ABSTRACT BOOK
AAFE 2024

LVI REUNIÓN ANUAL DE LA ASOCIACIÓN ARGENTINA DE FARMACOLOGÍA EXPERIMENTAL

23-24 de octubre de 2024

UNIVERSIDAD NACIONAL DEL SUR

Bahía Blanca, Argentina

AAFE

Asociación Argentina de Farmacología Experimental
Abstract book AAFE 2024. - 1a ed - Bahía Blanca : Asociación Argentina de Farmacología Experimental - AAFE, 2024.
Libro digital, PDF

Archivo Digital: descarga y online
ISBN 978-631-90806-0-5

1. Farmacología. I. Título
CDD 615

INDEX

Comisión Directiva

Presidente
Ventura Simonovich

Vicepresidenta
Susana Gorzalczany

Secretaria
Guillermina Hernando

Prosecretaria
Natalia Alza

Tesorero
Jerónimo Laiolo

Protesorero
Santiago Zugbi

Vocales
Daniela Quinteros
Hugo Hector Ortega

Revisores de cuentas
Mariano Hector Nuñez
Paula Scibona

AAFE agradece el apoyo de:

Entidades oficiales

Organizadoras locales

Guillermina Hernando
Natalia Alza

Colaboradores locales

Juan Facundo Chrestia
Alcibeth Pulido Carrasquero
Carla Mayora Justel
Tamara Valladares
Melisa Conde
Leticia Cabral

Dirección de Comunicación Institucional UNS
por ceder la foto de la portada

PALABRAS DE BIENVENIDA DEL PRESIDENTE DE AAFE

Distinguidos colegas, autoridades, estudiantes y amigos de la farmacología:

Es para mí un inmenso honor darles la más cordial bienvenida a este nuevo Congreso número 56° de la Asociación Argentina de Farmacología Experimental. Reunidos aquí, en el corazón de la Universidad Nacional del Sur, donde todos los días es el espacio de intercambio científico y de conocimiento para alumnos, profesores e investigadores, celebramos la pasión por descubrir, innovar y mejorar a través de esta disciplina hermosa que es la farmacología.

Hoy estamos atravesando un proceso de cambio no solamente a nivel local, sino también regional y global en diferentes aspectos. El lado negativo es la falta de recursos, pero creo que siempre la restricción es el gran amigo de la creatividad.

Y es así que este congreso es posible gracias a la enorme creatividad de la comisión directiva de la AAFE y de la Universidad Nacional del Sur a la cual estamos enormemente agradecidos. En particular, quiero agradecer especialmente a Guillermina Hernando, Natalia Alza, Jerónimo Laiolo, Santiago Zugbi y Daniela Quinteros, sin su trabajo y empeño este congreso no habría sido posible.

El lado positivo es que hemos tenido que repensarnos de formas diferentes en términos de cómo encarar el financiamiento de la ciencia, así como también cómo podemos crear nuevos emprendimientos que puedan eventualmente ser capaces de ser invertidos y generar, no solo beneficios a la comunidad, sino también puestos de trabajo.

Me gusta pensar que una crisis es algo demasiado valiosa para dejarla pasar, y en la AAFE vimos está crisis actual como una ocasión para asociarnos a otros grupos que nos permiten pensar en modelos diferentes de trabajo. Nuestra asociación ya no es solo un grupo de investigadores que comparten una disciplina y se reúnen para un congreso, sino un espacio donde podemos ayudar a otros a crear valor con su investigación y así poder encontrar nuevos modelos de trabajo en conjunto con otros a los cuales si nos manteníamos en nuestro espacio quizás no hubiéramos alcanzado.

Soy optimista también en la proyección de nuestra Asociación en términos internacionales. Hemos logrado fortalecer nuestras relaciones con las Sociedad de Farmacología de Chile y la Sociedad Brasilera de Farmacología y Terapéutica, nuestro programa se ve enriquecido con disertaciones de miembros de ellas.

Tenemos dos días muy intensos, como si fuera una olimpiada donde un atleta trabaja años para poder competir minutos, veremos en las presentaciones y posters el trabajo de años resumido en pocos minutos. Les agradecemos hayan elegido venir a presentar los mismos aquí, y esperamos enriquecernos de ustedes.

Por último, creo que la interacción es uno de los puntos más lindos de nuestro congreso, ojalá puedan lograr no solamente disfrutarlo sino también se lleven una red enriquecida para poder seguir creando y resolviendo los problemas que la ciencia nos pone cada día delante.

Quiero agradecer nuevamente a las autoridades de la Universidad Nacional del Sur, a CONICET y a la Fundación Williams por el apoyo y soporte para la organización de este congreso.

¡Bienvenidos!

Dr. Ventura Simonovich
Presidente

CONFERENCIAS/LECTURES

CONFERENCE I - *Wednesday 23th October 10:45 – 11:45*
Chair: Hugo Ortega

THE FUTURE OF PHARMACOLOGY: FROM ARTIFICIAL INTELLIGENCE TO CELL THERAPIES

Ventura Simonovich
Clinical Pharmacology Section, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. Department of Research, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

The field of pharmacology is undergoing a transformative evolution, driven by advancements in technology and innovative therapeutic approaches. This dissertation explores the future of pharmacology by examining the interaction between pharmacologists and emerging trends, particularly artificial intelligence (AI), and advanced treatments including cell therapies. AI, with its advanced machine learning algorithms and predictive analytics, is poised to revolutionize how pharmacologists approach drug discovery, clinical trials, and personalized treatment regimens. By leveraging AI to analyze vast datasets, pharmacologists can identify novel drug candidates, predict therapeutic outcomes, and minimize adverse effects, thereby accelerating the development of new medications.
Simultaneously, cell therapies, including stem cell and CAR-T cell therapies, are set to redefine treatment paradigms for a wide range of diseases, from cancer to genetic disorders. These therapies offer targeted, personalized interventions that address diseases at the cellular level, promising enhanced efficacy and reduced side effects. The interaction of pharmacologists with AI in the context of cell therapies further amplifies their potential, enabling precise patient selection, optimized treatment protocols, and real-time monitoring of therapeutic responses.
This dissertation examines key advancements, current applications, and future prospects in pharmacology, focusing on how pharmacologists can leverage AI and cell therapies to revolutionize the field. The role of clinical pharmacologists in the clinical development is critical, and the evolution of the roles in the clinical development addressing ethical considerations, regulatory frameworks, and economic implications of these technologies.

CONFERENCE 2-*Wednesday 23th October 18:30-19:30*
Chair: Cecilia Bouzat

REACTIVATION OF LATENT PROGENITORS DUE TO A SPINAL CORD INJURY

María Victoria Falco, Gabriela Fabbiani, **Raúl E Russo**
Departamento de Neurofisiología Celular y Molecular. Instituto de Investigaciones Biológicas Clemente Estable. Avenida Italia 3318, CP 11600 Montevideo, Uruguay.

The ependyma of the adult spinal cord is a latent stem cell niche that contributes to the glial scar after spinal cord injury. The mechanisms by which injury

reactivates the ependymal stem cell niche remain poorly understood. Ependymal cells are coupled via connexin (Cx) 43 and Cx26 in the active niche of neonatal mice, but uncouple with downregulation of Cx26 in the adult. Injury induces re-coupling and the upregulation of Cx26, suggesting a role for Cx signalling in the reactivation of the ependymal stem cell niche.[1] We hypothesized that Cx26 is a main regulator of the response of ependymal cells to tissue damage. To analyse the specific role of Cxs in ependymal cells we used transgenic mice to selectively delete Cx26 or Cx43 by crossing mice with floxed Cx26 or Cx43 genes with a FoxJ1CreER-tdTomato transgenic line. We found that in $Cx26^{fl/fl}$ mice, recombination with tamoxifen produced a significant reduction of Cx26 and proliferation in ependymal cells at 5 days post injury (DPI). Similar to injury, the activation of P2X7r triggered the proliferation of ependymal cells and the up-regulation of Cx26,[2] but failed to promote proliferation in $Cx26^{fl/fl}$ mice. As expected, the deletion of Cx26 in ependymal cells strongly reduced their contribution to the glial scar. Surprisingly, the deletion of Cx43 also reduced proliferation, an effect probably mediated by a lack of Cx26 expression in $Cx43^{fl/fl}$ mice. Our findings suggest that Cx26 is a potential target to improve the contribution of the ependymal stem cell niche to self-repair.

CONFERENCE 3 - *Tuesday 24th October 10:00-11:00*
Chair: Ventura Simonovich

PHARMACOINFORMATICS: NEW CHALLENGES AND HORIZONS IN DRUG DESIGN

David Ramírez
Departamento de Farmacología, Universidad de Concepción, Chile

Drug design has traditionally faced multiple obstacles, from the identification of therapeutic targets to the optimization of bioactive compounds. This has generated the need to use key tools that are located at the intersection of pharmacology and bioinformatics, giving rise to the field of pharmacoinformatics. This discipline is revolutionizing drug design by integrating large volumes of omics data (genomics, proteomics, metabolomics) with advanced computational analysis techniques.

Pharmacoinformatics offers innovative solutions through the use of machine learning algorithms, structural bioinformatics, simulation and molecular modeling, among other computational tools, that allow deeper and more precise analysis of biological data. These approaches facilitate the identification of new therapeutic targets, the prediction of the efficacy and safety of compounds, as well as the personalization of treatments based on individual genomic profiles.

By using pharmacoinformatics, integrative analysis of omics data has allowed the identification of key biomarkers and metabolic pathways in complex diseases such as cancer and neurodegenerative diseases. Furthermore, simulation of drug-protein interactions and rational structure-based drug design have

demonstrated significant impact on compound optimization. These advances are transforming the development of more effective and specific treatments, bringing us closer to an era of personalized and precision medicine.

CONFERENCE 4 - *Tuesday 24th October 17:00-18:00*
Chair: Natalia Alza

RESOLUTION COMPONENTS AND LIPID METABOLISM AS EMERGING TARGETS IN NEURODEGENERATION

Gabriela A. Salvador
Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB-UNS-CONICET).
Departamento de Biología, Bioquímica y Farmacia (DBByF-UNS)

Neurodegenerative disorders are characterized by the progressive and selective loss of vulnerable neurons in specific brain areas. Some major harmful challenges associated with neuronal dysfunction and death are proteotoxicity, oxidative stress, and neuroinflammation. By using metabolomics, we detected that phospholipids are selectively hydrolyzed in astrocytes and neurons by several phospholipases A2 in response to toxicity threats. In addition, ferroptosis-associated stimuli produced an imbalance in arachidonic acid (AA) and docosahexaenoic acid (DHA) content. This fatty acid rewiring activated AA- and DHA-dependent resolution pathways to mitigate pro-inflammatory signaling, and lipid droplet accumulation thus promoting cell survival. The inflammation/resolution balance is governed by many specialized pro-resolving lipid mediators acting as ligands of the GPCR receptor FPR2/ALX. In line with this, we also demonstrated that neurons and astrocytes secrete lipid ligands for FPR2/ALX-mediated resolution. Proteotoxic stimulus and oxidative stress also triggered lipid droplet accumulation in neurons and glia. Active lipid droplet hydrolysis and free cholesterol accumulation are associated with gliosis and movement disorders when massive dopaminergic neuronal death occurs in mice midbrain. Thus, depending on the neuronal injury level, lipid droplets can act as protective against damage or as promoters of cellular death. We hypothesize that lipid droplets act as yin/yang effectors of neurodegeneration working as dynamic fatty acid donors or sinks to intervene in resolution or pro-inflammatory signaling. Our results shed light on new targetable metabolic pathways for treating neurodegenerative disorders.

SYMPOSIUM 1 – *Wednesday 23th October 14:15-15:30*
DEVELOPMENT OF INNOVATIVE FORMULATIONS FOR THE IMPROVEMENT OF LEISHMANIASIS
Chair: Daniela Quinteros

TECHNOLOGICAL PLATFORM BASED ON BIOCOMPATIBLE POLYMERS AND BIOADHESIVES CARRYING DRUGS TO OPTIMIZE THE PHARMACOTHERAPY OF CUTANEOUS LEISHMANIASIS

Alvaro Jimenez Kairuz

Departamento de Ciencias Farmacéuticas, FCQ-UNC y Unidad de Investigación y Desarrollo en tecnología Farmacéutica (UNITEFA), CONICET-UNC.

My presentation will be focused on the development of topical formulations containing amphotericin B based on the technological platform that has been developed in the group for several years. We addressed concepts of optimized drug development, capabilities and quality criteria that allowed establishing the pharmacotechnical and biopharmaceutical advantages over the conventional pharmacotherapy. The talk will highlight the experimental capabilities and multidisciplinary integration that determined the efficacy both *in vitro* and at a preclinical level and the efficient development of a pharmaceutical product for topical use with high potential for the pharmacotherapy of this neglected disease.

TOPICAL TREATMENT FOR CUTANEOUS LEISHMANIASIS: FROM LIPID BIOPHYSICS TO THE FIRST-IN-HUMAN TEST

Ma. Laura Guzman[1], Ma. Florencia Peralta[2], Marcelo Quipildor[3], Francesca Papera[4], Paola A. Barroso[6], Ma. Eugenia Olivera[1], **Dolores C. Carrer[4]**

[1]Unidad de Investigación y Desarrollo en Tecnología Farmacéutica (UNITEFA)–CONICET y Depto. de Ciencias Farmacéuticas, Fac. de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba; [2]Centro de Investigación y Tecnología Química (CITeQ - UTN - CONICET), Córdoba; [3]Hospital San Vicente de Paul, Orán, Salta; [4]Instituto Ferreyra – INIMEC – CONICET y Universidad Nacional de Córdoba, Córdoba; [6]Instituto de Patología Experimental – CONICET y Universidad Nacional de Salta, Salta.

Cutaneous leishmaniasis (CL) is a neglected parasitic zoonosis that causes skin ulcers and is endemic in 98 countries. It mainly affects low-income people in low-income countries and treatments are inadequate, toxic and painful. The main treatments are systemic. An effective topical treatment would present great advantages, including minimization of toxicity and ease of (self)administration.
Using ultraflexible lipid formulations, we studied the effects of the incorporation of different drugs on the physicochemical properties of the membrane, in vitro efficacy, and efficacy in an animal model of CL. A formulation containing miltefosine showed excellent efficacy in a murine model of the disease. A first-in-human trial led us to modify the formulation in the context of real-life use in a

resistant CL patient. We are currently studying topical safety *in vivo*, and the extent of drug penetration to the rest of the body from topical application.

TOWARDS THE ESTABLISHMENT OF CRITICAL QUALITY ATTRIBUTES OF LIPOSOMAL NANO-FORMULATIONS OF AMPHOTERICIN B FOR THE TREATMENT OF VISCERAL LEISHMANIASIS

Cristian Casado[1], Rocío Massó[1], Ezequiel Ardanaz[1,2], Micaela Escobar Manzanelli[1], Consuelo Coronel Arrechea[1,2], Kiyomi Mizutamari[1], Ismael Bianco[1,2]

[1]*Centro de Excelencia en Productos y Procesos de Córdoba (CEPROCOR),* [2]*CONICET.*

Liposomal amphotericin B (AMB) is considered the “gold standard” in the treatment of visceral leishmaniasis. However, there are few similar approved formulations. Due to the low solubility in both aqueous and hydrophobic media, and its ability to form aggregates, AMB presents high toxicity. Thus, it is known that the chemical composition of the formulation and the manufacturing process are critical in the toxicity of AMB.

In this presentation, we will describe our work for establishing the key stages in the manufacturing process and their impact on the critical quality attributes of the final product.

The manufacturing process can be divided into 6 stages: 1) Dissolution of lipids and AMB in solvent and subsequent drying, 2) Hydration and removal of residual solvent, 3) High pressure homogenization, 4) Extruding, 5) Sterilization by filtration, 6) Aliquoting and freeze-drying.

Each stage requires the evaluation of numerous chemical, physicochemical and biological activity parameters, with the final aim of defining critical quality attributes. These impact on: a) the definition of the standardized operating procedure (SOP) for manufacturing and b) the definition of the technical specifications of the product and ranges.

The final objective of this work is to develop a liposomal formulation of AMB with reduced toxicity leading to expanding its therapeutic window thus increasing doses with fewer adverse effects.

SYMPOSIUM 2 – *Wednesday 23th October 15:30-16:45*
THE THERAPEUTIC POTENTIAL OF PLANTS AND DERIVED NATURAL PRODUCTS ON NEURODEGENERATIVE DISEASES
Chair: Natalia Alza

A JOURNEY THROUGH THE THERAPEUTIC POTENTIAL OF MEDICINAL PLANTS, FLAVONOIDS, AND DERIVATIVES IN NEURODEGENERATIVE DISEASES: A PHYTOPHARMACOLOGICAL PERSPECTIVE FUSED WITH TRADITIONAL KNOWLEDGE

Mariel Marder

Instituto de Química y Fisicoquímica Biológicas Prof. Dr. Alejandro C. Paladini (IQUIFIB). UBA-CONICET. Laboratorio de Neuro-Fito-Farmacología Medicinal. Facultad de Farmacia y Bioquímica. Buenos Aires, Argentina.

Neurodegenerative diseases (NDD) such as Alzheimer's (AD) and Parkinson's (PD) involve progressive dysfunction of the central nervous system (CNS). Current treatments are largely symptomatic and palliative due to the absence of etiological therapies. The complexity and presence of comorbidities require treatments targeting multiple CNS sites to improve therapeutic outcomes. The multifactorial nature of these diseases excludes monotherapy, driving the search for multipotent treatments that address various aspects of the onset and progression of NDD.

Our laboratory is focused on the search for new multi-action therapies, whether natural or their derivatives, to treat NDD and their comorbidities such as anxiety, stress, depression, and insomnia. We focus on molecules mimicking nature's architecture, which offer safer options with extensive biological interactions. These include medicinal plants (standardised extracts from native species), their active principles (flavonoids), and synthetic derivatives (like flavones and chalcones). Our goal is to develop treatments that are more specific, cost-effective, have fewer side effects, and offer broader therapeutic potential compared to current medications. Recently, we have investigated derivatives of 2'-hydroxychalcones and extracts from medicinal plants known for CNS activity, including Argentine valerians, peperina, marcela, and ceibo, among others.

In my talk, I will detail our research journey, highlight key milestones, and explain how we selected these promising treatments. We utilize techniques such as bioactive natural product extraction, chemical synthesis of derivatives, biochemical studies (binding to brain receptors like $GABA_A$, enzymatic inhibition for monoamine oxidases and cholinesterases), amyloid aggregation inhibition, oxidative stress analysis, cell assays, and behavioural tests in mice. Our primary goal is to enhance the quality of life for patients affected by these devastating diseases.

UNRAVELING THE NEUROPROTECTIVE MECHANISMS MODULATED BY YERBA MATE IN PARKINSON'S DISEASE

Juan Esteban Ferrario

Universidad de Buenos Aires, Facultad de Ciencias Exactas y Naturales, Instituto de Biociencias, Biotecnología y Biología traslacional (iB3) and CONICET, Buenos Aires, Argentina.

Yerba mate (YM) has positive effects on health and has been considered as a medicinal plant since pre-Hispanic times, mainly related to its acute effects as energizing. However, in recent years its prolonged consumption has been associated with some physiological systems. YM is a psychostimulant on the nervous system, and its extended use has been inversely associated with the incidence of developing Parkinson's disease (PD) in two independent epidemiological studies. Furthermore, in our laboratory we demonstrated that YM extract provides significant survival of dopaminergic neurons in primary cultures, supporting the hypothesis that YM could have some degree of neuroprotective capacity.

In order to give further experimental support to these evidences and to understand the cellular mechanism beyond YM intake, we conducted research both on neuronal cell line exposed to YM and on a Drosophila melanogaster alpha-synuclein (aSyn)-expressing model of PD fed with YM. In the fly model of PD, we evaluated behavior (geotaxis and locomotion), synaptic formation (GRASP: GFP Reconstitution Across Synaptic Partners) and gene expression of molecular markers related to cellular metabolism. Additionally, using the SH-SY5Y neuronal line, we investigated the regulation of proteins related to cellular metabolism. We observed a decrease in the amounts of aSyn by WB in flies fed with YM, as well as an increase in neuronal connectivity between dopaminergic and mushroom body neurons in aged wild-type flies determined by GRASP. Furthermore, we found in culture that YM regulates the expression of key markers of cellular metabolism related to neuronal health and survival, in particular AMPK and its downstream pathway.

Our results provide the first insights into the neuronal changes that take place following exposure to YM, suggesting that it improves synaptic connectivity as well as the regulation of energy and cellular metabolism. Further research is still needed, but the current results help to understand how natural compounds can act positively on neuronal health and thus influence the natural history of neurodegenerative pathologies such as Parkinson's disease.

CHOLINERGIC POTENTIATION FROM NATURAL EXTRACTS: REDISCOVERING CAFFEINE

Silvia Susana Antollini

INIBIBB-CONICET-UNS, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, Bahía Blanca (8000), Argentina.

Cholinergic signaling is crucial in a wide range of physiological processes. It involves the neurotransmitter acetylcholine, the acetylcholine receptor (though there are two types of receptors, muscarinic and nicotinic, we focus on the nicotinic receptors, nAChR), and the enzyme acetylcholinesterase (AChE). Alzheimer's disease (AD) features the loss of cholinergic signaling within the central nervous system as a crucial element in their pathophysiological mechanism. For this reason, current treatments for these pathologies aim to enhance cholinergic potentiation. We explored extracts from six plants known for their medicinal properties. The methanolic extract of *Camellia sinensis* leaves, or its phytochemical derivatives, demonstrated both anticholinesterase activity and nAChR agonist properties. Caffeine turned out to be the active principle. Although its AChE inhibitory effect is well-known, its cholinergic agonist activity was not. Therefore, we performed an in-depth characterization of this activity on nAChR. Considering caffeine as a multifactorial agent targeting multiple sites for AD treatment, we initiated the synthesis of a series of bifunctional caffeine derivatives consisting of a theophylline ring connected to amino groups via various intermediate chains. All of these were more potent AChE inhibitors than caffeine. Some of them also activated the nAChR, although not all stabilized the nAChR in its desensitized conformation. Using different biophysical strategies, we defined that the agonist behavior of the compounds on nAChR depends on the accessory group, while the stabilization of the receptor in a desensitized state depends on the interactions of the intermediate chain at the binding site. Thus, these new compounds can inhibit AChE and activate nAChR with greater potency than caffeine, advancing the understanding of the modulation mechanisms of these pharmacological targets for the design of new therapeutic interventions in cholinergic deficiency.

SYMPOSIUM 3 – *Wednesday 23th October 17:15-18:30*
APPLICATION OF ARTIFICIAL INTELLIGENCE IN PHARMACOLOGY AND HEALTH
Chair: Guillermina Hernando

EXPLAINABLE ARTIFICIAL INTELLIGENCE AND DRUG DISCOVERY. HOW CAN WE INTERPRET THE PREDICTIONS OF A MODEL IN TERMS OF MEDICINAL CHEMISTRY?

Ignacio Ponzoni

Instituto de Ciencias e Ingeniería de la Computación, UNS-CONICET; Departamento de Ciencias e Ingeniería de la Computación, UNS, 8000 Bahía Blanca.

Artificial intelligence (AI) is gaining an increasing impact in many applications associated with computer-assisted drug discovery. This is mainly due to the strong development of deep learning (DL) techniques, which have allowed the acquisition of predictive modeling capabilities never achieved before. However, models trained using DL are often opaque, providing almost null information on how they make certain decisions during their predictive process. Therefore, it is essential, if we want the general adoption of these AI-drive approaches by the medicinal chemistry community, that these models can be clearly understood by their end users in terms of their knowledge in the chemical domain. For this reason, research and development of explainable artificial intelligence (XAI) techniques have become a highly relevant topic to overcome this challenge. In this dissertation, we will discuss some of the most widely used explanation methodologies for AI-based models currently in the field of drug discovery. In particular, an intuitive overview of two families of XAI approaches will be presented, those based on feature attribution and those based on graph topologies. Additionally, the main visualization strategies designed for supporting XAI approaches in drug discovery will be discussed. Finally, key insights on each of these categories of methods, providing an analysis of the potential benefits of their adoption in medicinal chemistry, will be presented as general conclusions.

INNOVATIVE ONCOLOGICAL THERAPIES: A MIXED EXPERIMENTAL AND COMPUTATIONAL APPROACH

Camila Contestabile Monti[1], Agustina Verschoor[1], Fabiana Alejandra Rossi[2,3], Ignacio Cassol[1], **Mario Rossi**

[1,2,3,1]Facultad de Ingeniería, Universidad Austral, Pilar, Argentina, [2]Instituto de Investigaciones en Medicina Traslacional (IIMT), CONICET-Universidad Austral, [3]Facultad de Ciencias Biomédicas, Universidad Austral, Pilar, Argentina.

Artificial intelligence (AI) is revolutionizing the fields of pharmacology and health by facilitating the discovery of new drugs, personalized medicine and identification of new therapeutic targets. Due to AI's ability to analyze large

amounts of biomedical data, it makes it possible to discover complex patterns that can be exploited to develop more effective and targeted therapies.
In particular, our interest is focused on the area of molecular oncology, identifying and characterizing modulators that attack the migratory and invasive features of tumor cells. The inhibition of these processes is essential to prevent metastasis, one of the greatest challenges in oncology. This approach drives us apart traditional methods focused on cell viability, allowing us to intervene in critical aspects that determine cancer progression.
To achieve this goal, we adopted a mixed strategy, combining experimental and computational approaches that have allowed us to identify previously approved drugs that mimic the effects of inhibition of key genes involved in cell migration, contributing to the identification of new therapeutic pathways with a potential rapid clinical implementation.
In summary, our strategy led us to integrate bioinformatic tools in drug repositioning, paving the way for the identification of new possible therapeutic interventions with a high potential to significantly improve clinical outcomes in oncology patients.

IMPACT OF ARTIFICIAL INTELLIGENCE ON HEALTH: OPPORTUNITIES AND CHALLENGES FOR RESEARCH. EXPERIENCE FROM ITALIANO HOSPITAL

Sonia Benitez

Jefe de Área de Investigación e Innovación tecnológica - Coordinadora Programa de Inteligencia Artificial - Depto. de Informática en Salud - Hospital Italiano de Buenos Aires.

Even though the implementation of Artificial Intelligence (AI) still presents ethical and regulatory challenges, it is expected to profoundly transform biomedical research and patient care, offering greater accuracy, efficiency and accessibility in the treatment and prevention of diseases, as well as in the development of innovative therapies.
AI can improve diagnostic accuracy through advanced machine learning algorithms, which can analyze medical images, clinical and genomic data on an unprecedented scale. In research, it is expected to accelerate the discovery of new drugs and therapies by analyzing large amounts of complex data efficiently. From identifying compounds to predicting clinical outcomes, AI can optimize research processes, reducing time and costs. Neural networks and predictive algorithms can help model diseases, virtually test new molecules and predict possible side effects, among others.
This talk will explore foundational concepts of AI tech, how AI can assist biomedical research in general & pharmacology in particular, what is AI research in healthcare, and through this point show the experience at Hospital Italiano de Buenos.

SYMPOSIUM 4 – *Tuesday 24th October 14:15-15:30*
INNOVATIVE MATERIALS IN PHARMACOLOGY
Chair: Verónica Lassalle

DESIGN OF HYBRID NANOMATERIALS TO SOLVE HIGH SOCIAL IMPACT PROBLEMS

Verónica L. Lassalle

Instituto de Química del Sur, Departamento de Química, Universidad Nacional del Sur-CONICET.

The Dengue virus (DENV) is one of the most important pathogens transmitted by mosquitoes to humans. It is currently considered a very serious and increasing public health problem in our country and in several underdeveloped countries. The perspectives are alarming and the strategies to stop the spread of the virus, for the moment, are restricted to the use of repellents to prevent against the vector. In summer, and coinciding with the stationary period of the different arboviruses (such as dengue, zika and chikungunya), a higher incidence of episodes that can lead to severe skin diseases occurs which are associated with exposure to ultraviolet (UV) solar radiation. Nowadays, the approaches adopted to solve this problem are oriented to reduce sun exposure during peak hours and the application of adequate amounts of sunscreen periodically. In this context, it is clear that there are two problems of great impact, which manifest themselves in the same period of the year, affecting the public health system in the short and long term. The objective of our research is to develop a multifunctional cosmetic formulation that simultaneously provides protection as a sunscreen and insect repellent, including protective action against dengue vectors. The aim is to provide innovative, eco-friendly and more efficient tools that can be inserted into the routine of the population, without restriction in terms of age and pre-existent skin pathologies. A dual formulation was synthesized from natural ingredients to form microemulsions (ME) that, in addition to generating the repellent action, confer antioxidant and anti-inflammatory properties. The MEs have been loaded with inorganic nanoparticles, based on Zn oxide and/or Ti oxide which provide the sun protection action, generating besides, a synergy in the repellent effect. The formulations have been characterized in terms of their physicochemical properties; and its repellent and solar protector actions have been validated through in vitro tests.

IMPROVEMENT OF INHALABLE THERAPY: INTEGRATION OF AEROSOL TECHNOLOGY INTO PRODUCT DESIGN

María Verónica Ramirez Rigo[1,2]

[1]Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS), [2]Planta Piloto de Ingeniería Química (UNS-CONICET).

The promise of inhalable therapies lies in their ability to treat respiratory diseases more efficiently, delivering medication directly to the site of action with minimal side effects. In this presentation, we explore how integrating advanced aerosol technology into product design can significantly enhance drug delivery. Overcoming the anatomical and physiological barriers of the respiratory system is a significant challenge, and the success of inhalable therapies hinges on the seamless integration of two critical components: the drug formulation and the aerosol delivery device.

Our research focuses on developing innovative inhalable particulate systems. By co-processing drugs and excipients suitable for the pulmonary route, we produce microparticles with precise properties such as size, morphology, density, and crystalline form. Utilizing spray drying techniques, we fine-tune these particles to achieve superior encapsulation efficiency, drug release profiles, and aerodynamic performance.

We employ different configurations of drying equipment, adjusting operating conditions and materials to design the ideal product. Our work delves into polymeric matrices and high-dose drug particulate systems, among others, characterizing them through crystallography, thermal analysis, microscopy, and laser diffraction. Key assessments include density, rheological properties, interaction with pulmonary surfactant, dissolution, and stability. The aerodynamic performance of the formulation-device systems is evaluated using simulated breathing conditions for different patient groups.

This research provides valuable insights into aerosol technology, paving the way for the rational design of inhalable powder formulations and their integration with medical devices. These advancements hold the potential to improve healthcare practices by enhancing respiratory therapies.

DEVELOPMENT OF MUCOADHESIVE POLYMERIC FILMS FOR THE TREATMENT OF ORAL AND VAGINAL MYCOSES

Darío Leonardi

Instituto de Química de Rosario (IQUIR-CONICET), Facultad de Ciencias Bioquímicas y Farmacéuticas – Universidad Nacional de Rosario (UNR)

Oropharyngeal candidiasis is the most common opportunistic infection affecting patients with acquired immunodeficiencies (HIV-AIDS) and those undergoing chemotherapy. This disease is commonly treated orally with antifungal tablets and topically using nystatin mouthwashes or miconazole nitrate gel.

Formulations such as mouthwashes and gels require multiple daily applications as they are easily cleared by saliva. An alternative to the aforementioned topical treatment could be based on small-sized and thin buccal polymeric matrices, which would offer flexibility, ease of application, and allow adhesion at the site of action, reducing the number of daily applications and potentially leading to better patient compliance. Similarly, mucoadhesive polymeric matrices could be used for the treatment of vaginal mycoses.

SYMPOSIUM 5– *Tuesday 24th October 14:15-15:30*
ION CHANNELS AS THERAPEUTIC TARGETS
Chairs: Cecilia Bouzat and Guillermina Hernando

DECIPHERING THE MOLECULAR FUNCTION OF THE α7 NICOTINIC RECEPTOR FOR ITS IMPLEMENTATION AS A CLINICAL DRUG TARGET

Cecilia Bouzat

Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB-CONICET-UNS), Depto. de Biología, Bioquímica y Farmacia, UNS, Bahía Blanca, Argentina.

The α7 nicotinic receptor is a pentameric ligand-gated ion channel widely expressed in the central nervous system, where it plays key roles in cognition, attention, and memory. It is also found in non-neuronal cells, contributing to anti-inflammatory and neuroprotective processes. The enhancement of α7 activity is emerging as a promising therapeutic strategy for neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, as well as neurological and inflammatory conditions. Despite promising preclinical and clinical data, no α7-specific ligand has been approved for clinical use yet. Our objective is to elucidate the molecular function of α7 and its modulation under physiological and pathological conditions, in order to advance its potential as a therapeutic target. We expressed α7 in mammalian cells and assessed its function using single-channel and macroscopic current patch-clamp recordings. Through this approach, we identified natural and synthetic compounds that act as novel α7 positive allosteric modulators, exhibiting neuroprotective properties and offering new molecules with therapeutic potential. Additionally, we characterized new mechanisms of α7 modulation, including interactions with oligomeric amyloid beta peptides associated with Alzheimer's disease, cannabidiol, phosphorylation, calcium, and other nicotinic receptor subunits. These findings provide critical insights to be considered in future clinical trials. By investigating α7 function from a molecular perspective, our results lay the groundwork for its implementation as a viable therapeutic drug target.

ADDING NOVEL WORDS TO BRAIN LANGUAGE. PROTONS AS NEUROTRANSMITTERS

Osvaldo D. Uchitel

Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE UBA CONICET).

Extracellular pH changes may constitute significant signals for neuronal communication. During synaptic transmission, changes in pH in the synaptic cleft take place. In recent years, protons have been recognized as neurotransmitters that participate in neuronal communication in synapses of several regions of the CNS such as amygdala, nucleus accumbens, and brainstem. Protons are released by nerve stimulation and activate postsynaptic acid-sensing ion channels (ASICs). Several types of ASIC channels are expressed in the peripheral and central nervous system. The influx of Ca^{2+} through some

subtypes of ASICs, as a result of synaptic transmission, agrees with the participation of ASICs in synaptic plasticity. Pharmacological and genetic inhibition of ASIC1a results in alterations in learning, memory, and fear. The recognition of endogenous molecules, such as arachidonic acid, cytokines, histamine, spermine, lactate, and neuropeptides, capable of inhibiting or potentiating ASICs suggests the existence of mechanisms of synaptic modulation that have not yet been fully identified and that could be tuned by new emerging pharmacological compounds with potential therapeutic benefits.

NEW PERSPECTIVES ON THE PHARMACOLOGICAL MODULATION OF GLYCINERGIC NEUROTRANSMISSION

Gonzalo E. Yévenes[1,2], Ana M. Marileo[1,2], Victoria P. San Martin[1,2], Cesar O. Lara[1,2], Anggelo Sazo[1,2], Krishna Gaete[1,2], Omayra Contreras[1,2], Carlos F. Burgos[1], Patricio Castro[1], Jorge Fuentealba[1], Luis G. Aguayo[1], Gustavo Moraga-Cid[1]

[1]Universidad de Concepción, Departamento de Fisiología, Facultad de Ciencias Biológicas, Concepción, Chile, [2]Millennium Nucleus for the Study of Pain (MiNuSPain), Santiago, Chile

The inhibitory synapses in the central nervous system are crucial for regulating neuronal excitability. Both GABAergic and glycinergic neurotransmission are essential for neuronal inhibition, utilizing various mechanisms such as fast synaptic inhibition, tonic current activation, and presynaptic modulation. Given its significance, the mechanisms of action of many clinically important drugs, including general anesthetics, anxiolytics, hypnotics, and new antidepressants, involve the modulation of inhibitory neurotransmission. These drugs primarily achieve their therapeutic effects through direct actions on postsynaptic GABAA receptors. However, the pharmacological modulation of glycinergic neurotransmission has not yet been applied clinically. Recent evidence suggests that enhancing key proteins in glycinergic transmission, such as glycine receptors (GlyRs) and glycine transporters, can effectively alleviate pain. Our recent findings indicate that GlyR subtypes are differentially influenced by a variety of compounds, including synthetic molecules and natural alkaloids. We discovered that these compounds modulate GlyRs through different mechanisms, utilizing distinct binding modes and allosteric pathways. Additionally, these compounds target different elements of glycinergic neurotransmission. Ongoing studies with genetically-engineered mice suggest that GlyR subtypes contribute asymmetrically to the maintenance of chronic pain. Finally, the potential role of GPR158, a recently discovered metabotropic glycine receptor, reveals additional possibilities for GlyR modulation and pharmacological advances. Our current research aims to provide a comprehensive understanding of the alterations in glycinergic neurotransmission associated with chronic pain, paving the way for the development of advanced biomedical tools.

