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## MISIÓN

La Revista de Farmacología de Chile es considerada el órgano oficial de difusión científica y de opinión de la Sociedad de Farmacología de Chile. En un principio esta revista nació como un remozado libro de Resúmenes del XVIII Congreso Latinoamericano de la Asociación de Farmacología realizado en Chile el año 2008. Desde 2009 y hasta ahora la Revista de Farmacología de Chile ha recibido varios trabajos originales de investigación y diversas revisiones de temas farmacológicos relevantes. La Revista de Farmacología de Chile aborda temas relacionados con la farmacología básica y experimental, así como investigaciones clínicas. Las áreas temáticas principales son: farmacocinética, farmacodinamia, farmacología cardiovascular, farmacología pulmonar, farmacología endocrina, Neurofarmacología, farmacología clínica, estudios preclínicos, estrés oxidativo, fitofarmacología, ciencias farmacéuticas, química-médica y toxicología. También la revista actualmente permite divulgar opiniones sobre los principales temas de salud relacionados con medicamentos en Chile, la presentación de líneas de investigación de laboratorios nacionales en donde se realizan investigaciones farmacológicas, información de curso y programas de postgrados nacionales en farmacología y la publicación de Resúmenes científicos del Congreso Anual SOFARCHI.

### Audiencia:

La Revista de Farmacología de Chile está dirigida a farmacólogos nacionales e internacionales interesados en la divulgación de la farmacología. También está dirigida a estudiantes de pregrado de carreras universitarias del área de la salud y ciencias biomédicas, y a estudiantes de postgrado que cursen maestrías y doctorados en farmacología.

### Periodicidad:

Se editarán hasta 3 números anuales (abril, agosto y diciembre) en formato digital. El número de diciembre incluirá trabajos originales y los Resúmenes del Congreso Anual de la Sociedad de Farmacología de Chile.

### Temas a Publicar:

- Artículos originales en Farmacología Básica, Farmacología Clínica, Farmacoterapia y Toxicología.
- Artículos originales de investigación nacional e internacional en Farmacocinética y Farmacogenética.
- Artículos de revisión de temas farmacológicos importantes sobre las diversas temáticas de la disciplina.
- Artículos de Información de nuevos fármacos incorporados al arsenal terapéutico nacional.
- Opiniones oficiales de la sociedad sobre los aspectos regulatorios y nuevas políticas de medicamentos.
- Artículos sobre nuevas metodologías docentes, aplicadas en Farmacología.
- Información detallada de nuevos reportes de reacciones adversas reportadas a nivel internacional y nacional.
- Libros y revistas de los temas.
- Promoción de actividades académicas, congresos y cursos nacionales e internacionales en farmacología.
- Publicitar las ofertas de trabajo de inserción académica en Universidades Chilenas y extranjeras, así como las oportunidades de inserción laboral en la industria privada ligada al desarrollo de fármacos.

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Contacto: Avenida Independencia 1007, Independencia, Santiago, Chile. Teléfono: 56-2-29786050; Correo Electrónico: [consultas.sofarchi@gmail.com](mailto:consultas.sofarchi@gmail.com); [farmacologia@med.uchile.cl](mailto:farmacologia@med.uchile.cl)

Editores en Jefe: Dra. Angélica Escobar, Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso. Avenida Gran Bretaña 1111, Playa-Ancha, Valparaíso, Chile. Teléfono: 56-32-2508050; Correo Electrónico: [angelica.escobar@uv.cl](mailto:angelica.escobar@uv.cl); Dr. Rodrigo Castillo, Departamento Medicina Interna, Universidad de Chile, Huerfanos 3255, Santiago, Chile. Teléfono: 56-2-26815537, Correo Electrónico: [rodrigouch@uchile.cl](mailto:rodrigouch@uchile.cl)



**XLVI CONGRESO ANUAL  
SOCIEDAD DE FARMACOLOGÍA DE CHILE**



**XLVI CONGRESO ANUAL**  
Sociedad de **FARMACOLOGÍA** de Chile

*Universidad Austral de Chile*  
**VALDIVIA**  
*2 al 5 de Diciembre del 2025*





## WELCOME

Dear Members and Participants:

On behalf of the Chilean Society of Pharmacology, we extend a warm and enthusiastic welcome to the XLVI Annual Congress of our esteemed Society of Pharmacology (SOFARCHI), which will be held in the Aula Magna of the Austral University in the beautiful city of Valdivia. We are delighted to welcome a diverse group of undergraduate and graduate students, researchers, academics, and distinguished national and international speakers to this exciting event.

This congress is the leading annual meeting in pharmacology in Chile, and your presence enhances its importance and quality. For our students, this is a unique opportunity to disseminate and learn about the latest advances in pharmacological research and to connect with other researchers from across the country. Furthermore, it is a chance to be inspired by the collective wisdom gathered here. For researchers, this is a fertile ground to present their advances and new research challenges, foster collaboration, and expand the boundaries of pharmacological knowledge.

Our deepest gratitude to all our speakers and symposium participants, whose presentations sparked intellectual curiosity and fostered enriching debates throughout the congress.

The Austral University of Chile, with its commitment to academic excellence and research, welcomes us to a magnificent natural setting for this exchange of knowledge. This highlights the spirit of collaboration, cultural diversity, and scientific research that define our society.

Let us enjoy this week filled with networking, engaging presentations, and friendships that extend far beyond the realm of science.

Welcome to the XLVI Annual Congress of the Chilean Society of Pharmacology.

Sincerely,

**Patricio Iturriaga**  
**President**  
**SOFARCHI**



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## CONFERENCIAS / LECTURES



### 1. DR. KATIA GYSLING: A LIFE DEDICATED TO NEUROPHARMACOLOGY AND PEOPLE FORMATION

**Dra. Katia Gysling: una vida dedicada a la neurofarmacología y a la formación de personas**

#### Resumen:

More than thirty years of friendship and fruitful collaboration give me the privilege of paying tribute to Katia Gysling, one of the most admired and beloved scientists in our Chilean Society of Pharmacology. Katia devoted much of her career to understanding how the brain integrates stress signals with motivational circuits. Her work helped uncover how the corticotropin-releasing factor (CRF) system, including its binding protein (CRF-BP) and receptors (CRFR1 and CRFR2), modulates mesolimbic dopaminergic activity, establishing a molecular link between stress and addiction. Notably, Katia's research was pioneering in demonstrating how other brain nuclei, such as the BNST and septum, participate in the responses to stress and drugs of abuse. Throughout her career, her research group explored how stress and addictive drugs reshape the communication between CRF and dopamine, producing long-lasting changes in synaptic plasticity. In recent years, those studies progressed toward identifying heteromers between CRFR2 and D1 receptors, providing a molecular basis for the functional convergence between neurochemical systems traditionally studied in isolation. Together with her most recent students, Katia also explored differences in the CRF system between youth and adulthood, seeking mechanisms that could explain greater vulnerability to adversity during early life. Beyond her scientific contributions, Katia Gysling trained a generation of neuropharmacologists, sharing her passion for science with rigor and generosity. This lecture aims to honor her legacy by revisiting the main findings we shared and highlighting how her ideas continue to inspire new approaches to understanding the interaction between stress and addiction.

**Autores:** María Estela Andrés

**Afiliación:** Pontificia Universidad Católica de Chile

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** mandres@uc.cl

**Agradecimientos:** Fondecyt, ANID

**Socio Patrocinante:** Georgina Renard



### 2. PENTAMERIC LIGAND-GATED ION CHANNELS: BRIDGING MOLECULAR INSIGHTS AND CLINICAL PROMISE

**Canales iónicos pentaméricos activados por ligando: Uniendo conocimientos moleculares y promesa clínica**

#### Resumen:

Pentameric ligand-gated ion channels (pLGICs) are essential for translating neurotransmitter recognition into electrical signals in both vertebrates and invertebrates, contributing to fundamental processes such as movement, memory, cognition, and synaptic plasticity. These receptors are expressed not only in the nervous system but also in various non-neuronal cells, and are implicated in a wide spectrum of disorders, making them key pharmacological targets for clinically relevant drugs. In vertebrates, the pLGIC family includes cation-selective channels—nicotinic acetylcholine receptors (nAChRs) and serotonin type 3 receptors—as well as anion-selective channels such as glycine and GABAA<sub>A</sub> receptors, whereas in invertebrates the repertoire is even more diverse. Remarkably, the free-living nematode *Caenorhabditis elegans*—a model for both human diseases and anthelmintic drug discovery—possesses one of the largest and most varied pLGIC families, making it an ideal system for investigating their function and therapeutic potential. Using a combination of experimental approaches, including high-resolution patch-clamp recordings primarily focused on nicotinic and serotonin receptors, we characterized their kinetic and functional properties and identified novel modulatory compounds, providing valuable insights into their potential as therapeutic targets. Extending this framework to *C. elegans*, we bridged molecular and organismal levels to uncover functional features of nematode pLGICs—some conserved and relevant to human diseases, others uniquely nematode-specific and emerging as anthelmintic targets. These findings highlight new molecular targets and lead compounds for the development of novel therapies. Our work offers insights into receptor function under both physiological and pathological conditions, paving the way for innovative therapeutic applications.

**Autores:** Bouzat, C.

**Afiliación:** Instituto de Investigaciones Bioquímicas de Bahía Blanca, CONICET, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur. Bahía Blanca, Argentina.

