMETRIOSIS (EDT)**

del Valle Sofía<sup>1</sup>, Ruiz Ignacio<sup>2</sup>, Oppenheimer Florencia<sup>2</sup>, Leiros Gustavo<sup>2</sup>, Ricci Analía<sup>3</sup>, Meresman Gabriela<sup>1</sup>.

1.Laboratorio de Fisiopatología Endometrial, IBYME-CO-NICET; 2.Instituto de Ciencia y Tecnología César Milstein; 3.Instituto de Ciencia y Tecnología Dr. César Milstein (FPC-CONICET)

EDT is a gynecological disease characterized by the presence of endometrial tissue outside the uterine cavity affecting 10-15% of menstruating people. The available *in vitro* models for studying EDT are insufficient to clarify the complex epithelium-stroma interactions within tissues. Therefore, our aim was to develop and characterize 3D endometrial constructs that could be used as experimental models for studying this disease. We generated 3D constructs using type I collagen (5 mg/ml) as extracellular matrix, and genipin (120  $\mu$ M), a cross-linking reagent. First, 1x10<sup>6</sup> t-HESC endometrial stromal cells were embedded in the hydrogel, then 5x10<sup>5</sup> ECC-1 endometrial epithelial cells were seeded onto the collagen scaffold. They were incubated for 9 days at 37 °C with 5% CO<sub>2</sub> in DMEM-F12 medium. We examined how the construct's percentage of contraction changed depending on whether genipin was present or not, as well as how toxic it was using the LIVE/DEAD Viability/Cytotoxicity kit. We also performed histological analysis by using Periodic Acid-Schiff (PAS) and hematoxylin-eosin (H&E) staining and characterized the cellular organization by immunodetection of epithelial and stromal cells with cytokeratin and vimentin, respectively. 3D constructs without genipin formed glandular structures positive for cytokeratin which shared morphological similarities with endometrial tissue. These structures were also positive for PAS staining, suggesting active secretory activity. The stromal phenotype was confirmed with positive immunodetection for vimentin. Genipin did not cause cytotoxicity since cell viability was equivalent to basal (95%). Furthermore, it significantly reduced collagen contraction improving the mechanical handling of the constructs. H&E staining revealed the formation of a partially columnar continuous epithelium over the stroma. This innovative model will allow us to study the complex interactions of different cell types within a relevant biological microenvironment.

**5. 471. GENETIC CONTAMINATION IN A COLONY OF BALB/cJ AND THE REFRESH OF THE COLONY AS A CRITICAL POINT**

María Alfonsina Lizárraga, Diego Manuel Posik, Guillermo Giovambattista.

IGEVET - Institute of Veterinary Genetics "Eng. Fernando N. Dulout" (UNLP - CONICET LA PLATA). Faculty of Veterinary Sciences, National University of La Plata, Argentina

The genetic quality of laboratory animals is essential for the reproducibility of scientific research. There are many genetically defined lines of mice, such as inbred strains and congenic. These lines have important characteristics, such as genetic isogenicity, phenotypic uniformity, which is the axis of the reproducibility of the experiments. The control and preservation of the genetic quality of the laboratory animal should be a priority. The aim of this work was to evaluate the authenticity of mouse strain BALB/cJ from of colony from an experimental conventional animal care facility of the region and highlight the importance of genetic monitoring and show the consequences of an absence of refresh of the colony periodically. This strain BALB/cJ arrived at this animal care facility ground in the year

2000. Thereafter polygamous mating were made, until 2020. For twenty years a refresh of the colony of animals was not made. It is important to highlight that the periodicity of the colony refresh should be made from F5 to F10 generations, to have an optimal management of the colony. Microsatellite analysis by PCR is one of the most widely used methods in genetic quality controls of inbred lines. Tail samples (3-5mm) were taken from female (N=4), and genomic DNA was obtained by organic extraction. We analyzed 12 microsatellite loci that were located on twelve different autosomal chromosomes and polymorphic. Selected from the information database; www.informatics.jax.org. This panel allows the discrimination of the main strains present in Argentina: BALB/c, C3H/He and DBA/2J, C57BL/6J. The results showed evidence of genetic contamination with the positive control DBA/2J and C3H/HeJ strains; 10 of the 12 microsatellites analyzed were homozygous for the expected alleles and genotypes compatible with the positive control the BALB/cJ strain. On the contrary, the remaining two microsatellites presented the following genotypes: D2Mit493(97pb), compatible alleles for the DBA/2J strain and D12Mit12(164pb), for the C3H/HeJ strain. The results were reported to the experimental conventional animal care facility of the region, and based on this report the entire colony was renewed with new genetically controlled animals.

It is necessary to encourage routine genetic checks, every two years, to ensure that the results obtained are reproducible and have scientific validity and to encourage, technicians and professionals to continue training in the science of laboratory animals.

**6. 513. ASSESSMENT OF DEVELOPMENT AND REPRODUCTIVE TOXICOLOGY (DART): AN IN VITRO APPROACH**

Ernesto Gulin<sup>1</sup>, María Soledad Lorenzo<sup>1</sup>, Alejandro Maruri<sup>1</sup>, Pablo Torres<sup>2</sup>, Daniel Lombardo<sup>1</sup>

<sup>1</sup> Universidad de Buenos Aires (UBA), Facultad de Ciencias Veterinarias (FCV), Instituto de Investigación y Tecnología en Reproducción Animal (INITRA), Cátedra de Histología y Embriología. Buenos Aires, Argentina.

<sup>2</sup> Universidad de Buenos Aires (UBA), Facultad de Ciencias Veterinarias (FCV), Instituto de Investigación y Tecnología en Reproducción Animal (INITRA), Cátedra de Física Biológica. Buenos Aires, Argentina.

Reproductive toxicity can be studied by a holistic approach on experimental animals in extensive and expensive trials. However, using an integrated *in vitro* approach, the reproductive cycle can be split into its main biological components integrating results and providing comprehensive information on the potential effects of chemicals on gametes and embryonic development, decreasing the number of animal studies and providing a more detailed toxicological profile.

This work aims to introduce the setting up of an *in vitro* platform for DART testing, applying a battery of assays based on standardized reproductive biotechnologies. To evaluate the toxicity on male gametes, bovine spermatozoa were exposed to increasing concentrations of the test substance, studying viability with vital stains along with motility and velocity parameters assessed by computer-assisted sperm analysis (CASA). The bovine oocyte *in vitro* (bIVM) was applied to assess the effect of substances during oocyte maturation. Cumulus-oocyte complexes (COCs) obtained from ovaries of slaughter cows were selected and incubated in IVM medium with increasing compound concentrations. After 22 h, the viability and nuclear maturation were evaluated. The obtaining results allowed determining the concentration that reduced the IVM of oocytes by 50% compared to the untreated control. *In vitro* fertilization of bovine oocyte (bFIV) and early embryonic development were used as a model to evaluate the toxic effect of the fertilization process. Bovine gametes were co-incubated with increasing concentrations of the test substance. After 18 h, pronucleus formation was registered to determine the concentration that reduced the bFIV by 50% compared to the untreated control. This initial battery of *in vitro* models is part of developing a biotechnological platform for DART testing, promoting the technological cooperation between academia and industry partners within a 3Rs approach.