"Supported by ANID-FONDECYT 1211082, ANID-FONDECYT 1211095, ANID-FONDECYT 11221211, and by the Millennium Nucleus for the Study of Pain NCN19_038 (MiNuSPain)".

YOUNG INVESTIGATOR SYMPOSIUM– *Tuesday 24th October 13:00-14:15*
Chairs: Susana Gorzalczany and Jerónimo Laiolo

ANTIMICROBIAL ACTIVITY AND SAFETY PROFILE OF COPPER(II) COMPLEXES WITH SULFADIAZINE AND 1,10-PHENANTHROLINE

Rocío Belén Marinich[1], Lorena Elizabeth Guevara[1], Cristian Villa Pérez[2], Delia Beatriz Soria[2] and **Juan José Martínez Medina[1]**

[1]INIPTA, CONICET/UNCAUS, Universidad Nacional Del Chaco Austral, Comandante Fernández N° 755, Presidencia Roque Sáenz Peña (3700), Chaco, Argentina,
[2]CEQUINOR, CONICET/UNLP, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Bv. 120 Nº 1465, 1900, La Plata, Argentina.

Introduction: Sulfadiazine (SDZ) is a bacteriostatic sulfonamide that inhibits the enzymatic activity of dihydropteroate synthetase. Antimicrobial and safety profiles of SDZ could be modulated upon complexation with copper.
Objectives: The aim of this work is to assess the antimicrobial and toxicological properties of the binary and ternary Cu(II) complexes $Cu(SDZ)_2$ and $Cu(SDZ)_2$phen, with 1,10-phenanthroline as a co-ligand.
Methods: The minimum inhibitory concentration (MIC, in μg mL^{-1}) of both complexes was assessed firstly against bacterial and fungal ATCC strains by the agar dilution method. The broth dilution method against ATCC strains and the clinical isolates of *E. coli* and *S. aureus* (MRSA) provided by local hospitals was carried out to evaluate MIC and minimum bactericidal/fungicidal concentration (MBC/MFC). Besides, complexes' safety was evaluated by the Ames test (mutagenicity), *Artemia salina* assay (acute toxicity), and *Allium cepa* assay (phytotoxicity).
Results: In the agar dilution method, the complexes showed MIC values with clinical relevance (≤ 1000) against ATCC strains, thus being the $Cu(SDZ)_2$phen complex the most active one. In the broth dilution method, this complex showed relevant antibacterial activity against ATCC and *S. aureus* (MRSA) clinical isolates strains (MIC values from 31 to 500), as well as against yeast of the *Candida* genus (MIC values from 9 to 125). Moreover, the ternary complex showed bactericidal (CBM/CIM ≤ 4) and fungicidal activity (CFM/CIM ≤ 4) in most of the cases. Complexes did not induce frameshift mutations (*S. typhimurium* TA98) or base-pair substitution mutations (*S. typhimurium* TA100). Besides, mortality in *A. salina* nauplii was not detected until 600 μg mL^{-1}. The concentration that inhibits 50% of root length on *A. cepa* is close to 3 μM.
Conclusion: Including the co-ligand 1,10-phenanthroline, $Cu(SDZ)_2$phen, enhances the antimicrobial activity compared with the binary complex.

PHARMACOLOGICAL EFFECTS AND MECHANISMS OF *HUMULUS LUPULUS* (HOPS): A POTENTIAL ALTERNATIVE TREATMENT TO ESTROGENS

Germán A. Colareda[1], Juan M. Fernández[2], Nahuel E. Wanionok[2], Lucía C. Lojano-Gutierrez[1], Soledad I. Matera[1], Osvaldo L. Córdoba[3], María L. Flores[4], Romina G. Diaz[5], Alicia E. Consolini[1]

[1]Grupo de Farmacología Experimental y Energética Cardíaca, Cátedra de Farmacología, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata (UNLP), Argentina, [2]Laboratorio de Investigaciones en Osteopatías y Metabolismo Mineral (LIOMM), Facultad de Ciencias Exactas, UNLP-Centro de Investigaciones Científicas (CIC), Argentina, [3]Química Biológica II GQBMRNP, AAI y LACROMI – Centro Regional de Investigación y Desarrollo Científico Tecnológico (CRIDECIT), Facultad de Ciencias Naturales y Ciencias de la Salud, UNPSJB, Comodoro Rivadavia, Argentina, [4]Farmacognosia, GQBMRNP, AAI y LACROMI – Centro Regional de Investigación y Desarrollo Científico Tecnológico (CRIDECIT), Facultad de Ciencias Naturales y Ciencias de la Salud, UNPSJB, [5]Centro de Investigaciones Cardiovasculares "Dr. Horacio E Cingolani", Facultad de Ciencias Médicas, UNLP-CONICET.

Estrogens have cardiac and bone-protective effects, but adverse effects limit their clinical use. Phytoestrogens are plant-derived compounds with structural similarity to estradiol, many can act as selective estrogen receptor modulators. Genistein (GST), a well-studied phytoestrogen, exhibits bone-protective, LDL-lowering, and antitumor properties. Our lab has demonstrated the cardioprotective effects of GST and daidzein in ischemia-reperfusion (I/R) models. A tincture of *Humulus lupulus L. (Hops-T)*, was characterized by HPLC-DAD, and an abundant prenylated flavonoid (xanthohumol) and traces of isoflavones were found. In vitro experiments on bone marrow progenitor cells showed that Hops-T promotes osteogenic proliferation and inhibits adipogenesis. In endothelial cells (EA.hy926) it increased NO production and eNOS expression. Furthermore, concentration-response curves were performed in the isolated bladder, uterus, duodenum, and ileum in the presence of different concentrations of Hops-T. The tincture non-competitively inhibited carbachol and calcium-induced contractions in all tissues studied (IC50 between 6 and 22 µg dry extract/ml). On the other hand, rats were orally treated with Hops-T for one week. Hearts were isolated, perfused by the Langedorff technique, and subjected to 30´I/45´. Maximal left ventricular pressure (P, mmHg), total heat rate (Ht, mW/g), and muscle economy (P/Ht) were determined. Hops-T improved post-ischemic contractile recovery (PICR) and P/Ht during reperfusion. Although western blot analysis ruled out the involvement of cardioprotective pathways (p-AKT, p-PKCε, GSK3b, and BCL-2), cardioprotection was inhibited by L-NAME and 5-HD, demonstrating the involvement of NO synthases and mKATP channels.
In conclusion, Hops-T has cardioprotective effects, mediated by activation of mKATP and NO. Besides, it has an antispasmodic effect, enhances osteoblastogenesis, and stimulates endothelial cell proliferation.

PHARMACOLOGICAL MODULATION OF BK CHANNELS VIA ACCESSORY SUBUNITS AND ITS NEURONAL IMPACT

Federico Orsi, Juliana Monat, Verónica Milesi, **Pedro Martín**

Instituto de Estudios Inmunológicos y Fisiopatológicos (IIFP), Universidad Nacional de La Plata – CICPBA – CONICET.

Different β accessory subunits are associated with the large conductance voltage- and Ca^{2+}- dependent K^+ channel (BK channel) in a tissue-specific manner. In particular, BK channel/β4 subunits complexes (α/β4) control neuronal excitability in granule cells of the hippocampal dentate gyrus (GCDG) and, β4 deficient mice display a temporal lobe epilepsy (TLE). Thus, compounds that increase α/β4 activity are of interest for improving epilepsy treatment. Then, based on the β-dependent activating effect of arachidonic acid (AA) and leukotrienes on BK channel, we explore the effect of Montelukast (MTK) on this channel heterologously expressed in HEK cells with or without its β accessory subunits (β1, β2, and β4). MTK is a $CysLT_1$ receptor antagonist used as an anti-asthmatic drug that could share the affinity properties with the leukotrienes and its precursor, the AA. Using the patch clamp technique we found that MTK shifts the activation curves of α/β1 and α/β4 to more hyperpolarized voltages in a concentration-dependent manner (1 μM MTK: $\Delta V_{1/2}$ (α/β1)= -76.9 mV ± 8.2; n=7; p<0,05 and $\Delta V_{1/2}$ (α/β4)= -68.2 mV ± 6.5; n=6; p<0,05) without affecting α/β2 channel and, only at concentrations greater than 1 μM, slightly shifts the homomeric BK channel curve ($\Delta V_{1/2}$= -19.3 mV ± 5.6; n=4; p<0,05). MTK delays α/β4 deactivation, suggesting an open channel stabilization (for 1 μM MTK, at -60 mV: τ_{MTK}= 27.6 ± 3.7 ms vs. $\tau_{control}$= 2.0 ± 0.3 ms n= 5, p<0.05). Finally, we found MTK-sensitive GCDG in mouse brain slices, where the drug decreases in about a 90% the number of action potential spikes induced by 80 pA injection. The reduction in neuronal excitability was associated to reduction in the input resistance by 1 μM MTK ($IR_{control}$= 560.0 ± 31.1 MΩ, n=28 vs. IR_{MTK}= 346.2 ± 24.7 MΩ, p<0.05). Our results indicate that MTK directly activates the α/β4 channel and suggest that this effect could reduce DGGC excitability and may be a putative new treatment for TLE

AAFE AWARD to the best work in pharmacology - *24th October 11:30-13:00*
Chair: Guillermina Hernando
Juries: Daniela Quinteros, Sergio Sánchez Bruni and Ventura Simonovich

FUNGICIDAL PROPERTIES OF MENTHOL-THYMOL NADES AGAINST MULTIDRUG-RESISTANT CANDIDA ALBICANS AND CHEMOSENSITIZATION WITH FLUCONAZOLE

Melisa Fabiana Negro[1,2], Pamela Bustos[1,2], Lautaro Belezze[1], Magdalena Espino[3], María Gabriela Ortega[1,2], María de los Ángeles Fernández[3], María Fernanda Silvac[3], Mariana Andrea Peralta[1,2]

[1]*Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, UNC,* [2]*UNITEFA-CONICET, Facultad de Ciencias Agrarias, UNCuyo,* [3]*IBAM-CONICET*

Oral candidiasis is an infectious disease caused by an overgrowth of fungi, mainly *Candida albicans*. Given the increasing emergence of resistance to traditional antifungals, new therapeutic strategies focus on the search for new bioactive compounds. Natural deep eutectic solvents (NADES) are mixtures of primary metabolites and are considered environmentally friendly. Menthol (Men) and thymol (Thy) NADES have great potential for various applications.
The main objective of this study was to investigate the antifungal efficacy of NADES MT against an azole-resistant *C. albicans* clinical strain by evaluating its potential as a chemosensitizer combined with fluconazole (FLZ), assessing the synergistic effect and determining the generation of Reactive Oxygen Species (ROS) as a possible mechanism of action.
MT was prepared using Men and Thy in a 1:1 M ratio. Antifungal activity was assessed by plate microdilution, according to CLSI standards, on resistant *C. albicans* (RCa). To determine the fungicidal capacity of MT, the viability of RCa was assessed by counting colony-forming units (CFU). Intracellular ROS generation was defined by fluorometry with the fluorescent probe H 2 -DCFDA. The checkerboard method was chosen to establish possible interactions between MT and FLZ on RCa, according to CLSI protocol M27-A4.
MT's MIC (minimum inhibitory concentration) was determined at 180 µg/ml. MT significantly decreased cell viability at 180 µg/ml, RCa survival was reduced by 98.9%, while a complete fungicidal effect was observed at 360 µg/ml. It was determined that the fungicidal action mechanism of MT could be related to a pro-oxidative effect due to the generation of ROS in RCa. The MIC of MT was reduced by half while for FLZ the MIC decreased 256 times achieving the chemosensitization of RCa to FLZ.
MT is presented as a potent antifungal with the possibility of being investigated for infections caused by RCa, future research on its antifungal action mechanism is proposed.

COMBINED ALBENDAZOLE-CLORSULON TREATMENT AS STRATEGY TO CONTROL FASCIOLA HEPATICA. PHARMACOKINETIC AND EFFICACY EVALUATION IN OVINE

Valentina Chiappetta[1], Candela Cantón[1], César Pruzzo[2], Lucila Moriones[1], Carlos Lanusse[1], Luis Alvarez[1], Laura Ceballos[1]

[1]*Laboratorio de Farmacología, Centro de Investigación Veterinaria de Tandil (CIVETAN), UNCPBA-CICPBA-CONICET, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Facultad de Ciencias Veterinarias, Tandil, Buenos Aires, Argentina.* [2]*Centro de Diagnóstico Veterinario (CEDIVE), Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata, Chascomús, Buenos Aires, Argentina.*

Introduction: *Fasciola hepatica* causes fasciolosis, a growing zoonotic disease affecting livestock and humans worldwide. The WHO has recognized it as a significant emerging neglected disease. Anthelmintic treatments are the main strategy to control fasciolosis in livestock, based in drugs such as triclabendazole (TCBZ), albendazole (ABZ), clorsulon (CLOR), nitroxinil, closantel, and rafoxanide. Only TCBZ is available for human treatment. The intensive use of TCBZ in veterinary medicine has exerted significant selection pressure, leading to the development of resistant populations of *F. hepatica*. The combined use of drugs has been proposed as a strategy to preserve efficacy and delay the development of resistance. The goal of the work was to evaluate the potential pharmacokinetic interaction and efficacy of ABZ-CLOR co-administration in *F. hepatica* infected sheep. Methods: PK study: includes three groups of healthy sheep (n=6): Group ABZ, (7.5 mg/kg bw orally); Group CLOR (2 mg/kg bw subcutaneous); and Group ABZ+ CLOR, (same doses). Blood samples were taken previously and between 1 to 48 h post-treatment. Plasma was analyzed by HPLC. Efficacy controlled test: 16 sheep artificially infected with *F. hepatica*, were allocated into four (4) experimental groups: Control Group (without treatment) and treated groups, which received the same treatment mentioned in the PK study. Fifteen days after treatment animals were sacrificed and adult *F. hepatica* specimens were counted to evaluate the efficacy. Results: higher plasma availability was observed for ABZ-sulfoxide in the co-administered group compared to those in Group ABZ. CLOR PK behavior was not affected by co-administration with ABZ. The clinical efficacy was 85%, 92% and 100% for groups ABZ, CLOR and ABZ+CLOR, respectively. Conclusion: this study shows a PK interaction and improved efficacy after ABZ+CLOR co-administration, which can help to effectively control *F. hepatica* in sheep.

ANTI-INFLAMMATORY ACTIVITY OF FLAVONOID RICH FRACTIONS OF *Nectandra angustifolia* ETHANOLIC EXTRACT

Leandro Adrian Ferrini[1,2], Gonzalo Ojeda[2], Ana Maria Torres[2], Maria Victoria Aguirre[1], Marita Hernández Garrido[3], Maria Luisa Nieto Callejo [3], Juan Pablo Rodríguez[1]

[1]*Laboratorio de Investigaciones Bioquímicas de la Facultad de Medicina (LIBIM), Instituto de Química Básica y Aplicada del nordeste argentino (IQUIBA-NEA), CONICET, Corrientes, Argentina,* [2]*Laboratorio de Productos Naturales (LabProdNat), Instituto de Química Básica y Aplicada del nordeste argentino (IQUIBA-NEA), CONICET, Corrientes, Argentina,* [3] *Laboratorio de enfermedades inflamatorias y degenerativas, Instituto de Biomedicina y Genética Molecular (IBGM), Universidad de Valladolid, Valladolid, España.*

We have previously shown that the ethanolic extract of *Nectandra angustifolia* (NaE), from its aerial parts (leaves and stems), has notable anti-inflammatory effects in both *in vitro* and *in vivo* studies. These effects were demonstrated in LPS-stimulated macrophage cultures (RAW 264.7) and the BV2 microglial cell line. This study further explores NaE's anti-inflammatory properties, focusing on its mechanisms in microglia using an in vitro approach.

NaE was fractionated by flash chromatography and thin layer chromatography (TLC). Selected fractions (F4, F5, F6, F9) were tested for their activity. Concentrations were based on previous work with NaE. Screening involved measuring nitric oxide production (Griess reaction), IL-6, TNFα (ELISAs), and iNOS and COX-2 expression (western blot). No significant differences were observed compared to NaE at 50 µg/mL. Thus, fractions F5 and F6 were further tested at 25 µg/mL, showing improved results over the whole extract, with F5 selected for deeper analysis.

Fraction F5 inhibited p65 subunit translocation to the nucleus, as seen by confocal microscopy, and reduced phosphorylation of p65 and IκBα. Western blot analysis also showed decreased phosphorylation of c-JUN compared to LPS. This suggests an upstream inhibition mechanism. Inhibitors of laminin receptor 67 and TGR5 were also tested but did not affect the observed bioactivity.

We examined IL-4 polarization effects, finding that F5 did not induce arginase-1 expression nor alter it after IL-4 stimulation. Additionally, we investigated flavonoid localization within treated cells. Staining showed flavonoids present inside cells, with increased fluorescence after 24 hours.

In summary, our study highlights the anti-inflammatory activity of a fraction of NaE. The localization of flavonoids and further mechanistic insights will guide future research on their interactions with upstream targets in LPS-triggered inflammatory pathways.

PHARMACODYNAMIC EVALUATION OF RIFAXIMIN AGAINST *Staphylococcus aureus* ISOLATED FROM DAIRY COWS EMULATING BIOLOGICAL CONDITIONS

Florencia Aliverti[1], Julia di Filippo[1], Laura Marchetti[1], Daniel Buldain[1,2], Nora Mestorino[1]

[1]*Laboratory of Pharmacological and Toxicological Studies –LEFyT- Faculty of Veterinary Science, Universidad Nacional de La Plata. Argentina.* [2]*CONICET, Argentina.*

Rifaximin (RIF) is a semi-synthetic non-systemic antimicrobial (ATM) with antibacterial activity against both Gram+ and Gram- bacteria, used to treat subclinical mastitis (SCM) caused by S. aureus. There is limited information on its pharmacodynamics against this bacterium. This study aims to establish RIF's in vitro ATM activity at different pH values (emulating intracellular conditions) and in serum and milk against S. aureus isolates, and to evaluate its post-antibiotic effect (PAE). This study was conducted on a dairy farm in General Belgrano, Buenos Aires, Argentina. 35 animals suspected having SCM were selected, through monthly dairy control and California Mastitis Test (CMT). Milk samples from individual mammary quarters were collected for microbiology analysis, and cultured on CHROMagar Staph aureus®. Isolates recognized as S. aureus by color (pink to mauve) were identified by metabolic, biochemical tests and Gram staining. S. aureus ATCC 29213 was the control strain. RIF minimum inhibitory concentration (MIC) ranges obtained against S. aureus (n = 6) were 0.008-0.031, 0.004-0.0625, 0.008-0.0625, 0.008-0.031, and 0.008-0.125 µg/mL at pH 7.4, 6.5, 5.0, serum, and milk, respectively. Minimum bactericidal concentration (MBC) ranges were 0.016-0.0625, 0.008-0.125, 0.016-0.125, 0.016-0.0625, and 0.016-0.25 for the same conditions. The MBC/MIC ratio was consistently 2. RIF exhibited a longer PAE at pH 7.4 for 10xMIC compared with 3xMIC (0.88±0.02 vs. 0.59±0.01 h); acidic conditions prolonged this effect (0.98±0.04 and 2.37±0.01 h at pH 6.5 and 5, respectively). RIF demonstrated bactericidal activity against S. aureus at different pH or in biological fluids. It has a concentration-dependent PAE, being longer at acidic pH. These results provide information that cannot be derived from standard sensitivity tests. The effects found in vitro testing may be nullified by different in vivo factors (pH, for example) that are intrinsic to the drug, the host, and the strain.

AMORPHOUS SILICA NANOPARTICLES: NOVEL CHEMOTHERAPEUTIC OPTION FOR TRIPLE NEGATIVE BREAST CANCER

Agustina Ibarra[1], Valentina Clemente[1], Anabel Barrientos[2], Eliana N. Alonso[1], Georgina P. Coló[1], María E. Fermento[1], María M. Facchinetti[1], Alejandro C. Curino[1], María J. Ferronato[1*], Mariela Agotegaray[3*].*These authors contribute equally to this work.

[1] *Laboratorio de Biología del Cáncer, Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS) – CONICET, Departamento de Biología, Bioquímica y Farmacia (UNS), Bahía Blanca, Argentina.* [2] *Servicio de Patología del Hospital Interzonal General de Agudos Dr. José Penna, Av. Láinez 2401, 8000 Bahía Blanca, Argentina.* [3] *Laboratorio de Nanomateriales Híbridos Aplicados, Instituto de Química del Sur, Universidad Nacional del Sur (UNS) - CONICET, Departamento de Química (UNS), Bahía Blanca, Argentina.*

Triple-negative breast cancer (TNBC) is a heterogeneous group of tumors with difficult clinical management, due the lack of response to current available therapies for other BC tumors. Nanotechnology represents a strategy to obtain the selective delivery of drugs to cancer cells, thus reducing their adverse effects and increasing their efficacy. The aim of this work was to develop amorphous silica nanoparticles (SiNPs) containing folic acid (FA) as active targeting agent to obtain biocompatible carriers for drugs involved in TNBC. Modified Stöber process was applied to synthesize the amino-functionalized SiNP Si@NH_2 employing 3-aminopropyltriethoxiilane (APTES) as source of –NH_2 group. Then, folic acid (FA) was covalently linked to Si@NH_2 obtaining Si@FA. FTIR spectra confirmed functionalization with NH_2 and FA. DLS and TEM micrographs revealed monodisperse spherical shape for both SiNPs, with biocompatible sizes. Both SiNPs reduced the viability of TNBC MDA-MB-231 and 4T1 cell lines ($p < 0.001$; crystal violet assay) and Si@FA did not affect the growth of the mammary non-malignant HC11 cells. In addition, Si@FA induced ROS generation ($p < 0.01$; DCDCDHF assay) and displayed anti-proliferative and subsequently pro-apoptotic effects in MDA-MB-231 cells ($p < 0.001$; flow cytometry with PI-Annexin V staining). No effect was observed in the ROS generation and cell cycle of HC11 cells after Si@FA treatment. Moreover, SiNPs reduced TNBC cell migration ($p < 0.001$; wound healing assay) and did not affect HC11 motility. Finally, none of SiNPs caused signs of sub-acute toxicity in mice administered at 30 mg/kg over a month such as a decrease in body weight, alterations in the hematocrit and changes in the histology of spleen, brain, heart, liver, lung and kidney of the animals. In conclusion, these nanosystems displayed intrinsic antitumor activity without causing toxic in vivo effects, resulting in a promising therapeutic alternative for TNBC.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

1. SURVEY ON KNOWLEDGE AND USES OF HERBAL DRUGS SOLD IN VARIOUS STORES IN THE CITY OF SANTA FE (SANTA FE)

Mara García[1], Candela Zacaríaz[1], Candela Uzuriaga[1], Marcos Araya[1], Aldana Clebot[1,2], María Laura Fiasconaro[1,2] and **Carolina Masin**[1,2]

[1]*Carrera de Farmacia (FCS – Universidad Católica de Santa Fe), Santa Fe,* [2]*Instituto de Desarrollo Tecnológico para la Industria Química (CONICET-UNL), Santa Fe.*

The objective of study was to survey the most in-demand commercial samples of herbal drugs and analyze aspects of their commercialization in urban stores in the city of Santa Fe, Santa Fe province.
The work was designed as a descriptive, experimental, cross-sectional study. To collect data and obtain information, semi-structured surveys were conducted with both general consumers and sellers of the most commonly traded herbal drug products/species in the city of Santa Fe. The surveys respected anonymity. For better comprehension of the information, qualitative analyses and statistical techniques (quantitative) were applied.
Of the total surveyed consumers, 72% reported using medicinal plants, with 73% applying them for health conditions, 24% in gastronomy, and 3% using them for fashion purposes. Among the 10 most demanded herbal drugs are boldo, chamomile, eucalyptus, mint, mallow, garlic, dandelion, onion, carqueja, nettle, and ambay. Most respondents purchase herbal products/drugs primarily from dietary/herbal stores, followed by pharmacies. Regarding general inquiries about medicinal plants, most respondents turn to the internet, followed by family or friends. Regarding the places where herbal drugs are sold, 72% were found to be pharmacies, while the remaining 28% were dietary or natural store types. In the latter, there was a record of non-compliance with current regulations on the presentation and labeling of herbal drugs.
This preliminary study contributes to expanding the knowledge and use of herbal drug products, medicinal species, and commercialization aspects in the city of Santa Fe.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

2. ANNUAL EVALUATION OF MEDICINAL PHYTOCHEMICALS IN LEAVES OF *BAUHINIA FORFICATA* L

Candela Uzuriaga[1], Celeste Houriet[1], Agostina Amherdt[1], Carolina Masin[1,2], María Laura Fiasconaro[1,2]

[1]*Carrera de Farmacia (FCS – Universidad Católica de Santa Fe), Santa Fe.* [2]*Instituto de Desarrollo Tecnológico para la Industria Química (CONICET-UNL), Santa Fe.*

Global interest in medicinal plants has increased, regardless of socioeconomic development. Argentina is home to a wide range of plant species initially used by indigenous peoples as sources of medicine, and among them is *Bauhinia* spp. The presence of secondary metabolites in *Bauhinia* spp., underlines its medicinal importance. To date, no research has been found that correlates the concentration of these metabolites with annual seasonality. *Bauhinia forficata* L. leaves are used in folk medicine for their hypoglycemic, antioxidant and diuretic properties. This study aimed to evaluate the effect of annual seasonality on the production of secondary metabolites in *B. forficata* leaves in the city of Santa Fe, Argentina.

Leaf samples were collected from different georeferenced points of the city during one year. Each sample was air-dried, ground and macerated for 48 hours using 98% ethanol to obtain crude extracts by rotary evaporation. A phytochemical screening was performed for alkaloids (Mayer test), flavonoids (Shinoda test), triterpenoid-steroids (Liebermann-Buchard test), tannins (ferric chloride test) and saponins (foam test). In addition, total soluble proteins (TSP) were quantified using the Bradford method and total soluble sugars (TSS) using the anthrone reagent.

The results indicated that leaves of *B. forficata* showed secondary metabolites of medicinal interest, which varied according to the season. In summer and autumn, the leaves showed a notable presence of alkaloids (associated with cytotoxic and immunomodulatory properties), while in winter and spring flavonoids and tannins (associated with diuretic, hypoglycaemic and antioxidant purposes) were identified. Moreover, higher levels of TSS were found in winter and spring samples, while TSP concentration was highest in summer. These results increase scientific knowledge about this species and its seasonal use for medicinal purposes.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

3. BIOACTIVE METABOLITES FROM *Grindelia chiloensis* WITH ANTICHOLINESTERASE ACTIVITY

Florencia A. Musso, Valeria Cavallaro, Silvana A. Rodríguez, Brunella Biscussi, Martina Donozo and Ana Paula Murray

INQUISUR-CONICET-UNS, Departamento de Química, Universidad Nacional del Sur, Bahía Blanca, 8000, Argentina.

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases among the elderly, characterized by a progressive decline in memory, which impairs patients' cognitive abilities. AD is a complex and multifactorial disorder, and one of the most prominent theories regarding its etiology is the cholinergic hypothesis. This hypothesis is based on the degeneration of cholinergic neurons and the deficiency of the neurotransmitter acetylcholine (ACh). It has been demonstrated that ACh is hydrolyzed by the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Therefore, current pharmacological treatments aim to increase ACh levels in the brain using enzyme inhibitors such as rivastigmine, donepezil, and galantamine, resulting in improved nerve transmission and reduced disease symptoms.
Given this background and the various adverse effects associated with the drugs mentioned, natural alternatives for AD treatment, such as the use of medicinal plants, are being explored. In previous studies conducted by our research group, the ethanolic extract (EE) of the plant species *Grindelia chiloensis* (Cornel.) Cabrera showed significant inhibitory activity against AChE and BChE enzymes (IC_{50} of 960 µg/mL for AChE and 372 µg/mL for BChE). To isolate the bioactive metabolites, the EE was partitioned using solvents of different polarities, resulting in three subextracts: dichloromethane (DS), *n*-butanolic (nBS), and aqueous (AS). Of these, DS exhibited the highest inhibitory activity against the enzymes (AChE inhibition: 54% at 0.5 mg/mL; BuChE inhibition: 60% at 0.5 mg/mL). Fractionation of DS by column chromatography led to the isolation of several labdane-type diterpenes, among which grindelic acid and 6-oxogrindelic acid, both previously reported in other species of the same genus, were identified as major components. The identification of other compounds isolated from DS, as well as the bioactivity of each of them, will be presented.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

4. POSSIBLE MOLECULAR TARGETS FOR THE USE OF *Nicotiana glauca* AS A THERAPEUTIC STRATEGY AGAINST RHABDOMYOSARCOMA

Natalia María Frattini, Nicolás Olegario Blanco, Lucía Pronsato, Andrea Vasconsuelo and Lorena Milanesi

Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS). Instituto de Ciencias Biológicas y Biomédicas del Sur (INBIOSUR), CONICET.

Rhabdomyosarcoma is a malignant tumor common in children and adolescents. It arises from alterations in the regulation of growth and differentiation of precursor cells of myogenesis. It is characterized by its resistance to apoptosis; In general, oncological therapies are not effective. We demonstrated that the liposoluble extract from *Nicotiana glauca (N.g.)* induces apoptosis in the embryonal rhabdomyosarcoma cell line RD. *N.g.* is a plant belonging to the Solanaceae family. Species of this family have been shown pharmacological properties.

The objective of this work was to study the molecular mechanism involved in the apoptotic effect observed in RD cells in response to *N.g.* liposoluble extract treatment. RD cells were treated with the liposoluble extract dissolved in DMEM medium (1:1000) without bovine fetal serum. Exposure times were 1, 2 and 4 hours for Western Blot and RT-qPCR assays. Data analysis was performed using standard statistical packages. PERP is a proapoptotic gene, whose expression was upregulated after 2 hours of treatment (286.7% respect to the control). Also, the participation of the antioxidant enzyme Glutathione peroxidase 1 (Gpx 1) was demonstrated. Higher mRNA levels were detected, with respect to the control, after treatment (23.4%, 76.2% and 127.8% for 1, 2 and 4 hours of treatment, respectively). Western Blot showed an increase in Akt activation, a kinase involved in cell survival, as part of the molecular mechanism involved. The extract increased phosphorylation/activation of Akt after 2 and 4 hours with respect to the control (52.13% and 61% respectively).

These results show an initial defensive response against *N.g.* liposoluble extract in RD cells, which is not sufficient to prevent cell death by apoptosis. This data provides possible molecular targets for the use of *N.g.* as a therapeutic strategy against rhabdomyosarcoma.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

5. ANTITUMOR ACTIVITY OF *PLEUROTUS OSTREATUS* I-FRACTION IN A TRIPLE-NEGATIVE BREAST CANCER MURINE MODEL

María Julia Ferronato[1,2], Exequiel Gonzalo Alonso[1,2], Agustina Ibarra[1,2], Valentina Clemente[1,2], Juan Manuel Cuestas[3], Pablo Postemsky[4], Olivia López[5,6], Diego Boldrini[5,7], María Eugenia Fermento[1,2], Georgina Pamela Coló[1,2], Alejandro Carlos Curino[1,2], María Marta Facchinetti[1,2], **Eliana Noelia Alonso**[1,2]

[1]*Laboratorio de Biología del Cáncer, Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS)-CONICET, Bahía Blanca, Argentina,* [2]*Departamento de Biología, Bioquímica y Farmacia, UNS,* [3]*Laboratorio de Ecosistemas Naturales y Agropecuarios (LENA) (CIC/UNS),* [4]*Laboratorio de Biotecnología de Hongos Comestibles y Medicinales, Centro de Recursos Naturales Renovables de la Zona Semiárida (CERZOS), UNS-CONICET,* [5]*Planta Piloto de Ingeniería Química (PLAPIQUI), UNS-CONICET,* [6]*Departamento de Química, UNS,* [7]*Departamento de Ingeniería Química, UNS.*

Pleurotus ostreatus is an edible mushroom recognized by the Argentine Food Code. The antitumor activity of its polysaccharides, free or bound to proteins, has been demonstrated in different types of cancer. However, its potential in Triple-Negative Breast Cancer (TNBC) is unknown yet. In this context, we have shown that I-Fraction: a polysaccharide-enriched extract obtained from *P. ostreatus* exerts antitumor activity on 4T1 and MDA-MB-231 TNBC cell lines in cultive. Therefore, the objectives of this work are to determine the antitumor activity in vivo of I-Fraction in TNBC and to deepen its physical-chemical characterization. To this end, we employed a 4T1 syngeneic murine model in which BALB/c mice bearing TNBC tumors were treated with I-Fraction extract (25 mg/kg or 50 mg/kg) or vehicle (PBS 1x), 5 times a week for 3 weeks (total doses = 15; subcutaneously in the periphery of the tumor). We found that treatment with 50 mg/kg of I-Fraction retarded tumor growth in vivo. From the eleventh dose, I-Fraction-treated mice had significantly smaller tumors than vehicle-treated mice ($p < 0.05$). In addition to this, the ex vivo tumor volume and weight developed under treatment with 50 mg/kg of I-Fraction were significantly lower compared to vehicle treatment ($p < 0.01$). Furthermore, we found a lower number of lung metastases per animal in 50 mg/kg I-Fraction-treated mice than in the vehicle-treated mice ($p = 0.001$). Also, the treatment with I-Fraction did not affect the weight of the mice or their internal organs, nor did it alter hematological and biochemical parameters. On the other hand, by thermogravimetric analysis, we determined that I-Fraction contains a moisture of 6.6%, a residue of 12.8% at 700 ºC and a degradation start temperature of 139.3 ºC. Furthermore, differential scanning calorimetry thermograms showed an exothermic event at 280.7 ºC (ΔH=225.6 J/g). In conclusion, these results demonstrate the antitumor activity in vivo of *P. ostreatus* I-Fraction in TNBC.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

6. EXPLORING THE PHYTOCHEMICAL COMPOSITION OF AN AQUEOUS EXTRACT OF *NELTUMA CALDENIA* LEAVES

Eliana Noelia Alonso[1,2], Mario Simirgiotis[3], Agustina Ibarra[1,2], Valentina Clemente[1,2], Exequiel Gonzalo Alonso[1,2], Agustina Gutiérrez[2,4], Pablo Marinangeli[4,5], María Eugenia Fermento[1,2], Georgina Pamela Coló[1,2], Alejandro Carlos Curino[1,2], María Marta Facchinetti[1,2], **María Julia Ferronato**[1,2].