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** inbouzat@criba.edu.ar



### 3. MAPPING GLP-1R SIGNALING IN HUMAN POMC NEURONS: A CENTRAL MECHANISM OF ANTI-OBESITY DRUG ACTION

**Mapeo de la señalización del receptor GLP-1 en neuronas POMC humanas: un mecanismo central de la acción de los fármacos contra la obesidad**

**Resumen:**

Obesity shortens the lifespan of millions of people worldwide by increasing the risk of severe chronic diseases. Pharmacotherapies, in combination with lifestyle interventions, are a promising strategy to help obese patients reduce their body weight. Specifically, glucagon-like peptide-1 receptor (GLP-1R) agonists have emerged as an effective and approved therapy to promote weight loss by reducing appetite and food intake. In rodents, GLP-1R agonists such as liraglutide and semaglutide (also known as Ozempic® or Wegovy®) reach the hypothalamus and activate proopiomelanocortin (POMC) neurons, key regulators of energy balance that suppress food intake when stimulated. However, how GLP-1R signaling is integrated in human POMC neurons remains poorly understood, limiting the development of pharmacotherapies that selectively enhance their anorexigenic function. To uncover GLP-1R signaling in these neurons, we generated a human model of POMC neurons from pluripotent stem cell lines and examined their response to GLP-1R activation. We found that GLP-1R agonists persistently increase the excitability of human POMC neurons and identified candidate intracellular mechanisms that sustain this enhanced

excitability. These findings provide new insight into the central mechanisms underlying GLP-1R agonist action in neurons and reveal potential molecular targets to further potentiate the appetite-suppressing and weight-reducing effects of GLP-1R-based therapies.

**Autores:** Mazzaferro, S.

**Afiliación:** Institute of Metabolic Science, Department of Clinical Biochemistry. University of Cambridge

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** sm2676@medschl.cam.ac.uk



### 4. THE THERAPEUTIC POTENTIAL AND MOLECULAR SIGNATURE OF CANNABIDIOL IN DEPRESSION

**Potencial terapéutico y mecanismo molecular del cannabidiol en la depresión**

**Resumen:**

Cannabidiol (CBD) is a non-psychoactive compound from cannabis sativa which has demonstrated strong potential in the treatment of psychiatric disorders. We originally reported that CBD has antidepressant properties in preclinical models, which has been supported by evidence published by other research groups over the past decade. Despite that, there is a lack of supporting clinical evidence and the mechanism of action behind CBD's antidepressant properties remains poorly understood. To address this gap, our group investigated the multimodal profile of CBD in vivo (using animal models of depression) and in vitro (in primary neuronal cell cultures). To highlight the functional relevance of our findings, our data were compared with the molecular profile of ketamine, a prototype fast-acting antidepressant drug with demonstrated efficacy in humans. Our results provide new evidence about the effects of CBD on behaviour and neuroplasticity, potentially unravelling new pathways with relevance for the antidepressant effect.

**Autores:** Joca, S

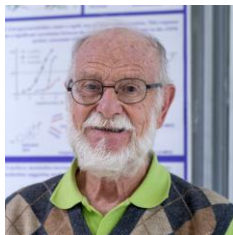
**Afiliación:** Aarhus University

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** sjoca@biomed.au.dk

**Agradecimientos:** Lundbeck Foundation, AUFF, AIAS.

**Socio Patrocinante:** Georgina Renard



**5. HISTORICAL PERSPECTIVE OF MECHANISMS OF DRUG ACTION: FROM OCCUPATION THEORY TO BIASED SIGNALING, 100 YEARS OF PHARMACOLOGICAL THINKING AND EXPERIMENTATION.**

**Perspectiva histórica de mecanismos de acción de medicamentos: desde la teoría de la ocupación a señalización influenciada, 100 años de pensamiento farmacológico y de experimentación**

**Resumen:**

Over the years, the molecular understanding of receptors working has been slow and dependent on physicochemical advances of protein structure and activity research. The initial concept of receptors was first used by Cambridge physiologists, referring to the “receptive” substance for nicotine (Langley., J. Physiol., 1905). This nomenclature mutated to receptors within short. The first serious proposal on drug mechanism of action came from J. A. Clark in Pharmacology at Edinburgh’s School of Medicine, who argued that drugs interact with cell surface receptors following the mass forming a concentration-dependent [drug-receptor] complex. Small doses cause a threshold effect, while increasing drug dosing elicit proportionally larger responses, until achieving the maximal response, interpreted as full occupancy. Clark’s proposal was summarized as concentration-response curves, where potency values were obtained and allowing comparison with structurally related compounds. Forty years later, a Clark’s disciple published an amendment to Clark’s theory introducing the concept of intrinsic activity since partial agonists and antagonists conceptually escaped Clark’s principles (Stephenson, Br. J. Pharmacol , 1956). Years later, radiotracers allowed calculating drug binding affinities to cells or isolated tissues and classifying receptors based on ligand selective affinity for endogenous and exogenous compounds. Years after, the opportunity emerged to study the multiplicity of intracellular signaling pathways elicited following receptor occupation. Finally, the cloning of receptors pushed a step forward by modelling ligand interactions with cloned and crystallized receptors. The outbreak of bioinformatics allowed visualizing [drug-receptor] complexes while molecular dynamic calculations supported the obtainment of binding affinities. Biased signaling prompted the dynamics of receptor conformations and the versatility of receptor signaling.

**Autores:** Huidobro-Toro J.P.

**Afiliación:** Laboratorio de Farmacología, Facultad de Química y Biología, Universidad de Santiago de Chile

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** [juan.garcia-huidobro@usach.cl](mailto:juan.garcia-huidobro@usach.cl)

**Agradecimientos:** FONDAF 200001

**Symposium Neuropharmacology** «Innovating in pharmacology: neuroimmune, aging, natural compounds for neuroprotection, and intestinal microbiota-based therapies».

Chair: **Dr. Javier Bravo**

**NEUROPROTECTIVE AND ANTIOXIDANT EFFECTS OF FERMENTED SPENT COFFEE GROUNDS EXTRACT AGAINST ALZHEIMER'S-RELATED OXYSTEROL 27-HYDROXYCHOLESTEROL.**

**Efectos neuroprotectores y antioxidantes del extracto fermentado de Borra de Café contra 27-hidroxicolesterol asociado con la Enfermedad de Alzheimer.**

**Resumen:**

Oxidative stress is a central contributor to Alzheimer's disease (AD), with the oxysterol 27-hydroxycholesterol (27-OHC) recognized as a physiologically relevant driver of redox imbalance and amyloidogenic processes. Spent coffee grounds (SCG), an abundant by-product of the coffee industry, are rich in hydroxycinnamic acids such as chlorogenic (CGA), caffeic (CA), and quinic acids (QA), yet their bioactivity remains underexploited without targeted valorization strategies. In this study, SCG was subjected to a three-step bioprocess comprising solid-state fermentation (SSF), hydroalcoholic extraction, and sequential ultrafiltration (UF <3 and <10 kDa) to obtain enriched low-molecular-weight fractions. Phenolic composition and enrichment were determined by high-performance liquid chromatography and total phenolics, and the biological activity was assessed in SH-SY5Y neuronal cells exposed to H<sub>2</sub>O<sub>2</sub> or 27-OHC. Endpoints included cell viability, reactive oxygen species (ROS), superoxide dismutase (SOD) activity, and amyloid-beta peptide A $\beta$ -40 expression as a relevant biomarker of amyloidogenic stress. SSF increased total phenolics up to 4.2-fold, with compositional shifts from CGA to CA and QA. The <3 kDa fraction obtained on day 10 showed the strongest activity, lowering ROS by nearly 90%, restoring SOD activity, and reducing A $\beta$ -40 accumulation by approximately 50% under 27-OHC stress, while pure phenolic standards produced weaker effects. These findings provide proof of concept that SCG fractions enriched through SSF and UF exert multitarget protective effects against oxidative and amyloidogenic stress. The study highlights the valorization of SCG as a sustainable source of functional neuroprotective ingredients, bridging food chemistry, biotechnology, and neurodegeneration research.

**Autores:** Alejandra Arancibia-Díaz, Carolina Astudillo-Castro, Claudia Altamirano, Mauricio Vergara-Castro, Carmen Soto-Maldonado, Andrés Córdova, Sofía Trujillo-Fernandez, María Elvira Zúñiga-Hansen, Ana María Vega, Paloma Fuentes.

**Afiliación:** Pontificia Universidad Católica de Valparaíso

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** alejandra.arancibia@pucv.cl

**Agradecimientos:** FONDECYT POSTDOCTORADO N°3250833

**Socio Patrocinante:** Javier Bravo

**MICROBIAL-BASED STRATEGIES TO PROMOTE HEALTHY AGING.**

**Estrategias basadas en microbios para promover un envejecimiento saludable**

**Resumen:**

Aging is accompanied by a series of physiological changes that significantly diminish quality of life. One of the most profound effects of aging is immunosenescence, a gradual deterioration of immune function characterized by a reduced capacity to mount effective immune responses. Emerging evidence indicates that gut microbiota dysbiosis contributes to this decline by impairing immune regulation, increasing susceptibility to infections, and promoting chronic inflammation. Although the gut microbiota plays a central role in maintaining human health and orchestrating immune homeostasis, its contribution to immunosenescence, and consequently to the immune response to vaccination in older adults, remains poorly understood. To explore this relationship, we conducted a pilot study aimed at characterizing the association between gut microbiota composition and vaccine responsiveness in healthy older adults. Our findings suggest that the gut microbiota may serve as a critical determinant of immune competence in aging, influencing the ability to generate effective vaccine-induced immunity. These results point to the modulation or restoration of gut microbiota as a promising strategy to enhance vaccine responses, reduce infection risk, and promote healthier aging.