[1]*Laboratorio de Biología del Cáncer, Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS) – Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Bahía Blanca, Argentina,* [2]*Departamento de Biología, Bioquímica y Farmacia, UNS,* [3]*Instituto de Farmacia, Facultad de Ciencias, Campus Isla Teja, Universidad Austral de Chile, Valdivia, Chile,* [4]*Laboratorio de Fitotecnología, Centro de Recursos Naturales Renovables de la Zona Semiárida (CERZOS), UNS – CONICET,* [5]*Departamento de Agronomía, UNS.*

Neltuma caldenia, commonly known as "caldén", is an endemic tree from Espinal region of Argentina. Previously, we evaluated the antitumor activity of an Aqueous Extract from *Neltuma caldenia* (AENc) leaves in Triple-Negative Breast Cancer (TNBC) cells studying its effects on cell viability, cell cycle, apoptosis and cell migration. In this work, phytochemical components of the AENc were screened by HPLC and GC-MS analysis. In addition, the content of proteins, carbohydrates, total phenolic acids and flavonoids were determined by colorimetric assays. The separation and identification of secondary metabolites from AENc were carried out on an UHPLC-ESI-QTOF-MS system and the analysis of the chromatographic peaks showed the presence of phenolic compounds; mainly flavonoids as quercetin, isorhamnetin, isovitexin, kaempferol, rutin, isorhoifolin, tricin, luteonin and catechin. Regarding GC-MS, interpretation of mass spectrum was conducted using the NIST database and the analysis showed the presence of volatile compounds: L-gala-L-ido-octose, 2-butyl-2,7-octadien-1-ol, 7-methyl-tetradecen-1-olacetate, 12-methyl-(E,E)-2,13-octadienol, 2-butenal-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl), dihydroactinidiolide and (E,E,Z)-1,3,12-nonadecatriene-5,14-diol. Additionally, the protein content of the AENc was 8.71 ± 1.26 mg/g (Bradford method; R^2 albumin calibration curve: 0.9883); the carbohydrates content was 0.29 ± 0.02 mg/g (phenol-sulfuric acid method; R^2 glucose calibration curve: 0.9938); the total phenolic acids content was 152 ± 0.3 mg/g (Folin-Ciocalteu method; R^2 gallic acid calibration curve: 0.9984) and the flavonoids content was 13.6 ± 0.023 mg/g (aluminium chloride method; R^2 quercetin calibration curve: 0.9980). In conclusion, the AENc is mainly composed of phenolic compounds which could be, at least in part, responsible for its antitumor properties in TNBC cells. Further studies are necessary in order to quantify the metabolites found in the AENc accurately.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

7. THERAPEUTIC POTENTIAL OF ALOE ARBORESCENS MILLER PARENCHYMA ETHANOLIC EXTRACT ON OSTEOPROGENITOR CELLS AND MYOBLAST (C2C12)

Nicolás Olegario Blanco, Natalia María Frattini, Lucía Pronsato, Andrea Vasconsuelo and Lorena Milanesi

Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur. Instituto de Ciencias Biológicas y Biomédicas del Sur, CONICET.

Research on natural products derived from plants with therapeutic potential in bone diseases is increasing due to their lower side effects and longer exposure time compared to synthetic drugs. *Aloe arborescens* Miller (*A. a.*) is a plant that possesses compounds with the potential to stimulate osteogenic activity, although its study is limited. This work evaluates the effects of the ethanolic extract of *A. a.* parenchyma on the viability, proliferation, migration, and mineralization of primary cultures of neonatal rat calvaria, and on the viability and proliferation of the murine myoblast cell line C2C12. Calvarial and C2C12 cells were treated with different dilutions of the ethanolic plant extract (1/2000-1/5000). In calvarial cells, migration was analyzed by wound assay and mineralization with alizarin red staining. Viability and proliferation were assessed with neutral red and crystal violet stains, respectively, for both cell types. Data were statistically analyzed by ANOVA and Bonferroni's multiple comparisons *post hoc* test. In calvarial cells, it was evidenced that 1/2000 (24, 48, and 72 h) and 1/5000 (72 h) dilutions showed a positive effect on cell viability ($p \leq 0.01$). A 27% ($p \leq 0.01$) increase in cell proliferation (1/5000, 72 h) was observed. The extract significantly stimulated migration (24 h) ($p \leq 0.01$). Both dilutions caused an increase in calcium deposits in these cells (higher effect with 1/5000 dilution at 25 days). The extract did not decrease the viability of C2C12 cells nor did it modify cell proliferation ($p \leq 0.01$). In conclusion, our results suggest that the ethanolic parenchymal extract of *A. a.* is non-toxic, has a positive impact on viability, stimulates proliferation and migration, and induces mineralization in osteoprogenitor cells, reflecting osteogenic differentiation. Furthermore, it has no toxic or proliferative effects on myoblasts, indicating that *A. a.* could represent a therapeutic alternative in bone pathologies without affecting muscle.

Pharmacognosy/Pharmacobotany
Chairs: Verónica Lasalle and Susana Gorzalczany

8. ANTIGIARDIAL EFFECTS OF *ATTALEA BUTYRACEA* FRUIT EXTRACT: MECHANISMS OF CELLULAR DEATH IN *GIARDIA LAMBLIA* TROPHOZOITES

Juan García-Bustos[1], Gabriel Luna Pizarro[2], Rocío G. Patolsky[2], Mariana Belén Joray[3], Constanza Feliziani[2], María Carolina Touz[2] and **Jerónimo Laiolo**[2,4]

[1]Universidad de La Amazonia, Caquetá, Florencia 180002, Colombia, [2]Instituto de Investigación Médica Mercedes y Martín Ferreyra, Consejo Nacional de Investigaciones Científicas y Técnicas (INIMEC-CONICET), Universidad Nacional de Córdoba, Córdoba 5016, Argentina, [3]Centro de Investigación y Desarrollo en Inmunología y Enfermedades Infecciosas, Consejo Nacional de Investigaciones Científicas y Técnicas (CIDIE-CONICET-UCC), Universidad Católica de Córdoba, Córdoba X5016DHK, Argentina, [4]Universidad Católica de Córdoba, Avda. Armada Argentina 3555, X5016DHK, Córdoba, Argentina.

Colombian plants, renowned for their rich tradition in traditional medicine, have garnered increasing attention for their potential therapeutic properties. Among these, Amazonian plant extracts have been explored for their effects on various health conditions, including gastrointestinal disorders. This study investigates the *in vitro* activity of 15 crude extracts from Colombian Amazonian plants against *Giardia lamblia*, a protozoan responsible for giardiasis—a prevalent gastrointestinal illness affecting diverse populations globally.

The *in vitro* efficacy of these extracts was assessed using the MTT colorimetric assay at a concentration of 500 µg/mL. The *Attalea butyracea* fruit extract (**P-2**) demonstrated the highest activity, with a median inhibitory concentration (IC_{50}) of 62.10 ± 6.57 µg/mL, leading to a detailed analysis of its mechanisms of action. Treatment with the IC_{50} of **P-2** resulted in an increased percentage of trophozoites in early apoptosis, while a dose of $2xIC_{50}$ significantly elevated late apoptosis and necrosis compared to the control. Observations from immunofluorescence and confocal microscopy revealed chromatin condensation and, in some cases, nuclear DNA degradation in treated trophozoites. Additionally, oxidative stress was induced, evidenced by a significant rise in reactive oxygen species (ROS). The structural integrity of the parasite was further confirmed to be affected by **P-2** through indirect immunofluorescence (IFI) and transmission electron microscopy (TEM).

These findings highlight the promising giardicidal activity of *Attalea butyracea* fruit extract and provide valuable insights into its mechanisms of action. The results underscore the potential of Colombian plant extracts as effective therapeutic agents for giardiasis, paving the way for further research and development of novel treatments.

Pharmaceutical Technology
Chairs: Cecilia Bouzat and Daniela Quinteros

9. DESIGN OF BIOPOLYMERS FILMS CARRYING STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF OPHTHALMIC DISEASES

Karina L. Bierbrauer[1,2], Laura R. Comini[1,2], Marcos Cometto[1], **Leandro E. Nieto**[1], Vanina A. Alamino[1,2], Victoria Leonhard[1,2], Dante M. Beltramo[1,2], Roxana V. Alasino[1,2]

[1]*CEPROCOR - Ministerio de Producción, Ciencia e Innovación Tecnológica - Gobierno de la Provincia de Córdoba,* [2]*CONICET - CCT Córdoba.*

Prednisolone is a steroidal anti-inflammatory drug that is useful for treating a wide range of inflammations and disorders typical of autoimmune disease. In the case of ocular diseases, particularly after surgery or processes that cause ocular inflammation, the administration of this type of drug is highly recommended. The goal is to rapidly reduce eye inflammation, leaving it without discomfort so that the patient finds quick relief. Although there are many formulations on the market designed to solve this problem, the usual administration dosage is complicated, resulting in poor patient adherence and often suspension of pharmacological treatment. Moreover, the amount of drug that reaches the posterior area of the eye (target site of the pharmacological action) is between 1 and 5% of the initial drug contained in a drop. This fact can be attributed to the low permeability of prednisolone through the conjunctival sac as well as cleaning mechanisms such as tearing. As a result, an alternative to the pharmaceutical drop instillation becomes necessary. Based on the previous description, we present the results obtained from the characterization and subsequent release study of prednisolone previously loaded in Eudragit E100 films, an acrylic co-polymer, with PEG400 as plasticizer. The techniques and studies performed for the characterization were FTIR, DSC, swelling, mechanical properties, and mucoadhesiveness; for the last two we used a texturometer. Additionally, we conducted prednisolone release tests using a Franz cell, quantifying the permeated active principle by UV-vis spectroscopy as a function of time. The findings indicated that Eudragit E100 films had good mechanical properties and released prednisolone slowly and steadily. These films have the potential to be used as ocular implants because they would simplify dosing and make therapeutic treatment easier.

Pharmaceutical Technology
Chairs: Cecilia Bouzat and Daniela Quinteros

10. PHARMACODYNAMIC-PHARMACOKINETIC RELATIONSHIPS AS A FUNDAMENTAL BASIS FOR ACHIEVING SUCCESSFUL PHARMACEUTICAL DOSAGE FORMS OF FUROSEMIDE

María Luisa Rodríguez[1], Pietro Fagiolino[2], Santiago Palma[3] and Manuel Ibarra[2]

[1]*Biopharmacy and Pharmaceutical Technology, Polo Tecnológico de Pando Institute, Faculty of Chemistry, Universidad de la República, Canelones, Uruguay,* [2]*Pharmaceutical Sciences Department, Faculty of Chemistry, Bioavailability and Bioequivalence Centre for Medicine Evaluation, Universidad de la República, Montevideo, Uruguay,* [3]*Pharmaceutical Sciences Laboratory, Department of Pharmaceutical Sciences, Faculty of Chemical Sciences, Universidad Nacional de Córdoba, Córdoba, Argentina*

Acidic drugs face absorption challenges in oral administration due to pH variations in the gastrointestinal (GI) tract, leading to ionization and reduced uptake. Furosemide (FUR), a potent diuretic with a low pKa exemplifies this issue, as its absorption is limited to the upper small intestine (absorption window). To enhance bioavailability and its diuretic effect, gastroretentive drug delivery systems (GRDDS) are designed for complete dissolution in the stomach.
Several clinical studies on different FUR formulations were analyzed. Since this drug is mainly excreted through urine, a large part of the in vivo pharmacokinetic research involves tracking its urinary excretion rate. The relation between drug excretion rates and the intensity of urine output; diuretic efficiency and drug delivery rates; and the benefit of sustained drug delivery were analyzed.
The diuretic effect of FUR increases its urinary excretion rate because of an increase in both the intrinsic excretion clearance (urine output) and the renal tissue bioavailability. Consequently, urinary recovery does not accurately represent the systemic bioavailability of the formulations, but rather reflects their diuretic effects. Extended drug input resulted in a more effective diuretic response compared to administering the entire dose rapidly, as long as the drug concentration at the site of action remained above the minimum effective level for a longer period. A rate-limiting step must be established, specifically the drug release from the formulation to prevent a loss of systemic bioavailability. The formulation should not progress through the GI tract beyond the absorption window and also have to ensure that the concentration at the site of action is as efficient as possible (around the EC50%).
It was concluded that the most effective strategy for developing GRDDS of FUR involves incorporating two components within the formulation: a rapidly releasing loading dose and an extended-release maintenance dose.

Pharmaceutical Technology
Chairs: Cecilia Bouzat and Daniela Quinteros

11. DEVELOPMENT OF FUROSEMIDE CONTROLLED-RELEASE FLOATING TABLETS USING A SOLID DISPERSION STRATEGY

María Luisa Rodríguez[1], **Federico Rosano**[1], Santiago Palma[2] and Pietro Fagiolino[3]

[1]*Biopharmacy and Pharmaceutical Technology, Polo Tecnológico de Pando Institute, Faculty of Chemistry, Universidad de la República, Canelones, Uruguay,* [2]*Pharmaceutical Sciences Laboratory, Department of Pharmaceutical Sciences, Faculty of Chemical Sciences, Universidad Nacional de Córdoba, Córdoba, Argentina,* [3]*Pharmaceutical Sciences Department, Faculty of Chemistry, Bioavailability and Bioequivalence Centre for Medicine Evaluation, Universidad de la República, Montevideo, Uruguay.*

Furosemide has a narrow absorption window in the upper GI tract due to its low solubility and ionization in the gut. Evidence suggests that a modified-release gastroretentive (GR) system is an effective strategy to improve its oral bioavailability and diuretic effect. Solid dispersions (SD) have been proposed as an alternative to enhance the solubility of poorly soluble drugs. This research aimed to develop a GR tablet with extended release of furosemide, using flotation and tablet size to ensure gastric retention, and incorporating Poloxamer 188 (P188) as an SD carrier to improve drug dissolution.

Using a Quality by Design approach, the quality target product profile was defined, and critical material attributes and process parameters were identified through risk assessment. These included matrix formers, carbogenic/acidogenic agents, diluents, P188 content, and compression force. Pre-formulation studies, including dissolution tests, XRD, DTA, and confocal Raman microscopy, showed that the SD of furosemide and P188 enhanced the dissolution rate of the drug compared to its physical mixture, likely due to the reduced crystallinity of P188. Additionally, furosemide was found to be homogeneously distributed without altering its crystalline structure.

A melt granulation process was developed to produce GR tablets, adjusting formulations to optimize drug release, buoyancy, and matrix stability. Formulation 12 (F12) achieved the desired controlled release at gastric pH, with 5 hours of buoyancy and minimal matrix erosion (EI= 67.3%). F12 met specifications for mass uniformity, dosage strength, friability, hardness, and dimensions. After buoyancy testing, the matrices measured 23 mm in length and 10.50 mm in diameter (n=3), making it a promising formulation retained by both flotation and size. The developed formulation is expected to have prolonged gastric retention in vivo and the manufacturing process is scalable to an industrial level.

Pharmaceutical Technology
Chairs: Cecilia Bouzat and Daniela Quinteros

12. PRODUCTION OF INHALABLE POROUS PARTICLES BY SPRAY DRYING: A COMPARATIVE ANALYSIS OF THREE- AND TWO-FLUID NOZZLES

Marcos Andrés Serain[1,2,3], Verónica Bucalá[1,2] and Loreana Gallo[1,3]

[1]*Planta Piloto de ingeniería Química, PLAPIQUI (UNS-CONICET),* [2]*Departamento de Ingeniería Química (DIQ-UNS),* [3]*Departamento de Biología, Bioquímica y Farmacia (BByF-UNS).*

Spray drying (SD) technology is employed to produce porous particles (PPs) for pulmonary drug delivery. This technique enables precise control over particle properties through the optimization of operating conditions and the selection of specific atomization nozzles. The present study compares the use of a two-fluid nozzle (2-FN) with three-fluid nozzle (3-FN) to assess the impact on the production of inhalable PPs. SD tests were done using a Buchi-290 spray dryer. For both the 2-FN y 3-FN configurations, the drying air flowrate was set at 35 m^3/h, and the inlet air temperature at 170 °C. Atomization flowrates of 601 and 742 l/h were tested. The feed volumetric flowrate was fixed at 3 ml/min for the 2-FN. In the 3-FN, two synchronized liquids were simultaneously pumped through the nozzle at a feed rate of 1.5 ml/min each, maintaining a total flowrate of 3 ml/min for comparison purposes. In both setups, the liquid feed was prepared by dissolving salbutamol sulfate (10%, w/v) and ammonium bicarbonate (pore-forming agent, 1.25%, w/v) in water. After SD, the resulting powders exhibited a moisture content below 2.44%, indicating effective drying. Process yields exceeded 58%, which is acceptable for a laboratory-scale dryer. SEM images showed that all samples had smooth surfaces with pores. Powders produced with the 3-FN had higher tapped density and particle size compared to those from the 2-FN. The aerosolization properties showed that all samples achieved an emitted dose above 92%. The mass median aerodynamic diameter was higher than 5 µm (limit value for inhalable particles) with the 3-FN. In concordance, the fine particle fraction for these powders was about half (30%) compared to that obtained with the 2-FN (62%). The 2-FN setup and selected operating conditions yielded better powder characteristics compared to those using 3-FN. Further research is needed to adjust the operating conditions and feed formulation to produce 3-FN particles suitable for inhalation.

Pharmaceutical Technology
Chairs Cecilia Bouzat and Daniela Quinteros

13. EVALUATION OF THE AERODYNAMIC PERFORMANCE OF TWO NATIONAL VALVED HOLDING CHAMBERS FOR ASTHMA TREATMENT

Yamila L. de Charras[1,2], Tatiana M. Odoux[1], Fernanda Cabrera[1], Diego E. Bertin[1,2] and M. Verónica Ramírez-Rigo[1,3]

[1]*Planta Piloto de Ingeniería Química (PLAPIQUI – CONICET – UNS),* [2]*Departamento de Ingeniería Química, Universidad Nacional del Sur,* [3]*Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur.*

Valved Holding Chambers (VHCs) are medical devices recommended to reduce oropharyngeal deposition and minimize side effects when pressurized metered-dose inhalers (pMDIs) are prescribed. Some of the aerosol is lost on the walls of the VHC, and only respirable particles (1-5 µm), produce the desired therapeutic effect. Although several VHCs are available on the market, the specific performance of national ones is unknown, so the dose is adjusted based on the patient's response. The aim of this study was to evaluate the aerodynamic performance of two national VHCs for asthma treatment.

Comparative evaluations were conducted on two VHCs of the same brand (AC-305 y AC-403), one cylindrical (AH) and one pear-shaped (AP), against a reference cylindrical VHC (ACP). The emitted fraction by the device and their Particle Size Distribution (PSD) were determined using a multistage cascade impactor (NGI) operated at a flow rate of 30 L/min. A pMDI containing salbutamol was used. The drug was recovered and quantified by HPLC-UV.

The particle size distribution of the emitted aerosol, measured by the NGI, presents a MMAD of 2.2 ± 0.1 µm for both VHCs under study. This value is slightly lower than the reference (2.5 ± 0.1 µm), which implies that they have a greater tendency towards fine particles. In addition, an emitted fraction of 27.5 ± 2.4% was determined for AH and 27.6 ± 3.6% for AP, showing no relevant differences in terms of VHC geometry. Although the emission value is around 35% lower than the reference, the evaluated VHCs present a 15% higher fraction of fine particles and a 47% lower fraction of coarse particles on average. These results indicate that the VHCs under study present a lower oropharyngeal deposition and higher aerosol quality in terms of respirable particles.

In conclusion, the national VHCs demonstrate good aerodynamic performance.

Pharmaceutical Technology
Chairs: Cecilia Bouzat and Daniela Quinteros

14. INDOMETHACIN DRY POWDER INHALER AS AN ALTERNATIVE TO INHALED CORTICOSTEROIDS IN PEDIATRIC ASTHMA TREATMENTS

Nazareth Ceschan[1,2], Andrea Dugour[3], Beatriz Behernd[4], Juan Figueroa[3], Hugh Smyth[4], María Ramírez Rigo[1,2]

[1]Planta Piloto de Ingeniería Química (PLAPIQUI, UNS-CONICET), Camino La Carrindanga, Km 7, Bahía Blanca (8000), Argentina, [2] Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, San Juan 670, Bahía Blanca (8000), Argentina, [3] Instituto de Ciencia y Tecnología Dr. Cesar Milstein (CONICET) - Fundación Cassará, [4]College of Pharmacy, The University of Texas at Austin, 2409 University Avenue, Austin, TX (78712) United States

Asthma is a chronic respiratory condition affecting millions globally, especially children. This illness is mostly treated with inhaled corticosteroids (IC). However, these treatments often face challenges related to adherence and adverse effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are not traditionally used for asthma although they are not contraindicated. This work proposes an indomethacin (a NSAID) dry powder inhaler (DPI) for pediatric asthma treatment as an alternative to traditional IC therapies.

Indomethacin (IN) microparticles were obtained by jet-milling and the aerodynamic performance and anti-inflammatory effect was studied. Three different inhalers, each with different intrinsic resistances (low, medium, and high), were tested at two pressure drops (4KPa, as per pharmacopeia, and 1KPa, to mimic pediatric respiratory patterns). The anti-inflammatory effect of IN was studied in the CALU-3 cell line and compared to budesonide (BUD), a widely used IC, by measuring IL-6 and IL-8 production after a pro-inflammatory stimulus.

Particles dispersed readily through inhalers with different resistances. The mass median aerodynamic diameter was adequate for the application. The emitted fraction was high at a 4KPa pressure drop but decreased at lower pressures. The fine particle fraction of IN, indicating the amount of drug entering the lungs, was independent of inspiratory flow rate and inhaler resistance, making it suitable for patients with different respiratory capabilities, such as children. IN showed an anti-inflammatory effect similar to BUD in the asthma model, reducing the production of IL-6 and IL-8. No significant differences were found between BUD and IN at different concentrations.

In conclusion, the IN microparticles obtained by milling are suitable for pulmonary administration using devices with varying resistances. The studied system demonstrates potential for treating airway inflammation in children, providing an alternative to IC.

Pharmaceutical Technology
Chairs: Cecilia Bouzat and Daniela Quinteros

15. SILDENAFIL CHEWABLE GELS: A NOVEL ALTERNATIVE FOR THE TREATMENT OF PEDIATRIC PULMONARY ARTERIAL HYPERTENSION

Romina B. Pereyra[1,2], Nicolas A. Lopez[1,2], María B. Figuerón[1] and Noelia L. González Vidal[1,2]

[1] *Dpto de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS), Bahía Blanca, Argentina.* [2] *Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Bahía Blanca, Argentina.*

Pulmonary arterial hypertension is an increase in the pressure of the vessels that supply blood to the lungs and is associated with high mortality rates. Sildenafil (SIL) is a therapeutic option for pediatric treatment. The aim of this work was to develop chewable gels (CG), a patient-friendly pharmaceutical form for children, containing SIL at a dose of 20 mg per unit. Also, gelatin, plasticizers (glycerin and sorbitol), sucralose, citric acid, benzoate sodium, and menthol were used for CG design. Four formulations (F_1-F_4) were obtained by molding, after application of a 2^2 experimental design, with evaluation of the experimental factors impact over critical properties by ANOVA. After the stabilization process (drying in a vacuum oven at 25°C), CG were entirely characterized. ANOVA results indicated that gelatin and plasticizer concentration were significant factors for the quality of developed CG. The final weight of CG was around 3.5 ± 0.15 g/unit. There were no significant differences between the pH of formulations (4.49 ± 0.03), which is acceptable since low values ensure the preservative activity of sodium benzoate. On the other hand, F_3 showed the lowest syneresis (24.08 ± 0.31 %), the highest volume (2.66 ± 0.17 cm^3) and the most appropriate texture parameters (hardness 83.34 ± 1.56 N; gumminess 74.30 ± 2.34 N, springiness 4.75 ± 0.11 mm and cohesiveness 0.87 ± 0.001). Besides, this formulation exhibited a disintegration time of 16 minutes and an appropriate *in vitro* dissolution profile, achieving a maximum value of 98.5 ± 0.13 % dissolved at 90 minutes. In conclusion, F_3 demonstrated favorable characteristics, including optimal dissolution profile and disintegration time, which support its potential effectiveness for oral administration of SIL. These attributes indicate that the CG can be a viable and practical alternative for the treatment of pediatric pulmonary arterial hypertension, potentially enhancing patient compliance and therapeutic efficacy.

Molecular Pharmacology
Chairs: Pedro Martin and Hugo Ortega

16. ELUCIDATING CANNABIDIOL BINDING SITES ON THE α7 NICOTINIC ACETYLCHOLINE RECEPTOR

Juan Facundo Chrestia[1], Franco Viscarra[2,3], Isabel Bermudez[2], and Cecilia Bouzat[1]

[1]*Departamento de Biología, Bioquímica y Farmacia, Instituto de Investigaciones Bioquímicas de Bahía Blanca, Universidad Nacional del Sur-Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina,* [2]*Department of Biological and Medical Sciences, Oxford Brookes University, UK,* [3]*Structural Bioinformatics and Computational Biochemistry, Department of Biochemistry, Oxford University, UK.*

The α7 nicotinic receptor is an ACh-gated channel present in the nervous system and in non-neuronal cells. Reduced activity of α7 has been linked to neurological and neurodegenerative disorders, while increased activity could contribute to cancer progression. α7 is a target of cannabidiol (CBD), which is of great interest due to its widespread use, therapeutic properties, and lack of psychoactive effects. By patch clamp recordings, we showed that CBD mediates two distinct actions on α7 function occurring at different time scales. CBD rapidly inhibits the frequency of activation episodes, while after several minutes, it causes an additional delayed effect evidenced by the appearance of prolonged activation episodes. To predict the binding sites of CBD, we performed molecular dynamics simulations of α7 and CBD in coarse-grained representation. α7 resting and desensitized states were embedded in a POPC:POPA:CHOL membrane and simulated in the presence of CBD molecules. Several potential binding sites were identified for both receptor states. Representative structures were backmapped to atomistic representation and each one was simulated to gain deeper insight into the stability and interactions. In both states, the most stable binding site was located in the top portion of the extracellular domain. Contact analysis was performed and several residues were selected for mutagenesis studies. Compared to the wild-type receptor, electrophysiological recordings with mutants showed different responses to CBD, ranging from reduced sensitivity for the rapid inhibitory effect to increased sensitivity for the kinetic changes. These results confirm the involvement of the candidate residues in the allosteric mechanism underlying CBD´s effect on α7 and suggest that different residues govern the different effects.

Molecular Pharmacology
Chairs: Pedro Martin and Hugo Ortega

17. *CAENORHABDITIS ELEGANS* BETAINE-SENSITIVE NICOTINIC RECEPTORS: A POTENTIAL TARGET FOR ANTIPARASITIC DRUGS

Ornella Turani, Guillermina Hernando, Noelia Rodríguez Araujo, and Cecilia Bouzat.

Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, 8000 Bahía Blanca, Argentina.

Parasitic nematodes have developed resistance to most anthelmintic drugs, generating problems in human and animal health. Consequently, there is an urgent need to identify novel drugs and targets. *Caenorhabditis elegans*, with its extensive and diverse family of nicotinic acetylcholine receptors (nAChRs), offers a valuable model for this purpose. Many of these receptors, which are critical for worm locomotion, remain uncharacterized, making them potential targets for novel anthelmintic drugs. ACR-23, whose endogenous agonist is betaine (BE) and is modulated by the nematocidal drug monepantel (MNP), is a poorly characterized nAChR present in body-wall muscle and mechanosensory neurons of nematodes. Since it is not conserved in vertebrates, ACR-23 is an interesting pharmacological target for anthelmintic drugs. Our goal is to elucidate the molecular function and pharmacology of ACR-23 to investigate its potential as a novel anthelmintic drug target. By performing locomotion assays with wild-type worms we showed that exogenous BE significantly increased worm motility. This effect was not observed in *acr-23* mutants, indicating that the hypermotility is mediated by ACR-23. Exposure to MNP produced the opposite effect, as motility was reduced in a concentration-dependent manner. Additionally, MNP produced spastic paralysis and inhibited egg hatching. Locomotion assays with mutant worms demonstrated that MNP-induced paralysis is mediated by ACR-23 and DEG-3/DES-2, a nAChR present in sensory neurons involved in nociception and chemotaxis. By patch-clamp recordings from cultured *C. elegans* L1 muscle cells, we described for the first time BE-elicited single channels and macroscopic currents. Our study provides novel insights into the molecular function and pharmacology of the nAChR family and contributes to the understanding of the molecular basis of anthelmintic action. This paves the way for the development of novel drugs.

Molecular Pharmacology
Chairs: Pedro Martin and Hugo Ortega

18. DRUG REPURPOSING STRATEGY TARGETING THE HUMAN 5-HT$_3$A RECEPTOR

Noelia Rodriguez Araujo, Ignacio Bergé, Jeremías Corradi and Cecilia Bouzat

Instituto de Investigaciones Bioquímicas de Bahía Blanca, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, 8000 Bahía Blanca, Argentina.

Drug repurposing strategies offer a rational approach to reducing the time and costs associated with new therapies. In this study, piperazine (PZE) and hydroxyzine (HZE) were tested as novel modulators of the human 5-HT$_3$A receptor. This receptor belongs to the pentameric ligand-gated ion channel family and is emerging as a pharmacological target for neurological, psychiatric and gastrointestinal disorders. PZE is an anthelmintic drug that acts through nematode GABA and MOD-1 receptors while HZE, a derivative of PZE, is a first-generation H1 receptor antagonist used for skin allergies and shows mild anxiolytic, sedative, and antiemetic effects. By whole cell recordings, we observed that the preincubation with PZE inhibited 5-HT-evoked currents of 5-HT$_3$A receptors. The co-application of PZE and 5-HT did not alter the peak current, suggesting a non-competitive inhibition. PZE caused an increase in the EC_{50} value and a decrease in the maximum response to 5-HT, further supporting the proposed inhibitory mechanism. Molecular docking of PZE into the 5-HT3A receptor suggested two major binding sites, distinct from the 5-HT binding site, reinforcing that PZE may act as a negative allosteric modulator. Candidate residues at these sites, located at the interface between the transmembrane (TMD) and the extracellular domains, and at the top of the TMD were mutated to confirm their contribution. Regarding HZE, our electrophysiological studies demonstrated that the preincubation with this drug in the low micromolar concentration range strongly decreased macroscopic responses of 5-HT$_3$A. Thus, the 5-HT$_3$A receptor may mediate several effects observed with HZE and could represent an important pharmacological target. By identifying new targets and mechanisms, our drug repositioning strategy facilitates the discovery of novel therapeutic applications for clinically approved drugs in a rational and efficient manner.

Molecular Pharmacology
Chairs: Pedro Martin and Hugo Ortega

19. PHARMACOLOGICAL INHIBITION OF P300 EXERTS AN ANTITUMOR ROLE IN THYROID CANCER

Valentina Clemente[1,2], Agustina Ibarra[1,2], Karen Schweitzer[1,2], Eliana Noelia Alonso[1,2], María Julia Ferronato[1,2], Georgina Pamela Coló[1,2], Guillermina Ana Gallardo[1,2], Alejandro Carlos Curino[1,2], María Eugenia Fermento[1,2] and María Marta Facchinetti[1,2].

[1]*Laboratorio de Biología del Cáncer, Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS)-Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Bahía Blanca, Argentina.* [2]*Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS), Bahía Blanca, Argentina.*

Thyroid Cancer (TC) is the most prevalent endocrine tumor worldwide. p300 is a protein that functions as a transcriptional cofactor, histone acetyltransferase, and lysine acetyltransferase for proteins involved in functions other than transcription. A relationship of p300 with cancer has been demonstrated, however, its role is still unclear since it has been documented as a tumor suppressor and/or as an oncoprotein. In our laboratory, we have established an association between p300 and breast cancer, observing a protumoral role. Due to the limited studies on p300 and TC, it is interesting to investigate p300 expression and the cellular and molecular mechanisms through which this protein could be involved in tumor progression of TC. The objective of this work was to study the effect of inhibiting the acetylase function of p300 on the processes of apoptosis and metastasis in human TC cells. The treatment of human papillary TC cell line, TPC-1, with VV59 (inhibitor of p300 acetylase function) or its vehicle (DMSO) produced a decrease in the number of cells compared to the vehicle (crystal violet assay and manual counting, $p<0.0001$). When we analyzed the cell cycle by flow cytometry, we detected an increase in the sub G0/G1 phase and a decrease in the G0/G1 phase in cells treated with VV59 compared to those treated with the vehicle ($p<0.001$). In addition, we detected a decrease in p53 protein expression (Western Blot) and an increase in the cytoplasmic levels of p53 and p300 (immunofluorescence) in cells treated with VV59 compared to cells treated with vehicle. On the other hand, we detected that pharmacological inhibition of p300 decreases cell migration (wound healing assay, $p<0.0001$), invasion (matrigel assay, $p<0.0001$), and cell adhesion (crystal violet assay, $p<0.0001$). Taken together, these results demonstrate an antitumoral role for the pharmacological inhibition of p300 acetylase function in the human TC cell line.

Molecular Pharmacology
Chairs:

20. HEMEOXYGENASE-1 INDUCES THYROID CANCER PROGRESSION DEPENDING ON SUBCELLULAR LOCALIZATION AND ENZYMATIC ACTIVITY

Exequiel Gonzalo Alonso[1], Marilina Mascaró[1], Karen Schweitzer[1], Lucía Fernández Chávez[1], Georgina Pamela Coló[1], Eliana Noelia Alonso[1], María Julia Ferronato[1], Eugenia Fermento[1], María Marta Facchinetti[1], Alejandro Carlos Curino[1].

[1]*Laboratorio de Biología del Cáncer – Instituto de Investigaciones Bioquímicas Bahía Blanca (INIBIBB) Universidad Nacional del Sur (UNS-CONICET). Departamento de Biología, Bioquímica y Farmacia.*

Thyroid cancer (TC) is the most common endocrine tumor worldwide. Heme Oxygenase-1 (HO-1) is responsible for heme degradation and has shown pro- or antitumor properties depending on the tumor type. In this work, we aimed to study the role of HO-1 in TC biology. For this purpose, we assessed HO-1 expression and localization by Western Blot and indirect immunofluorescence, respectively; cell viability by crystal violet method, cell migration by wound healing assay and cellular protrusions by actin filaments staining. Pharmacological activation of HO-1 with 80μM hemin induced HO-1 overexpression, nuclear localization and increased cell migration and protrusions in TPC-1 ($p<0.0001$) and 8505c ($p<0.0001$) cell lines. In the Nthy-Ori-3-1 non-malignant cell line, only HO-1 cytoplasmic localization was observed and cell migration was unaffected. Pharmacological inhibition of HO-1 with 16μM ZnPP induced HO-1 expression, cytoplasmic localization and reduced migration in TPC-1, 8505c and Nthy-Ori-3-1 ($p<0.001$) cells. To evaluate nuclear HO-1 contribution in TC cell viability, we treated TPC-1 cells with 10μM E-64 (a cysteine-protease inhibitor shown to inhibit HO-1 nuclear translocation) or its combination with hemin. Both the treatment with E-64 alone and with E-64+hemin showed a reduction in HO-1 nuclear expression. In addition, E-64+hemin showed a decrease in cell viability compared with hemin treatment alone (48-72h, $p<0.0001$). Since MAPK is the main signaling pathway involved in TC, we analyzed pERK levels and observed that it increased after hemin treatment. Moreover, 80μM hemin, 10μM U0126 (MEK inhibitor) or their combinations, failed to alter HO-1 expression, thus showing that HO-1 is located upstream of the MEK-ERK pathway. In conclusion, our results indicate a protumor role for HO-1 in TC depending on its subcellular localization and enzymatic activity suggesting that both the canonical and non-canonical pathways of HO-1 are involved in TC progression.

Molecular Pharmacology
Chairs: Pedro Martin and Hugo Ortega

21. MOLECULAR INSIGHTS INTO NATURAL COMPOUNDS: ELECTROPHYSIOLOGICAL EFFECTS OF TRANS-CINNAMALDEHYDE AND EUGENOL ON NICOTINIC ACETYLCHOLINE RECEPTORS

Guillermina Hernando, Juan Facundo Chrestia, and Cecilia Bouzat

Instituto de Investigaciones Bioquímicas de Bahía Blanca, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, 8000 Bahía Blanca, Argentina.

Natural extracts and essential oils, often containing a diverse array of bioactive compounds, are appealing sources for identifying new potential drug candidates in drug discovery. Bioactive compounds have been used in traditional medicine for centuries to treat a variety of diseases. In recent times, there has been a resurgence of interest in these bioactive compounds due to their medicinal properties. Research has shown that many of these compounds act on neurotransmitter receptors, particularly Cys-loop receptors such as the nicotinic acetylcholine receptor (nAChR). nAChRs are a family of acetylcholine-gated ion channels found in the central and peripheral nervous systems, playing key roles in processes like muscle contraction, memory, and attention.

The primary goal of this project was to investigate the molecular effects of two naturally occurring phenylpropanoids found in *Cinnamomum verum* oil, trans-cinnamaldehyde (TCA) and eugenol (EGN), on two types of mammalian nAChRs, both of which are involved in various pathological conditions. Since TCA and EGN are multitarget compounds, it is essential to understand the molecular mechanisms underlying their potential therapeutic and adverse effects.