**Autores:** Erick Riquelme

**Afiliación:** Pontificia universidad Católica de Chile

**Área de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** [EMRIQUEL@UC.CL](mailto:EMRIQUEL@UC.CL)

**Agradecimientos:** Fondecyt 1231629 CECAN

**Socio Patrocinante:** JAVIER BRAVO

## TARGETING THE GUT MICROBIOTA TO TREAT NEUROPSYCHIATRIC DISORDERS

### Apuntando a la microbiota intestinal para tratar trastornos neuropsiquiátricos

#### Resumen:

The monoamine hypothesis remains the leading explanation for the mechanisms underlying major depressive disorders, with the most common medications being selective serotonin reuptake inhibitors (SSRIs), which block the re-uptake of neurotransmitters such as serotonin (5-HT) in the brain. These SSRIs are taken orally and are efficiently absorbed in the intestine. However, recent studies have demonstrated that SSRIs also impact the gut microbiota, showing antibiotic-like effects and affecting certain gut symbionts sensitive to fluoxetine (FLX). This evidence suggests that SSRIs may influence brain function partly through alterations in the gut microbiota. To explore this, a variant of FLX was developed by modifying its secondary amine with methyl iodide (MeI), creating a quaternary ammonium salt (FLX+) with reduced ability to cross the intestinal barrier. This chemical modification was confirmed through <sup>1</sup>H-NMR, which detected structural changes, and Log P coefficient measurements that indicated increased hydrophilicity compared to the original drug. Furthermore, *in silico* and *in vitro* analyses showed that the modified compound continues to interact with the serotonin transporter (SERT), albeit with decreased potency relative to FLX. Behavioural studies in rats and zebrafish revealed that FLX+ does not exhibit antidepressant or anxiolytic-like effects, in contrast to FLX, suggesting that FLX+ is unable to cross the intestinal or blood-brain barriers. These findings partially fulfil the goal of creating a tool to investigate how SSRIs affect gut microbes and to better understand the role these microbial changes may play in alleviating mood disorder symptoms.

**Autores:** Bravo J.A.

**Afiliación:** Grupo de NeuroGastroBioquímica. Instituto de Química, y Centro de Investigación Interdisciplinaria en Biomedicina, Biotecnología y Bienestar (C3B), Pontificia Universidad Católica de Valparaíso. Valparaíso, Chile

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [javier.bravo@pucv.cl](mailto:javier.bravo@pucv.cl)

**Agradecimientos:** Pontificia Universidad Católica de Valparaíso DI Grants 039.350/2023, 039.304/2023, 039.324/2023, and 039.469/2024

**Socio Patrocinante:** Javier A. Bravo.

## MICROBIOTA-DEPENDENT T-CELL RESPONSE TO PATHOGENIC ALPHA-SYNUCLEIN PLAYS A CRITICAL ROLE TRIGGERING THE DEVELOPMENT OF SENSORY AND MOTOR IMPAIRMENT ASSOCIATED WITH PARKINSON'S DISEASE

### La respuesta de linfocitos t contra alfa-sinucleína patógena juega un papel crítico desencadenando el deterioro motor y sensorial asociados con la enfermedad de parkinson

#### Resumen:

Previous studies have shown that both the T-cell response and the microbiota play critical roles in the development of Parkinson's Disease (PD), which involves motor impairment and chronic pain. Nevertheless, the relationship between the microbiota and the development of the T-cell response in PD remains unexplored. Our results show that the depletion of either gut microbiota or T-cells, but not B-cells, abrogated the development of motor deficits, sensory disturbances, neuroinflammation, and gut inflammation in the transgenic SNCA mouse model. SNCA mice developed an autoreactive T-cell response to  $\alpha$ -synuclein-derived neo-antigens accumulated in the gut mucosa, a process that was dependent on the microbiota. The adoptive transfer of lymphocytes into lymphopenic or antibiotic-treated SNCA mice rescued the disease manifestation. SNCA mice displayed a gut dysbiosis involving the selective reduction of some short-chain fatty acids and increased intestinal permeability. Importantly, the conditional genetic deficiency of the  $\alpha$  short-chain fatty acid receptor in T-cells abrogated the development of sensory disturbances and motor impairment. Our findings indicate that the development of sensory disturbances and motor impairment in SNCA mice depends on the interaction of T-cells with the microbiota through bacterial short-chain fatty acids. Our data suggests that gut microbiota dysbiosis triggers increased intestinal barrier permeability and the subsequent synuclein pathology in the colonic mucosa, activating inflammatory T-cells specific to  $\alpha$ -synuclein-derived neo-antigens.

**Autores:** Zulmary Manjarres<sup>1,2</sup>, Valentina Ugalde<sup>1,3</sup>, Ornella Chovar-Vera<sup>1,4</sup>, Luis Rodríguez<sup>1,4</sup>, Carolina Prado<sup>1,4</sup>, Ivania Valdés<sup>2</sup>, Paula Díaz<sup>2</sup>, Alejandra San Martín-Isasi<sup>2</sup>, Alexandra Espinoza<sup>1,3</sup>, Erick Riquelme<sup>2</sup>, Margarita Calvo<sup>2</sup>, Rodrigo Pacheco<sup>1,4</sup>

**Afiliación:** 1Fundación Ciencia & Vida, Santiago, Chile. 2Pontificia Universidad Católica de Chile, Santiago, Chile. 3Fundación Arturo López Pérez OECS Cancer Center, Santiago, Chile. 4Universidad San Sebastián, Santiago, Chile.

**Área de la Farmacología:** Immunopharmacology

**Dirección de Correo:** [rpacheco@cienciavida.org](mailto:rpacheco@cienciavida.org)

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**Socio Patrocinante:** Javier Bravo

**Symposium Cancer Pharmacology** «Novel targets in cancer pharmacology: basic, clinical, and technological approaches».

Chair: **Dr. Rodrigo Castillo**

**TRANSACTIVATION BETWEEN P2Y2 AND HER2 RECEPTORS AND ITS POTENTIAL ROLE IN GASTRIC CANCER**

**Transactivación entre los receptores P2Y2 y HER2 y su posible papel en el cáncer gástrico**

**Resumen:**

Gastric cancer (GC) remains one of the most prevalent malignancies in Chile, ranking as the leading cause of cancer-related deaths in men and the third in women. Despite advances in surgery and chemotherapy, current treatments are limited by drug resistance and severe side effects, emphasizing the need for new molecular targets. Only a few targeted therapies, mainly those acting on the epidermal growth factor receptor 2 (HER2), have been approved, leaving an important gap in understanding other signaling pathways involved in GC progression. Recent studies by our group have identified a novel role of purinergic signaling, mediated by extracellular nucleotides such as ATP and UTP, in promoting tumor cell proliferation. Among these, the G protein-coupled receptor P2Y2 (P2Y2R) is highly overexpressed in GC biopsies. Activation of P2Y2R enhances tumor cell growth, whereas its inhibition reduces proliferation. Importantly, G protein-coupled receptors can indirectly activate receptor tyrosine kinases, such as HER2, through a process known as transactivation, which has been associated with epithelial-mesenchymal transition (EMT) and increased tumor aggressiveness in other cancers. To explore this mechanism in GC, we analyzed P2Y2R/HER2 transactivation using GC-derived cell lines and primary tumor cultures. qPCR assays confirmed elevated expression of both receptors in GC compared with healthy gastric mucosa. Stimulation with UTP induced a concentration-dependent increase in cell proliferation, while inhibition with Lapatinib, a HER2 blocker, reversed this effect. Moreover, immunodetection of phosphorylated EGFR and AKT confirmed activation of HER2 signaling following P2Y2R stimulation, supporting the existence of functional P2Y2R/HER2 transactivation in this model. These findings provide the first evidence of P2Y2R/HER2 transactivation in GC and suggest that this signaling axis may contribute to tumor progression and EMT. Understanding this interaction could lead to the dev

**Autores:** Claudio Coddou<sup>1,2</sup>, Daniela Cerda<sup>1,2</sup>, Antonia Covarrubias<sup>1,2,3</sup>, Denisse Reyna-Jeldes<sup>1,2</sup>

**Afiliación:** 1Laboratorio de Señalización Purinérgica, Departamento de Ciencias Biomédicas, Facultad de Medicina, Universidad Católica del Norte, Coquimbo, Chile 2Núcleo para el estudio del cáncer a nivel básico, aplicado y clínico, Universidad Católica del Norte 3Facultad de Ciencias Agropecuarias, Universidad del Alba, La Serena 1700000, Chile

**Area de la Farmacología:** Gastrointestinal pharmacology

**Dirección de Correo:** ccoddou@ucn.cl

**Agradecimientos:** Fondecyt Regular grant #1251487

**FROM GENE TO CURE: RECOMBINANT L-ASPARAGINASE PRODUCTION FOR LEUKEMIA THERAPY**

**Del gen a la cura: producción de l-asparaginasa recombinante para el tratamiento de la leucemia**

**Resumen:**

L-Asparaginase (L-ASNase) is a cornerstone biopharmaceutical for the treatment of Acute Lymphoblastic Leukemia (ALL). Its therapeutic action relies on depleting serum asparagine, which starves neoplastic cells that lack asparagine synthetase. However, the clinical use of native L-ASNases from bacterial sources like *Escherichia coli* and *Erwinia chrysanthemi* is often compromised by severe adverse effects. These include hypersensitivity reactions (immunogenicity) and significant off-target glutaminase activity, which causes further toxicity. The "Gene to Cure" paradigm leverages recombinant DNA technology to engineer superior L-ASNase "bio-betters" with improved therapeutic profiles. This journey begins upstream with the heterologous expression of the L-ASNase gene in optimized microbial hosts such as *E. coli*, *Pichia pastoris*, and *Bacillus subtilis*. Production is enhanced through molecular and metabolic strategies, including codon optimization, promoter engineering, and the development of optimized fermentation media supplemented with key amino acids like arginine and aspartate to maximize yield. Simultaneously, the enzyme itself is re-engineered. In silico immunoinformatic tools are employed to predict and map the T-cell and B-cell epitopes responsible for allergenicity. Guided by these data, enzyme engineering techniques such as site-directed mutagenesis, directed evolution, and the design of chimeric "humanized" enzymes are used to modify the gene. These modifications successfully silence immunogenic regions and reduce glutaminase activity. Downstream strategies, including PEGylation and glycosylation, further enhance plasma half-life and stability. This integrated "gene-to-cure" pipeline is essential for developing highly efficient, safe, and robust recombinant L-ASNase therapies.

**Autores:** Farias J.G

**Afiliación:** Universidad de La Frontera

**Area de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** jorge.farias@ufrontera.cl

**Agradecimientos:** This work was supported by the state of São Paulo Research Foundation (FAPESP Grant number 2023/18416-0), FAPESP-UFRO (grant number 2020/06982-3) and by the Chilean National Research and Development Agency (ANID) Fondecyt program (grants number 11230701 and 1240197).

## **CARDIOVASCULAR RISK IN A COHORT OF CHILDHOOD CANCER SURVIVORS: PILOT STUDY OF EXERCISE TRAINING AND SGLT2 INHIBITORS IN CARDIOMETABOLIC MARKERS**

**Riesgo cardiovascular en una cohorte de supervivientes de cáncer infantil: estudio piloto del entrenamiento físico y los inhibidores de SGLT2 en marcadores cardiometabólicos**

### **Resumen:**

In Chile, there are 400 new cases of childhood cancer per year, with an overall survival rate of approximately 60%, leading to an increase in cancer childhood survivor (CCS). Pediatric Antineoplastic Drug Program (PINDA) protocol includes anthracyclines, chemotherapeutic agents with a high cardiotoxic risk. This protocol currently excludes interventions with cardiometabolic benefits, such as physical training. Aerobic exercise increases cardiorespiratory fitness (CRF), and is associated with better cardiovascular outcomes. SGLT2 inhibitor therapy has demonstrated cardioprotective effects in heart failure (HF) patients, and results in cardioprotection. We hypothesize that a combined exercise intervention will improve CRF in a cohort of CCS, reducing cardiovascular, metabolic, and inflammatory risk factors, markers of cardiotoxicity, and that a pilot with a complementary SGLT2 inhibition intervention could enhance cardioprotection. Clinical study at Salvador and Calvo Mackenna Hospitals (2024 -2026 will include: i) control group (18 to 25 years) from Salvador Hospital (n=15); and ii) a CCS group (n=30), treated with anthracycline chemotherapy from Calvo Mackenna Hospital. Both groups will undergo continuous supervised training for 12 m. Specific objectives are: i) to determine baseline CV and cardiorespiratory parameters (O<sub>2</sub> consumption – peak VO<sub>2</sub>) in CCS and matched healthy controls; ii) CRF and cardiac function at baseline, 6 and 12 m; iii) to determine pro-inflammatory cytokines (IL-6 and TNF-alpha), myokines (PGC 1alpha, and irisin) and cardiometabolic risk (lipid profile, insulin) in blood samples and RNA levels in peripheral blood mononuclear cells (PBMCs) at baseline, 6 and 12 m. Conclusion. Optimizing cardiovascular risk by controlling cardiovascular risk factors, implementing structured physical training, and exploring adjunctive SGLT2 inhibitor therapy will reduce the pro-inflammatory and adverse cardiometabolic profile associated with CV risk in CCS.

**Autores:** Castillo RL\*, FigueroaEG, González-Candia A, Paris C, Verdugo V, Lang M, Cruz-Montecinos C, Armijo M, Acevedo P, Carrasco RA

**Afiliación:** Medicina Interna Oriente, Facultad de Medicina, Universidad de Chile; Escuela de Obstetricia, Facultad de Ciencias para el Cuidado de la Salud, Universidad San Sebastián; Institute of Health Sciences, University of O'Higgins, Rancagua; Oncología Hospital Luis Calvo Mackenna; Cardiología, Hospital Salvador ; Kinesiología, Univ de Chile; Department of Cardiology, Univ. Zurich, Switerland.

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** rodrigouch@uchile.cl

**Agradecimientos:** # FIIS Grant 2023 – Faculty of Medicine, University of Chile.

**Symposium Metabolic Pharmacology** «Experimental models for studying mitochondria metabolism in long-term diseases».

Chair: **Dr. Mario Herrera-Marschitz**

**HUMAN BRAIN ORGANIDS AS AN IN VITRO MODEL SYSTEM FOR NEURODEGENERATIVE AND MITOCHONDRIAL DISEASES**

**Organoides derivados de cerebro humano: Un modelo in vitro para estudiar trastornos neurodegenerativos y trastornos mitocondriales.**

**Resumen:**

Neurodegenerative and mitochondrial diseases pose major challenges to global health. Neurodegenerative disorders are marked by progressive neuronal dysfunction and cognitive decline, while mitochondrial diseases, often caused by genetic defects in nuclear or mitochondrial DNA, impair cellular energy metabolism and contribute to neurological manifestations. The incidence of these conditions rises steeply with age, and by 2050 more than 150 million people worldwide are expected to suffer from dementia alone. Despite their growing impact, underlying mechanisms remain poorly understood, and current treatment options are limited. To address this gap, organoid cultures have emerged as powerful in vitro model systems for investigating disease mechanisms. At the Karolinska Institutet Stem Cell & Organoid Unit, we are developing advanced 3D brain organoid systems that better replicate the human brain microenvironment. Our platform combines hydrogel encapsulation with spinning bioreactors and microgravity-based rotary wall vessel bioreactors to support long-term maturation and functional modeling. The objective of this lecture is to present recent advances in brain organoid technologies and to highlight their application in modeling neurodegenerative diseases and mitochondrial disorders associated with genetic defects. These models provide innovative opportunities to study disease mechanisms and support translational research, including the development of novel therapeutic strategies, for example, in Alzheimer's disease and mitochondrial dysfunction, related pathologies.

**Autores:** Inzunza J.

**Afiliación:** Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** jose.inzunza@ki.se

**Agradecimientos:** Karolinska Institutet funds.

**Socio Patrocinante:** Prof. M. Herrera-Marschitz

**STUDYING THE EFFECT OF PERINATAL ASPHYXIA (PA) ON IMPAIRED MITOCHONDRIAL RESPIRATION MONITORED WITH REAL-TIME SEAHORSE: REVERSED BY THE NAD<sup>+</sup> DONOR NICOTINAMIDE RIBOSIDE.**

**Estudios sobre el efecto de asfisia perinatal en metabolismo mitocondrial monitoreado con seahorse: efecto de reemplazo de nad<sup>+</sup> con nicotinaamida riboside.**

**Resumen:**

Perinatal asphyxia (PA) is a leading cause of neonatal morbidity, linked to mitochondrial dysfunctions and long-term neurological impairments. Methodological limitations have made difficult to assess the bioenergetics alterations induced by PA, identifying regional vulnerability regarding brain tissue, targeting for novel therapeutic strategies. The present study describes a novel approach for monitoring and evaluating mitochondrial respiration in organotypic cultures from rat neonates exposed to global PA, using an integrated real-time platform (Seahorse XFe96/Cytation5 integration). Oxygen consumption rate (OCR) was monitored under oligomycin (as an inhibitor of ATP-synthase); carbonylcyanide-p-trifluoromethoxyphenylhydrazon (as a decoupler, FCCP), and rotenone/antimycin A (as inhibitors of complex I and III, Rot/AA) conditions, estimating: (i) basal mitochondrial respiration; (ii) ATP-linked respiration; (iii) maximal mitochondrial respiration; and (iv) spare respiratory capacity, finding a significant decrease in these parameters, in substantia nigra and neostriatum, but not in neocortex, although the regions were cultured together for each group, suggesting a regional dependent compromise of mitochondrial efficiency and adaptive capacity. The effect of PA on mitochondrial functioning was prevented by treating the neonates with the NAD<sup>+</sup> donor nicotinamide riboside (0.8 mmol/kg, i.p., 1h after delivery). The present findings highlight the heterogeneous impact of PA on mitochondrial respiration and support the idea of protection by NAD<sup>+</sup>-replacement.

**Autores:** Herrera-Marschitz M., Urrea F.A., Morales P., Ezquer F.A., Díaz-Urbina E., Almarza C., Davidson H., Lobos P.

**Afiliación:** Mol&Clin Pharmacology, Nucleo Inmunología & Farmacología, ICBM, Medical Faculty, University of Chile

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** mh\_marschitz@uchile.cl

**Agradecimientos:** This study was supported by FONDECYT Chile (No. 1231443, MHM; No. 1231443, FAU; FE; No. 1190562; No. 3240639, PL); FONDEQUIP EQM220164 (FAU, MHM); VID-UChile (No. UM-03/22, FAU); Puente-ICBM (No570419; Focco ICBM2025, PMR).