Through single-channel recordings, we observed that TCA exerts a negative modulatory effect on both α7 and muscular nAChRs. In α7 receptors, TCA significantly reduces activity by decreasing the frequency of activation episodes without affecting the amplitude or open duration. In contrast, for muscular nAChRs, both TCA and EGN induce a concentration-dependent reduction in open channel duration within the micromolar range. This reduction is accompanied by a shift towards shorter durations in the main closed component.

The modulation of nAChRs by these compounds is pharmacologically significant and should be considered when evaluating the therapeutic potential of TCA and EGN. Our findings provide valuable insights into how natural compounds affect Cys-loop receptors, which are underexplored but critical targets for various therapeutic strategies.

Medicinal Chemistry/Biopharmacy
Chairs: Verónica Lasalle and Susana Gorzalczany

22. SYNTHESIS, BIOLOGICAL EVALUATION AND IN SILICO ANALYSIS OF NEW METHYLXANTHINE DERIVATIVES AS POTENTIATORS OF THE CHOLINERGIC SYSTEM

Juan Pablo Munafó[1], Brunella Biscussi[2], Santiago Gundin[2], Diego Obiol[3], Marcelo Costabel[3], Cecilia Bouzat[1], Ana Paula Murray[2] and Silvia Antollini[1]

[1]*INIBIBB-CONICET-UNS, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, Bahía Blanca (8000), Argentina.* [2]*INQUISUR-CONICET-UNS, Departamento de Química, Universidad Nacional del Sur, Bahía Blanca (8000), Argentina.* [3]*IFISUR-CONICET, Departamento de Física, Universidad Nacional del Sur, Bahía Blanca (8000), Argentina*

Cholinergic deficiency is commonly associated with several diseases, such as Alzheimer's and Myasthenia Gravis. To address this question, one of the strategies involves the synthesis of hybrid molecules that integrate different pharmacophores. In previous research, caffeine was used as a basis to create caffeine-pyrrolidine hybrids, which were shown to be effective both as acetylcholinesterase (AChE) inhibitors and in potentiating the nicotinic acetylcholine receptor (nAChR).

In the present study, a new series of caffeine derivatives with various primary and secondary amines as accessory groups were evaluated. These compounds were efficiently synthesized using a microwave reactor, with alkylbrominated intermediates of theophylline and theobromine as starting reagents along with the corresponding amine. All methylxanthine hybrids were found to be AChE inhibitors, with some exhibiting potency comparable to that of tacrine. To assess the impact of these compounds on the nAChR, fluorescence spectroscopy and single-channel measurements were performed to evaluate their effects on the receptor's conformational state and functionality. Some of the compounds acted as partial agonists, although not all were capable of stabilizing the receptor in a desensitized state. To understand the molecular mechanisms underlying these results, we conducted molecular docking studies on both AChE and nAChR.

The agonist activity of the synthesized caffeine analogs on the nAChR was found to depend on the accessory group, while the stabilization of the receptor in a desensitized state was associated with interactions involving the intermediate chain of the hybrid compounds at the binding site. Thus, we obtained a group of molecules that behave as cholinergic potentiators more efficiently than caffeine and also identified key features crucial for modulating the pharmacological targets under study.

Medicinal Chemistry/Biopharmacy
Chairs: Cecilia Bouzat and Daniela Quinteros

23. ANTICANCER ACTIVITY AND SAFETY ASSESSMENT OF A TROXERUTIN-OXIDOVANADIUM(IV) COMPLEX ON LUNG CANCER CELLS

Alexandra Velásquez Bravo[1], **Juan José Martínez Medina**[2], Libertad López Tevez[2], Andrés Gonzalo Restrepo[1], Luciano Huamaní[1], Pablo Gonzalez[3], Evelina Ferrer[1], Patricia Williams[1] and Luciana Naso[1]

[1]*CEQUINOR, CONICET/UNLP, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Bv. 120 Nº 1465, 1900, La Plata, Argentina.* [2]*INIPTA, CONICET/UNCAUS, Universidad Nacional Del Chaco Austral, Comandante Fernández Nº 755, Presidencia Roque Sáenz Peña (3700), Chaco, Argentina.* [3]*Departamento de Física, Facultad de Bioquímica y Ciencias Biológicas, Universidad Nacional del Litoral and CONICET, Santa Fe S3000ZAA, Argentina.*

Introduction: Lung cancer is the second most common malignant tumor worldwide. While chemotherapy effectively reduces tumor volume, it also has severe side effects. In this context, natural compounds are considered potential alternatives to chemotherapeutic drugs.
Objective: The primary objective is to synthesize, characterize, and assess the anticancer activity of a new compound between the flavonol troxerutin (Trox) and the oxidovanadium(IV) cation (VOtrox), based on the hypothesis that flavonoids structurally modified by complexation exhibit enhanced biological properties.
Methods: VOtrox was synthesized in absolute methanol at pH=7 and characterized using spectroscopic techniques (FTIR, EPR, UV-vis), elemental and thermogravimetric analysis. The effects of the compounds on lung cancer cell viability (A549 cell line) were measured by MTT assay. To investigate the mechanism of action, morphological changes, intracellular reactive oxygen species ROS content (CM-H_2DCFDA probe), mitochondrial membrane potential (MMP) ($DIOC_6$ probe), and GSH depletion were used. The Ames test to evaluate genetic damage and the *Artemia salina* test to predict acute toxicity were used.
Results: The proposed structure of the complex, $[VO(trox)_2].8H_2O$, was supported by physicochemical analysis. The metal coordinated through the 5-hydroxy (ring A) and 4-carbonyl (ring C) of troxerutin. VOtrox is stable in aqueous solution for at least 30 h. At 100 µM, VOtrox reduced 35% A549 cell viability which is consistent with the morphological changes noted: cell shrinkage and nuclear condensation. The complex increased ROS levels and decreased MMP and GSH content in a dose-dependent manner (*ca*. 250%, 30%, and 29% at 100 µM, respectively) compared to the untreated cells. The compound did not exert acute toxicity or mutagenic action at concentration up to 600 µg mL^{-1}.
Conclusion: Antitumor activity of troxerutin enhances upon coordination.

Medicinal Chemistry/Biopharmacy
Chairs: Cecilia Bouzat and Daniela Quinteros

24. GREEN SYNTHESIS OF HETEROCYCLES AND BIOACTIVITY EVALUATION FOR THE TREATMENT OF NEUROLOGICAL DISEASE

Valentina Pastore[1], Valeria Palermo[2], Eliana Nope[2], Marina Rademacher[1], Victoria Suarez[1], Malena Mihura[1], Gabriel Sathicq[2], Gustavo Romanelli[2], Mariel Marder[1].

[1]*Instituto de Química y Fisicoquímica Biológicas Prof. Dr. Alejandro C. Paladini (IQUIFIB). UBA-CONICET. Facultad de Farmacia y Bioquímica. Buenos Aires, Argentina.* [2]*Grupo de Investigación en Síntesis Orgánica Ecoeficiente, Centro de Investigación en Ciencias Aplicadas "Jorge J. Ronco" (CINDECA). CICPBA-CONICET-UNLP. La Plata, Buenos Aires, Argentina.*

In this work, we present the synthesis of molecules belonging to heterocyclic families, known for their extensive and proven biological activities, using multicomponent reactions aligned with the principles of Green Chemistry. This approach emphasizes a high degree of Atomic Economy, avoiding the isolation or purification of intermediates. The work includes the synthesis of derivatives: dihydropyridines such as nifedipine, recognized for its calcium channel blocking action; 3,4-dihydropyrimidin-2(1H)-ones/thiones, a family with notable anticancer activity exemplified by monastrol; tetrahydropyridines, compounds exhibiting a range of biological activities such as antimicrobial, antioxidant, antifungal, and neuroprotective properties; and 2-amino-4H-pyrans, known for their pharmacological activity as antifungal, anti-inflammatory, and anticancer agents. The bioactivity of the synthesized series was explored with a focus on therapeutic targets in the central nervous system, aiming to treat diseases such as epilepsy, Parkinson's, and Alzheimer's. Initially, *in silico* assays were conducted using validated and freely accessible programs that allow the evaluation of physicochemical descriptors and parameters related to drug absorption, distribution, metabolism and excretion. The potential for interaction with various therapeutic targets was assessed using tools such as SwissADME, SwissTargetPrediction, and Way2Drug. Preliminary results showed that 11 selected candidates exhibited *in silico* activity against targets including monoamine oxidases, acetylcholinesterases, and voltage-gated ion channels, all of which are related to the aforementioned diseases. Following the selection of the most promising candidates, we initiated cell viability assays in the human neuroblastoma cell line (SH-SY5Y), where the compounds were tested at different concentration ranges based on their solubility. Initial results suggested that these compounds do not affect cell viability, indicating their suitability for further evaluation in systems requiring living cells. This comprehensive approach combines green synthesis with the exploration of biological activities, contributing to the development of high-value, low-impact drugs with potential for treating highly relevant diseases.

Therapeutics
Chairs: Verónica Lasalle and Susana Gorzalczany

25. EXPLORING THE THERAPEUTIC POTENTIAL OF CAMP SIGNALING MODULATION IN BREAST CANCER CELLS

Tamara Valladares[1], Carla Mayora Justel[1,2], Isabel Luthy[3], Carmen Esandi[1,2], Ariana Bruzzone[1].

[1]*Instituto de Investigación Bioquímica de Bahía Blanca (INIBIBB-UNS-CONICET),* [2] *Departamento de Biología, Bioquímica y Farmacia- UNS,* [3]*Instituto de Biología y Medicina Experimental (IBYME-CONICET).*

In Argentina, breast cancer is the most common type of cancer in women. cAMP is a key regulator of cellular processes. Previous studies from our lab and others show that in both normal and tumor breast tissues: 1) high intracellular cAMP (icAMP) levels reduce proliferation, tumor growth, and cell migration; 2) alterations in the cAMP pathway are common in processes linked to tumor progression; 3) cAMP is often exported extracellularly (ecAMP), though its role remains unclear. This study investigates how modulators of cAMP production, degradation, or exclusion affect breast cancer cells.
MCF-7, T47D, and MDA-MB-231 cell lines were obtained from ATCC. Cell viability was evaluated via MTT reduction assay, and western blot was used to analyze p-ERK and total ERK for signaling changes. PDE gene expression was assessed by RT-qPCR.
Our results show that MDA-MB-231 cells express higher levels of phosphodiesterase 4 (PDE4D) than MCF-7 cells, confirming lower icAMP concentrations in MDA-MB-231. Adenylate cyclase stimulation with forskolin (10 µM) significantly reduced cell viability and decreased ERK phosphorylation in all three cell lines. In MCF-7 cells, PDE inhibition with IBMX (10 µM) or Probenecid (10 µM) decreased both cell viability and ERK phosphorylation. Additionally, extracellular cAMP (10 µM) and adenosine (100 µM), a cAMP metabolite, reduced cell viability and p-ERK levels. Theobromine (10 µM), an adenosine A1 receptor and PDE inhibitor, produced similar effects.
This study highlights the role of cAMP modulation and its metabolites in regulating tumor cell proliferation. Key mediators in cAMP signaling may serve as potential pharmacological targets for cancer therapy.

Therapeutics
Chairs: Verónica Lasalle and Susana Gorzalczany

26. THE HEMIN TREATMENT IMPAIRS THE CELL SURVIVAL OF HORMONE-DEPENDENT AND HORMONE-INDEPENDENT HUMAN BREAST CANCER THROUGH THE REGULATION OF "HO-1/IRON" AXIS

Florencia Magalí Gómez[1], Karen Schweitzer[2], Alejandro Carlos Curino[2], María Marta Facchinetti[2], Gisela Giorgi[1]

[1]*Laboratorio de Fisiología Humana, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, Bahía Blanca, Argentina.* [2]*Laboratorio de Biología del Cáncer, Instituto de Investigaciones Bioquímicas Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS)-CONICET, Departamento de Biología, Bioquímica y Farmacia (UNS), Bahía Blanca, Argentina.*

We have previously reported that the overexpression of Heme Oxygenase-1 (HO-1), an enzyme that catalyzes heme degradation and releases iron, impairs breast cancer (BC) cell survival in human triple-negative (MDA-MB-231) BC cell lines, most likely through ferroptosis induction. In this study, we aimed to evaluate the effect of hemin, a drug commercially available that modulates the activity of HO-1, in the modulation on hormone-dependent and independent BC cell survival and to assess the involvement of HO-1. To this end, we treated the T47D and MDA-MB-231 cell line with hemin (36h). We studied cell viability (crystal violet), iron storage (Prussian blue), ROS levels (DFCA), lipid peroxidation (MDA accumulation) and the expression of the iron importer ZIP14 (immunocytochemistry). We found that hemin treatment decreased T47D and MDA-MB231 cell viability ($p<0.01$ in both) and increased iron storage ($p<0.05$ in both), ROS levels ($p<0.05$ and $p<0.001$ respectively), MDA accumulation ($p<0.01$ in both) and ZIP14 expression. The treatment with iron chelator (deferoxamine) reversed the reduction of cell viability induced by hemin in both cell lines ($p<0.001$ in both). When HO-1 was inhibited with SNPP in MDA-MB231 cells, we detected an increase in the cell viability ($p<0.01$). Similarly, the overexpression of an enzymatically inactive HO-1 in T47D increased the cell viability ($p<0.05$). In conclusion, the hemin effect on the BC cells would be independent of the breast tumor subtype. In hormone-dependent and independent BC, the hemin impairs cell viability through the HO-1 induction that produces an increase in free iron accumulation, ROS production and lipid peroxidation, being the enzymatic activity of HO-1 necessary for the hemin effect on cell viability.

Therapeutics
Chairs: Pedro Martin and Hugo Ortega

27. THE BISPHOSPHONATE ALENDRONATE PROTECTS VASCULAR ARCHITECTURE UNDER STRESS CONDITIONS INDUCED BY OBESITY

Pablo Cutini, Sabrina Cepeda, Marisa Sandoval, Virginia Massheimer

Instituto de Ciencias Biológicas y Biomédicas del Sur (INBIOSUR), CONICET-Universidad Nacional del Sur (UNS). Departamento de Biología, Bioquímica y Farmacia. UNS. Bahía Blanca. Argentina.

Alendronate (ALN) is a bisphosphonate used as first line therapy for bone-related diseases. Indeed, various extraosseous effects have been reported. We previously demonstrated a favorable vascular action of ALN through the inhibition of cellular events that trigger atherosclerosis disease. The final stage of atheroma formation is vascular calcification (VCa). In turn, as a defense mechanism, the vascular system induces neovascularization. Obesity is a risk factor that promotes VCa and impairs angiogenic process, so we investigated the effect of ALN on VCa and angiogenesis under stress conditions induced by obesity. To that end, thoracic aorta was isolated from female Wistar rats fed with a high-fat diet (27%) or standard diet (4% fat) for 10 weeks. Primary cultures of endothelial cells (EC) and vascular smooth muscle cells (VSMC) were performed. VSMC treatment with 10 µM ALN reduced the expression of osteogenic markers RUNX2 and TNAP (92 and 69% vs. control, respectively, $p<0.05$) and matrix mineralization (38% vs. control, $p<0.05$, alizarin staining) induced by osteogenic medium. ALN treatment induced a marked reduction in VCa in aortic explants isolated from obese rats (24% vs. control, $p<0.05$, Von Kossa staining). In order to evaluate angiogenesis, EC proliferation (MTT assay) and capillary formation (tube formation assay) were studied. EC derived from obese rats showed lower proliferation rate and capillary formation than lean rats (51 and 26% respectively, $p<0.05$). Treatment with ALN reversed these results: ALN increased cell growth (13% vs. control, $p<0.01$), and stimulated tube formation (18% vs. control, $p<0.05$). The proangiogenic effect is mediated by VEGF, since the presence of a VEGF receptor antagonist (1 µM SU5416), completely suppressed tube formation induced by ALN. In conclusion, ALN could exert a potential beneficial action on events that compromise vascular architecture through the downregulation of VCa and the impairment of arterial remodeling.

Therapeutics
Chairs: Pedro Martin and Hugo Ortega

28. EFFECT OF METFORMIN TREATMENT ON COGNITIVE IMPAIRMENTS INDUCED BY HIGH FAT DIET (HFD) FEEDING AND/OR EXPOSURE TO CHRONIC MODERATE STRESS (CMS).

Andres Prochnick, Mara Anais Garrido Palacios, Adriana Laura Burgueño, Ana María Genaro, **Miriam Ruth Wald**.

Instituto de Investigaciones Biomédicas. UCA- CONICET.

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) have been linked with increasing age, advanced glycosylation end products, obesity, and insulin resistance. These clinical links lead to investigating the effects of an antidiabetic therapy such as metformin (MET), that has been proposed as an improvement of cognitive dysfunction. Previously, we showed that the exposure to high fat diet (HFD) and/or chronic moderate stress CMS induced a cognitive impairment. Here we investigated the effect of MET treatment on this cognitive ability. For this purpose, 4 weeks-old mice were fed with standard diet (SD) or HFD. Then, 8 weeks later, a group of animals were exposed to CMS. After 12 weeks a subgroup of animals was treated with MET (250 mg/kg*day). These treatments lasted until the subjects were 32 weeks-old. Results indicated that although MET treatment did not affect body weight, improved glucose tolerance ($p<0.01$). Respecting lipid metabolism, no significant differences were found. Concerning behavior, MET reverted the impairments induced by HFD and HFD+CMS in working memory in the Y-maze test ($p< 0.05$) and spatial memory in object recognition test ($p< 0.01$). Taking into account, the Barnes test provides information about spatial memory and learning in a more complex context and allows evaluating short- and long-term memory. The testing phase is performed one day after the last training session, on day 5 and after one week, day 12. We observed that MET improved the latency to find the target hole altered by HFD+CMS exposure at day 5 ($p<0.05$). When we tested at day 12, MET improved long-term memory ($p<0.01$). We conclude that although MET does not produce the expected weight loss, it improves glucose tolerance. Moreover, MET protects spatial and working memory and learning that is impaired under HFD feeding and CMS exposure.

Bioinformatics and Therapeutic Targets
Chairs: Pedro Martin and Hugo Ortega

29. ADVANCING PHARMACOMETRIC ACCESSIBILITY: A UNIFIED PLATFORM FOR DATA INTEGRATION AND AUTOMATED MODEL OPTIMIZATION

Julián Otálvaro[1,2], Ivone Jimenez[2], Michael Neely[1], Andres Zuluaga[2]

[1]*Laboratory of Applied Pharmacokinetics and Bioinformatics LAPKB, CHLA-USC, L.A California,* [2]*Grupo de Investigación en Farmacología y Toxicología, LIME: Laboratorio Integrado de Medicina Especializada, MINCIENCIAS (111589786169), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia*.

Pharmacometrics integrates pharmacology, mathematics, and statistics to quantify drug behavior and optimize therapeutic regimens, playing a vital role in drug development, clinical trials, and personalized medicine. Despite its importance, widespread adoption among practitioners is hindered by challenges such as the high cost of quality data and the specialized knowledge required to use existing tools.

To overcome these barriers, we have developed an integration platform that harnesses the robust capabilities of Pmetrics, a leading non-parametric population pharmacokinetic and pharmacodynamic modeling tool. Our platform enhances Pmetrics' accessibility by offering a user-friendly, step-by-step interface that eliminates the need for complex software installations, making it easier for both new researchers and seasoned pharmacometricians to use its advanced analytical capabilities.

A key feature of the platform is its ability to facilitate the sharing of pharmacometric datasets, which can significantly reduce the cost of acquiring PK/PD data by enabling the reuse of existing datasets. Users can upload, search for, and share data within the community, fostering cooperation while ensuring proper credit is given to data owners.

Additionally, the platform includes an AI-based model fitting tool that automates the selection of models, parameter ranges, and error models, enhancing the efficiency and accuracy of pharmacometric analysis. We are also working on adding covariate selection, further expanding the platform's capabilities.

Once modeling is complete, the platform seamlessly integrates with the web version of BestDose™, allowing practitioners to make informed decisions about patient regimens directly from the platform. This integration bridges the gap between pharmacometric analysis and clinical application, ensuring that insights gained from Pmetrics can be directly applied to optimize patient care.

By reducing the complexity and cost associated with pharmacometrics, this platform aims to democratize access to this crucial field, empowering a broader range of practitioners to utilize pharmacometric insights in their work.

Clinical Pharmacology
Chairs: Pedro Martin and Hugo Ortega

30. REAL-WORLD IMPLEMENTATION OF THE OPTIMMAS PROGRAM IN HIGH-RISK PATIENTS AT THE UNIVERSITY OF ANTIOQUIA HEALTH PROGRAM

María A. Montoya-Giraldo, Luisa Díaz, Gabriel J. Restrepo, Andres F. Zuluaga

Grupo de Investigación en Farmacología y Toxicología, LIME: Laboratorio Integrado de Medicina Especializada, MINCIENCIAS (111589786169), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia.

Objective: The OPTIMMAS program seeks to optimize medication use and reduce adverse outcomes in high-risk patients through a multidisciplinary approach, with a particular focus on addressing polypharmacy and substance abuse.
Materials and Methods: The program was implemented in the University of Antioquia's Health Program in 2023, targeting a population of 302 high-risk patients identified through clinical screening. Of these, 62 patients (21%) were specifically flagged for substance abuse issues, including benzodiazepines, opioids, and other psychoactive substances. Data were collected over a year, with regular medication reviews, patient education sessions, and monitoring of clinical outcomes. Key metrics included the total number of medications dispensed, hospitalization rates, and the incidence of substance misuse.
Results: OPTIMMAS led to a significant reduction in medication-related issues, with a 9% decrease in the total number of medications dispensed annually. Among the 62 patients with identified substance abuse, 45% showed improved adherence to prescribed therapies, while 30% required targeted interventions due to high-risk behaviors. Hospitalization and mortality rates decreased by 6%, demonstrating the program's impact on patient safety and health outcomes. Notably, the intervention helped in identifying and mitigating the misuse of psychoactive substances, contributing to better management of these complex cases.
Conclusion: The real-world data from the OPTIMMAS program highlight its effectiveness in reducing inappropriate medication use and improving clinical outcomes in a high-risk population, with success in addressing substance abuse issues. These findings support the expansion of similar multidisciplinary programs to other healthcare settings, emphasizing the need for continuous monitoring and individualized patient care.

Pharmacokinetics and Pharmacodynamics
Chairs: Cecilia Bouzat /Daniela Quinteros

31. POPULATION PHARMACOKINETIC MODELING OF AMPICILLIN IN NON-CRITICAL HOSPITALIZED PATIENTS RECEIVING INTRAVENOUS INFUSION

Andres F. Zuluaga, Ivone E. Jimenez, Andrés Hincapié, Laura Vargas, María A. Montoya-Giraldo

Grupo de Investigación en Farmacología y Toxicología, LIME: Laboratorio Integrado de Medicina Especializada, MINCIENCIAS (111589786169), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia.

Objective: This study aimed to develop a population pharmacokinetic (pop-PK) model to describe the pharmacokinetics of ampicillin in non-critical hospitalized patients receiving a 3 g intravenous infusion over two hours.
Materials and Methods: Fifteen hospitalized patients were included in the study. Blood samples were collected at multiple time points during and after the 2-hour infusion. One and two-compartment models with first-order elimination were used for the pharmacokinetic analysis. Covariates such as patient weight, age, and renal function were considered to understand their impact on drug clearance and volume of distribution. Data were analyzed using non-linear mixed-effects modeling with Pmetrics.
Results: The dataset comprised 75 observations across 15 patients. The one-compartment model demonstrated good convergence after 74 cycles. The observed-predicted plot for individual predictions showed an R^2 of 0.983, indicating a good fit between the observed and predicted concentrations. The model exhibited a bias of 0.008 and an imprecision of 5.27, suggesting an appropriate level of precision.
The final parameter estimates (median) included a constant of elimination of 0.8 h^{-1} and an apparent central volume of distribution (V) of 35.6 L. The absorption rate constant (Ka) was estimated at 1.04 h^{-1}. The model also identified significant variability in these parameters (CV% ranging from 34 to 159), with covariates such as renal function and body weight significantly impacting the clearance of ampicillin. The median trough concentration of patients (initial condition) was 35.7 ± 12 mg/L.
Conclusion: The developed pop-PK model for ampicillin in non-critical hospitalized patients receiving intravenous infusion demonstrated an acceptable fit and reliable parameter estimate, suggesting its utility for individualized dosing in this population. Further validation with a larger sample size is recommended to confirm these findings and refine dosing guidelines.

Pharmacokinetics and Pharmacodynamics
Chairs: Cecilia Bouzat Cecilia Bouzat /Daniela Quinteros

32. POPULATION PHARMACOKINETICS OF METFORMIN IN COLOMBIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A COMPREHENSIVE ANALYSIS AND CLINICAL IMPLICATIONS

Ivone E Jiménez, Laura Vargas, Andrés Hincapié, Andrés F Zuluaga

Department of Pharmacology and Toxicology, University of Antioquia, Medellín, Colombia.

Achievement of treatment goals of patients with diabetes in Colombia remains substantially low under metformin monotherapy. The objective of this study was to determine the population pharmacokinetics of metformin in adults after an oral dose of 500, 850, or 1000 mg, evaluating whether clearance affects drug kinetics.

The population pharmacokinetics of metformin was performed in 29 subjects with type 2 diabetes mellitus. Plasma concentrations of metformin were quantified by high-performance liquid chromatography. A population pharmacokinetic metformin model was developed using non-linear mixed effect modeling based on the concentration-time data, utilizing Pmetrics software. Covariates considered in the analysis included age, fat mass, weight, clearance, and SLC22A1 polymorphisms.

A two-compartment pharmacokinetic model with first-order elimination better-described drug kinetics (R^2 = 0.96 for the individual obs.-pred plot. The mean population pharmacokinetic parameters were apparent clearance of 5.5 L/h, apparent volume of distribution of 74.03 L, absorption rate constant of 0.379 $hour^{-1}$, lag-time of 0.437 hours, intercompartmental clearance of 61.73 L/h, and bioavailability of 0.58. Covariate analyses revealed that body weight is an individual factor influencing the apparent oral clearance: $CL=CL1*(wt/70)^{0.75}$., suggesting that individualized dosing adjustments based on body weight could enhance treatment efficacy.

Nanotechnology
Chairs: Verónica Lasalle and Guillermina Hernando

33. DESIGN, DEVELOPMENT AND CHARACTERIZATION OF CARVACROL-LOADED LIQUID CRYSTALLINE NANOPARTICLES BASED ON THE COMBINATION OF PHYTANTRIOL AND GLYCEROL MONOOLEATE TO ADJUST NON-CLASSICAL LIGHT AND DRUG DELIVERY APPLICATIONS

Ayelen Inda[1,2], Carolina del Valle Bessone[1,3], Carolina Aloisio[4], Sofía Martinez[1], Cecilia Tettamanti[1], Camila Costa Giobbatto[1], Guillermo Bracamonte[5], Rafael Oliveira[6], Daniel Allemandi[1], Soledad Ravetti[2], **Daniela Quinteros**[1]

[1]*Unidad de Investigación y Desarrollo en Tecnología Farmacéutica (UNITEFA), CONICET and Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba (UNC), Córdoba Argentina.* [2]*Instituto Académico Pedagógico de Ciencias Humanas, Centro de Investigación y Transferencia Villa María (CIT VM), Villa María, Córdoba, Argentina.* [3]*Escuela de Ciencias de la Salud. Universidad Nacional de Villa Mercedes, Villa Mercedes San Luis, Argentina.* [4]*Ingeniería de Procesos Sustentables, Universidad Tecnológica Nacional, Facultad Regional San Francisco, San Francisco, Córdoba and CONICET, Argentina.* [5]*Instituto de Investigaciones en Fisicoquímica de Córdoba (INFIQC). Centro Laser del INFIQC, y Departamento de Química Orgánica del INFIQC, Facultad de Ciencias Químicas, UNC.* [6]*Centro de investigaciones en química biológica (CIQBIC), Facultad de Ciencias Químicas, UNC.*

The main was to design, develop and characterize of nanoparticulate lipid liquid systems (NLCL) loaded with carvacrol (CAR) from the bilipid combination of phytantriol and glycerol monooleate PHY/GMO (1:1).
From the construction of the ternary phase diagram (PPD), the optimal proportions of the different components PHY/GMO, PLX and water are selected to obtain NLCL using the aqueous titration method. The NLCL PHY-GMO systems were synthesized by TOP-DOWN method and characterized by particle size, PDI, z-potential, % encapsulation and pH. The structure of the nanocarriers was determined by SAXS. The stability was evaluated for 90 days and the release of CAR from the NLCL PHY-GMO CAR was studied. Finally, the fluorescence properties of NLCL were determined by 3D fluorescence and by confocal microscopy. The whole development was compared with the NLCL systems of the individual components ($NLCL_{GMO}$ and $NLCL_{PHY}$).
PPD showed the maximum range for obtaining NLCL systems, PHY/GMO: 20-100%, PLX: 20-100%; W:0-80% was found. The lipid/surfactant ratio of 4:6 was found to be the best ratio for obtaining NLCLPHY-GMO systems. The particle size for NLCLPHY-GMO, NLCLPHY and NLCLGMO was between 130.7 ± 3.5 and 289.0 ± 47.7. The PDI was less than 0.2. The PZ of the formulations was found between -20 to -30 mV and a pH close to neutrality. In terms of structure, the NLCL systems presented a cubic phase, Pn3m for NLCLPHY and the NLCL PHY-GMO and

NLCLGMO systems Im3m. The NLCL PHY-GMO CAR system was shown to be stable for 90 days and showed a 10% release of CAR from the nanostructure over 24 h, with an encapsulation efficiency of 88%. In terms of fluorescen properties, optical activities were observed and were confined to the UV-visible and near-infrared regions. The fluorescence was increased with the addition of CAR. The bilipid systems showed autofluorescence and reflected light when imaged by confocal microscopy.

NLCL were developed based on the bilipid combination, which exhibited physicochemical properties compatible with nanometric systems. With good CAR encapsulation efficiency and sustained release over time. They are stable systems with autofluorescent optical properties.

Nanotechnology
Chairs: Verónica Lasalle and Guillermina Hernando

34. DEVELOPMENT OF HYDROGELS LOADED WITH ZnO NANOPARTICLES AND MORIN FOR THE TREATMENT OF SKIN DISORDERS: SYNTHESIS, PHYSICOCHEMICAL CHARACTERIZATION, AND ANTIVIRAL PROPERTIES

Ana Karen Jaimes[1,3], Victoria Ayala-Peña[2], Vera Álvarez[3] and Verónica Lassalle[1]

[1]*INQUISUR, Departamento de Química, Universidad Nacional del Sur-CONICET, Bahía Blanca, 8000, Argentina.* [2]*Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur-CONICET, Bahía Blanca, 8000, Argentina.* [3]*INTEMA, Universidad Nacional de Mar del Plata-CONICET, Mar del Plata, 7600, Argentina.*

Skin disorders affect a large portion of the global population, causing different levels of damage. This situation leads to serious problems to the public health systems, highlighting the need for more effective and accessible treatments. In this context, biopolymers with several bioactive properties have emerged as a promising strategy for treating various skin conditions. In this work, hydrogels (HGs) based on gelatin were synthesized using a freeze-thaw method, incorporating chitosan to add functionality and other biological properties, and gum arabic as a crosslinker. The gel fraction was determined to be 59.5%. The swelling behaviour was explored in an acetate buffer (pH 5.11) to simulate the dermal environment reaching a percentage of about 1044% after 360 minutes, and the water contact angle averaged 97.7° revealing the hydrophilic nature of the HGs. HGs were loaded with morin, a natural compound with antitumor, antioxidant and anti-inflammatory properties, and with ZnO nanoparticles (NPs) that possess antimicrobial, antiviral, antifungal, antioxidant, anti-inflammatory, and anticancer properties. The objective was to assess a multifunctional platform by the generation of a synergistic effect among the polymeric, inorganic and the natural drug to treat dermal disorders, especially those arising from viral pathogens. The obtained HGs were characterized using FTIR spectroscopy, atomic absorption spectroscopy, and scanning electron microscopy. Antioxidant activity of the unloaded HG, HG loaded with ZnO NPs and HG loaded with both ZnO NPs and morin, yielding values of 2, 12, and 86%, respectively. Additionally, morin and ZnO NP release tests were conducted in a medium simulating the skin environment (pH 5.5 and 32°C) and antiviral activity studies were performed. The results indicated that the proposed platforms are suitable for use as topical drug delivery systems.

Nanotechnology
Chairs: Verónica Lasalle and Guillermina Hernando

35. STUDY OF THE PHYSICOCHEMICAL PROPERTIES OF MPEG-PLA LIPID NANOPARTICLES LOADED WITH NUCLEIC ACIDS (NP-MPEG-PLA-NA) FOR DELIVERY TO THE CENTRAL NERVOUS SYSTEM (CNS)

Tatiana A. Guarnieri[1,2,3,4]; Jenny L. Fiedler[2] and Javier O. Morales[1,3,4]

[1]*Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, Universidad de Chile, Santiago 8380494, Chile.* [2]*Laboratory of Neuroplasticity and Neurogenetics. Faculty of Chemical and Pharmaceutical Sciences. Department of Biochemistry and Molecular Biology. Universidad de Chile, Independencia, 8380492, Santiago, Chile.* [3]*Advanced Center for Chronic Disease, ACCDiS, Universidad de Chile.* [4]*Center of New Drugs for Hypertension and Heart Failure, CENDHY, Universidad de Chile.*

Recently, several nucleic acids (NA) have been reported to show therapeutic potential in animal models of diseases affecting the central nervous system (CNS). However, intravenous (IV) administration does not efficiently facilitate their passage through the blood-brain barrier. This study aims to develop mPEG-PLA lipid nanoparticles (NPs) loaded with NA for intranasal administration to enhance their delivery to the CNS. In this work, we investigate the physicochemical properties of empty NPs (mPEG-PLA) and NA-loaded NPs (NP-mPEG-PLA-NA), including hydrodynamic diameter (HD), polydispersity index (PdI), zeta potential (ZP) and stability. NP were synthesized using biodegradable and biocompatible PEG and PLA polymers through a double emulsion method and were loaded with various test nucleic acids at three different N/P ratios. HD, PdI, and ZP parameters were evaluated using Dynamic Light Scattering (DLS). The resulting NP concentration was quantified using Nanoparticle Tracking Analysis (NTA), and NPs were visualized by Transmission Electron Microscopy (TEM). A total of eight NP syntheses were performed, including empty NP, with no significant differences observed between loaded and unloaded NP. Our findings revealed that the average size of both loaded and unloaded NP ranged between 140 and 200 nm. The PdI, ranging from 0.2 to 0.3, indicates that the obtained NP are narrowly dispersed systems. The resulting ZP, between -30 and -25 mV, suggests a high level of electrostatic repulsion between particles, reducing the tendency for aggregation. Additionally, NP-mPEG-PLA-NA remained stable for over four weeks when stored at 4 °C, showing only minimal variations during this period. This study presents preliminary results in the development of therapeutic NP-mPEG-PLA loaded with nucleic acids for intranasal administration in animal models of CNS disorders.