**NEURODEGENERATIVE DISORDERS: NOVEL  
PHARMACOLOGICAL OPPORTUNITIES**

**Desórdenes neurodegenerativos: Nuevas oportunidades farmacológicas.**

**Resumen:**

Alzheimer's disease (AD) is characterized by cognitive impairment and the presence of neurofibrillary tangles and senile plaques in the brain. Neurofibrillary tangles are composed of hyperphosphorylated tau, while senile plaques are formed by amyloid- $\beta$  ( $A\beta$ ) peptide. The amyloid hypothesis proposes that  $A\beta$  accumulation is primarily responsible for the neurotoxicity in AD. The other pathological features of AD comprise abnormal microvasculature, interneural dysfunction, increased inflammatory response, elevated production of reactive oxygen species, and impaired brain glucose metabolism. Among all these pathologies, mitochondrial dysfunction, regardless of it being an inciting insult or a consequence of the alterations, is related to all the associated AD pathologies. Observed altered mitochondrial morphology, distribution and movement, increased oxidative stress, dysregulation of enzymes involved in mitochondrial functioning, impaired brain metabolism, and impaired mitochondrial biogenesis in AD subjects suggest the involvement of mitochondrial malfunction in the progression of AD. We will focus on synaptic mitochondria as a primary target for  $A\beta$  toxicity and/or formation, generating toxicity at the synapse and contributing to synaptic and memory impairment in AD. We will also discuss that synaptic mitochondrial dysfunction occurs in aging and correlates with age-related memory loss. Therefore, synaptic mitochondrial dysfunction could be a predisposing factor for AD or an early marker of its onset.

**Autores:** Inestrosa-C N

**Afiliación:** Centro de Excelencia en Biomedicina de Magallanes (CEBIMA) Universidad de Magallanes, Punta Arenas

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** ninestrosa@bio.puc.cl

**Agradecimientos:** FONDECYT

**Socio Patrocinante:** Prof. M. Herrera-Marschitz

**Symposium Metabolic Pharmacology** «Obesity: Emerging Pathophysiological Mechanisms and Novel Therapeutic Opportunities».

Chair: **Dr. Ramón Sotomayor-Zarate**

**MOLECULAR EFFECTS OF OBESOGENIC DIETS IN POMC NEURONS: CAN WEIGHT LOSS REVERSE OBESITY-INDUCED EFFECTS?**

**Efectos moleculares de dietas obesogénicas en neuronas POMC: ¿La pérdida de peso puede revertir estos efectos?**

**Resumen:**

Obesity, driven by chronic energy imbalance, affects ~16% of adults worldwide. Calorie restriction (CR) is widely used for weight loss, yet nearly half of individuals regain weight. Proopiomelanocortin (POMC) neurons are key regulators of appetite and energy balance, but in obesity they become less responsive to metabolic cues. Here we asked whether obesity-induced molecular alterations in POMC neurons are sex-dependent and, in males, whether these alterations are reversible after CR-mediated weight loss. Obesity was induced in Tg(POMC:eGFP) mice with a 12-week high-fat diet (HFD), followed by 6 weeks of 60% CR. Fluorescence-activated cell sorting was used to isolate POMC neurons for RNA-seq and RRBS-seq, and transcriptomic deconvolution was applied to refine cell-type specific expression. HFD produced robust, sex-dependent transcriptional reprogramming in POMC neurons. In males, integrated methylome and transcriptome analyses indicated that obesity modulates pathways related to synaptic communication, sensory signal detection, and neuronal excitability. Following CR, most differentially expressed genes shifted toward baseline levels; however, a subset of biological processes remained dysregulated. Notably, CR also elicited condition-specific epigenetic and transcriptional signatures enriched for response to signaling, cell adhesion, and membrane transport, suggesting active remodeling rather than simple reversion. Collectively, our results show that although calorie restriction (CR) tends to normalize gene expression in POMC neurons, alterations at the level of biological processes persist after weight loss. These residual traces may act as a 'memory' of the obese or post-diet state, influencing feeding behavior and promoting weight regain.

**Autores:** Ríos J.1, Opazo V.1, Medina J.1, Manríquez I.1, González-Gómez G.1, Cooper A.1, Bruna C.2, García MA.3, Tarifeño-Saldivia E.1

**Afiliación:** 1 Gene Expression and Regulation laboratory (GEaRLab), Departamento de Bioquímica y Biología Molecular, Facultad de Ciencias Biológicas, Universidad de Concepción, Chile. 2 Departamento de Bioquímica y Biología Molecular, Facultad de Ciencias Biológicas, Universidad de Concepción, Chile. 3 Laboratorio de Biología Celular, Departamento de Biología Celular, Facultad de Ciencias Biológicas, Universi

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** etarisa@udec.cl

**Agradecimientos:** FONDECYT Iniciación N°11190401, FONDECYT Regular N°1241887

**Socio Patrocinante:** Ramón Sotomayor-Zarate

**MATERNAL HIGH-FAT DIET EXPOSURE IMPAIRS OFFSPRING HIPPOCAMPAL SYNAPTIC TRANSMISSION AND COGNITIVE FUNCTION.**

**La exposición materna a una dieta rica en grasas deteriora la transmisión sináptica hipocámpal y la función cognitiva de la descendencia.**

**Resumen:**

Introduction: Maternal exposure to high-fat diets (mHFD) has been associated with cognitive impairments in offspring, accompanied by molecular and structural changes in the hippocampus. However, the extent to which these behavioral deficits result from altered synaptic plasticity and transmission remains unclear. Methods: Female mice were fed a 60%-fat diet beginning one month prior to mating and continuing through gestation and lactation. The offspring were evaluated during the juvenile period (postnatal days 30–45) using the novel object recognition (NOR) and object location memory (OLM) tasks to assess cognitive performance. The efficacy of synapses was measured in CA1 pyramidal neurons of the hippocampus using whole-cell electrophysiological recordings, which allowed for the assessment of synaptic efficacy and long-term potentiation (LTP). Results: Offspring who were exposed to mHFD displayed impaired recognition and spatial memory, as indicated by reduced discrimination indices in the NOR and OLM tests. Electrophysiological analyses revealed increased inhibitory synaptic efficacy and decreased LTP magnitude in hippocampal slices, indicating disrupted excitatory/inhibitory balance and impaired synaptic plasticity. Discussion: These findings demonstrate that exposure to the mHFD during critical developmental periods compromises offspring cognition through alterations in hippocampal synaptic plasticity. The observed imbalance between excitatory and inhibitory signaling may underlie the cognitive deficits associated with maternal obesity, identifying potential targets for therapeutic intervention.

**Autores:** Fuenzalida M1,2,4, Cerna C1,2, Vidal N1,2, Ahumada J4, Rodríguez G1, Thomas S3.

**Afiliación:** Laboratorio de Plasticidad Neuronal, Instituto de Fisiología, Universidad de Valparaíso

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** marco.fuenzalida@uv.cl

**Agradecimientos:** This work was supported by FONDECYT grant N° 1241173, ANID-MILENIO NCN2023\_032, and CIDI grant N°1 CENFI-UV awarded to MF

**Socio Patrocinante:** Ramon Sotomayor-Zarate

## ROLE OF THE HIPPOCAMPUS–LATERAL SEPTUM–LATERAL HYPOTHALAMUS PATHWAY IN THE REGULATION OF FOOD INTAKE AND THE DEVELOPMENT OF OBESITY

### Papel de la Vía Hipocampo–Septum Lateral–Hipotálamo Lateral en la Regulación de la Ingesta de Alimentos y el Desarrollo de la Obesidad

#### Resumen:

Obesity, as a global pandemic, leads to critical health complications, including cardiovascular and metabolic diseases, neuropsychiatric disorders, cognitive deficits, and dementia. The hyperphagia seen in obese patients is linked to the dysfunction of brain circuits that regulate eating behaviors. Particularly, the Hippocampus (Hipp)–Lateral Septum (LS)–Lateral Hypothalamus (LH) pathway has not been thoroughly studied in this context. In our study, we utilized a high-fat diet (HFD)-induced obesity model over six weeks, observing increased neuroinflammatory markers within the Hipp-LS-LH pathway, specifically those related to the NLRP3 inflammasome and glial cells (GFAP, Iba1). Our findings revealed that HFD reduces the GLP-1R protein level in the LS, notably in male rats, with standard dietary restoration recovering normal GLP-1R levels. However, the combination of dietary change with the anorexigenic drug phentermine fails to reverse the initial GLP-1R reduction, suggesting a mechanism for weight regain. On a neurochemical level, continuous HFD exposure diminishes the activity of GABAergic neurons within the LS and their inhibitory control over the LH. This observation indicates that the Hipp-LS-LH pathway's dysregulation plays a role in the pathophysiology of obesity. Our research highlights that the dysfunction in the Hipp-LS-LH pathway involves various neuropeptides and neurotransmitters in obese conditions, thus offering potential pharmacological targets for obesity treatment. Through evaluating these targets, we aim to contribute to developing therapeutic strategies that address both the neurological and behavioral aspects of obesity, ultimately aiding in the management and reduction of obesity's global impact.

**Autores:** Covarrubias, M.J.; Olivares-Barraza, R.; Marcos, J.L.; Silva-Olivares, F.; Velásquez, V.B.; Sotomayor-Zárate, R.