Nanotechnology
Chairs: Verónica Lasalle and Guillermina Hernando

36. ASSESSMENT OF BIOGENIC SILICA POTENTIAL FOR BIOMEDICAL APPLICATIONS

Francisco E Navarro[1], Marina Busso[1], Mariela Agotegaray[2], Fernanda Horst[2], M Cecilia Damiani[1,3], Miguel Sánchez[4], Cecilia A Popovich[1,3,5]

[1]*Departamento de Biología, Bioquímica y Farmacia (UNS) San Juan 670, (8000) Bahía Blanca. Argentina.* [2]*Departamento de Química – INQUISUR, UNS-CONICET. Avda. Alem 1253, (8000), Bahía Blanca, Argentina.* [3]*Centro de Recursos Naturales Renovables de la Zona Semiárida (CERZOS) (CONICETUNS), Camino de La Carrindanga Km 7, (8000) Bahía Blanca, Argentina.* [4]*Instituto de Física del Sur (IFISUR), Departamento de Física, UNS, CONICET, Av. L.N. Alem 1253, B8000CPB - Bahía Blanca, Argentina.* [5]*CEDETS (CIC-UPSO), Ciudad de Cali, (8000) Bahía Blanca. Argentina.*

Diatoms are eukaryotic microalgae, which present a cell wall made of amorphous silica called frustule. Studies in micro/nano-technology show that frustules are potential materials for various applications, such as drug delivery, biosensors, and rapid bleeding control. The aim of this study was to evaluate the physicochemical properties and blood tissue biocompatibility of frustules extracted from *Halamphora coffeaeformis*, a diatom native from Bahía Blanca Estuary, to assess their potential application in biomedical fields. Frustules were obtained from two different culture methods: photobioreactor (F-PBR) and open raceway pond (F-RAC). Both cultures underwent an oxidation treatment with hydrogen peroxide at 80ºC for 12h. Afterwards, the frustules were subjected to three calcination treatments at 300ºC, 500ºC, and 800ºC, based on mass loss and stabilization identified through thermogravimetric analysis. Significant changes were observed in the composition and surface properties of the frustules after the treatments. In general, the percentages of Si and O tended to increase as temperatures rose, while C content decreased. This trend corresponded with a reduction in C=O and C-H groups at higher temperatures. BET surface area values were highest at 300ºC for both cultivation methods, with F-RAC (68.6 m^2/g) significantly surpassing F-PBR (27 m^2/g). Additionally, z-potential measurements indicated higher stability for F-PBR (-33 mV) compared to F-RAC (-20 mV), suggesting better dispersion stability in an aqueous medium and fewer aggregates. The preliminary hemocompatibility study, displayed by evaluation of hemolysis and osmotic fragility on red blood cells, showed biocompatibility of frustules with erythrocytes. In conclusion, *H. coffeaeformis* frustules, particularly those from photobioreactor cultivation and calcined at 300ºC, possess favorable physicochemical properties and biocompatibility with blood tissue. These characteristics highlight their potential as drug carriers.

Nanotechnology
Chairs: Verónica Lasalle and Guillermina Hernando

37. STUDY OF THE PHYSICOCHEMICAL PROPERTIES AND STABILITY OF NANOSTRUCTURED LIPID CARRIERS (NLC) MODIFIED WITH EDGE ACTIVATORS (EA): USE OF SODIUM DEOXYCHOLATE (SDC), SODIUM DEOXYGLYCOCHOLATE (SDGC) AND SODIUM DEOXYTAUROCHOLATE (SDTC)

Gabriela N. Otavalo[1,2,3] and Javier O. Morales[1,2,3]

[1]*Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, Universidad de Chile, Santiago 8380494, Chile.*[2]*ACCDiS – Advanced Center for Chronic Diseases. Santiago, Chile.* [3] *CENDHY – Center of New Drugs for Hypertension and Heart Failure. Santiago, Chile*

Bile salts (BS) are identified as EA for their capacity to boost membrane flexibility and deformability of nanocarriers through tight junctions which in turn improves bioavailability of drugs. This study is the first to analyze the incorporation of BS as EA into NLC. Here, we investigated the effect of specific BS (SDC, SDGC, and SDTC) on NLC's physicochemical properties such as hydrodynamic diameter (HD), polydispersity index (PdI), Zeta potential (ZP), and stability. NLCs were synthesized using a blend of solid lipid glycerides, fatty acid esters of PEG, and a mix of capric and caprylic triglycerides, along with different concentrations of BS (2, 6 and, 10 mM) utilizing a modified method combining low-energy hot emulsification with an injection technique. We evaluated HD and PdI using Dynamic Light Scattering and ZP by Laser Doppler Electrophoresis. Stability was assessed over four weeks at 4 °C. In total, 10 NLC syntheses were produced including empty NLCs. One-way ANOVA with $p< 0.05$ was used to determine statistical significance of observed differences. Our findings revealed a significant impact of BS on the physicochemical properties of NLC. Increasing the concentration of SDC led to a rise in HD, while the inclusion of conjugated BS (SDGC and SDTC) resulted in a decrease. The PdI demonstrated a downward trend as BS concentration increased, indicating that the NLCs were monodisperse systems, attributable to the stabilizing function of BS. Furthermore, a notable increase in value of ZP was observed with the increasing BS concentration, suggesting higher electrostatic repulsion and reduced particle aggregation. The NLC-BS demonstrated high stability, with minimal variation in physicochemical characteristics over four weeks at 4 °C. In conclusion, the incorporation of BS into NLCs led to a general reduction in HD and PdI, an increase in ZP, and high stability over time. These insights can be instrumental in enhancing permeation across biological membranes.

Nanotechnology
Chairs: Verónica Lasalle and Guillermina Hernando

38. DEVELOPMENT OF MAGNETIC NANOSYSTEMS WITH POTENTIAL FOR THE TREATMENT OF INNER EAR PATHOLOGIES

Giuliana Paolillo[1], María Julia Martín[1,2], María Gabriela Montiel Schneider[2], Guillermo Spitzmaul[1] and Verónica Lassalle[2]

[1]*Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Av. La Carrindanga Km. 7, 8000 Bahía Blanca, Argentina.* [2]*Instituto de Química del Sur (INQUISUR), Departamento de Química, UNS-CONICET, Av. Alem 1253, 8000 Bahía Blanca, Argentina.*

Hearing loss (HL) affects more than 5% of the global population, and projections suggest it could impact up to 50% of young individuals in the coming years. Most cases of HL are associated with local inflammation. Current treatments for HL are limited due to the inner ear's protective barriers, with intratympanic (ITT) administration being the most efficient method for drug delivery. However, the round window membrane (RWM) still poses a significant barrier for most drugs.

Our research focuses on overcoming this limitation through the implementation of nanotechnology. We propose the ITT injection of magnetic nanoparticles (MNPs) loaded with Diclofenac (Dfc), followed by their guidance to the inner ear via the RWM using an external magnetic field (EMF). Previously, we developed iron-oxide MNPs coated with folic acid (FA). This work aims to formulate MNPs loaded with Dfc, MPNs@FA.Dfc. The loading process was optimized for the physical adsorption of Dfc via weak interactions. Thus, Dfc can be easily released in the perilymph, which is the inner ear's target fluid. Drug loading capability and efficiency as well as the release kinetics were quantified by HPLC. Hydrodynamic diameter, Z potential and iron content estimation served to evaluate the influence of Dfc loading on these properties. Additionally, the FA-Dfc interaction was confirmed by FTIR analysis. The cytotoxicity and internalization of loaded MNPs were analyzed *in vitro* in HEK293 cell cultures. Finally, the ability of MNPs@FA.Dfc to cross the RWM was studied in dissected murine cochleae. To that end, MNPs were deposited in the RWM niche and then exposed to an EMF. We found by inductively coupled plasma-optical emission spectrometry a significant increase in the total Fe in the treated tissue. This result is consistent with the entry of MNPs. Statistical analysis was conducted using ANOVA test. These studies are of fundamental importance for future *in vivo* trials employing the developed nanosystem.

Nanotechnology
Chairs: Verónica Lasalle and Guillermina Hernando

39. CHARACTERIZATION OF A NANOPARTICULATE FORMULATION OF A POORLY SOLUBLE DRUG

Ana Paula Sanguinetti[1,2,3], **Laura Astorga**[1,2], Cristian Lillo[1,2,3] and Jorge Montanari[1,2,3]

[1]*Universidad Nacional de Hurlingham (UNAHUR), Laboratorio de Nanosistemas de Aplicación Biotecnológica (LANSAB), Hurlingham, Buenos Aires, Argentina*. [2]*Comisión de Investigaciones científicas de la provincia de Buenos Aires (CIC), La Plata, Buenos Aires, Argentina*. [3]*Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Ciudad Autónoma de Buenos Aires, Argentina*.

Ricobendazole, also known as albendazole sulfoxide, is a widely used antiparasitic in the veterinary field. It presents significant difficulty in terms of solubilization, requiring solutions with extreme pH levels to be included in veterinary formulations. Formulating it in a nanoparticulate system would pave the way for more targeted use with lower and more effective doses, for example, against helminths. To achieve this, it was proposed to encapsulate Ricobendazole in solid lipid nanoparticles based on the lipid Gelot 64® (Gattefossé), which consists of a mixture of glyceryl monostearate and PEG-75 stearate (MW 3500) (C_{18}) dispersed in solid lipid nanoparticles.
The synthesis method of Solid Lipid Nanoparticles (SLN) consists, in the first step, of melting the lipid with soy lecithin and the lipophilic drug at 5°C above the lipid melting point, followed by homogenization with UltraTurrax for 3 minutes at 25,000 rpm. Then, in a second step, a hot aqueous solution of Tween 80 is added to this dispersion, and three more homogenization cycles are performed with UltraTurrax for 3 minutes at maximum power. After this, the resulting emulsion is allowed to cool to room temperature to permit solidification and the formation of the SLN. The colloidal stability was studied using Turbiscan Lab, and flow parameters and viscosity were calculated by rheology. The size of the formulations obtained was estimated by dynamic light scattering at different dilutions. To determine the size and encapsulation efficiency (%EE), a quantification method for this drug was developed by HPLC, adapting a pre-existing analytical method. The formulations generated monodisperse nanoparticle populations with an approximate size of 300nm, a Z-potential of -12 mV, and an %EE of around 70%.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Adrian Lifschitz and Santiago Zugbi

40. ACUTE LOCAL TOXICITY OF A TOPICAL LIPOSOMAL FORMULATION FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS

Francesca Papera and Dolores C. Carrer

Instituto Ferreyra – INIMEC – CONICET - Universidad Nacional de Córdoba, Córdoba, Argentina

Cutaneous leishmaniasis (CL) is a parasitic disease transmitted by the bite of a phlebotomine insect, which acquires the parasite by feeding on an infected mammal (zoonosis). There is a significant need for new therapies for CL, as the available medications are inadequate due to their toxicity. A topical formulation would be highly advantageous. The assessment of local toxicity is one of the requirements that topical formulations must meet, according to regulatory agencies such as ANMAT and the FDA.

The formulation under evaluation is a hydrogel containing phospholipids (PC) and miltefosine (Milt) that has shown excellent efficacy in preclinical trials. The formulations were prepared under sterile conditions and aliquoted into 1 ml syringes. In adult male Wistar rats, we assessed local irritation using a modified Draize test (ISO 10993-23:2021 and OECD 402). The animals were divided into 3 groups of 5 animals each, with one animal included as a sham control. The Treatment group received a single dose of PC-Milt in hydrogel at 4 different concentrations (90 µL/cm^2; 0.1-0.5-1.0-1.5% w/v of Milt) and a positive control (10% SDS in hydrogel) applied to the shaved skin on their backs. Each animal in the Control group received the vehicle (hydrogel), the vehicle with PC in two different concentrations (corresponding to Milt concentrations of 0.5%-1.5% w/v), and the positive control. Animals were weighed, observed, and photographed at 4, 24, 48, and 72 hours after application. Skin biopsies were taken at 24 and 48 hours.

Preliminary visual observation results showed that the values observed according to the ISO 10993-23:2021 score were below 1. This means that none of the tested concentrations of PC-Milt or the vehicle and excipient controls caused irritation. The results of the biopsies are under analysis. The preliminary conclusion is that the tested formulations do not produce skin irritation in this animal model.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Adrian Lifschitz and Santiago Zugbi

41. *IN VITRO* COMBINED EFFECT OF *Origanum vulgare* AND *Rosmarinus officinalis* ESSENTIAL OILS AGAINST *Escherichia coli* AND *Salmonella typhimurium* ISOLATED FROM BROILER CHICKENS

Federico Toso[1,2], Daniel Buldain [2,3], Julia di Filippo[2], Verónica Prio[4], Laura Marchetti[2], Nora Mestorino[2]

[1]*Facultad de Ciencias Veterinarias, Universidad Nacional de La Pampa.* [2]*Laboratorio de Estudios Farmacológicos y Toxicológicos –LEFyT-, Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata, 60 y 118 S/N.* [3]*CONICET.* [4]*Cátedra de Producción de Aves y Pilíferos, Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata.*

Antibiotic growth promoters (AGP) are administered in broiler chicken diets to increase production efficiency. Human health can be negatively impacted by the rise in antimicrobial resistance resulting from this practice. AGP for production has been banned in the European Union and restricted in Argentina. Essential oils (EOs) are potential alternatives to AGP. This study aimed to evaluate the pharmacodynamic interaction of *Rosmarinus officinalis* (RO) and *Origanum vulgare* (OV) EOs alone and in combination against *Escherichia coli* (n= 6) and *Salmonella typhimurium* (n= 6) isolated from healthy poultry by cloacal swabs. *E. coli* ATCC 25922 and *S. typhimurium* ATCC 14028 were used as control strains. The EOs were obtained by steam distillation of fresh leaves and herbaceous branches plants from San Javier, Córdoba, Argentina. Minimum inhibitory concentrations (MICs) of ROEO and OVEO were determined by microdilution at pH 7.4, 6.5, 6, 5.5 and 5 (emulating chicken GIT conditions, from crop (pH 4.5) to rectum (pH 6.3)). The fractional inhibitory concentration (FIC) index was obtained by the checkerboard method for both microorganisms at each pH. Synergism (S) exists if FIC ≤ 0.5, partial synergism (PS) if 0.5 < FIC < 1, indifference (I) if 1 ≤ FIC < 2 and antagonism (A) if FIC ≥ 2. The MICs were between 6.5-3.12, 100-50, 12.5-6.25 and 100-50 µL/mL for OVEO and ROEO, against *E. coli* and *S. typhimurium* respectively. MICs were not modified by varying pH. Combining the EOs, a PS effect (FIC 0.5-0.75) against both bacteria was obtained at pH 7.4. However, at lower pH, clearly synergistic effects were achieved, for *E. coli* at pH 5 (FIC 0.075-0.49) and for *S. typhimurium* at pH 6 (FIC 0.48-0.49). With this study we confirmed the antibacterial activity and synergistic effect of OVEO and ROEO against avian *E. coli* and *S. typhimurium*. These EOs used alone or in combination could be an alternative to reduce the AGP usage and the losses caused by these bacteria in poultry production.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Adrian Lifschitz and Santiago Zugbi

42. SOLUBILITY AND ANTIMICROBIAL ACTIVITY OF CLARITHROMYCIN WAS IMPROVED BY THE DEVELOPMENT OF A NEW SALT CONTAINING P-AMINOBENZOIC ACID

Antonela Bartolilla, Camila Gomez, Brenda Basiglio, Melisa Fumarola, Marcela Longhi, Ariana Zoppi, Virginia Aiassa

Unidad de Investigación y Desarrollo en Tecnología Farmacéutica (UNITEFA-CONICET), Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina.

Clarithromycin (CLM) is a semisynthetic broad-spectrum antimicrobial that presents unfavorable physicochemical and biopharmaceutical properties that limit their efficacy. The aim of this work was to optimize these unfavorable properties of CLM. For it, a salt combining CLM with p-aminobenzoic acid (PABA) was developed and characterized to enhance its solubility and antimicrobial efficacy. CLM:PABA salt was prepared in a 1:1 molar ratio by the solvent evaporation method, using methanol. The salt was characterized by infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and X-ray diffraction (PRDX). The dissolution was assessed by *in vitro* dissolution tests. Antimicrobial activity of CLM and CLM:PABA salt against *Staphylococcus aureus* ATCC 29213 and clinical strain 773 was determined by the agar diffusion method according to CLSI guidelines. Antibiofilm activity was determined by the MTT assay using CLM concentrations equivalent to 10, 100 and 1000 x MIC. The characterization of the system by FTIR revealed a new band at 1541 cm^{-1}, confirming the formation of a CLM:PABA salt. SEM analyses showed a different morphology, and X-ray diffraction revealed different patterns between the salt and pure drugs. *In vitro* dissolution tests showed a significant increase in dissolution rate and percentage dissolved in the salt. CLM:PABA salt showed a significantly higher inhibition halo than pure CLM in both strains, suggesting a synergistic effect with PABA. In addition, both CLM and CLM:PABA salt reduced the viability of the biofilm, whereas salt showed a marked decrease in cell viability compared to pure CLM [1000xMIC]. In conclusion, this salt demonstrated a better dissolution profile and greater antibacterial and antibiofilm activity than pure CLM, suggesting a promising antimicrobial potential and a possible increase in its therapeutic effect.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Adrian Lifschitz and Santiago Zugbi

43. ANTIBIOTIC RESIDUES IN SWINE FECAL MATTER: EFFECT ON EDAPHIC BACTERIA COUNTS

Joaquín Mozo[1,2*], Julieta Decundo[1,3], Guadalupe Martínez[1,3], Susana Dieguez[1,4], Alejandro Soraci[1,3], Denisa Pérez Gaudio[1,3]

[1]*Lab. de Toxicología, Depto. de Fisiopatología, Centro de Investigación Veterinaria de Tandil, FCV-UNCPBA, Tandil, Argentina,* [2]*Depto. de Producción Animal, FCV-UNCPBA, Tandil, Argentina,* [3]*Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina,* [4]*Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CICPBA), La Plata, Argentina*.

The use of antibiotics in animal production has raised concerns about environmental residues and persistence. In intensive pig farming, antibiotics are widely used, leading to reduced effectiveness and resistant strains that can transfer to other animals or humans. These compounds may not be fully absorbed or metabolized, allowing them to enter the environment through excreta. Significant concentrations of antibiotics have been detected in manure, potentially contaminating groundwater, surface waters, and soil, altering its microbiome. Despite these risks, systematic monitoring is lacking. This study aimed to assess the impact of residual amoxicillin (AMOXI) and oxytetracycline (OTC) in pig feces on soil total aerobic mesophilic bacteria (TAMB).

Fecal samples (100 g) from pigs not treated with antimicrobials were fortified with known concentrations of AMOXI and OTC to simulate post-administration levels. Untreated feces were included as a control. Samples were placed outdoors, for a 30 day-period, on natural grassland at the CIVETAN experimental unit in Tandil, Bs. As., Argentina. Post-experiment soil samples (0-10 cm depth) were collected beneath each fecal deposit and analyzed using serial dilution, plating on nutrient agar, and incubation at 28°C for 24-48 hours. A one-way ANOVA was conducted to detect differences between groups.

Results showed that soils beneath antibiotic-supplemented feces had higher average TAMB counts (AMOXI: 2.14×10^7 CFU/g; OTC: 2.5×10^7 CFU/g) compared to controls (1.29×10^7 CFU/g), with statistically significant differences ($p<0.01$). These findings align with previous studies by Binh et al. (2007) and Chen et al. (2013), indicating that AMOXI and OTC increase total bacterial counts in soils exposed to these antibiotics. This likely occurs at the expense of other microbial populations targeted by these drugs.

In conclusion, antibiotics in pig feces can reach the soil and alter its microbial composition.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Adrian Lifschitz and Santiago Zugbi

44. *Escherichia coli* O157:H7 ISOLATED FROM FEEDLOT-GROUND BEEF: BACTERICIDAL ACTIVITY OF AP7121 AND SYNERGISTIC EFFECT WITH EDTA

Laureano Schofs[1,2], Mariana Bistoletti[3], Leonardo García Allende[4], Sabina Lissarrague[1,3], Guadalupe de Yaniz[1,2], Beatriz Baldaccini[3], Sergio Sánchez Bruni[1,2], Mónica Sparo[2,4]

[1]*Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA). Tandil, Buenos Aires, Argentina.* [2]*Centro de Investigación Veterinaria de Tandil (CIVETAN). CONICET-UNCPBA-CICPBA. Tandil, Buenos Aires, Argentina.* [3]*Facultad de Ciencias de la Salud, Instituto de Investigación en Ciencias de la Salud, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Olavarría, Buenos Aires, Argentina.* [4]*Hospital Privado de Comunidad, Servicio de Gastroenterología y Endoscopía, Mar del Plata. Argentina.*

The emergence of multidrug-resistant *Escherichia coli* strains highlights a need for new therapeutic options. In Argentina, feedlot systems have acquired significant relevance as providers of meat products, such as ground beef. *E. coli* O157:H7 is one of the most important foodborne pathogens, with major implications in the meat products industry. AP7121 is a bacteriocin produced by the probiotic strain *Enterococcus faecalis* CECT7121. In this study, we aimed to investigate its bactericidal activity against *E. coli* O157:H7 (n=5) isolated from feedlot-ground beef and the synergistic effect with EDTA. 5 isolates of *E. coli* O157:H7 were isolated and characterized from feedlot-ground beef sold in Tandil County (Argentina) markets. Minimum Inhibitory Concentration (MIC) for AP7121, EDTA, and their combination against *E. coli* was performed (micro-dilution method). *In vitro,* the bactericidal activity of AP7121 alone or combined with EDTA (512 mg/L) was studied by carrying out time-kill curves to assess a synergistic effect. Samples were obtained for viable cell counts (0, 4, 8, and 24 h). MIC and time-kill curves were carried out three times. AP7121 (MIC_{AP} > 128 mg/L) alone did not show an inhibitory effect against *E. coli*; MIC_{EDTA} was > 16000 mg/L. EDTA was not bactericidal. AP7121 combined with EDTA showed a lower MIC (MIC_{AP} 2-4 mg/L) with bactericidal activity against all *E. coli* isolates. A synergistic effect was observed at 4-8 and 24 h (-2.4 to -4.5 Δlog_{10} CFU/mL). AP7121 constitutes a candidate as a natural tool, combined with EDTA, against *E. coli* O157:H7. EDTA perturbs the cell membrane, allowing AP7121 to have a bactericidal effect against *E. coli*.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Adrian Lifschitz and Santiago Zugbi

45. A NOVEL-FRIENDLY PEDIATRIC FORMULATION OF VANCOMYCIN FOR ORAL ADMINISTRATION

Nicolas López[1], Marcelo Avena[2] and Vidal Noelia Gonzalez[1]

[1]*CONICET-Departamento de Biología, Bioquímica y Farmacia-Universidad Nacional del Sur (UNS), Bahía Blanca, Argentina,* [2]*INQUISUR--Universidad Nacional del Sur (UNS), Bahía Blanca, Argentina*

Pseudomembranous colitis is an inflammation of the colon associated with an overgrowth of the bacterium *Clostridium difficile*. Administration of oral vancomycin (VAN) is needed for a correct treatment. However, in Argentina, formulations for oral administration of VAN are not developed. In this sense, the content of a vial (for i.v. route) is reconstituted with water and administered orally. This work aimed to develop a new oral formulation of VAN for children.

Chewable gels (CG), also known as 'gummies', are considered suitable alternatives to traditional oral dosage forms like tablets and capsules, due to their merits which include administration without water, softness/flexibility, improved drug release, appealing organoleptic properties, better patient compliance, simple manufacturing process and usefulness for persons of different ages.
In this work, CG were elaborated with VAN (200 mg/unit), gelatine as gelling agent, citric acid as acidifier, sodium benzoate as preservative, glycerine and sorbitol as plasticizers, and vanilla essence. After stabilization (completion of the syneresis process) for 15 days, they were characterized in terms of weight, syneresis, dimensions, pH, water activity, texture profile analysis, *in vitro* dissolution, uniformity of content and disintegration time.
The average weight of each CG was 3.04 g, with a size of 22 mm width/length and 9.5 mm height, and the average syneresis was 29.66%. Texture parameters resulted in an average hardness of 4.99 N, a gumminess of 4.49 N, an adhesiveness of 1.08 N and an elasticity of 0.16 mm. The average pH value was 4.28, necessary to prevent bacterial growth. The VAN content was set at 91.8 % and, according to the *in vitro* dissolution profiles, a 100 % of drug concentration was dissolved after 30 min.
In conclusion, the developed CG of VAN would be a good option to fill the therapeutic gap for treatment of *Clostridium difficile* infections in pediatric patients.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Adrian Lifschitz and Santiago Zugbi

46. BIOACTIVITY OF A FORMULATION OBTAINED FROM THE HYDROLYZED ESSENTIAL OIL OF *CYMBOPOGON NARDUS* IN *AEDES AEGYPTI* MOSQUITOES

María Rosana Ramirez[1], Jorge Oyhenart[2], Juan Carlos Yori[3]

[1]*Consejo Nacional de Investigaciones Científicas y Técnicas – CONICET- CCT-Nordeste.* [2]*Instituto de Ciencias de la Tierra y Ambientales de La Pampa (Conicet–Facultad de Ciencias Naturales Universidad Nacional de La Pampa), La Pampa, Argentina.* [3]*Instituto de Investigaciones en Catálisis y Petroquímica (Consejo Nacional de Investigaciones Científicas y Técnicas - Universidad Nacional del Litoral), Santa Fe, Argentina.*

Citronella oil is obtained from two perennial herbs of the species *Cymbopogon* (Poaceae). This plant is grown and commercialized in the province of Misiones, Argentina. The essential oil obtained from this species is mainly used as a mosquito repellent, is not considered harmful to humans, but can cause skin irritation. The most abundant repellent molecules found in the group are citronellal, citronellol and geraniol. The high citronellal content also makes it possible for plants of this genus to be used for the production of para-menthane-3,8-diol (PMD), because citronellal is a precursor of this compound. In this work, the extraction and hydrolysis of *C. nardus* oil was carried out. The virgin oil was obtained by hydrodistillation. On the other hand, part of the virgin oil was hydrolyzed by treatment with sulfuric acid. The chemical profile of both the virgin oil and the hydrolysed oil samples was determined by gas chromatography. The main compounds detected in the hydrolysed sample were PMD and compounds of the isopulegol family. The hydrolyzed sample was then diluted in water with ethanol and a formulation was prepared (confidential) and evaluated for its potential repellent activity against *Aedes aegypti* mosquitoes. Tests showed that the formulation (14 % PMD) exhibits protection for 25 minutes, and 85% repellency for about two hours after topical application. Indicating that at the concentration tested the protection time of the formulation against *Aedes aegypti* was proportional to the amount of PMD applied. However, the constitution of the formula should be modified to provide greater efficacy and protection time.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Verónica Lasalle and Guillermina Hernando

47. ROLE OF FUCOIDAN-RICH EXTRACTS IN SOME VIRAL INFECTIONS

Camila Uboldi[1], Tatiana Golovca[1], Agustín Nelo Buzzi[1], Macarena Giuliani[1], Verónica Lassalle[3,4], Ezequiel Latour[2], Fernando Dellatorre[2,4], Victoria Belén Ayala[1,4].

[1]*Departamento de Biología, Bioquímica y Farmacia de la Universidad Nacional del Sur. Bahía Blanca, Buenos Aires, Argentina.* [2]*Universidad Tecnológica Nacional, Facultad Regional Chubut. Grupo de Investigación y Desarrollo Tecnológico en Acuicultura y Pesca (GIDTAP). Puerto Madryn, Argentina.* [3]*Departamento de Química, INQUISUR, Universidad Nacional del Sur, Bahía Blanca, Argentina.* [4]*Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET). Argentina.*

Currently, there is a diversity of viral infections that, even though they have vaccines or treatments, continue to be highly prevalent. Such are the cases of genitourinary viruses like HPV (human papillomavirus) or herpesviruses. The latter are also strongly associated with upper body infections. On the other hand, the use of antiviral drugs has been limited due to the generation of drug-resistant viral strains. Additionally, in certain age groups, their implementation is not recommended due to their high toxicity and limited effectiveness. In the present time, the trend in scientific and clinical research is towards the use of natural antiviral compounds as a more attractive option, as they are biodegradable and have minimal or no side effects, as fucoidans. Which are sulfated polysaccharides obtained from brown seaweed.
Objectives: To employ fucoidan-rich extracts from *Undaria pinnatifida* and *Myriogloea major* algaes as potential antivirals. For this purpose, we used the HSV-1 (herpes simplex type 1 virus) virus for Vero cell culture infection. We used the Hela cells to study the effect of HPV-transformed cells.
Results: The treatment with extracts from *Undaria pinnatifida* showed antiviral activity against HSV-1 at 100 µg/ml in approximately 100% after 24 hours post-infection. Additionally, it was observed that treatment with a dose of 100 µg/ml reduced amyloid beta peptide synthesis under infected conditions by almost 100% at 24 hours using immunocytochemistry techniques. Treatments with extracts and fractions obtained from *Myriogloea major* at 1 µg/ml were able to reduce the viral titer of HSV-1 by 100%. Also, the fractions showed a differential cytotoxicity against Hela and Vero cells, being significantly more cytotoxic against cells derived from cervical carcinoma.
These data together suggest that fucoidan extract could be proposed as a potential medicinal compound for use in certain viral-origin pathologies.

Pharmaceutical Technology
Chairs: Verónica Lasalle and Guillermina Hernando

48. OPTIMIZING GRANULE FORMULATIONS FOR PEDIATRIC TUBERCULOSIS TREATMENT USING QBD PRINCIPLES

Laura Carolina Luciani Giacobbe[1*], Tomás Lobos Silhanek[2], María Eugenia Olivera[1].

[1]*Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba y Unidad de Investigación y Desarrollo en Tecnología Farmacéutica, CONICET-UNC. Haya de la Torre y Medina Allende, Córdoba, Argentina. CP: X5000HUA,* [2]*Facultad de Ciencias Químicas, Universidad Nacional de Córdoba. Av. Medina Allende N°1998, X5000 Córdoba.*

Quality by Design (QbD) is an approach to pharmaceutical development that enhances consistency and quality by understanding and controlling the product and process. This study analyzed how composition attributes and high shear wet granulation parameters affect granules of rifampicin (RIF), isoniazid (ISO), and pyrazinamide (PIR) to design optimized formulations such as dispersible granules and tablets for pediatric tuberculosis treatment.

A factorial design of experiments (DoE) using a DIOSNA P1-6 granulator investigated granulation parameters: impeller speed, liquid/solid ratio, and massing time, and their impact on granule properties. For ISO and PIR, a 2^3 factorial design was employed, while a 2^4 design was used for RIF, including carboxymethyl cellulose ratio as an additional factor. The evaluated responses were yield, bulk and tapped densities, Carr index, Hausner ratio, repose angle, porosity, and dissolution at 5 minutes. The experimental data was analyzed using Design Expert® software (statistical significance assessed via ANOVA; $p < 0.05$).

Results indicated that the experimental models generally fit well with the responses, except for dissolution, which remained consistently high (≥ 82%) across all formulations, supporting efficacy. Granule properties were sensitive to massing time, with longer times enhancing outcomes. The liquid/solid ratio significantly influenced granule properties; for hydrophilic solids (ISO and PIR), increasing this ratio improved desirability, while for hydrophobic RIF, higher ratios reduced desirability due to limited liquid accommodation. Though higher agitation speeds were preferred, acceptable performance was attained at lower speeds.

Numerical optimization identified optimal granulation conditions for each active ingredient. The optimized formulations demonstrated suitable compressibility, high porosity, and consistent density, interesting for developing dispersible granules and tablets that meet the critical quality attributes for pediatric use.

Pharmaceutical Technology
Chairs: Verónica Lasalle and Guillermina Hernando

49. ENHANCED ANALGESIA WITH SUBTHERAPEUTIC MORPHINE USING SELF-NANOEMULSIFYING SYSTEMS (SNEDDS) OF AN OMEGA-3 ENRICHED MARINE OIL IN ACUTE PAIN MANAGEMENT

Karem Alejandra Arrigoni-Rodriguez[1], Florencia Elorriaga[2], Carlos Laino[2], and María Eugenia Olivera[1*]

[1]*Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba y Unidad de Investigación y Desarrollo en Tecnología Farmacéutica, CONICET-UNC. Haya de la Torre y Medina Allende, Córdoba, Argentina. CP: X5000HUA,* [2]*Instituto de Biotecnología, Centro de Investigación e Innovación Tecnológica Universidad Nacional (CENIIT), Universidad Nacional de La Rioja, La Rioja, Argentina*.

The combination of a subtherapeutic dose of morphine (MOR) with omega-3 fatty acids (O3) generated a synergistic analgesic effect and reduced adverse events associated with MOR in a murine model (patent P-20120100854). This study aimed to evaluate the antinociceptive efficacy of a self-nanoemulsifying drug delivery system (SNEDDS) containing O3-enriched marine oil (OM), both alone and in combination with MOR (SNEDDS-MOR), in a murine model of acute pain.
The SNEDDS was prepared by combining OM with surfactants and co-surfactants. Male Wistar rats were used to evaluate the antinociceptive effects using the hot plate test. Six groups of rats received a single oral dose of the following treatments: OM (720 mg O3/kg), MOR (12 mg/kg, subtherapeutic dose), OM-MOR, SNEDDS and SNEDDS-MOR (same doses as the non-combined treatments). A saline solution (10 mL/kg) served as the control. The latency to nociceptive responses (LR) was measured 90 minutes post-administration. The rats underwent a Rotarod test to evaluate their motor coordination and to rule out a possible sedative effect of formulations. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test.
The saline, MOR, OM and OM-MOR groups showed similar LR, indicating no significant analgesic effects. In contrast, SNEDDS and SNEDDS-MOR significantly prolonged LR compared to control ($p<0.05$), demonstrating enhanced antinociceptive efficacy and a synergistic effect with the combination of OM and MOR. No significant differences in motor coordination between treated groups and controls confirmed that the observed analgesia was not due to sedation.
The study demonstrated that OM-based SNEDDS can significantly potentiate the analgesic effects of subtherapeutic doses of MOR, offering a promising approach to pain management that could minimize opioid-related adverse effects. Further studies are warranted to confirm these findings and explore their application in clinical settings.

Pharmaceutical Technology
Chairs: Verónica Lasalle and Guillermina Hernando

50. STABILITY AND AERODYNAMIC ANALYSIS OF pMDIs WITH SPRAY-DRIED MOMETASONE MICROPARTICLES

Nazareth Ceschan[1,2], Hugh Smyth[3], María Ramírez Rigo[1,2]

[1]*Planta Piloto de Ingeniería Química (PLAPIQUI, UNS-CONICET), Camino La Carrindanga, Km 7, Bahía Blanca (8000), Argentina,* [2] *Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, San Juan 670, Bahía Blanca (8000), Argentina,* [3] *College of Pharmacy, The University of Texas at Austin, 2409 University Avenue, Austin, TX (78712) United States*

Asthma is a chronic respiratory condition that affects millions worldwide, particularly children, and is primarily treated with inhaled corticosteroids (IC). Pressurized metered-dose inhalers (pMDIs) often contain drug suspensions in propellants. Physical instability of these formulations can result in low airway deposition and high drug retention in the oropharynx, leading to swallowing of the medication. Stabilizing excipients can impair formulation and aerodynamic performance (AP); engineered particles with controlled properties offer an alternative. This study aims to produce and examine the stability and aerosolization behavior of excipient-free pMDIs containing spray-dried (SD) microparticles of mometasone (M), an IC used in asthma.
Particle morphology was analyzed by scanning electron microscopy (SEM). For pMDIs production, particles were put into aluminum canisters, sealed with a metered valve and filled with pharmaceutical-grade HFA 134a. The AP of pMDIs was evaluated using a cascade impactor. Stability was preliminarily assessed by dispersing the particles in saline solution (model dispersing medium) and measuring particle size distribution (PSD) at predetermined time intervals
SD particles were rounded with slightly rough surfaces. *Ca*. 43% of the M dose would reach deep lung regions, with oropharynx loss of 11%, as determined in the AP experiment. The mass median aerodynamic diameter was 3.5µm, adequate for the proposed application, while aerodynamic particle size distribution was narrow, with geometric standard deviation lower than 3. SD particles of M demonstrated adequate stability in saline solution: that PSD did not importantly change over time (1, 10 and 30 minutes). These results were confirmed by testing an aged pMDI, which showed no important changes in aerodynamic parameters. In conclusion, stable pMDIs with adequate AP were obtained using SD particles combined with pharmaceutical-grade HFA 134a.

Pharmaceutical Technology
Chairs: Nora Mariel Marder and Ventura Simonovich

51. DEVELOPMENT OF A RISK MANAGEMENT MATRIX TO EVALUATE THE ASSOCIATED RISKS IN THE DEVELOPMENT OF A DRY POWDER INHALER

María Caldarola[1,2], Cecilia Arnaboldi[1], Tatiana Odoux[2], Fernanda Cabrera[2], Nazareth Ceschan[1,2]

[1]*Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur, San Juan 670, Bahía Blanca (8000), Argentina,* [2] *Planta Piloto de Ingeniería Química (PLAPIQUI, UNS-CONICET), Camino La Carrindanga, Km 7, Bahía Blanca (8000), Argentina*

Standardized procedures and instructions (P&I) ensure uniformity in the production and quality control of new drugs and devices. Creating and implementing these documents associated with Drug Design and Development (D&D) ensures effective transfer from lab to production scale, with focus on Risk Management (RM). This work aimed to a) develop P&I for RM and b) analyze the risks associated with production and transfer to industrial production (IP) of a prototype of a high dose dry powder inhaler.

P&I applicable to RM for prototype development were written considering various approaches, like Failure Mode and Effects Analysis, Preliminary Hazard Analysis, and Hazard and Operability Studies. The RM for the prototype under development identified risks categorized into technical, economical and administrative ones. Each risk was described by identifying its origin, probability of occurrence, and impact on prototype development. A risk index was obtained by multiplying probability of occurrence and impact.

Most risks were classified as technical (13 out of 16 risks) while only three were administrative or economical. Risks related to quality and availability of initial materials have a low chance of occurrence but a high impact on product development. On the other hand, risks related to prototype technical development have a higher chance of occurrence and impact. Mitigation actions were proposed to reduce the risk of product development through their implementation. Most mitigation actions are related to the implementation of documents to allow traceability

In conclusion, the systematic analysis of risks for the inhalation drug prototype not only details potential challenges but also sets a precedent for risk management in similar projects. The instructions and documents will contribute to greater efficiency in the research and production of drugs intended for IP.

Pharmaceutical Technology
Chairs: Nora Mariel Marder and Ventura Simonovich

52. PEDIATRIC FORMULATIONS AND BITTER TASTE OF DRUGS IS NOT A GOOD COMBINATION: HOW TO OVERCOME IT?

Candela Juan[1,2], Noelia Gonzalez Vidal[1,2], and Loreana Gallo[1,3]

[1]*Departamento de Biología, Bioquímica y Farmacia - Universidad Nacional del Sur (UNS), Bahía Blanca, Buenos Aires, Argentina*. [2]*Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Bahía Blanca, Buenos Aires, Argentina*. [3]*Planta Piloto de Ingeniería Química (PLAPIQUI, UNS-CONICET), Bahía Blanca, Buenos Aires, Argentina*.

Losartan potassium (LP) is an antihypertensive drug with bitter taste. The study aimed to obtain solid dispersions (SD) of LP with Eudragit® L100 or E PO and adjuvants (such as colloidal silicon dioxide, SiO_2), by spray drying, to be incorporated in orally disintegrating tablets (ODT). The ODT disintegrate in the oral cavity, avoiding swallowing issues, being adequate for pediatrics.

Eleven SD were developed, although three SD with ≥ 90 % encapsulation efficiency and ≥ 70 % process yield were produced as ODT, accompanied by menthol, Neotame®, pineapple flavor, and excipients required for direct compression. The ODT were evaluated in terms of disintegration time, hardness, friability, uniformity of weight and content, wetting time, water absorption ratio, and *in vitro* dissolution. Besides, a palatability study was conducted with 10 volunteers that compared the taste of ODT_{LP}: composed of LP and excipients, ODT_E: composed only with excipients, and ODT_{SD}: composed of selected SD and excipients. Statistical analysis included ANOVA and Mann-Whitney U test with a level of probability '*p*' of 5 %.

Only two formulations ($ODT_{SD\text{-}L100}$ and $ODT_{SD\text{-}E\ PO/SiO2}$) exhibited adequate disintegration time, hardness, and friability. $ODT_{SD\text{-}E\ PO/SiO2}$ also had successful results in the dissolution study, achieving 95.4 % drug release at pH 1.2, while only 40.2 % was dissolved at pH 6.8, restricting drug release in the oral cavity. In the palatability study, the formulations were scored from 0 ("non-bitter") to 3 ("extremely bitter"). ODT_E demonstrated non-bitter taste. Significant differences were found between $ODT_{SD\text{-}E\ PO/SiO2}$ with a score of 1.20, and ODT_{LP}, with a score of 2.50 (*p*-value = 0.0031).

In conclusion, spray drying technology managed to reduce the bitter taste of LP, when flavorings and sweeteners were insufficient. The developed $ODT_{SD\text{-}E\ PO/SiO2}$ could be considered a good candidate for administering LP to pediatric patients, due to the potential improvement in treatment adherence.

Phytopharmacology
Chairs: Adrian Lifschitz and Santiago Zugbi

53. CARDIOPROTECTIVE MECHANISMS DURING ISCHEMIA-REPERFUSION AND EVALUATION OF ANTIDEPRESSANT ACTION OF *Salvia guaranitica* TINCTURE

Maria Victoria Piersante [1], Soledad Inés Matera[1], Maria Inés Ragone[1,2] and **Alicia Consolini**[1]

[1]Cátedra de Farmacología I y II, GFEYEC, Farmacia, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata. 47 y 115, La Plata, CP: 1900, Buenos Aires; [2]Consejo Nacional de Investigaciones Científicas y Técnicas.

Salvia guaranitica A. St.-Hil. ex Benth (Sg) (Lamiaceae) is a native plant from Argentinian Mesopotamia, and it is used as antispasmodic and sedative. In previous communications we have shown that the ethanolic extract of leaves has flavonoids, isoflavones and terpenes, and it induced antispasmodic effects on intestinal smooth muscle, sedation in mice and cardioprotection in a model of ischemia/reperfusion (I/R) in isolated rat hearts. Now, the aim was to evaluate the mechanisms of cardioprotection and if it has antidepressant activity. Methods: Wistar rats were orally treated with 1% ethanolic extract of *S. guaranitica* (Sg) (*ad libitum*) during 1 week. Then, isolated hearts were arterially perfused and introduced in a flow calorimeter to measure left intraventricular pressure (LVP, mmHg) and heat rate (Ht, mW/g). Maximal LVP of contraction (P), the diastolic one (LVEDP), and muscle economy (Eco=P/Ht) were measured during a protocol of 30 min I/45 min R. For mechanisms, before I/R wortmannin 100µM (Wrt, inhibitor of PI3K/Akt), clonazepam 10 µM (Clzp, blocker of mNCX), or nMPG 2mM (ROS scavenger) were perfused. In mice, Sg effects were evaluated in the forced-swimming test, in doses of 10, 30 and 100 mg/kg via i.p. vs saline and fluoxetine. Statistics: *p<0.05. Results: In rat hearts, Wrt reduced the postischemic contractile recovery (PICR) of hearts from oral Sg treated rats, from 53.5±6.6 to 31±11% of Pi*) as well as in Eco. Clzp did not affect PICR nor Eco, but nMPG increased PICR up to 87±21%*. In mice, Sg 10 mg/kg reduced the immobility time of swimming respect to saline (from 82±17 to 55±16* s) similar to fluoxetine (55±18* s). Conclusions: a) cardioprotection of oral Sg in rats was due to activation of the PI3K/Akt pathway, but not to activation of the mNCX; b) Sg cardioprotection is attenuated by the ROS production during I/R; c) Sg showed antidepressant effect at low doses in mice.

Phytopharmacology
Chairs: Adrian Lifschitz and Santiago Zugbi

54. EFFECTS OF POLEO (*Lippia Turbinata Griseb*) ON ISOLATED WISTAR RAT DUODENUM MUSCLE

Mariano Goddio Biancotti, Nilda Brizuela, Carlota Grigorjev.

Cátedra de Farmacología General. Facultad de Ciencias Médicas, UNC. Santa Rosa 1085. Córdoba. Argentina

The practice of traditional and complementary medicine is increasing. However, most of the plants used lack scientific support. Poleo (*Lippia Turbinata Griseb*) is used as an antispasmodic and also as a uterine stimulant (abortifacient). Objective: in this study we evaluated the effects on tone, amplitude and frequency of contractions induced by Poleo extract in isolated duodenum muscle. Virgin female rats of the Wistar line, aged 3-4 months, were used. Poleo extract in alcoholic solution in 30% dilution was used to know the effects of the active principles on the tissue to be studied. An isolated experimental model organ was used to simulate the physiological conditions in which the tissue is found within the organism. The duodenum muscle was extracted from the sacrificed animal and placed in the organ bath until its contractile activity was stabilized. Then, Poleo extract was added in volumes of 50, 100 and 200 microliters. Muscle contractility variations were recorded through a voltage transducer connected to a Beckman Type RB electrophysiograph. From these recordings, statistical comparison of the results was performed using the Student's T method. Exposure of the duodenum to Poleo extract produced a significant decrease in the tone and amplitude (dose dependent), and maintained the frequency of contractions ($p<0.01$). Preliminary results would explain the "popular" use of Poleo as an antispasmodic agent. However, future studies are needed to elucidate its pharmacodynamics.

Phytopharmacology
Chairs: Adrian Lifschitz and Santiago Zugbi

55. ANTI-INFLAMMATORY POTENTIAL AND THIN LAYER CHROMATOGRAPHY PROFILES OF THREE PLANT SPECIES GROWN IN CHACO PROVINCE, ARGENTINA

Franco Daniel Paz Seputic[1], María Virginia Radovancich[2], **Juan José Martínez Medina**[1,2], Carola Analía Torres[1,2] and María Beatriz Nuñez[1,2]

[1]*Instituto de Investigaciones en Procesos Tecnológicos Avanzados (Consejo Nacional de Investigaciones Científicas y Técnicas - Universidad Nacional del Chaco Austral, Roque Sáenz Peña, Chaco, Argentina),* [2]*Departamento de Ciencias Básicas y Aplicadas, Universidad Nacional del Chaco Austral*.

The aims of this study were to evaluate the anti-inflammatory activity (AA) of hydroethanolic extracts from *Lantana camara* L. (*Lc.*), *Lippia turbinata* Griseb. (*Lt.*) and *Mentha spicata* L. (*Ms.*) leaves and to identify their constituents.
AA was evaluated *in vitro* using enzymatic inhibition by 5-lipoxygenase and hyaluronidase and heat-induced hemolysis inhibition in erythrocytes. Enzymatic reaction products and hemoglobin were quantified spectrophotometrically with different concentrations of extracts or reference substances to generate dose-response curves and determine the half-maximal inhibitory concentration (IC_{50}). To identify phenolic acids (PA) and flavonoids or their derivatives, thin layer chromatography (TLC) plates were loaded with the extracts and their hydrolyzed ethyl acetate fractions, together with pure PA and flavonoids. TLC plates were eluted with different mobile phases: ethyl acetate:formic acid:acetic acid:water (100:11:11:26) for flavonoid glycosides, toluene:diethyl ether:acetic acid (10.9:7.3:1.8) for flavonoid aglycones, and chloroform:ethyl acetate:acetone:formic acid (8:6:4:2) for PA. Plates were visualized under UV light (366 nm), before and after spraying with the polyethylene glycol reagent for natural products, and the retention factors (Rf) of the pure compounds and the separated bands in the extracts were measured.
All the extracts showed AA. *Lc*. was the most active against 5-lipoxygenase (IC_{50}= 42.3 µg/mL). *Ms*. was the most active against hyaluronidase (IC_{50}= 38.9 µg/mL) and protecting erythrocytes (IC_{50}= 514.7 µg/mL). PA and flavonoids were tentatively identified by their Rf values and chromatographic characteristics in comparison with the pure compounds as follows: luteolin derivatives, rosmarinic acid and caffeic acid in *Ms.,* luteolin derivatives in *Lt.* and caffeic acid derivatives in *Lc*.
These results encourage us to further investigate AA of the extracts on cellular culture and *in vivo* models.

Phytopharmacology
Chairs: Nora Mariel Marder and Ventura Simonovich

56. EFFECT OF EXTRACTION METHOD ON THE YIELD AND BIOLOGICAL ACTIVITIES OF ESSENTIAL OILS OF AROMATIC PLANTS

Emanuel Hosni[1], **Silvana Rodriguez**[1], Ana Paula Murray[1] and Anabela Lorenzetti[1]

[1]*INQUISUR – CONICET, Departamento de Química, UNS, Bahía Blanca, Argentina*.

The global demand for essential oils (EO) from plants has grown exponentially. EO are used in various industries, from food to medicine, due to their numerous health and personal care benefits. Among aromatic and medicinal plant species, the production of *Origanum* cv EMMA INTA, commonly known as oregano, is prominent in Argentina. Natural deep eutectic solvents (NADES) have emerged as an environmentally alternative to traditional organic solvents, offering characteristics such as low toxicity, metabolite solubility, biodegradability, and preservative properties. This study focuses on the use of NADES as extractants and co-solvents in the oregano hydrodistillation process to evaluate the quality, yield, and biological activities of the EO. Three different NADES based on carbohydrates were used to increase the EO yield. The EO quality was evaluated through chemical composition analysis using gas chromatography-mass spectrometry (GC-MS) and the study of biological activities, including acetylcholinesterase inhibition and antioxidant activity. The AChE inhibition of the EO was assessed spectrophotometrically using the Ellman method, and antioxidant activity through DPPH reduction. Essential oils were extracted from the aerial parts of the plants through hydrodistillation and NADES extraction, with different yields and compositions observed among the different NADES. The highest oil yield (1.25%) was obtained for the NADES composition malic acid: fructose: glucose: water 1:1:1:5. The essential oils, containing carvacrol, terpinolene, α-terpinene, and γ-terpinene as main components, exhibited effective antioxidant activity, with an IC_{50} range of 34.96 to 58.65 µg/mL. Maximum acetylcholinesterase inhibition was observed with an IC_{50} value of 47.3 µg/mL. These findings suggest that oregano essential oils could have pharmacological applications in preventing oxidative stress-induced diseases.

Phytopharmacology
Chairs: Adrian Lifschitz and Santiago Zugbi

57. MINT ESSENTIALS OILS AS ANTICHOLINESTERASE AGENTS

Luana Ostertag[1], **Silvana Rodriguez**[1] and Ana Paula Murray[1]

[1]*INQUISUR – CONICET, Departamento de Química, UNS, Bahía Blanca, Argentina*.

The inhibition of the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) is relevant for the discovery of new alternatives in the treatment of Alzheimer's disease. This study aims to investigate the inhibition of the activity of both enzymes and antioxidant activity by the essential oils of three aromatic species cultivated at the Southwest of Buenos Aires province: *Mentha piperita* (1), *Mentha arvensis* (2) and *Minthostachys verticillata* (3).
The chemical composition of the essential oil (EO) obtained from the aerial parts by hydrodistillation, were analyzed by GC-MS. The antioxidant activity was assessed using the DPPH method, and the inhibition of AChE and BChE was determined using the Ellman's method to determine the inhibitions of AChE and BChE.
Twelve compounds were identified in EO2 and EO3 and seven compounds in EO1, with the predominance of oxygenated monoterpenes. The major compounds for EO1 were *trans* – caryophyllene (34.61%), followed by isomenthone (30.50%) and isopulegol (27.86%). While EO2 were menthone (62.03%) and D-limonene (12.83%) and EO3 were trans-caryophyllene (26.92%), carvone (28.21%) and caryophyllene oxide (24.36%).
The EOs showed moderate DPPH radical scavenging activity in the range of IC_{50} values of 0.69 mg/ml to 0.76 mg/ml). EO2 exhibited the highest inhibition of BChE compared to EO3 and EO1 were on the range of IC_{50} values 45.59 to 31.30 ηg/ml, while EO3 was the most efficient against AChE (IC_{50} = 160.6 ηg/ml).
These results suggest that essential oils of Mentha species and/or their components could be potential candidates for further studies for the development of effective anti-Alzheimer agents.

Phytopharmacology
Chairs: Adrian Lifschitz and Santiago Zugbi

58. CHROMATOGRAPHIC PROFILE, GASTROINTESTINAL AND ANTIDEPRESSANT-LIKE EFFECTS OF *VERBENA BONARIENSIS*

Brenda Heidenreich[1,2], Maria Inés Ragone[1,3], **Valentina Pastore**[2,3,4]

[1]*Cátedra de Farmacología I y II, GFEYEC, Farmacia, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, UNLP, La Plata, Buenos Aires, Argentina;* [2]*Cátedra de Farmacognosia, Farmacia, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, UNLP, La Plata, Buenos Aires, Argentina;* [3] *Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET);* [4]*Instituto de Química y Fisicoquímica Biológicas Prof. Dr. Alejandro C. Paladini (IQUIFIB). UBA-CONICET. Facultad de Farmacia y Bioquímica. Buenos Aires, Argentina.*

Verbena bonariensis, a native Argentine specie, is traditionally used for gastrointestinal and central nervous system disorders. Our aim is to evaluate the effects of *V. bonariensis* extracts on intestinal smooth muscle in rats and on behavior in mice. Additionally, a phytochemical analysis was conducted. The following extracts were prepared: infusions 5% w/v (W), tinctures 20% w/v (T) and decoctions at 5% w/v (D) from the aerial parts and flowers of *V. bonariensis* (Vb) or *V. officinalis* (Vo). Concentration-response curves of carbachol (Cbh) were performed in isolated rat intestines in the absence and presence of single and increasing concentrations of VbT and VbD. To evaluate the depression-like effect, the tail suspension test (TST) was performed. Mice were injected i.p. with: saline solution (SF), 1.25 mg/kg clomipramine (Clp, positive control), 15 mg/kg VbW or 30 mg/kg VbW. In the intestine, VbT at 1, 3 and 10% w/v reduced the maximum contraction of Cbh in a dose-independent manner up to 68.35±4.54%, while VbD did not change it. In the TST, VbW 30 mg/kg significantly decreased the immobility time similar to Clp. The chromatographic profile was performed, comparing *V. bonariensis* vs *V. officinalis* as describe in European Pharmacopoeia 8th Edition for *V. officinalis*. Additionally, extracts' antioxidant activity was measure as their ability to scavenge DPPH radicals (% DPPH quenched, (0.02-0.25 mg/mL)): VbD=10.47-64.58 *vs* VoD=5.71-56.22. The results suggest that: a) *V. bonariensis* extracts do not present direct antispasmodic activity in the isolated intestine. However, the popular use as an antidiarrheal could be due to an autonomic effect; b) VbW showed an antidepressant-like effect at a dose of 30 mg/kg validating its traditional use; c) TLC revealed a different chromatographic profile between *V. bonariensis* vs *V. officinalis* with verbascoside apparently absent in *V. bonariensis;* d) both species exhibit significant antioxidant potential at low concentrations.

Phytopharmacology
Chairs: Nora Mariel Marder and Ventura Simonovich

59. MECHANISM OF CARDIOPROTECTION AFTER ORAL TREATMENT WITH SOY ISOFLAVONES OR MACA (*Lepidium meyenii*) AFTER ISCHEMIA/REPERFUSION IN RATS

Soledad Inés Matera[1,2], Juliana Fantinelli[2,3] and Alicia Consolini[1]

[1]*Grupo de Farmacología Experimental y Energética Cardíaca, Cátedra de Farmacología, Farmacia, GFEYEC, Dpto Cs. Biológicas, Facultad de Ciencias Exactas. Universidad Nacional de La Plata. 47 y 115, La Plata, CP: 1900, Buenos Aires;* [2]*Consejo Nacional de Investigaciones Científicas y Técnicas.* [3]*Centro de Investigaciones Cardiovasculares "Dr Horacio E Cingolani".*

Soy isoflavones (SI) and maca flour (*Lepidium meyenii*) are dietary supplements. Both products contain the phytoestrogens genistein and daidzein, which individually had demonstrated cardioprotection against ischemia and reperfusion (I/R), associated to mKATP channels activation. We have previously shown that oral SI was cardioprotective, in part by reducing ROS production, while maca cardioprotection was limited by fibrillation occurrence in both sex. This work evaluated the SI and maca mechanisms of action by using selective blockers of: PI3K/Akt activation (wortmannine, Wt), ROS production (Tiopronin, MPG), and PKC (chelerythrine, Che). Methods: Wistar rats were orally administered with SI 100mg/kg/day or maca 1g/kg/day during 1 week. Hearts were isolated and arterially perfused inside a flow calorimeter, and stimulated at 5 Hz. After stabilization, each drug was perfused before I (and during R for MPG). Hearts were exposed to 30 min I/60 min R. Left intraventricular pressure (LVP) and total heat flow (Ht, mW/g) were measured. Maximal LVP of contraction (P) and muscle economy (Eco= P/Ht) were calculated. Results were compared by 2-way ANOVA (* $p<0.05$). Results: Wt produced a tendency to reduce post-ischemic contractile recovery (PICR) in hearts from SI-treated male rats (up to 34±13% vs 44±11%*). Wt delayed for 45 min the PICR in maca-treated male rat hearts despite finally it reached the control PICR. MPG ameliorated the PICR in maca-treated female rat hearts (up to 50±8% vs 32±5%*). Che abolished the cardioprotection of SI-treated female rat hearts (up to 5±5% vs 45±8%*). Conclusions: SI cardioprotection depends on both PI3K/Akt and PKC activations; the lack of protection and fibrillation in maca treated female rat hearts was due to ROS production, but in male rat hearts cardioprotection of maca involved PI3K/Akt activation.

Phytopharmacology
Chairs: Nora Mariel Marder and Ventura Simonovich

60. POTENTIAL NEUROPROTECTIVE EFFECTS OF ARGENTINE MEDICINAL PLANTS THROUGH CHOLINESTERASE INHIBITION FOR NEURODEGENERATIVE DISEASE TREATMENT

Marina Rademacher[1], Carolina Marcucci[1], Victoria Suarez[1], Lourdes Pin[1], Leonardo Martín Anconatani[2], Rafael Alejandro Ricco[2], Natalia Colettis[1], Ignacio Agudelo[2], Valentina Pastore[1], Mariel Marder[1].

[1]*Instituto de Química y Fisicoquímica Biológicas Prof. Dr. Alejandro C. Paladini (IQUIFIB). UBA-CONICET. Facultad de Farmacia y Bioquímica. Buenos Aires, Argentina.* [2]*Universidad de Buenos Aires. Facultad de Farmacia y Bioquímica. Departamento de Farmacología. Cátedra de Farmacobotánica. Buenos Aires, Argentina.*

Our laboratory studies Argentine medicinal plants with potential effect on the central nervous system for treating neurodegenerative diseases and their comorbidities, such as anxiety and insomnia. Among the multiple mechanisms involved in the development of these pathologies, and particularly Alzheimer's disease, the enzymes butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) play prominent roles. The death of cholinergic neurons leads to a decrease in the neurotransmitter acetylcholine, resulting in a progressive dysfunction of cognitive functions. Inhibiting these enzymes is a strategy used to prolong the half-life of ACh, thereby alleviating symptoms. We selected the following species: *Achyrocline saturejoides* (Marcela, flowering aerial parts), *Erythrina crista-galli* (Ceibo, leaves), *Minthostachys verticillata* (Peperina, sterile aerial parts), *Heteropterys glabra* (Tilo del campo, fruit), *Aloysia citrodora* (Cedrón, sterile aerial parts), *Stigmaphyllon bonariense* (Papa de río, secondary stem). Authenticated samples were dried, ground, and extracts prepared according to the Argentine Pharmacopeia 7th edition (infusions 5% w/v, tinctures 10% w/v). Previous studies have explored their phytochemical composition and antioxidant properties. Their cytotoxicity was tested on SH-SY5Y cells (β-hexosaminidase), showing no effect on viability up to 100 µg/mL. The BChE and AChE inhibition activity of the extracts was evaluated (Ellman's method) and IC_{50} was calculated: [%AChE inhibition (1 mg/mL): 151-51,5; IC_{50}(mg/mL): 0,3-3,2; %BChE inhibition (1 mg/mL): 13,3-94,0; IC_{50}(mg/mL): 0,1-0,5]. Extracts were more effective on BChE than AChE, with tinctures generally being more active than infusions, except for Ceibo. Marcela's tincture was the most active on BChE, while some infusions, notably Peperina, were more active on AChE. These results suggest that Argentine medicinal plants may offer promising compounds for treating neurodegenerative diseases and their comorbidities.

Pharmacognosy
Chairs: Nora Mariel Marder and Ventura Simonovich

61. ACTIVE PRINCIPLES PRESENT IN *LEPECHINIA MEYENII* (WALP.) EPLING ETHANOL EXTRACT AS ANTIANGIOGENIC DRUG CANDIDATES

Brisa E. Alanis[1], Érika A. Ripani[3], Jerónimo Laiolo[2], Macarena Funes Chabán[1], Mariano Vera[3], María C. Carpinella[1] and **Mariana B. Joray**[1]

[1]*Centro de Investigación y Desarrollo en Inmunología y Enfermedades Infecciosas CONICET-UCC,* [2]*Instituto de Investigación Médica Mercedes y Martín Ferreyra CONICET-UNC,* [3]*Instituto de Investigaciones en Biodiversidad y Biotecnología CONICET-UNMdP*.

Pathological angiogenesis is a common feature to a large number of diseases. The limited efficacy of available treatments, their adverse effects and the development of resistance make it imperative to find new therapeutic agents. In this regard, natural products continue to play a significant role in drug discovery. This work studied the antiangiogenic activity of the ethanol extract of *Lepechinia meyenii*. Through chemical fractionation, three compounds were isolated. Tube formation assay using bovine aortic endothelial cells was the experiment of choice to assess angiogenesis *in vitro*. Cell proliferation and cell migration were investigated through the MTT and the scratch assay, respectively. The inhibitory effect over the microsomal enzyme prostaglandin E2 synthase (mPGE2S-1) was studied by molecular and massive dynamic simulations. Cytotoxicity on peripheral blood mononuclear cells and erythrocyte cells was evaluated by means of MTT and hemolysis assay, respectively. *In silico* prediction of pharmacological properties was performed using the SwissADME online tool.
Chemical fractionation of *L. meyenii* extract yielded the antiangiogenic compounds carnosic acid (**1**), carnosol (**2**) and rosmanol (**3**). Among these, **1** showed the highest activity (IC_{50} = 5.7 µM). No adverse effect was observed over cell proliferation, while this compound efficiently blocked cell migration. The isolated compounds did not show toxic effects on peripheral blood mononuclear cells and did not affect erythrocyte membrane integrity. Based on experimental evidence that supports mPGE2S-1 as the molecular target of **1,** its inhibitory effect over this enzyme was further investigated.
This work highlights the native flora of Argentina as a source of new antiangiogenic agents. As far as we know, there has been no previous description of the antiangiogenic activity of *L. meyenii*. These results position the isolated compounds as promising candidates for the development of new angiogenesis inhibitors.

Bioinformatics and Therapeutic Targets
Chairs: Nora Mariel Marder and Ventura Simonovich

62. PHARMACOLOGICAL INHIBITION OF P300 DISPLAYS ANTIMETASTATIC ACTIVITY IN TRIPLE NEGATIVE BREAST CANCER

Guillermina Ana Gallardo[1,2], María Julia Ferronato[1,2], Eliana Noelia Alonso[1,2], Georgina Pamela Coló[1,2], Valentina Clemente[1,2], María Marta Facchinetti[1,2], Alejandro Carlos Curino[1,2], María Eugenia Fermento[1,2]

[1]*Laboratorio de Biología del Cáncer, Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS)-Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Bahía Blanca, Argentina.* [2]*Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS), Bahía Blanca, Argentina.*

Triple negative breast cancer (TNBC) is a molecular subtype of BC that is known for having a poor prognosis and limited therapeutic options. Therefore, it is necessary to investigate potential therapeutic targets for this pathology. A relationship between p300 and cancer has been demonstrated; but its role remains unclear, as it has been documented both as a tumor suppressor and an oncoprotein. Previously, we have shown that pharmacological inhibition of p300 has an antitumoral effect in the hormone-independent breast cancer cell line, LM3 and its syngeneic murine model. Further, we observed that pharmacological inhibition of p300 reduces migration, invasion and adhesion processes in TNBC MDA-MB-231 cells, indicating the need to further investigate the involved molecules. It is known that E-cadherin and β-catenin are key proteins in adhesion processes between epithelial cells and a decrease in their membrane expression is linked to a pro-tumor phenotype. Therefore, we proposed to investigate the effect of pharmacological inhibition of p300 on stress fiber formation and E-cadherin and β-catenin expression in TNBC cell line and its xenograft model. MDA-MB-231 cells were treated with VV59 (inhibitor of p300 histone acetyltransferase activity) or its vehicle. We detected an increase in E-cadherin and in membrane β-catenin expression in cells treated with VV59 compared to vehicle (immunofluorescence, $p<0.01$). In addition, cells stained with fluorescently labeled phalloidin revealed a decrease in stress fibers in cells treated with VV59 compared to vehicle ($p<0.01$). In a murine xenograft model of MDA-MB-231 we detected an increase in E-cadherin and in membrane β-catenin expression (immunohistochemistry, $p<0.01$) in the tumors of animals injected with VV59 compared to the control group. Also, in such a group of mice, we found a significant reduction in the number of lung metastases with respect to the control group ($p<0.05$). These results suggest a prometastatic role of p300 in TNBC.

Pharmacokinetics and Pharmacodynamics
Chairs: Nora Mariel Marder and Ventura Simonovich

63. LONG-TERM POPULATION PHARMACOKINETICS OF TACROLIMUS IN ADULT TRANSPLANT RECIPIENTS IN COLOMBIA

Ivone E. Jimenez, Andrés Hincapié, **María A. Montoya-Giraldo**, Andres F. Zuluaga

Grupo de Investigación en Farmacología y Toxicología, LIME: Laboratorio Integrado de Medicina Especializada, MINCIENCIAS (111589786169), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia

Objective: Tacrolimus is an immunosuppressant used post-organ transplantation with significant pharmacokinetic variability. This study aimed to develop a nonparametric population pharmacokinetic (pop-PK) model to predict tacrolimus levels in adult transplant recipients four and two-thirds years post-transplant.
Materials and Methods: The study included 9 adult patients who were more than four years post-transplantation. Intensive sampling (6 samples per day) was performed, yielding 57 observations. A three-compartment model with first-order absorption was used. Covariates including body mass index (BMI), hematocrit, time since transplant, and genetic polymorphisms (CYP3A5 and ABCB) were considered for influencing clearance and distribution volumes, with allometric scaling to BMI.
Results: The final model yielded an R-squared of 0.37, indicating a moderate fit between predicted and observed values. Additionally, the model exhibited a bias of 0.151 and an imprecision of 2.05. The final mean parameter estimates included apparent clearance (CL/F) of 0.03 L/h, apparent central volume (V/F) of 0.12 L, apparent peripheral volume (Vp/F) of 3.86 L, relative bioavailability, and absorption rate constant (Ka) of 0.42 h. Subpopulations within the model were identified based on key parameters such as bioavailability and elimination rates. The identified covariates significantly impacted tacrolimus clearance and distribution volumes.
Conclusion: This nonparametric pop-PK model is a promising tool for individualized dosage predictions in long-term transplant recipients. However, further validation with a larger sample size and prospective evaluations is necessary to confirm its clinical utility.

Pharmacokinetics and Pharmacodynamics
Chairs: Nora Mariel Marder and Ventura Simonovich

64. IMPACT OF OBESITY ON THE POPULATION PHARMACOKINETICS OF ORAL ACETAMINOPHEN IN HEALTHY ADULTS IN MEDELLÍN, COLOMBIA

Andres F. Zuluaga, Ivone E. Jimenez, Andrés Hincapié, María A. Montoya-Giraldo, Laura Vargas, Hector J. Perez

Grupo de Investigación en Farmacología y Toxicología, LIME: Laboratorio Integrado de Medicina Especializada, MINCIENCIAS (111589786169), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia[1]

Objective: Acetaminophen is widely used as a first-line analgesic for both children and adults. This study aimed to develop a population pharmacokinetic (pop-PK) model to describe acetaminophen kinetics in adults with and without obesity following a 1000 mg oral dose, assessing how body composition influences drug disposition.
Materials and Methods: Twenty-four healthy adult volunteers, including obese and non-obese individuals, were recruited. Plasma acetaminophen concentrations were measured at multiple time points (0, 15, 30, 60, 90, 120, and 360 minutes) post-administration using a validated high-performance liquid chromatography (HPLC) method with ultraviolet detection. Pharmacokinetic parameters were estimated using non-linear mixed-effect modeling via Pmetrics software. Covariates such as age, fat mass, weight, BMI, clearance, and CYP2E1 polymorphisms were evaluated.
Results: The dataset comprised 144 observations from the 24 participants. A two-compartment model with first-order elimination best described the pharmacokinetics of acetaminophen, yielding an R-squared value of 0.96. Fat mass emerged as a significant covariate, particularly influencing the clearance of acetaminophen, which was estimated at 48.3 L/h/70 kg. The estimated central and peripheral volumes were 4.3 L and 71.2 L, respectively. The model also indicated a mean absorption lag time of 13 minutes and a bioavailability of 86%.
Conclusion: The study highlights the significance of fat mass as a covariate in acetaminophen pharmacokinetics. These findings suggest that dosing regimens for acetaminophen in obese patients should account for these population pharmacokinetic differences to optimize therapeutic outcomes.

Pharmacokinetics and Pharmacodynamics
Chairs: Nora Mariel Marder and Ventura Simonovich

65. EFFECTS AND MECHANISMS OF CARVEDILOL ON CALORIMETRICAL AND MECHANICAL RECOVERY OF HYPERTHYROID RAT HEARTS EXPOSED TO ISCHEMIA REPERFUSION

Maria Inés Ragone[1,2], Matias Bayley[1,2], Alicia Consolini[1]

[1]*Cátedra de Farmacología I y II, GFEYEC, Farmacia, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata. 47 y 115, La Plata, CP: 1900, Buenos Aires;* [2]*Consejo Nacional de Investigaciones Científicas y Técnicas.*

Carvedilol (Carv) prevents damage to mitochondrial function in cardiac ischemia-reperfusion (I/R) injury. Our aim was to evaluate the effects of direct perfusion and acute oral administration of Carv in the postischemic recovery of euthyroid (EuT) and hyperthyroid (HypT) rat hearts exposed to I/R and the mechanisms involved. Rats became HypT by daily injecting s.c. 20 µg/kg T3 for 15 days. EuT and HypT rats received orally 20 mg/kg Carv daily during 7 days (O-Carv) before isolating hearts. Moreover, isolated ventricles of HypT or EuT rats were perfused with Carv 0.03 µM before I/R. Isolated hearts were perfused inside a flow calorimeter and exposed to 30 min I/45 min R. Left intraventricular pressure (LVP, mmHg) and total heat release (Ht, mW/g) were measured and maximal developed pressure (P) and total muscle economy (P/Ht ratio) were calculated (mmHg.g/mW). The role of PI3K/Akt pathway was evaluated by perfusing wortmannin (Wrt, 100µM) before I/R in EuT-O-Carv and HypT-O-Carv. To evaluate the ROS contribution, hearts from HypT rats perfused with Carv were also perfused before I and during R with n-MPG 0.2 mM, a ROS scavenger. Results: perfused Carv improved the postischemic contractile recovery (PICR) to 60.5±9.9% of pre-I P (vs 31.8±3.8% in EuT,*$p<0.05$) and P/Ht to 4.1±1.0 mmHg.g/mW (vs 1.0±0.4* in EuT) but not in HypT. nMPG prevented the lack of cardioprotection of perfused Carv in HypT. O-Carv-HypT significantly improved PICR and P/Ht vs HpT-C (50.2±8.3 vs 23.5±3.4* % of pre-I and 3.6±0.29 vs 1.7±0.2* mmHg.g/mW, respectively) and EuT-O-Carv improved vs EuT (54.5±4.2 vs 19.8±4.6* % of pre-I and 4.4±0.7 vs 1.6±0.4* mmHg.g/mW, respectively). These last effects were reversed by Wrt. Results suggest that: a) Carv was directly cardioprotective in EuT hearts exposed to I/R; b) Carv lost its beneficial effects in hyperthyroidism due to ROS accumulation; c) Subacute oral Carv was strongly cardioprotective in EuT and HypT hearts and PI3K/Akt pathway is involved.

Pharmacokinetics and Pharmacodynamics
Chairs: Nora Mariel Marder and Ventura Simonovich

66. PHARMACODYNAMIC ASSESSMENT AND SKIN EXPOSURE OF TOPICALLY ADMINISTERED CHLORPYRIFOS IN CATTLE

Karen Larsen, Paula Ichinose, Victoria Miró, Hernán Moscuzza, Lucila Moriones, Adrián Lifschitz, Guillermo Virkel

Centro de Investigación Veterinaria de Tandil (CIVETAN), UNCPBA-CICPBA-CONICET. Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Facultad de Ciencias Veterinarias, Tandil, Buenos Aires, Argentina.