**Afiliación:** Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso

**Area de la Farmacología:** Neuropharmacology

Dirección de Correo: ramon.sotomayor@uv.cl

**Agradecimientos:** FONDECYT Grant 124-0141 and CIDI-UV 01/2024 to R.S.-Z.

**Socio Patrocinante:** Ramón Eduardo Sotomayor Zárate

## TIME-RESTRICTED FEEDING AS A POTENTIAL TREATMENT FOR SARCOPENIC OBESITY

### Alimentación Restringida en el tiempo como tratamiento potencial de la Obesidad sarcopénica

#### Resumen:

Sarcopenic obesity, characterized by low muscle mass and strength alongside obesity, increases the risk of poor health outcomes. Time-Restricted Feeding (TRF) is a dietary intervention that has shown promise in improving muscle function and mitochondrial health. To study the impact of TRF in obesity we used two murine models of obesity (genetically obese ob/ob mice and diet-induced obesity mice) and submitted them to 12/12 TRF protocol. Our results show that TRF improved glucose homeostasis, muscle function, and mitochondrial function. The intervention also attenuated the negative effects of obesity on physical performance and muscle mass obesity altered macrophage phenotype and skeletal muscle bioenergetics, while TRF modulated these effects. In diet-induced obesity mice, TRF reduced the M1 macrophage phenotype and increased markers of M2 macrophages. Additionally, TRF reversed the elevated expression of complex I and improved autophagy in skeletal muscle. The findings suggest that TRF may be a promising non-pharmacological intervention to mitigate the adverse effects of obesity on muscle function and mitochondrial health. Further studies are needed to characterize the specific role of macrophages in regulating the skeletal muscle microenvironment during aging and to explore the therapeutic potential of TRF in humans.

**Autores:** Briones-Manríquez Fernanda, Ibarra-Barahona Iván, Almarza Gonzalo, Araya María Jesus, Luz-Crawford Patricia, Pérez-Leighton Claudio, del Campo Andrea.

**Afiliación:** 1Laboratorio de Fisiología y Bioenergética Celular, Escuela de Química y Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Santiago,

**Area de la Farmacología:** Molecular pharmacology

Dirección de Correo: andrea.delcampo@uc.cl

**Agradecimientos:** ANID FONDECYT 1230428

**Socio Patrocinante:** Andrea del Campo

## SIMPOSIO / SYMPOSIUM

**Symposium Drug Delivery** «Bridging the Gap: Advanced In Vitro, Ex Vivo, and In Vivo Models for Characterizing and Predicting the Performance of Drug Delivery Systems».

Chair: **Dr. Javier Morales**

### DEVELOPMENT AND CHARACTERIZATION OF DRY POWDER FORMULATIONS FOR NOSE-TO-BRAIN DELIVERY. USE OF IN VITRO SETUPS MODIFIED USP CASCADE IMPACTORS, AND 3D-PRINTED NASAL REPLICA CASTS FOR DEPOSITION AND PERMEATION STUDIES

Desarrollo y caracterización de formulaciones en polvo seco para administración nariz-cerebro. Uso de sistemas in vitro basados en impactadores en cascada USP modificados y réplicas nasales impresas en 3D para estudios de deposición y permeación.

#### Resumen:

This work explores the nasal cavity as a promising route for both local and systemic drug delivery, providing rapid access to the central nervous system (CNS). In addition to well-established local applications such as corticosteroids and antihistamines, the presentation highlights recent therapeutic developments, including intranasal formulations as antineuroinflammatory options. The study emphasizes the critical role of device design and aerodynamic behavior in the efficiency of nose-to-brain delivery systems. We present the development and characterization of dry powder formulations tested through in vitro setups based on modified USP cascade impactors and 3D-printed nasal replica casts. These models enable the simulation of airflow patterns, inhalation maneuvers, and deposition profiles in different nasal regions. Furthermore, the integration of permeation studies allows the assessment of drug transport across nasal mucosa, supporting the rational design of micro- and nanoparticulate carriers for CNS targeting. Overall, this work aims to deepen our understanding of nasal delivery as a non-invasive alternative to traditional routes, bridging formulation design, device performance, and biological response through advanced modeling tools

**Autores:** Moraga-Espinoza D.F.

**Afiliación:** Laboratorio de tecnología farmacéutica, Facultad de farmacia, Universidad de Valparaíso

**Area de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** daniel.moraga@uv.cl

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### INTEGRATING IN VITRO, EX VIVO, AND DISEASE-SPECIFIC IN VIVO MODELS FOR THE DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEMS

Integración de modelos in vitro, ex vivo e in vivo-específicos de enfermedad para el desarrollo de nuevos sistemas de liberación de fármacos

#### Resumen:

This presentation will cover a range of models: In vitro buccal mucosa models, ex vivo buccal tissue models (e.g., porcine buccal mucosa) and critical bone defect models to study bone regeneration with 3D printed implants. Advancing barrier-permeating drug delivery systems demands model systems that are mechanistically informative yet translatable. This talk presents an integrated framework spanning in vitro, ex vivo, and disease-specific in vivo models used for formulation design. First, we outline a buccal delivery platform to enhance buccal epithelium residence and drive intact nanocarrier permeation. Standardized permeation workflows (Franz/ Ussing) quantify steady-state flux and  $P_{app}$  while monitoring tissue integrity, enabling structure–permeation relationships for small molecules and biologics and clarifying when hydrodynamics and/or ionization govern performance. Second, we pivot to regenerative delivery in bone: a rat calvarial critical-size defect model used to evaluate 3D-printed polycaprolactone implants functionalized with the pro-regenerative peptide Histatin-1. Micro-CT and histology demonstrate significant gains in neo-bone formation with organized lamellar deposition, with hematology and CRP indicating no adverse systemic inflammation. Together, these case studies illustrate how convergent, tiered models expose formulation to tissue interactions that simpler tests miss, and how “device-plus-delivery system” strategies can be rationally tuned for non-invasive mucosal delivery and localized regenerative therapy. We will complement with practical guidelines for model selection, assay standardization, and go/no-go criteria that shorten the path from formulation hypothesis to clinically meaningful effect.

**Autores:** Morales J. O.

**Afiliación:** Universidad de Chile

**Area de la Farmacología:** Pharmacokinetics / drug metabolism

**Dirección de Correo:** jomoraes@ciq.uchile.cl

**Agradecimientos:** FONDECYT Project 1231154, PIA/ANID ACT240058, PIA/ANID ACT250073, FONDAP Project 15130011  
Socio Patrocinante: NA

## MICROPHYSIOLOGICAL SYSTEMS ON A CHIP: NOVEL PLATFORMS FOR EVALUATING NANOMEDICINE EFFICACY AND TOXICITY IN DRUG DELIVERY

### Sistemas Microfisiológicos en Chip: Nuevas Plataformas para Evaluar la Eficacia y Toxicidad de Nanomedicinas en Liberación de Fármacos

#### Resumen:

Microphysiological systems (MPS), including organ-on-a-chip technologies, have emerged as powerful tools that replicate the structural and functional complexity of human tissues, offering physiologically relevant environments for drug testing. These systems enable the controlled study of nanoparticle transport, efficacy, and toxicity under dynamic conditions, providing an ethical and predictive alternative to animal models. In this work, particular emphasis is placed on the use of blood–brain barrier (BBB)-on-a-chip models for assessing the performance of nanomedicines in the context of neurodegenerative diseases. As a case study, we present recent findings on the design and evaluation of D3-peptide functionalized gold nanoprisms (GNPr-PEG-D3), which demonstrated the ability to cross the BBB, attenuate amyloid- $\beta$ -induced cytotoxicity, and preserve endothelial tight junction integrity in an Alzheimer's disease-on-a-chip model. These results highlight how nanoparticle geometry and surface chemistry modulate biological responses and emphasize the relevance of chip-based disease modeling for preclinical nanomedicine evaluation. Overall, this research underscores the potential of MPS platforms for advancing nanotherapeutic development by providing quantitative insights into nanoparticle–cell interactions, biodistribution, and off-target effects within human-relevant microenvironments.

**Autores:** N. Hassan

**Afiliación:** Universidad Tecnológica Metropolitana

**Area de la Farmacología:** Pharmacokinetics / drug metabolism

**Dirección de Correo:** nhassan@utem.cl

**Agradecimientos:** Fondecyt Regular 1230830

**Socio Patrocinante:** Javier Morales Montecinos, Universidad de Chile

## SIMPOSIO / SYMPOSIUM

**Symposium Immunopharmacology** «Immunometabolic Modulation: Emerging Pathways for Therapeutic Development».

Chair: **Dr. Rafael Burgos**

### COMPOUNDS OF NATURAL ORIGIN THAT PLAY A THERAPEUTIC ROLE IN DOGS (CANIS LUPUS FAMILIARIS)

**Compuestos de origen natural que desempeñan un papel terapéutico en perros (Canis lupus familiaris)**

#### Resumen:

Animal welfare and health are driving increasing research into the development of naturally derived compounds that have a therapeutic effect on companion animals, specifically dogs, while minimizing adverse effects. Naturally derived compounds that exhibit therapeutic effects in dogs must have scientific evidence supporting their effectiveness. Currently, there is scientific evidence supporting the use of phytotherapy in skin diseases, including those of immune, parasitic, and traumatic origin; diseases of the digestive system of infectious origin; and metabolic diseases, such as diabetes and obesity-related conditions, among others. However, there is limited evidence regarding their effect on the immune system, as most studies have focused on clinical trials to evaluate the antioxidant effect of diets containing naturally derived compounds. In our laboratory, we are evaluating the effect of delphinidin on the function of polymorphonuclear and mononuclear immune cells. To date, results have shown that delphinidin does not affect cell viability and significantly reduces the production of reactive oxygen species, metalloproteinase 9 activity, and neutrophil extracellular trap production. Furthermore, delphinidin has been shown to significantly reduce the production of key cytokines involved in the immune response. Its effects on chemotaxis, phagocytosis, myeloperoxidase production, and inflammatory pathways involved in the observed responses have also been studied. Our study continues to understand the effect of delphinidin in dogs and to explore its use as a nutritional supplement for the prevention or treatment of inflammatory conditions in dogs.