Chlorpyrifos (CPF) is currently being repurposed for the control of cattle mange and ticks. CPF is used topically as a pour-on formulation, or through dipping and aspersion methods. CPF and its oxon metabolite (CPF-ox) are irreversible inhibitors of acetylcholinesterases (AChEs) and butyrylcholinesterases (BChEs) in both target parasites and treated animals. This work evaluated the effects of CPF (in vitro and in vivo) and CPF-ox (in vitro) on AChE and BChE activities in cattle plasma, and the availability of CPF in cattle skin and plasma following its topical administration. CPF was administered (7.5 mg/kg) along the backline of 6 heifers on days 0 and 11 post-first dose. Plasma and skin samples were collected before the initial treatment up to 20 days post-administration. Drug concentrations in plasma and skin (retroauricular, backline, and croup regions) were measured by HPLC. The IC50s of CPF for the in vitro inhibition of AChE and BChE activities in plasma were greater than 1000 µM. CPF-ox was roughly 500 times more potent AChE inhibitor and 150 times more potent BChE inhibitor. The IC50 of CPF-ox for AChE activity (1.9±1.1 µM) was lower ($p=0.037$) than that for BChE activity (6.8±4.3 µM). CPF did not change plasma AChE and BChE activities in treated animals. CPF concentrations in plasma were between 0.07±0.03 µg/mL (day 0.25) to 0.16±0.11 µg/mL (day 20). Drug exposure in the skin, measured as AUC (µg/d.g), was higher ($p<0.05$) in the backline (2218±1872) compared to other skin areas (521±138). Notably, higher ($p<0.05$) CPF partial AUCs were observed following the second dose. The absence of inhibitory effects on cholinesterase activities in plasma indicates low plasma levels of CPF, underscoring its safety for treated animals. Although CPF was detected in various skin regions, its distribution was not uniform. Therefore, repeating the treatment at intervals of 8-11 days is crucial to increase skin drug exposure and enhance the efficacy against ectoparasites.

Pharmacokinetics and Pharmacodynamics
Chairs: Nora Mariel Marder and Ventura Simonovich

67. POTENTIAL IMPAIRMENT OF MONENSIN CYP3A-DEPENDENT LIVER METABOLISM BY MACROLIDE ANTIMICROBIALS

Paula Ichinose, María Victoria Miró, Marcela Valente, Laura Moreno-Torrejón, Karen Larsen, Carlos Lanusse, Adrián Lifschitz, Guillermo Virkel

Centro de Investigación Veterinaria de Tandil (CIVETAN), UNCPBA-CICPBA-CONICET. Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Facultad de Ciencias Veterinarias, Tandil, Buenos Aires, Argentina

Traditional macrolide antimicrobials are well-known inhibitors of cytochrome P4503A (CYP3A) isozymes in cattle liver. Monensin (MON), an ionophore antibiotic with a narrow safety margin, is detoxified via CYP3A. Consequently, the incompatibility between ionophores and certain macrolides is well-known in livestock animals. We hypothesized that this metabolic interaction could also occur with more recently introduced macrolides, such as tilmicosin (TIL), tulathromycin (TUL), and gamithromycin (GAM). This study aimed to evaluate the effects of TIL, TUL, GAM and MON on the CYP3A-dependent metabolism in cattle liver microsomes, and to assess the influence of the mentioned macrolides on the metabolism of MON itself. Testosterone 6β-hydroxylase (TST 6β-OH) activity (a marker of CYP3A-dependent metabolism) was assayed in liver microsomes from steers (n=4) incubated either in absence (controls) or presence of 25 and 125 µM of TIL, TUL, or GAM alone or in combination with 250 µM of MON. Triacetyl-oleandomycin (TAO) was used as the reference macrolide drug. MON (0.72 µM) metabolism was studied both in the absence and presence of all the aforementioned macrolides (5 µM). Incubated samples were analyzed by HPLC with UV detection (testosterone 6β-hydroxylase) or MS/MS detection (MON metabolism). An 81% inhibition ($p<0.05$) of TST 6β-OH activity was observed only in presence of TAO at both concentrations assayed. The rate of MON metabolism in control incubations was 19.4±1.6 pmol/min.mg. TAO inhibited MON liver metabolism (76%, $p<0.05$). Only minor inhibition (16-25%, $p<0.05$) of the ionophore metabolism was observed in the presence of TIL, TUL and GAM. These observations indicate that “new” macrolides (TIL, TUL and GAM) could not be considered as CYP3A inhibitors. Similarly, their potential impairment of MON hepatic metabolism would be of minor clinical relevance. Therefore, the concurrent administration of the novel macrolide antimicrobials with MON would be safe in cattle.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

68. IMPACT OF PH MODIFICATION ON THE EFFICACY *IN VITRO* OF ANTIMICROBIALS AND ALTERNATIVE THERAPIES IN CANINE OTITIS EXTERNA DUE TO *PSEUDOMONAS AERUGINOSA*

Andrea Buchamer[1], Guillermo Broglia[1,2], **Federico Toso**[1,3], Alan Paris[1], Daniel Buldain[1,4], Nora Mestorino[1], Laura Marchetti[1]

[1]*Laboratorio de Estudios Farmacológicos y Toxicológicos -LEFyT-, Facultad de Ciencias Veterinarias, UNLP,* [2]*Cátedra de Enfermedades de Caninos y Felinos Domésticos, Facultad de Ciencias Veterinarias, UNLP;* [3]*Cátedra de Farmacología, Facultad de Ciencias Veterinarias, UNLPam,* [4]*CONICET.*

Pseudomonas aeruginosa is frequently isolated from the external auditory canal (EAC) of dogs with chronic otitis externa (OE). pH of the EAC uploads from pH5 to pH6 when infection occurs favoring bacteria development. Aminoglycosides and fluoroquinolones are commonly used to treat OE, but resistant strains are increasing. Essential oils (EOs), such as *Melaleuca armillaris* EO, has proven antimicrobial (AM) activity. Other compounds, like N-acetylcysteine (NAC) has antibiofilm and antioxidant properties, although their AM activity has not been widely studied. This study aimed to evaluate the AM activity of gentamicin (GEN), enrofloxacin (ENR), *M. armillaris* and NAC at different pH values against *P. aeruginosa*.

109 ear swab samples were collected from 56 canines, with and without OE. Each ear was considered a sampling unit. *P. aeruginosa* were isolated and identified by metabolic and biochemical tests. 24 isolates were selected to compare susceptibility to ENR, GEN, NAC and EO, by broth microdilution at pH 5, 6 and 7.4.

MIC_{90} of GEN increased at acidic pH in resistant isolates (from 512 at pH7.4 to 1024 µg/mL pH5 and 6) and sensitives (2µg/mL (pH7.4), 8 µg/mL (pH6),16 µg/mL (pH5)). MIC_{90} of ENR did not change at any pH in resistant (64 µg/mL) and sensitive (1 µg/mL) isolates. NAC increased its potency at acidic conditions (MIC_{90}: 0.375 g/mL at pH 7.4 and 6; to 0.18 g/mL at pH 5). MIC_{90} of *M. armillaris* EO was 12.5 µL/mL at pH 7.4 and 6, and decreased at 6.25 µL/mL at pH 5. In NAC and EO the MBC was close to the MIC, showing a bactericidal behavior. The MBC_{90} for EO decreased similarly (25 µL/mL at pH 7.4 to 6.25 µL/mL at pH 5), while the NAC MBC_{90} was 0.375 g/mL independently of the pH.

NAC and *M. armillaris* EO are potential alternatives to be applied alone or in combination with traditional AMs to maximize efficacy of OE treatment. Therefore, it is essential to continue the study of pharmacodynamic interactions in vitro with different combinations of them.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

69. EFAVIRENZ:α-CYCLODEXTRIN:MEGLUMINE REDUCE *Staphylococcus aureus* HEMOLYSIS, AND BIOFILM FORMATION

Brenda Basiglio#, Melisa A. Fumarola#, Camila S. Gomez, Antonela Bartolilla, Marcela R. Longhi, Virginia Aiassa, Ariana Zoppi.

Unidad de Investigación y Desarrollo en Tecnología Farmacéutica (UNITEFA-CONICET), Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina. # These authors contributed equally to this work.

The pathogenicity of *Staphylococcus aureus* is closely related to virulence factors such as hemolysins and biofilm formation. Strategies that reduce the mortality caused by *S. aureus* infections may involve the use of drugs that decrease its virulence. Efavirenz (EFV) is an antiviral drug that has also shown antibiofilm and antihemolytic activity against *S. aureus,* which suggests its potential in the antibacterial treatment fields. However, because of its poor aqueous solubility, this drug has a low and variable oral bioavailability. In previous works, we demonstrated that the formation of EFV:α-cyclodextrin binary complex (BC) and EFV:α-cyclodextrin:meglumine multicomponent complex (MC) could enhance the drug's solubility and dissolution rate. The objective of this study was to evaluate the effect of EFV complexation on the virulence factors in *S. aureus*. Biofilm biomass was detected by crystal violet staining, and biofilm viability was assayed by MTT using two *S. aureus stains*, ATCC 29213 and clinical 9455. Hemolytic activity of *S. aureus* ATCC 29213 was determined by a human erythrocyte lysis assay. EFV significantly decreased the biomass and metabolic activity of the biofilm of both strains under study. When evaluating its BC and MC, it was seen that the complexation does not affect the antibiofilm activity of EFV. In addition, EFV showed great ability to reduce hemolysis produced by *S. aureus* ATCC 29213. Regarding its complexes, the BC reduced hemolysis but to a lesser extent, while the MC, which showed the best physicochemical and biopharmaceutical properties, produced a slightly greater reduction in hemolysis than pure EFV. These results demonstrate that EFV complexation does not alter its antibiofilm or antihemolytic activity against *S. aureus*. Therefore, these complexes constitute interesting alternatives for improved EFV formulations.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

70. SALICYLIC ACID ENHANCES THE EFFICACY OF KETOCONAZOLE COMBATING THE BIOFILM FORMATION OF *Candida* spp.

Camila S. Gomez, **Antonela Bartolilla**, Melisa Fumarola, Brenda Basiglio, Marcela Longhi, Ariana Zoppi, Virginia Aiassa

Unidad de Investigación y Desarrollo en Tecnología Farmacéutica (UNITEFA-CONICET), Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina.

Biofilm formation in fungi presents a significant challenge due to their resistance to antifungal treatments, often leading to chronic infections and increased mortality rates. *Candida* spp. is well-known for forming robust biofilms on medical devices and host tissues, complicating treatment. Ketoconazole (KTZ), a broad-spectrum antifungal agent, is limited by poor solubility, reducing its efficacy, especially against biofilms. Salicylic acid (SA) is known for its keratolytic and antimicrobial properties, and in our previous work, we developed a KTZ:SA co-amorphous system (1:1 molar ratio), achieving an increase in KTZ solubility.
This study aimed to evaluate the antibiofilm activity of the KTZ vs. KTZ:SA system on two *Candida* ATCC and four clinical strains. The improved solubility compared to pure KTZ was a crucial factor for enhancing antifungal activity. Previously, drug-drug interactions were identified through physicochemical characterization techniques, and the system showed an amorphous nature.
The minimum inhibitory concentration (MIC) of KTZ was determined by the microdilution method following *Clinical Laboratory Standards Institute* guidelines. Higher concentrations derived from MIC results were used to assess biofilm activity using the XTT assay. The assay revealed a significant reduction in cell viability relative to the control or pure KTZ in all strains, demonstrating the efficacy of the KTZ:SA system against biofilms. Laser scanning confocal microscopy was used to examine the impact of pure KTZ, SA, and the KTZ:SA system on morphology and cell counts in the biofilms of clinical strains of *C. albicans*. Imaging showed that the system, and even SA alone, affected the biofilms in terms of morphology and cell count. Microscopy also revealed the increased solubility of KTZ in the system.
In summary, the KTZ:SA co-amorphous system shows promise as an effective treatment against *Candida* biofilms.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

71. SWINE FECES AS A SOURCE OF RESIDUAL AMOXICILLIN AND OXYTETRACYCLINE CONCENTRATIONS IN RUNOFF WATER

Joaquín Mozo[1,2*], Julieta Decundo[1,3], Guadalupe Martínez[1,3], Susana Dieguez[1,4], Alejandro Soraci[1,3], Denisa Pérez Gaudio[1,3]

[1]*Lab. de Toxicología, Depto. de Fisiopatología, Centro de Investigación Veterinaria de Tandil, FCV-UNCPBA, Tandil, Argentina,* [2]*Depto. de Producción Animal, FCV-UNCPBA, Tandil, Argentina,* [3]*Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina,* [4]*Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CICPBA), La Plata, Argentina*.

In intensive pig farming, the irrational use of antibiotics has diminished their effectiveness and fostered the emergence and spread of antibiotic-resistant strains. Since these antibiotics are not completely metabolized, they can be released into the environment through animal waste, resulting in detectable levels in manure, soil, and both groundwater and surface waters. Nevertheless, thorough monitoring is still lacking. This study aimed to investigate the presence of residual amoxicillin (AMOXI) and oxytetracycline (OTC) which transfer from pig feces to runoff water.

Fecal samples (100 g) from untreated pigs were fortified by triplicate with AMOXI and OTC, considering therapeutic doses and bioavailability (20 mg/kg and 36% and 40 mg/kg and 6%, respectively) to simulate real levels. The excreta were left outdoors on a sloped area with natural vegetation for 30 days. Runoff water samples were collected after precipitation events using passive collectors placed downslope. Analytical studies were conducted using HPLC-UV at the Toxicology Laboratory, Department of Physiopathology, CIVETAN.

Five precipitation events occurred during the assay period on days 4, 8, 9, 11, and 21. For AMOXI, average residual concentrations (0.06 µg/ml) were observed from day 4 to 11, with the highest (0.10 µg/ml) on day 9. For OTC, residuals (0.13 µg/ml) were detected from the first rainfall through day 21, with peaks (0.14 µg/ml) on days 8, 9, and 11. Although AMOXI concentrations appear lower than those of OTC, it is important to consider the different initial fortification doses; when adjusted for these differences, AMOXI levels are 2.36 times greater than those of OTC.

Notably, AMOXI was present in higher proportions over a shorter period, while OTC persisted longer, being detected in the last rainfall sample. In conclusion, both antibiotics were found in runoff water, indicating potential risks to ecosystems and public health, emphasizing the need for systematic monitoring.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

72. *IN VITRO* EFFICACY TEST OF *CYMBOPOGON NARDUS* OIL AGAINST *TRITRICHOMONAS FETUS* TROPHOZOITES

María Rosana Ramirez[1], Estefanía Sereno Bruno[2], Juan Carlos Yori[3], Jorge Oyhenart[2]

[1]*Consejo Nacional de Investigaciones Científicas y Técnicas – CONICET- CCT-Nordeste.* [2]*Instituto de Ciencias de la Tierra y Ambientales de La Pampa (Conicet–Facultad de Ciencias Naturales Universidad Nacional de La Pampa), La Pampa, Argentina.* [3]*Instituto de Investigaciones en Catálisis y Petroquímica (Consejo Nacional de Investigaciones Científicas y Técnicas - Universidad Nacional del Litoral), Santa Fe, Argentina.*

Tritrichomonas foetus is a sexually transmitted parasite (protozoan) that causes reproductive failure in livestock. The indiscriminate use of antimicrobials has led to organisms resistant to therapy. In addition, the risk of antibiotic residues in foods such as milk and meat, and its consequences for human health, have led to a ban on their use in animal feed in several regions of the world. Since there are still no affordable vaccines or safe treatments, new therapies against this infectious disease of livestock need to be found. In this sense, plant extracts are a potential source of active compounds. The aim of this work was to determine whether the natural oil of *Cymbopogon nardus* has lethal properties in vitro against *T. foetus* and to compare its effect with hydrolyzed oil. To carry out this work, both virgin oil of C. nardus and hydrolyzed oil were used. These were tested against the parasite *T. foetus* strain B1, *in vitro*. The virgin oil was obtained by hydrodistillation. On the other hand, part of the virgin oil was hydrolyzed by treatment with sulfuric acid. Subsequently, virgin oil, hydrolyzed oil or metronidazole were added in appropriate dilutions to the culture media containing the parasite. The growth of trophozoites was controlled after 24 hours of exposure to drugs. Both virgin and hydrolyzed oil were found to kill *T. foetus* cells in culture. The mean maximum effective concentrations (EC50) were 0.4 µg/mL and 0.1 µg/mL, respectively. Therefore, it is possible to suggest that *C. nardus* essential oil is a potential pharmaceutical raw material to combat and/or control the *T. foetus* parasite.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

73. ESTABLISHING DRUG COMBINATIONS IN *C. ELEGANS*: INTEGRATING NATURAL AND COMMERCIAL ANTHELMINTICS FOR EFFECTIVE HELMINTHIASIS CONTROL

Alcibeth Pulido Carrasquero[1], Cecilia Bouzat[1] and Guillermina Hernando[1]

[1]*Instituto de Investigaciones Bioquímicas de Bahía Blanca, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, 8000 Bahía Blanca, Argentina.*

Helminthiases, caused by parasitic infections, are significant neglected diseases that impact millions worldwide, exacerbating poverty and inequality. Combination therapy, which involves using commercial drugs, new agents, or natural products, is an effective approach to broadening treatment effectiveness.

The primary goal of this study is to investigate the effects of combining natural compounds with commercial anthelmintics (levamisole, monepantel, piperazine and ivermectin). Combining bioactive phytochemicals with synthetic compounds has been proposed as a promising strategy for enhancing nematode control in human and veterinary medicine. The concurrent use of natural compounds and synthetic drugs can lead to pharmacodynamic interactions due to the effects of two compounds with different mechanisms of action on the target parasite.

The nematode *Caenorhabditis elegans* is a model system for anthelmintic drug discovery. We performed behavior assays of *C. elegans* strains to identify synergic anthelmintic activities of combinations of natural compounds with commercial anthelmintics. In the experiments, synchronized worms at the adult stage were exposed to various concentrations of selected individual agents on agar plates or multiwell plates. Changes in worm behavior or thrashing rate were observed under a stereoscopic zoom microscope and compared to control conditions. IC_{50} values were determined for the individual natural compounds and anthelmintics as well as for the different combinations. At least three combinations were necessary to assess whether the interactions were synergistic, additive, or antagonistic.

The results suggest that natural compounds, which act through mechanisms different from classical anthelmintics, may help counteract resistance in combined anthelmintic therapies. These findings highlight the potential of multitarget compounds as valuable tools in integrated pharmacological strategies for effective parasite control.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

74. POTENTIAL OF XENOBIOTIC METABOLIZING ENZYMES AS MARKERS FOR TICK RESISTANCE TO ECTOPARASITIC DRUGS

Karen Larsen[1], Paula Ichinose[1], Victoria Miró[1], Macarena Sarli [2], Jorgelina Torrents[2], Nicolás Morel[2], Santiago Nava[2], Adrián Lifschitz[1], **Guillermo Virkel**[1]

[1]*Centro de Investigación Veterinaria de Tandil (CIVETAN)(CONICET-CICPBA-UNCPBA), Facultad de Ciencias Veterinarias, Universidad Nacional del Centro, Tandil, Argentina.* [2]*Instituto de Investigación de la Cadena Láctea (IdICaL) (INTA-CONICET), Estación Experimental Agropecuaria Rafaela (INTA EEA Rafaela), Rafaela, Santa Fe, Argentina*

Ticks are hematophagous ectoparasites that significantly impact cattle production systems in tropical and subtropical regions. Their control primarily relies on chemical compounds, which can be applied alone or in combination. However, the sustained use of chemical acaricides has often led to the emergence of resistant tick populations. Research efforts are being conducted to understand the mechanisms underlying tick resistance to ectoparasitic drugs, which could also be used as resistance markers. Studies on the expression and catalytic activities of different cholinesterases have been conducted to understand the mechanisms of tick resistance to organophosphates like chlorpyrifos. This work evaluated acetyl-cholinesterase (AChE) catalytic activity in larvae from five (5) tick populations with varying in vitro susceptibility against a commonly used combination of the pyrethroid cypermethrin (CPM) and the organophosphate chlorpyrifos (CPF). The in vitro activity of CPM+CPF was evaluated using the Adult Immersion Test (AIT). AChE activity was measured in tick homogenates through a spectrophotometric method. Tick populations were classified as highly susceptible (n=3) and low susceptible (n=2) against the combination. AChE activity (19.9 ± 4.75 nmol/min.mg) in highly susceptible populations was approximately two times higher ($p<0.001$) than in low susceptible tick populations (11.4 ± 4.51 nmol/min.mg). Interestingly, AChE activity in low susceptible populations was less sensitive to inhibition by CPF or its active metabolite, CPF oxon. These preliminary results encourage further research into identifying biomarkers of tick resistance to acaricides, particularly to organophosphates and pyrethroid compounds.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

75. *EX VIVO* AND *IN VIVO* ASSESSMENT OF THE PHARMACOLOGICAL INTERACTION BETWEEN THE MONOTERPENE CINNAMALDEHYDE AND ANTIPARASITIC DRUGS

María Victoria Miró[1], Paula Ichinose[1], Mercedes Lloberas[2], Lucila Moriones[1], Carlos Lanusse[1], Guillermo Virkel[1], Adrián Lifschitz[1]

[1]*Laboratorio de Farmacología, Centro de Investigación Veterinaria de Tandil (CIVETAN), UNCPBA-CICPBA-CONICET, Campus Universitario, Tandil 7000, Argentina*. [2]*Laboratorio de Parasitología, Instituto Nacional de Tecnología Agropecuaria (INTA), Estación Experimental, Balcarce 7620, Argentina*

Given the growing development of drug resistance in gastrointestinal nematodes of ruminants as well as in soil-transmitted helminth parasites in humans, innovative parasite control strategies are needed. Numerous phytochemical compounds exhibit efficacy against parasites under laboratory conditions, but the *in vivo* effectiveness remains largely unexplored. This study investigated the effect cinnamaldehyde (CNM) on the pharmacological response of levamisole (LVM) and doramectin (DRM) against nematode naturally-infected lambs, through *ex vivo* and *in vivo* assessments. The modulation of the intestinal absorption/secretion by CNM (1.5 mM) was assessed by the diffusion-chamber model using Rho123 (0.5 µM) as substrate to measure their transport across the lamb´s ileum tissue. Two *in vivo* trials (T) were conducted to evaluate the pharmacological interaction between CNM/DRM and CNM/LVM in lambs infected with resistance nematodes. In T1 the oral co-administration of DRM (0.2 mg/kg) alone or combined with CNM (two doses of 100 mg/kg at 0 and 24 h), both as oral emulsion was evaluated. In T2, lambs received LVM (SC, 3.75 mg/kg) alone or in combination with CNM (two SC doses of 80 mg/kg at 0 and 3h). LVM plasma concentrations were measured by HPLC. The reduction in fecal egg count (FEC) was used as an indicator of the pharmacological response. The presence of CNM decreased Rho123 efflux across the lamb intestine, which may confirm a drug transport-related interaction. The presence of CNM increased the pharmacological response of DRM from 66.3 to 78.0% of FEC reduction. CNM enhanced LVM systemic exposure by increasing the LVM AUC by 20%, but a similar efficacy was obtained compared to the LVM alone treatment (55.5 and 51.4%). The presence of CNM may induce pharmacokinetic/pharmacodynamic interactions both *ex vivo* and *in vivo*. These findings provide valuable insights to the search for more effective and sustainable parasite control strategies in both veterinary and human medicine.

Antimicrobial/Antiparasitic/Antiviral Agents
Chairs: Juan J. Martinez Medina and Santiago Zugbi

76. *IN VITRO* AND *IN VIVO* ASSESSMENT OF MONOTERPENE DERIVATIVES FOR CONTROLLING CATTLE TICK *RHIPICEPHALUS (BOOPHILUS) MICROPLUS*

Victoria Miró[1], Macarena Sarli[2], Victoria Rossner[3], Jorgelina Torrents[2], Norma Cabaña[3], Lautaro Segovia[3], Viviana Gomez[3], Guillermo Virkel[1], Santiago Nava[2], **Adrian Lifschitz**[1]

[1]*Centro de Investigación Veterinaria de Tandil (CIVETAN)(CONICET-CICPBA-UNCPBA), Facultad de Ciencias Veterinarias, Universidad Nacional del Centro, Tandil, Argentina.* [2]*Instituto de Investigación de la Cadena Lactea (IdICaL) (INTA-CONICET), Estación Experimental Agropecuaria Rafaela (INTA EEA Rafaela), Rafaela, Santa Fe, Argentina.* [3]*Instituto Nacional de Tecnología Agropecuaria (INTA), Estación Experimental Agropecuaria Colonia Benítez, Chaco.*

Ticks are ectoparasites that significantly impact livestock health and productivity. Phytochemicals, natural compounds derived from plants, have gained attention as potential alternatives in the face of widespread resistance to synthetic acaricides. This study evaluated the *in vitro* and *in vivo* acaricidal activity of geraniol (GNL) and thymol (TML). Additionally, GNL exposure in ticks was measured using HPLC. *In vitro* GNL activity was assessed using the Adult Immersion Test (AIT) with a 1% GNL solution (1% acetone-0.02% Triton X) and an immersion time of 2 minutes. *In vivo* activity of GNL was evaluated in six calves experimentally infested with *Rhipicephalus (Boophilus) microplus*. Calves were treated with 1% GNL alone, cypermethrin 20 % alone, or a combination of both. Ticks exposed to GNL *in vitro* and *in vivo* (1-3 days post-treatment) were collected for HPLC measurement of GNL concentrations. *In vitro* TML activity was evaluated using the Larval Immersion Test (LIT) with concentrations ranging from 0.001% to 0.1% TML solution (1% acetone-0.02% Triton X). No significant differences were observed in the oviposition of engorged females after immersion in GNL (efficacy 31%). Similarly, no reduction in tick counts was observed after *in vivo* treatment with GNL in calves. Although ticks were exposed to similar concentrations of GNL (1%), exposure was significantly higher ($P < 0.05$) in the *in vitro* trial. GNL concentrations ranged from 0.96 to 2.60 µg/g in the *in vivo* trial and from 23.3 to 61.7 µg/g in the *in vitro* trial. TML showed high larvicidal activity with an LD50 of 0.01% (95% CI: 0.007-0.012) and an LD99 of 0.053% (95% CI: 0.031-0.251). While GNL did not exhibit significant acaricidal activity *in vivo* or *in vitro*, TML's effectiveness against tick larvae is promising. Further *in vivo* trials are necessary to confirm the efficacy of TML against *R. microplus*.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

77. EFFECT OF SIGMA-1 RECEPTOR ANTAGONISM ON ETHANOL-INDUCED PLACE AND TASTE AVERSION

Agustín Salguero[1], Ignacio Morón Henche[3], Cruz Miguel Cendán[2], Leandro Ruiz-Leyva[2,5] and Ricardo Pautassi[1,4]

[1]*Instituto de Investigación Médica M. y M. Ferreyra (INIMEC – CONICET-Universidad Nacional de Córdoba), Córdoba, 5000, Argentina,* [2]*Department of Pharmacology, Institute of Neuroscience, Biomedical Research Center (CIBM) Faculty of Medicine, University of Granada, Spain,* [3]*Department of Psychobiology and Centre of Investigation of Mind, Brain, and Behavior (CIMCYC), Faculty of Psychology, University of Granada, Spain,* [4]*Facultad de Psicología, Universidad Nacional de Córdoba, Córdoba, Argentina,* [5]*Department of Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA.*

Previous studies suggest that modulation of the sigma 1-receptor (S1R) can attenuate ethanol intake. This can be related to this system being involved in ethanol's motivational effects. This study assessed age-related differences in modulation of ethanol-induced conditioned taste (CTA, Experiment 1) and place (CPA, Experiment 2) aversion, by antagonism of S1R. In Experiment 1 adult rats were exposed to a conditioned Stimulus (CS, saccharine, 0.1%) and then administered the S1R antagonist S1RA (16 mg/kg). Ethanol (1.75 g/kg) was administered 30 min later. CS intake was repeatedly tested after the conditioning. In Experiment 2 adolescent rats were habituated to a two-compartment apparatus at postnatal day 31 (PD31), and conditioning took place at PDs 32-35. These rats were given daily pairings between the effects of ethanol (or vehicle) and the distinct compartments. In each conditioning session the rats received vehicle and were then placed in the inhibitory CS (CS-) compartment for 12 min. Then, they were administered S1RA (16 mg/kg, i.p.) or vehicle. Ethanol (2.5 g/kg, i.p.) was administered 30 min later, and the animals were immediately placed in the excitatory CS (CS+) compartment for 12 minutes. Results were analyzed using repeated measures ANOVAs. In Experiment 1 the administration of S1RA seemed to promote greater ethanol-induced CTA, thus suggesting a promoting effect of S1R on ethanol's aversion. Experiment 2 revealed a reliable CPA that was not altered by S1RA. These results suggest that S1R antagonism blocks the appetitive effects of ethanol or exacerbates the aversive effects of this drug.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

78. EXPLORING THE α7 NICOTINIC RECEPTOR IN HUMAN RETINAL PIGMENT EPITHELIUM CELLS AS A NOVEL THERAPEUTIC TARGET

Julieta Ailen Mader, María Florencia Fernández Delias, Juan Facundo Chrestia, María del Carmen Esandi, Cecilia Bouzat

Instituto de Investigaciones Bioquímicas de Bahía Blanca, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, 8000 Bahía Blanca, Argentina.

The α7 nicotinic acetylcholine receptor is highly expressed in the brain and is also present in non-neuronal cells, including immune and epithelial cells. It is involved in cognition, memory, pain, neuroprotection and inflammation and its potentiation has emerged as a therapeutic strategy for neurological, neurodegenerative, and inflammatory disorders. Given that the increase in oxidative stress in retinal pigment epithelial cells contributes to the development of age-related macular degeneration and that α7 activation exerts cell protective effects, we explored the presence and functional relevance of α7 in D407 retinal pigment epithelium cells, a model system for various retinal diseases. By real time PCR, and indirect immunofluorescence using confocal microscopy and flow cytometry we demonstrated the presence of α7 in these epithelial cells. To determine the presence of functional receptors, we measured the movement of intracellular calcium levels triggered by the activation of α7. A pulse of ACh together with an α7 positive allosteric modulator revealed a 3-fold increase in intracellular calcium measured with the fluo-3AM probe. To mimic the events occurring in age-related macular degeneration, we treated cells with ferric ammonium citrate (FAC) to induce stress damage and measured reactive oxygen species (ROS) with the fluorescent probe DCFH-DA. FAC treatment resulted in a significant increase in ROS levels with respect to the control. To determine if α7 protects against oxidative damage, we exposed cells to a specific α7 agonist, PNU-282987, before the FAC treatment. Notably, PNU-282987 exhibited protective effects against the damage, leading to a reduction in ROS levels compared to the treated cells. Overall, by identifying for the first time the presence of α7 in the D407 cell line and revealing its protective role against oxidative damage, we propose α7 as a promising therapeutic target for retinal neurodegenerative disorders.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

79. KETAMINE-INDUCED HYPERLOCOMOTION IS ENHANCED BY THE NEUROACTIVE STEROIDS ESTRADIOL AND PROGESTERONE IN MALE RATS WITH LOW TESTOSTERONE LEVELS

Natalia Belén González[2], Gerónimo Ciurleti[1], Clara Calcagno[1], Lucas Ortiz[1], Paloma Ramírez[3], Ricardo Cabrera[1,2,3].

[1]*Laboratorio de Investigaciones Neuroquímicas, Comportamentales y Endócrinas. (LINCE-INBIOMED- Universidad de Mendoza). LINCE-IMBECU-CONICET Mendoza. 5500.* [2]*Facultad Ciencias Médicas. Universidad de Mendoza. Mendoza. 5500.* [3]*Facultad de Ingeniería. Universidad de Mendoza. Mendoza. 5500*

Ketamine is an anesthetic drug that, as a drug of abuse in humans, generates psychotic episodes characterized by hallucinations, sensory dissociation, and delusional ideation. In rats, prolonged i.p administration of ketamine triggers psychotomimetic signs and adaptive changes in the SNC, as evidenced, among others, by an increase in locomotor activity. This sensitization phenomenon leads to modifications in neuronal networks mediated by dopamine, glutamate, and GABA in the mesocorticolimbic circuit. In our laboratory, we have demonstrated that neuroactive steroids play a neuromodulatory role in the differential response to drugs of abuse. This work aimed to study neuroadaptive phenomena induced by ketamine in parallel with neuromodulatory phenomena induced by s.c administration of Estradiol (E_2) and Progesterone (P_4) in an experimental model of psychosis in male rats. In previous works, we demonstrated that the decrease in testosterone concentration in orchidectomized male rats induced a notorious positive modulation of the nigrostriatal dopaminergic pathway, potentiated by the administration of E_2 and P_4. Adult male Sprague-Dawley orchidectomized rats were used. The experimental groups were Control (C), Control E_2 (4mg/kg) (CE), Control P_4 (0.1mg/kg) (CP), Ketamine (25 mg/kg)(K), Ketamine E_2 (KE), Ketamine P_4 (KP). Animals were evaluated in the open field following a stimulus dose of ketamine, using Ethowatcher to quantify meters/10 minutes. Data were expressed as mean±SEM and analyzed by T-test and/or ANOVA 1 and Bonferroni test. We observed a significant increase in locomotor activity in rats receiving ketamine (K) relative to (C)($P<0.0001$). Control animals receiving uncombined E_2 and P_4 (CE and CP) showed increased locomotor activity concerning C ($P<0.0001$). On the other hand, administration of E_2 or P_4 to the KE;KP groups induced a significant increase in the locomotor activity of the K group without supplementation ($P<0.0001$). We conclude that neuroactive steroids synergistically modify ketamine-induced sensitization, and genomic and non-genomic mechanisms would differentially support such synergy.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

80. THE NEUROACTIVE STEROIDS ESTRADIOL AND PROGESTERONE EXHIBIT NEUROPROTECTIVE PROPERTIES IN A MODEL OF NEURODEGENERATION. CUTANEOUS ELECTROMYOGRAPHY AS A SUBSTANTIAL TECHNOLOGICAL ADVANCE FOR EARLY DIAGNOSIS AND POST-TREATMENT PROGNOSIS

Paloma Ramírez[3], Natalia González[1], Manuela Casas[3], Mauco Aberastain[3], Pilar López[2], Ricardo Cabrera[1,2,3]

[1]*Laboratorio de Investigaciones Neuroquímicas, Comportamentales y Endócrinas. (LINCE-INBIOMED- Universidad de Mendoza). LINCE-IMBECU-CONICET Mendoza. 5500.* [2]*Facultad Ciencias Médicas. Universidad de Mendoza. Mendoza. 5500.* [3]*Facultad de Ingeniería. Universidad de Mendoza. Mendoza. 5500.*

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease in humans after Alzheimer's disease. It is characterized by the irreversible loss of dopaminergic neurons in the substantia nigra. Neurodegeneration is studied with experimental models in rodents by injecting the neurotoxic 6-hydroxydopamine (6-OHDA). Electromyography is used to diagnose and analyze the functional integrity of muscle fibers by recording myoelectric activity. The objective was to study the neuroprotective effect of Estradiol (E_2) and Progesterone (P_4) in a rodent model of hemiparkinsonism using cutaneous electromyographic recordings. Adult male Sprague-Dawley rats subjected to left nigrostriatal neurodegeneration were used. The experimental groups were Control (C), Hemiparkinsonian (HP), C+Estradiol+Progesterone (CEP), and HP+Estradiol+Progesterone (HPEP). Electromyographic measurements were performed using surface electrodes. Data was expressed as mean+SEM and was analyzed with ANOVA 2 followed by Bonferroni test. We observed that administering E_2 and P_4 to control animals did not present significant differences in muscle electrical activity to the control without supplementation. A decrease in the myoelectric signal was observed in the HP to the C ($p<0.0001$), parallel to a delay in the onset of locomotion. A significant increase in myoelectric signal was observed in the HPEP group receiving s.c. supplementation of E_2 and P_4 with respect to the HP group ($p<0.0001$), supporting our hypothesis of neuroprotective effect of E_2 and P_4. We observed a significant increase in myoelectric activity in the CEP group to the HPEP ($p<0.0001$). We conclude that the neuroprotective effect of the neuroactive steroids E_2 and P_4 is a therapeutic potential in treating neurodegenerative phenomena, in parallel to the possibility offered by cutaneous electromyography for monitoring the neuroprotective evolution over time as a therapeutic prognosis.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

81. CHOLESTEROL METABOLISM IMPAIRMENT: A BIOMARKER OF NEURODEGENERATION?

Athina Maniscalchi[1], Oriana N. Benzi Juncos[1,2], Melania I. Funk[1,2], Melisa Conde[1,2], Mariel Bonjour[1], Natalia Alza[1,3], and Gabriela A. Salvador[1,2]

[1]*Instituto de Investigaciones Bioquímicas de Bahía Blanca, Universidad Nacional del Sur (UNS), Consejo Nacional de Investigaciones Científicas y Técnicas.* [2]*Departamento de Biología, Bioquímica y Farmacia, UNS.* [3] *Departamento de Química, UNS.*

We have previously established an *in vivo* iron overload model using C57BL/6 mice characterized by movement disorders similar to Parkinson's disease phenotype. Midbrain analysis of iron-treated mice showed increased gliosis along with the loss of tyrosine hydroxylase labeling and the presence of ferroptosis markers. Associated with dopaminergic neuronal loss, we found cholesterol (Chol) accumulation in the midbrain ($p<0.05$). Free Chol increase was accompanied by the upregulation of SREBP1 and SREBP2 ($p<0.001$) transcription factors. To further investigate the link between Chol and ferroptosis, we used single-cell cultures of neurons, astrocytes, microglia, and primary glial cultures exposed to iron overload. Dopaminergic neurons (N27), astrocytes (C6), and mouse primary glial cultures showed increased Chol levels in intracellular compartments as well as in their secretomes after iron treatment ($p<0.001$). This rise coincided with the upregulation of genes associated with Chol *de novo* synthesis and transport, HMGCR and ABCA1 ($p<0.001$). In addition, neurons incubated with astrocytes' secretome enhanced even more their Chol content, probably due to the upregulation of the ABCA1 transporter. To study the link between Chol accumulation and ferroptosis, cells were exposed to the inhibitor ferrostatin-1. We found that ferrostatin-1 reduced Chol levels when cells were exposed to iron overload ($p<0.001$). Our findings indicate that altered Chol metabolism could be a biomarker of midbrain neurodegeneration triggered by ferroptosis, with motor impairment as an outcome.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

82. DIFFERENT ANTIOXIDANTS MODULATE SEVERAL STEPS OF FERROPTOSIS ASSOCIATED WITH NEURODEGENERATION

Melisa Conde[1,2], Oriana N. Benzi Juncos[1,2], Athina Maniscalchi[1], Melania I. Funk[1,2], Mariel Bonjour[1], Natalia Alza[1,3], and Gabriela A. Salvador[1,2]

[1]*Instituto de Investigaciones Bioquímicas de Bahía Blanca, Universidad Nacional del Sur (UNS), Consejo Nacional de Investigaciones Científicas y Técnicas.* [2]*Departamento de Biología, Bioquímica y Farmacia, UNS.* [3]*Departamento de Química, UNS.*

A recently described form of regulated cell death named ferroptosis has been associated with several neurodegenerative processes. The most prominent mechanisms related to ferroptosis are iron accumulation, lipid peroxidation, and mitochondrial disorganization associated with glutathione (GSH) depletion. We aimed to investigate the effect of well-known antioxidants in the above-described mechanisms related to neuronal death by ferroptosis. To this end, we used the pesticide maneb which has been described as a pro-ferroptotic stimulus and whose exposure is associated with Parkinsonism. We found that maneb can trigger dopaminergic neuronal death in a time- and concentration-dependent manner ($p<0.01$). Neuronal death was accompanied by diminished GSH content ($p<0.05$), and the typical mitochondrial pattern of ferroptosis ($p<0.001$). Moreover, maneb treatment was able to increase neuronal alpha-synuclein (aSyn) expression ($p<0.05$). Using this neurodegenerative framework, we evaluated two different antioxidants: *N*-acetylcysteine (NAC), a GSH precursor, and ferrostatin-1, a radical-trapping agent. We found that NAC was able to revert aSyn overexpression in maneb-exposed neurons ($p<0.05$) and that ferrostatin-1 was able to re-establish mitochondrial architecture to that of control neurons ($p<0.001$). Intriguingly, luteolin, a flavonoid that acts as a free radical scavenger, increased cell death in neurons exposed to maneb ($p<0.05$). This later could be explained by the inhibitory effect of lipoxygenases exerted by luteolin. Our results show that antioxidants with different mechanisms of action target several steps of ferroptosis, and could be the starting point for further studies aimed at preventing neuronal death by this form of regulated cell death.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

83. KETAMINE INDUCES BRAIN REGIONAL- AND TIME-DEPENDENT GLIAL ALTERATIONS THROUGH THE AT_1 RECEPTORS

María J. Piermarini[1], Victoria B. Occhieppo[1], Osvaldo M Basmadjian[1], Gustavo Baiardi[2] and Claudia Bregonzio[1].

[1]*Departamento de Farmacología Otto Orsingher, IFEC-CONICET, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba. Argentina,* [2]*Laboratorio de Neurofarmacología, (IIBYT-CONICET), Universidad Nacional de Córdoba, Argentina*

Schizophrenia, and other mental diseases, are related to neurotransmitter imbalance (dopamine and glutamate) and neuroinflammation. The administration of ketamine is a validated animal model of schizophrenia in rodents, which reproduces the typical symptoms of this pathology. Brain Angiotensin II modulates dopaminergic and glutamatergic neurotransmission through AT_1 receptors (AT_1-R). Previously, we showed the AT_1-R involvement in behavioral, neurochemical, and neuroinflammatory responses in a ketamine model of schizophrenia, 14 days after the last ketamine administration. Since our group has found that the alterations in several parameters are time withdrawal period dependent, our present aim was to compare the alterations induced by ketamine over the microglial and glial expression and the AT_1-R's role at days 7 and 14. Male Wistar rats were administered AT_1-R antagonist Candesartan/vehicle (3mg/kg p.o., days 1-10) and Saline/Ketamine (30mg/kg i.p.; 6-10). After 7 or 14 days of withdrawal, the animals were sacrificed for GFAP and CD11b immunohistochemistry. Data from the Prefrontal cortex (Pre-limbic and Infra-limbic areas) and Caudate putamen were analyzed using Two-way ANOVA, followed by the Bonferroni test. Ketamine administration induced long-lasting increased GFAP expression, blunted by the AT1-R blockade effect, was observed only on day 14. In Caudate putamen, the same increased GFAP expression was observed but at day 14, all the groups showed a normalized response, independently of the AT_1-R blockade. Regarding microglial cells, ketamine administration decreased CD11b expression in the Prefrontal cortex and caudate putamen, after 7 of withdrawal, independently of AT_1-R blockade. Further studies are needed to understand the AT1-R receptor role in the progression of glial response in this schizophrenia model/dopamine-glutamate imbalance model induced by ketamine.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

84. OXYTOCIN, VASOPRESSIN AND PROLACTIN AS POSSIBLE THERAPEUTIC TARGETS IN THE TREATMENT OF ADOLESCENT EMOTIONAL HEALTH

Gabriela C. Ciavatta and **Gabriela B. Acosta**

Instituto de Neurociencias Cognitiva y Traslacional (INCYT), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Instituto de Neurología Cognitiva (INECO), Universidad Favaloro. Marcelo T. de Alvear 1632, Piso 8, C1021ABA*, CABA, Argentina*.

Early life stress (ELS) is defined as a period of severe and/or chronic trauma, as well as environmental/social deprivation or neglect in the prenatal/early postnatal stage. Social attachment is intrinsically important and was described by different behavioral processes that are involved in the formation of parental, filial and couple bonds. The objective of this work was to analyze the impact of stressful experiences in early life stages on attachment in adolescents and its possible relationship with chemical mediators such as vasopressin (AVP), oxytocin (OXT) and prolactin (PRL) that would have an important role in this study. A cohort, observational, non-randomized, analytical, consecutive, open, prospective study was conducted. The Massie-Campbell Attachment Stress Scale was used. The sample size was 187 adolescents divided into 3 groups: Control, 1st year and 4th year of school. The results obtained with this attachment scale showed that in both groups studied a significant increase was observed both in the 1st year and in the 4th year of school with respect to the control group (Chi square df; 14.73.1 ****P < 0.001).
Oxytocin (OXT), vasopressin (AVP) and prolactin (PRL) were analyzed as possible therapeutic tools to prevent mental illness using scientific articles, including original studies, systematic reviews and meta-analyses. The peptides AVP and OXT are key hormones in the peripheral system and in the brain with opposite functions in the modulation of stress, anxiety and social behaviors, and they would also intervene in the formation of attachment bonds. OXT, AVP, and PRL were found to be involved in the initiation and maintenance of maternal behavior. These findings indicate that exposure to adverse childhood experiences significantly increases attachment behavior during adolescence. OXT, AVP, and PRL could become potential therapeutic targets for the treatment of early life stress. This new knowledge may facilitate the development of neuromodulator-targeted therapies with improved safety and efficacy profiles.

Neuroscience and Neuropharmacology
Chairs: Nora Mariel Marder and Susana Gorzalczany

85. ROLE OF A CANNABIS EXTRACT IN 2-ARACHIDONOYLGLYCEROL METABOLISM REGULATION DURING PHYSIOLOGICAL AGING

Sabrina Rosicler Salas[1,2], Pablo Gustavo Milano[1,2], Florencia Antonella Musso[3,4], Susana Juana Pasquaré[1,2] and Ana Clara Pascual[1,2]

[1]*Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB-CONICET-UNS).* [2]*Departamento de Biología, Bioquímica y Farmacia, UNS.* [3]*Instituto de Química del Sur (INQUISUR-UNS-CONICET).* [4]*Departamento de Química, UNS.*

The availability of the main neuroprotective endocannabinoid (EC), 2-arachidonoylglycerol (2-AG), was found to decrease in rat cerebral cortex (CC) synaptosomes (syn) during aging. It was also demonstrated that 2-AG metabolism can be modulated by its own receptors. Moreover, phytocannabinoids present in Cannabis sp. extracts (CE), capable of binding to cannabinoid receptors, are being used in several studies to treat neurodegenerative processes. The aim of the present work was to evaluate if a CE could modulate 2-AG metabolism and thus attenuate its deficit in aging. To this end, delta-9-tetrahydrocannabinol (THC) enriched CE were obtained from descarboxilated female flowers with ethanol as extraction solvent. The THC-free fraction (CE F/THC) was isolated from the CE using thin-layer chromatography. CC syn from adult (4-6 months) and aged (24-26 months) rats were obtained by differential centrifugation and purified in ficoll gradients, and then used to test the synthesis (diacylglycerol lipase -DAGL- and lysophosphatidate phosphohydrolase -LPAase- and hydrolysis (monoacylglycerol lipase, MAGL) of 2-AG. The syn were coincubated with THC enriched CE (1 µM THC), CE F/THC or 1 µM pure THC, and the respective radiolabeled substrate, simultaneously. Results showed that, none of the treatments modified the 2-AG metabolism in adult syn ($p \geq 0.05$). However, in aged syn, CE F/ THC caused a decrease in the MAGL (8%) and DAGL (84%) activities ($p < 0.05$). Additionally, THC-enriched CE reduced MAGL activity (7%), and pure THC caused a decline in DAGL activity (56%) ($p < 0.05$). These results demonstrate that the CE is capable of increasing the 2-AG availability in aged syn, possibly attenuating the deregulation of this EC observed in aging. This effect is observed only in the presence of the complete CE, demonstrating the synergy between the different components of the plant. These findings highlight the importance of using the entire CE in the success of Medicinal Cannabis.

Bioinformatics and Therapeutic Targets
Chairs: Pedro Martin and Hugo Ortega

86. ETIDRONATE AND ALENDRONATE AFFECTS DIFFERENTIALLY THE GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE ACTIVITY OF EGPE, A PARASITIC CELL LINE DERIVED FROM *ECHINOCOCCUS GRANULOSUS* G1 PROTOSCOLECES

Facundo Ariel Agüero[1,2], Andrea Maglioco[1,2], Alejandra Juárez Valdez[2,3], Emilio Roldán[1], Margot Paulino[4], Alicia Graciela Fuchs[1,3]

[1]*Centro de Altos Estudios en Ciencias Humanas y de la Salud-Universidad Abierta Interamericana.* [2]*Consejo Nacional de Investigaciones Científicas y Técnicas.* [3]*Instituto Nacional de Parasitología "Dr. Mario Fatala Chaben"-Administración Nacional de Laboratorios e Institutos de salud "Dr. Carlos Malbrán".* [4]*Departamento de Experimentación, Teoría de la Estructura de la Materia y sus Aplicaciones, Facultad de Química, Universidad de la República, Uruguay.*

Echinococcus granulosus is the etiological agent of Cystic echinococcosis (CE), a globally distributed parasitic zoonosis that affects livestock, ungulates and humans. In Argentina 1691 human cases were confirmed in 2018-2021. Our laboratory developed the EGPE cell line from protoscoleces of a bovine liver hydatid cyst. We use this cell line to investigate compounds with antiparasitic potential. Bisphosphonates (BF), toxic ATP analogs, are used for bone disease treatment and have shown antiproliferative effects on EGPE. We identified by mass spectrometry two isoenzymes of Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expressed by EGPE cells, purified by affinity columns with antibodies from hepatic CE patients. This enzyme catalyzes the sixth step of glycolysis, forming 1,3-bisphosphoglycerate (BPG) from glyceraldehyde-3-phosphate (G3P) and inorganic phosphate, reducing NAD^+. This enzyme is essential for the parasite's energy production. The aim was to evaluate the effect of two BF, etidronate (ETI) and alendronate (ALE), on GAPDH enzymatic activity in the EGPE line. We cultured 150 million EGPE cells for 48 hours with medium 199 (37ºC, 5%CO_2), in two conditions: with and without 10% hydatid fluid. The culture was lysed by mechanical disruption with a syringe and centrifuged at 4000 x g for 5 minutes at 4ºC. The supernatant was treated with ETI and ALE at 1 and 10 µM. GAPDH enzymatic activity was measured using a commercial kit (Abcam) as nanomoles of NADH/mg of protein. Highest GAPDH activity in the sample with hydatid fluid was observed in ETI 1µM, while in the sample without hydatid fluid was with ALE 10µM (91.16 and 1165 nmol NADH/mg, respectively). Molecular docking assays showed that phosphates of BF could occupy the phosphate sites of G3P and BPG in the *ab initio* models of GAPDH from *Echinococcus granulosus*. These results suggest that bisphosphonates could differentially increase GAPDH activity in *Echinococcus granulosus* relative to the basal level.

Pharmacokinetics and Pharmacodynamics
Chairs: Pedro Martin and Hugo Ortega

87. EFFECT OF FASTING AND FEEDING ON THE PHARMACOKINETICS OF A SINGLE ORAL DOSE OF CANNABIDIOL IN DOGS

Laureano Schofs[1,2], Maria Victoria Miró[2], Lucila Moriones[2], Juan Torres[1], Marko Jeran[3], Mónica Sparo[2,4], Luis Álvarez[1,2], Sergio Sánchez Bruni[1,2]

[1]*Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA). Tandil, Buenos Aires, Argentina.* [2]*Centro de Investigación Veterinaria de Tandil (CIVETAN). CONICET-UNCPBA-CICPBA. Tandil, Buenos Aires, Argentina.* [3]*"Jožef Stefan" Institute, Department of Inorganic Chemistry and Technology, Ljubljana, Slovenia.* [4]*Facultad de Ciencias de la Salud, Instituto de Investigación en Ciencias de la Salud, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Olavarría, Buenos Aires, Argentina.*

Cannabinoid research has gained attention in Human and Veterinary Medicine in recent years. Cannabidiol (CBD) is one of the major non-psychotropic cannabinoids found in *Cannabis sativa* L. CBD has shown a wide variety of pharmacological effects and a safety profile that make it suitable for treating many conditions in dogs. However, the pharmacokinetic (PK) behavior of CBD has not been fully elucidated. CBD is poorly absorbed after oral administration in dogs. Therefore, new strategies are needed to increase CBD bioavailability. The main goal of this work was to assess the effect of fasting and feeding on oral PK of CBD in dogs. Five healthy mixed-breed dogs (weight 20 ± 1.4 kg) were used in a controlled cross-over study. All dogs were fasted for 18 hours before being given orally 10 mg/kg of CBD (Kanbis®, Elea, Argentina). The *Fed group* received CBD concomitantly with commercial dry dog food, while the *Fasted group* received the same food six hours after receiving the CBD dose. After a wash out period of three weeks, animals´ treatments were reversed. Blood samples were taken previous CBD administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 28 and 36 hours after the treatment. CBD plasmatic concentrations were measured using a RP-HPLC method. Pharmacokinetic parameters were estimated using PK solution® software 2.0.2 (Summit Research Services, USA). A statistically significant difference ($p<0.01$) was found in C_{max}, $AUC_{0-\infty}$ and AUMC, resulting in an average increase of about 530, 680 and 580% respectively in the *Fed group*. Taking this into consideration, CBD should be given with food in order to maximize its oral bioavailability for treating dogs with systemic diseases. On the contrary, fasting could be useful for concentrating CBD in the gastrointestinal tract for local affections.

Pharmacokinetics and Pharmacodynamics
Chairs: Pedro Martin and Hugo Ortega

88. AMIODARONE POSTISCHEMIC CARDIOPROTECTION IN EUTHYROID RATS INVOLVES PKC PATHWAY, BUT IS AFFECTED BY OXIDATIVE STRESS UNDER HYPOTHYROIDISM

Matías Bayley[1,2], Maria Inés Ragone[1,2], Alicia Consolini[1]

[1]*Cátedra de Farmacología I y II, GFEYEC, Farmacia, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata. 47 y 115, La Plata, CP: 1900, Buenos Aires;* [2]*Consejo Nacional de Investigaciones Científicas y Técnicas.*

In previous works we showed that Amiodarone (Amd), a class 3 antiarrhythmic drug, had a protective effect in euthyroid (EuT) rat hearts exposed to ischemia/reperfusion (I/R), but not in hypothyroid (HypoT) rat hearts when given in a subacute oral treatment. The aims of this study were to: a) elucidate the mechanisms responsible of Amd effects under I/R in EuT hearts, and b) evaluate whether the loss of protection of Amd in HypoT rat hearts is due to accumulation of reactive oxygen species (ROS). The work was performed with EuT and HypoT Wistar rats administered with oral Amd 30 mg/kg/day during a week. The isolated hearts were perfused inside a flow calorimeter to measure left intraventricular pressure (LVP), changes in diastolic pressure (ΔLVEDP) and total heat flow (Ht, $mW.g^{-1}$) during the I/R protocol. Maximal LVP of contraction (P) and muscle economy (P/Ht) were calculated. The role of PI3K/Akt and PKC pathways were respectively evaluated with Wortmannin (Wrt, 100μM) and Chelerythrine (Che, 100μM) perfusion before I/R in EuT+Amd hearts. N-(-2-mercaptopropionyl) glycine (n-MPG, 0.2 mM), a ROS scavenger, was perfused before I and during R, to evaluate the ROS contribution in HypoT+Amd and EuT+Amd rat hearts. Che decreased post-ischemic P (to 9.9±4.1% of pre-I vs 53.6±6.3% in EuT+Amd; $p<0.01$), P/Ht (to 3.3±1.1mmHg.g/mW, $p<0.01$ vs EuT+Amd) and increased ΔLVEDP at the end of R. Wrt did not significantly modify the Amd effect in P, P/Ht and ΔLVEDP. Perfusion of n-MPG improved P (to 65.9±6.6% of pre-I vs 26.4±4.9% in HypoT+Amd; $p<0.01$), P/Ht (3.8±0.4mmHg.g/mW; $p<0.01$ vs. HypoT+Amd) and decreased ΔLVEDP during R, compared to HypoT+Amd. In EuT+Amd hearts, nMPG did not add positive effects to the already beneficial effects of Amd. Conclusions: a) PKC pathway plays a relevant role in Amd protection in EuT rats, but the PI3K/Akt pathway is not involved in its protective effect, b) the loss of protection of Amd in HypoT rat hearts is due to accumulation of ROS.

Clinical Pharmacology
Chairs: Pedro Martin and Hugo Ortega

89. ANTIBIOTIC RESISTANCE PATTERNS OF *Staphylococcus* spp. ISOLATES FROM THE NOSTRILS OF HEALTHY HORSES

Julia di Filippo[1], **Florencia Aliverti**[1], Taiel Konis[1,2], Federico Toso[1,5], Laura Marchetti[1], Daniel Buldain[1,3], Pablo Trigo[3,4], and Nora Mestorino[1]

[1]*Laboratorio de Estudios Farmacológicos y Toxicológicos –LEFyT-, Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata.* [2]*Instituto de Investigaciones en Reproducción Animal (INIRA), Facultad de Ciencias Veterinarias (FCV), Universidad Nacional de la Plata,* [3]*CONICET.* [4]*Instituto de Genética Veterinaria (IGEVET) Facultad de Ciencias Veterinarias, Universidad Nacional de La Plata.* [5] *Facultad de Ciencias Veterinarias, Universidad Nacional de La Pampa.*

Staphylococcus aureus (SA) and coagulase-negative *Staphylococci* (CNS) are significant reservoirs of multidrug resistance since they can colonize the nostrils of animals and humans asymptomatically. This study aimed to assess the antimicrobial (ATM) susceptibility of *Staphylococcus* spp., isolated from healthy horses (n=94) intended for assisted therapies in La Plata City, Argentina.

Nasal swabs from both sides of each animal were cultured in CHROMagar™ Staphylococcus, resulting in 272 suspected *Staphylococcus* spp. isolates. 87 (31.99%) were pink/mauve, while 185 (68.01%) were white or light blue colonies compatible with SA and CNS, respectively. Identification was done using metabolic and biochemical tests, including Gram staining.

An agar diffusion susceptibility test was carried out using *S. aureus* ATCC 25923, *S. epidermidis* ATCC 14990, and *S. saprophyticus* ATCC 15305 as control strains. ATMs were chosen based on their usage in equine and human treatments and line with CLSI recommendations. Vancomycin susceptibility was also assessed using the Brain Heart Infusion agar test.

Among the SA isolates, 6.90% (6/87) were resistant to penicillin, 2.30% (2/87) to cefoxitin (suspected MRSA), and 3.45% (3/87) to chloramphenicol. In contrast, among the CNS isolates, resistance was higher, 45.95% (85/185) to penicillin, 4.86% (9/185) to cefoxitin, and only 1.08% (2/185) to chloramphenicol. 1.15% (1/87) and 4.86% (9/185) were phenotypically resistant to erythromycin and clindamycin simultaneously (positive D test) among SA and CNS isolates, respectively. Additionally, 23.16% (63/272) of all isolates showed intermediate resistance (IR) to clindamycin. Finally, no resistance to vancomycin was found.

These findings highlight the importance of monitoring the resistance profile of *Staphylococcus* spp. in horses that frequently interact with humans. This is crucial in the "One Health" concept due to the pathogen's capacity to spread ATM resistance determinants across different species.

Clinical Pharmacology
Chairs: Pedro Martin and Hugo Ortega

90. INCIDENCE OF ISCHEMIC AND HEMORRHAGIC EVENTS DUE TO DUAL ANTIPLATELET THERAPY IN CORONARY ANGIOPLASTY

Mariano Goddio[1], Ignacio Ensinas[2], Nilda Y. Brizuela[1] and Juan P. Ricarte Bratti [1,2]

[1]*Farmacología General. Facultad de Ciencias Médicas. Universidad Nacional de Córdoba.* [2]*Servicio de Cardiología. Sanatorio Allende. Córdoba.*

Introduction: acute coronary syndromes (ACS) are usually treated with antiplatelet agents associated with coronary transluminal angioplasty (CTA). Despite advances in technology and antithrombotic therapies, ischemic and hemorrhagic events continue to occur in this scenario. These effects have been studied worldwide, but due to the hepatic activation that requires clopidogrel and prasugrel in our setting, we lack precise data.
Objectives: to quantify ischemic and hemorrhagic events in the one-year period of ACS according to the antiplatelet regimen chosen, and according to this, to categorize antiplatelet agents according to real antithrombotic potency and real hemorrhagic potency in our setting.
Material and Methods: adult patients with ACS who underwent CTA at Sanatorio Allende. A registry of ACS was carried out and the patients were followed for one year. This work was approved by the ethics committee of the Sanatorio Allende. Categorical data are shown as percentages and the chi-square test was used to establish differences between them.
Results: 122 patients were included in total, 84% of whom were men. Clopidogrel was used in 52% of patients, ticagrelor in 29%, and prasugrel in 19%. Ischemic events were recorded in 7% of patients with clopidogrel, 4.7% with ticagrelor, and 4.1% with prasugrel. Hemorrhagic events were observed in 5% of patients with clopidogrel, 4.5% with ticagrelor, and 5% with prasugrel. These data show that combined events, i.e. ischemic plus hemorrhagic events, were almost 12% for clopidogrel, and 9.1% for ticagrelor and prasugrel. The use of triple therapy, dual antiplatelet therapy plus anticoagulation, did not significantly increase hemorrhagic events.
Conclusion: Hemorrhagic events according to the antiplatelet regimen do not vary although ischemic events are more frequent with clopidogrel and less frequent with ticagrelor or prasugrel.

Phytopharmacology
Chairs: Pedro Martin and Hugo Ortega

91. CULTURES OF MARINE MICROALGAE: A POTENTIAL SOURCE OF NATURAL ANTIOXIDANTS

Ana V. Bauchi[1,2], M. Alejandra Sequeira[3,4], M. Belén Faraoni[3,4], M. Cecilia Damiani[1,2], M. Cecilia Popovich[1,2,4]

[1]*Centro de Recursos Naturales Renovables de la Zona Semiárida (CERZOS) (CONICET-UNS), Camino de La Carrindanga Km 7, B8000, Bahía Blanca. Argentina.* [2]*Departamento de Biología, Bioquímica y Farmacia (UNS), San Juan 670, B8000, Bahía Blanca. Argentina.* [3]*Instituto de Química del Sur (INQUISUR), Departamento de Química, Universidad Nacional del Sur-CONICET, Bahía Blanca, 8000, Argentina.* [4]*Investigador de la Comisión de Investigaciones Científicas (CIC) de la Provincia de Bs. As., Argentina.*

Marine diatoms have garnered significant attention as a potential source of natural antioxidants including fucoxanthin (Fx). In particular, numerous studies have shown that Fx has promising applications in human health, indicating its potential in pharmaceutical and nutraceutical industries. A significant Fx production by the marine diatom *Halamphora coffeaeformis*, isolated from Bahía Blanca Estuary (Argentina), was evidenced in our previous studies. We also verified that cultures of this species adapted at 100 µE m^{-2} s^{-1} of light intensity showed remarkable antioxidant activity. Under this scenario, the purpose of this study was to evaluate variations in the enhancement of antioxidant activity of extracts from *H. coffeaformis* cultures depending on different light condition adaptation. For this, an optimized protocol for 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt radical ($ABTS^{\bullet+}$) bleaching test was implemented. The diatom was cultured in f/2 medium at 60 µE m^{-2} s^{-1} of light intensity under a photoperiod of 12 h light:12 h dark. Fx-enriched extract was obtained by ethanolic treatment of *H. coffeaformis* biomass and its antioxidant activity was spectrophotometrically achieved by $ABTS^{\bullet+}$ scavenging activity measurements. The results showed an antioxidant activity of 47% for Fx-enriched extract at a concentration of 0.02 mg mL^{-1} and it represented half of that obtained by ascorbic acid (93%)**,** used as a reference positive control. In addition, it was evidenced lower activity for concentrations between 0.005 and 0.04 mg mL^{-1} compared to our previous studies with *H. coffeaeformis* cultures conditioned at 100 µE m^{-2} s^{-1}. In conclusion, this study demonstrates that pigment production in *H. coffeaeformis* can be improved by optimizing light intensity conditions and it also underscores the potential of this native species as a promising alternative source of natural antioxidants.

Pharmacogenetics
Chairs: Pedro Martin and Hugo Ortega

92. USE OF BIOINFORMATICS TOOLS IN THE STUDY OF THE ONSET OF PORPHYRIA CUTANEA TARDA IN HIV INFECTED INDIVIDUALS: EFFECT OF ANTIRETROVIRALS AND THE INFLUENCE OF DRUG METABOLIZING AND TRANSPORTING SYSTEM

Priscila Pagnotta[1,2], Johanna Zuccoli[3], Viviana Melito[1,3], Victoria Parera[3], Ana María Buzaleh[3]

[1]*Departamento de Química Biológica, FCEN, UBA.* [2]*Instituto de Biología y Medicina Experimental (IBYME).* [3]*Centro de Investigaciones sobre Porfirinas y Porfirias (CIPYP), UBA-CONICET.*

Porphyria Cutanea Tarda (PCT), due to the deregulation of Uroporphyrinogen decarboxylase, can be hereditary or acquired (A-PCT), with a high PCT-HIV association. We previously observed experimentally that genetic variants of *ABCB1, ABCG2* and *GST* could contribute to its onset. The aim was to evaluate *in silico* the role of genes of drug metabolizing and transporting system in A-PCT onset in relation to antiretroviral therapy. SNV of *ABCB1, ABCG2, GST* and *NR1I2*, and gnomAD, PharmGKB, Gene Expression Omnibus, UniProt, GenBank, PreADMET and SwissADME databases were considered. Free Wilson equations were used to design possible therapeutic alternatives. Population study demonstrated that allele frequency in Controls varied among different geographic regions. Genetic variants in *ABCB1*, *ABCG2*, *GST* and *NR1I2* are associated with toxicity and differential metabolism by antiretrovirals (Efavirenz, Nevirapine, Atazanavir, Nelfinavir, Tenofovir and Dolutegravir). In turn, individuals treated with protease inhibitors (PI) compared to those receiving non-nucleoside reverse transcriptase inhibitors (NNRTI) showed under expression of *ABCB1* (FC=0.83; p adj<0.05) and differential expression of 17 *ABC* (65% overexpressed) and 21 *CYP* (71% overexpressed) (GSE44228). Moreover, derivatives of Thiophene[3,2]pyrimidine could be use as therapeutic alternative for NNRTI and derivatives of (S)-tetrahydrofuran-tertiary amine-acetamide for PI with differential action on P-gp and CYP. We conclude that antiretrovirals alter drug metabolizing and transporting system, and variants of analyzed genes in this study could influence the manifestation of A-PCT in HIV infected individuals in relation to antiretroviral therapy due to hepatotoxicity. It is important to further explore experimentally this research to be applied in personalized medicine.

Pharmaceutical Technology
Chairs: Juan J. Martinez Medina and Santiago Zugbi

93. CHITOSAN-HYALURONIC ACID INTERPOLYMER FILMS FOR TOPICAL DELIVERY OF ACYCLOVIR AGAINST THE HERPES SIMPLEX

Johanna Karina Valenzuela Oses[1,2], Brenda Konigheim[3], Juan Javier Aguilar[3], Mónica Cristina Garcia[1,2]

[1]*Universidad Nacional de Córdoba, Facultad de Ciencias Químicas, Departamento de Ciencias Farmacéuticas, Córdoba, Argentina,* [2]*Consejo Nacional de Investigaciones Científicas y Técnicas, CONICET, Unidad de Investigación y Desarrollo en Tecnología Farmacéutica, UNITEFA, Córdoba Argentina,* [3]*Universidad Nacional de Córdoba, Facultad de Ciencias Médicas, Instituto de Virología "Dr. J. M. Vanella", CONICET, Argentina*.

Herpes simplex virus (HSV), known as herpes, is a common infection that represents an important public health problem worldwide. Acyclovir (ACI) is a reference drug for its treatment, but it has different limitations. Interpolymer-drug complexes (IPD) are an interesting therapeutic strategy to control drug release and improve the performance of ACI. In this work, ACI-loaded IPD-based polymeric films were developed and characterized for the topical treatment of HSV. The coacervation method was used for preparing the IPD, where ACI was added to neutralize 50% and 10% of chitosan (Ch) and hyaluronic acid (HA), respectively. IPD-ACI in dispersion were analyzed by dynamic light scattering and displacement studies, and lyophilized to characterize the solid state. Films were obtained by casting solvent, using glycerin (2% w/v) as a plasticizer, and further characterized through pharmaceutical and biological studies. Systems in dispersion exhibited sizes in the nanometer range (834 and 662 nm for IPD and IPD, respectively). IPE-ACI exhibited a high zeta potential value (59.6 mV), which indicated colloidal stability. Studies of ionic displacement by the addition of NaCl revealed ionic interaction between ACI and the polymer carrier. Thermal analyses showed the absence of free drug in IPD-ACI. X-ray diffraction and optical microscopy did not show peaks or birefringent phenomena under polarized light, respectively, confirming that the drug interacted completely with the polymer carrier. ACI was uniformly distributed in the films (coefficient of variation < 5%) and its release was controlled toward biorelevant fluids. IPD-ACI films interacted with mucin, revealing their bioadhesive properties, and showed biocompatibility against Vero cells (cell viability > 70%). After inoculation of cells with HSV–1 virus, a herpetic cell inhibition of 100% was achieved. IPD-ACI films show promising properties for the topical delivery of ACI for herpes treatment.

Pharmaceutical Technology
Chairs: Juan J. Martinez Medina and Santiago Zugbi

94. 3D- PRINTING CAPSULAR DEVICES FOR COMPOUNDING PHARMACY: MATERIALS CHARACTERIZATION AND DRUG STABILITY STUDY

Juan Francisco Peña[1,2], Loreana Gallo[1,3] and Ivana Cotabarren[1,2]

[1]*Planta Piloto de Ingeniería Química, PLAPIQUI (UNS-CONICET), Camino La Carrindanga Km 7, 8000 Bahía Blanca, Argentina; Departamento de Ingeniería Química, Universidad Nacional del Sur (UNS), Av. Alem 1253, 8000 Bahía Blanca, Argentina;* [2]*Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS),* [3]*San Juan 670, 8000 Bahía Blanca, Argentina.*

3D printing is revolutionizing the pharmaceutical industry by enabling personalized drug manufacturing with precise dosages and customized forms, facilitating controlled release profiles and innovative treatments. However, its implementation demands rigorous quality control to ensure safety and efficacy. In this context, magistral compounding combined with 3D printing, offers a promising approach to enhance the personalization of medications. This study aimed to physico-chemically characterize (i.e., FT-IR spectra, DSC thermograms and morphology) the materials used for the 3D printing of capsular devices (CDs), equivalent to size 0 hard gelatin capsules, with 0.4- and 0.9-mm wall thickness (CD-0-0.4 and CD-0-0.9). Losartan potassium, a common antihypertensive, was used as the model drug, and poly(vinyl alcohol) (PVA) was the printing filament. In addition, the stability of the drug inside the CDs was assessed under natural (25°C, 60% RH) and accelerated conditions (40°C, 75% RH) over 1 and 3 months. To this end, the FT-IR spectrum and DSC thermograms of the drug were analyzed and compared to initial values. The physicochemical characterization of the drug and PVA showed the chemical nature and morphology expected for those materials. Regarding drug stability inside CD-0-0.4, FT-IR spectrum and DSC thermogram confirmed no chemical changes in its chemical composition for natural (1 and 3 months) and accelerated conditions (1 month). Conversely, the CDs opened under 3 months accelerated conditions, preventing data acquisition. For CD-0-0.9, FT-IR and DSC confirmed no chemical changes in the drug chemical composition, only in natural conditions. In both accelerated conditions, the CDs opened. The difference in PVA mass between CD-0-0.4 and CD-0-0.9 allowed a higher water sorption that notably affected their structural integrity. In conclusion, CD-0-0.4 and CD-0-0.9 satisfactorily preserve the stability of the drug in natural storage conditions.