**Autores:** Hidalgo A. I; Vega M. C; Maldonado D. V; Hidalgo M. A; Burgos R. A

**Afiliación:** Laboratory of immunometabolism, Institute of Pharmacology and Morphophysiology, Faculty of Veterinary Sciences, Austral University of Chile

**Area de la Farmacología:** Immunopharmacology

**Dirección de Correo:** aihgvvet@gmail.com

**Agradecimientos:** Fondecyt Initiation project No. 11230785

### OBESITY-ASSOCIATED METABOLOMIC AND FUNCTIONAL REPROGRAMMING IN NEUTROPHILS FROM HORSES WITH ASTHMA

**Reprogramación metabólica y funcional asociada a la obesidad en neutrófilos de caballos con asma.**

#### Resumen:

Equine asthma is a chronic respiratory disorder characterised by neutrophilic airway inflammation, bronchial hyperresponsiveness, and reduced lung function. Obesity, increasingly common in domestic horses, has been proposed as a risk factor that may exacerbate inflammation. This study examined whether obesity alters neutrophil metabolism and inflammatory responses in asthmatic horses. Six horses in clinical remission were classified as obese or non-obese based on body condition score. Obese horses showed higher serum interleukin-1 $\beta$  (IL-1 $\beta$ ) levels and neutrophil counts, suggesting systemic inflammation. Neutrophils from obese horses exhibited stronger oxidative responses to zymosan and higher IL-1 $\beta$  gene expression after lipopolysaccharide stimulation, indicating a hyperinflammatory phenotype. Metabolomic analysis identified 139 metabolites, with significant differences in fatty acids, branched-chain amino acids, and tricarboxylic acid (TCA) cycle intermediates. Pathway analysis revealed alterations in fatty acid synthesis, amino acid metabolism, and glutathione pathways. Increased levels of itaconate, citraconic acid, and citrate in obese horses indicate profound metabolic reprogramming of neutrophils. These findings suggest that obesity promotes a metabolically active, pro-inflammatory neutrophil profile that may worsen airway inflammation. Addressing obesity may therefore be essential in the management of equine asthma and could inform future metabolic-targeted therapies in veterinary medicine.

**Autores:** Moran G.

**Afiliación:** Instituto de Farmacología y Morfofisiología, Facultad de Ciencias Veterinarias, Universidad Austral de Chile

**Area de la Farmacología:** Veterinary pharmacology

**Dirección de Correo:** gmoran@uach.cl

**Agradecimientos:** FONDECYT 1230101

## KETOSIS & IMMUNITY: INSIGHTS FROM DAIRY COWS

### Cetosis e Inmunidad: Perspectivas desde las Vacas Lecheras

#### Resumen:

Ketogenic diets have gained attention in recent years due to their potential benefits in managing metabolic diseases such as obesity and type II diabetes, as well as in cancer treatment. However, the impact of elevated ketone bodies, particularly beta-hydroxybutyrate (B-OHB), on immunity is still debated. While B-OHB may act as an anti-inflammatory metabolite, it could also hinder the immune response. Examining what occurs in dairy cows with ketosis could provide valuable insights. During the postpartum period, dairy cows experience a negative energy balance, leading them to mobilize body fat reserves. This process saturates the liver with fatty acids, which are partially oxidized to ketone bodies. High blood levels of B-OHB (ketosis) have been linked to inflammatory diseases, such as retained placenta, mastitis, and metritis. This link is primarily due to the impairment of neutrophil functions, such as migration, phagocytosis, and NETosis. One mechanism behind these effects is the restriction of glycolysis and ATP production in activated neutrophils. Likewise, other B-OHB targets have been also proposed to explain its effects, including its interaction with the hydroxycarboxylic acid receptor 2 (HCAR2) and the free fatty acid receptor 3 (FFAR3), as well as its ability to inhibit the NLRP3 inflammasome. Furthermore, B-OHB has been recognized as an epigenetic modifier that can influence histones and DNA through histone deacetylase (HDAC) inhibition or by beta-hydroxybutyrylation. Ultimately, the impact of B-OHB on neutrophil function and the occurrence of infectious diseases is strongly influenced by the overall metabolic state and productive context of the dairy cows through their production cycle.

**Autores:** Quiroga J.

**Afiliación:** Laboratorio de Inmunometabolismo, Instituto de Farmacología y Morfofisiología, Facultad de Ciencias Veterinarias, Universidad Austral de Chile

**Area de la Farmacología:** Veterinary pharmacology

**Dirección de Correo:** john.quiroga@uach.cl

**Agradecimientos:** FONDECYT Postdoctoral 3230482

## MITOCHONDRIAL DYSFUNCTION IN NEUTROPHILS UNDER INFLAMMATORY CONDITIONS INDUCED BY D-LACTATE: IMMUNOMETABOLIC CONSEQUENCES AND THERAPEUTIC PERSPECTIVES

### Disfunción mitocondrial en neutrófilos bajo condiciones inflamatorias inducidas por d-lactato: consecuencias inmunometabólicas y perspectivas terapéuticas.

#### Resumen:

Mitochondrial bioenergetics plays a crucial role in neutrophil functions, particularly in the generation of reactive oxygen species (ROS) and the formation of neutrophil extracellular traps (NETosis). These processes are essential for host defense but can become pathogenic when dysregulated. In ruminants, acute ruminal acidosis results from bacterial overgrowth and the excessive production of D-lactate, an isomer generated during microbial fermentation of carbohydrates. Unlike L-lactate, D-lactate is slowly metabolized in mitochondria by D-lactate dehydrogenase (D-LDH), yet it profoundly affects neutrophil metabolism. We have demonstrated that D-lactate stimulates mitochondrial ROS (mtROS) release and HIF-1 $\alpha$  stabilization, activating the PI3K/Akt/HIF-1 and GSK-3 $\beta$  pathways that coordinate glycolysis, gluconeogenesis, and glycogenolysis to sustain ETosis. These alterations contribute to an increased mitochondrial electron flux and enhanced production of mtROS, which act as signaling molecules that trigger inflammatory and metabolic responses in neutrophils. Recent evidence also highlights the involvement of mitochondrial complexes I and III as major sites of ROS generation under these conditions. This coupling between mitochondrial metabolism and inflammatory signaling defines a novel immunometabolic axis in neutrophils, wherein mitochondrial dysfunction amplifies tissue injury during metabolic acidosis. Understanding these mechanisms provides new therapeutic perspectives to modulate mitochondrial function, electron transport activity, and lactate metabolism, with implications for inflammatory diseases in ruminants and comparative immunometabolism.

**Autores:** Burgos R.A.1; Quiroga J.1; Manosalva C.2; Alarcón P.1; Bahamonde J. 1; Teuber S.1; Hidalgo M.A.1

**Afiliación:** 1 Laboratory of Inflammation Pharmacology and Immunometabolism, Institute of Pharmacology and Morphophysiology, Faculty of Veterinary Sciences, Universidad Austral de Chile, Valdivia, Chile. 2 Institute of Pharmacy, Faculty of Sciences, Universidad Austral de Chile, Valdivia, Chile.

**Area de la Farmacología:** Immunopharmacology

**Dirección de Correo:** rburgos1@uach.cl

**Agradecimientos:** FONDECYT Regular Project No. 1250695

**Socio Patrocinante:** Rafael A Burgos

## SIMPOSIO / SYMPOSIUM

**Symposium Drug Delivery** «Innovative Drug Discovery Strategies for Neurodegenerative Diseases».

Chair: **Dr. David Ramírez**

### A MIXED LIGAND AND TARGET VIRTUAL SCREENING FOR THE DISCOVERY OF BRAIN PERMEABLES SGK1 INHIBITORS AS PROTECTIVE AGENTS FOR NEURODEGENERATIVE DISEASES

**Descubrimiento de inhibidores de SGK1 con permeabilidad cerebral mediante un cribado virtual mixto entre ligando y estructura, como agentes protectores de enfermedades neurodegenerativas**

#### Resumen:

A major challenge in modern medicine is developing new therapies for aging-related diseases such as neurodegenerative disorders, whose prevalence increases with longer life expectancy. Although kinase inhibitors have achieved clinical success, their development for central nervous system (CNS) disorders remains limited due to the complexity of kinase networks and poor blood–brain barrier (BBB) permeability. Serum/glucocorticoid-regulated kinase 1 (SGK1) participates in multiple signaling pathways but remains an underexplored target in neurodegeneration. Following a mixed ligand- and structure-based virtual screening, we have identified a brain penetrant SGK1 inhibitor. A medicinal chemistry program based on hit expansion and optimization for BBB permeability, has generated a new family of SGK1 inhibitors as chemical probes that enable investigation of SGK1 role in neurological disorders and serve as promising starting points for drug development. These findings highlight SGK1 as a potential therapeutic target for neurodegenerative diseases, as Alzheimer's disease.

**Autores:** Madruga E. 1,2; Garcia-Rubia A. 1; Gil C. 1,2; Martinez A. 1,2\*

**Afiliación:** 1 Centro de Investigaciones Biológicas-CSIC, Madrid, Spain; 2 CIBERNED, ISCIII, Spain

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** ana.martinez@csic.es

**Agradecimientos:** MCIN/Agencia Estatal de Investigación (grant no. PID219-105600RB-I00), MCIN/AIE/10.13039/50110001033 and European Union NextGenerationEU/PRTR (grant no. PDC2022-133774-I00) Instituto de Salud Carlos III – Spain (grant no. CB18/05/00040, CIBERNED), Ministerio de Educación, Cultura y Deporte (grant no. FPU20/03743 to E.M.)

**Socio Patrocinante:** David Ramirez

### CONSTRUCTING NEUROPROTECTIVE AGENTS: SYNTHETIC STRATEGIES FOR HETEROCYCLIC CHALCONES Y SUS DERIVADOS

**Diseño y síntesis de agentes neuroprotectores: estrategias para la obtención de chalconas heterocíclicas y sus derivados**

#### Resumen:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid beta (A-beta) peptides, which exert neurotoxic effects by disrupting neuronal homeostasis and synaptic signaling. A-beta aggregates interact with nicotinic acetylcholine receptors (nAChRs), particularly the alpha7 subtype, impairing cholinergic transmission essential for cognition and memory. Positive allosteric modulators (PAMs) of alpha7 nAChRs have emerged as promising agents to counteract A-beta-induced neurotoxicity by enhancing receptor activity without competing with acetylcholine. In this context, novel heterocyclic chalcones were synthesized via Claisen–Schmidt condensation from a fomanoxine-derived benzodihydrofuran precursor and methyl aromatic ketones bearing diverse halogen substitution patterns. The compounds were obtained in good to excellent yields (50–98%) and evaluated for cytotoxicity and neuroprotective effects against A-beta(1–42) oligomers using PC-12 neuronal cells. Most derivatives were non-cytotoxic; notably, fluorinated chalcones exhibited significant neuroprotective activity, with the 2,4,5-trifluoro and 3-fluoro analogues restoring cell viability by over  $60 \pm 5\%$  and  $50 \pm 6\%$ , respectively. Furthermore, fluorine substitution at the 3,5-positions enhanced cytoprotection and inhibited A-beta aggregation, suggesting a dual mechanism of action. Complementary evaluation of 3-((6-(phenylethynyl)pyridine-3-yl)oxy)quinuclidine (EQ-04), a selective alpha7 nAChR PAM, revealed a 37% increase in cell viability at 1 nM and inhibition of A-beta aggregation. Together, these findings highlight the potential of both alpha7 nAChR modulators and heterocyclic chalcones as neuroprotective scaffolds for AD therapy, providing a foundation for future structure–activity optimization and in vivo studies.

**Autores:** Jiménez, C.1; López, J.2; Polo-Cuadrado, E.1; Fuentealba, J.3;

**Afiliación:** 1. Universidad de Concepción, Fac.Cs. Químicas, Depto. Química Orgánica; 2. Pontificia Universidad Católica de Chile, Depto Química Orgánica, Escuela de Química, Fac. Química y de Farmacia; 3. Universidad de Concepción, Fac. Cs. Biológicas, Depto Fisiología

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** cjimenez@udec.cl

**Agradecimientos:** Proyecto VRID- Multidisciplinario 220.023.056-M., FONDECYT (ANID) 1190652 and 1200908, ANID National Ph.D. Fellowship 21200635, ANID Operational Funding 242210098

## IDENTIFICATION OF MULTI-TARGET DIRECTED LIGANDS FOR ALZHEIMER'S DISEASE BY COUPLING VIRTUAL SCREENING AND EXPERIMENTAL VALIDATION

**Identificación de ligandos dirigidos a múltiples targets para la enfermedad de Alzheimer mediante la combinación de cribado virtual y validación experimental**

### Resumen:

Alzheimer's disease (AD) is a neurodegenerative disorder associated with the accumulation of beta-amyloid plaques, oxidative stress, and a decrease in cholinergic activity among other pathologies. Given the limitations of current treatments, multitarget strategies present a promising alternative. This study prioritized six key therapeutic targets associated with AD: acetylcholinesterase (AChE), beta-secretase 1 (BACE-1), cannabinoid receptor type 2 (CB2), glycogen synthase kinase 3 beta (GSK-3 $\beta$ ), monoamine oxidase A (MAO-A), and the neuronal acetylcholine receptor subunit alpha-7 (nAChR7). Ligand- and structure-based virtual screening methods were applied to identify potential multitarget directed ligands (MTDLs), reducing an initial database of 14 million compounds to 21 candidates that were tested experimentally. From this screening, the compound PJ17 exhibited a multitarget profile with sub-micromolar activity against AChE and GSK-3 $\beta$ . Unbiased molecular dynamics simulations revealed key common interactions between PJ17 and those targets. This offered valuable insights for the further hit-to-lead optimization of this promising MTDL. In addition, PJ17 showed a safe profile in cellular primary culture suggesting its use as a template to design multitarget drugs against AD.

**Autores:** Valenzuela-Hormazábal, P. 1; Valero-Rojas, J. 1,2; Martínez González, L. 3,4; Ramos-Inza, S. 3; Oviedo-Pino, V. 1; González-Ortega, C. 5; Hernando, G. 6; López, J. 7; Scorza, C. 8; Echeverry, C. 8; Gutierrez, M. 9; Reyes-Parada, M. 5,10; Martínez, A. 3,4; Ramírez, D. 1

**Afiliación:** 1 Departamento de Farmacología, Facultad de Ciencias Biológicas, Universidad de Concepción

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** dramirezs@udec.cl

**Agradecimientos:** Fondecyt Regular 1220656

**Socio Patrocinante:** David Ramirez

## PANEL COMMUNICATIONS

Day 2, 14.30°-16.00°, December 3rd, 2025 (wednesday)

### 1. INHALABLE POROUS GELATIN MICROCAPSULES AS AN ADVANCED DELIVERY PLATFORM FOR CIPROFLOXACIN AGAINST PSEUDOMONAS AERUGINOSA Biofilms

Microcápsulas porosas inhalables de gelatina como plataforma avanzada de administración de ciprofloxacino contra biopelículas de *Pseudomonas aeruginosa*

**Resumen:** Chronic lung infections represent a major public health challenge, particularly in patients with cystic fibrosis. Among these, *Pseudomonas aeruginosa* infections remain one of the most critical clinical concerns. Previously, we developed ciprofloxacin (CIP)-loaded gelatin microspheres forming amorphous solid dispersions (ASD) to enhance the drug's solubility and antibacterial efficacy against *P. aeruginosa*, achieving significant improvements. In the present study, we explored the coating of these microspheres to obtain ciprofloxacin microcapsules. Inhalable gelatin-based microcapsules containing CIP were prepared by spray drying, using palmitic acid as a coating material and D-mannose or NaCl as porogens. Their in vitro dissolution properties, aerodynamic performance, and antimicrobial activity against *P. aeruginosa* biofilms were evaluated. The porogen-containing microcapsules exhibited the highest CIP dissolution, reaching 40% of the dose within 6 h, compared to 30% for uncoated microspheres and only 3% for unprocessed CIP. The fine particle fraction of the microcapsules exceeded 60%. Moreover, porogen-containing microcapsules achieved the strongest inhibitory effects, reducing surviving biofilm colonies by  $-6.8$  log (D-mannose) and  $-6.1$  log (NaCl) after 6 h and completely eradicating biofilms after 24 h. In contrast, the coated formulation without porogen and unprocessed CIP showed surviving colonies at 24 h, with reductions of only  $-4.0$  log and  $-2.8$  log at 6 h, respectively. In conclusion, lipid-coated microencapsulation with porogens further improved CIP solubility and efficacy against *P. aeruginosa* biofilms. The combination of coating and porogen created an osmotic micro-pump effect that enhanced drug dissolution, while the microcapsules displayed excellent aerodynamic properties for inhalable dry powder delivery, with a fine particle fraction exceeding that of current commercial inhalation products (20–40%).

**Autores:** Pérez-Basáez P. 1; Moreno M. P. 1; Villicic A. 1; Monreal-Ortega L. 1; Moraga-Espinoza D. 1,2; Bahamondez-Canas T. F. 1,2

**Afiliación:** 1. Escuela de Química y Farmacia, Facultad de Farmacia, Universidad de Valparaíso, Valparaíso, Chile; 2. Centro de Investigación, Desarrollo en Innovación en Productos Bioactivos, Universidad de Valparaíso, Valparaíso, Chile

**Área de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** [tania.bahamondez@uv.cl](mailto:tania.bahamondez@uv.cl)

**Agradecimientos:** FONDECYT Regular 1251689 (2025)

**Socio Patrocinante:** Tania Bahamondez

### 2. INHALABLE POROUS GELATIN MICROCAPSULES AS AN ADVANCED DELIVERY PLATFORM FOR CIPROFLOXACIN AGAINST PSEUDOMONAS AERUGINOSA BIOFILMS

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dose within 6 h, compared to 30% for uncoated microspheres and only 3% for unprocessed CIP. The fine particle fraction of the microcapsules exceeded 60%. Moreover, porogen-containing microcapsules achieved the strongest inhibitory effects, reducing surviving biofilm colonies by  $-6.8$  log (D-mannose) and  $-6.1$  log (NaCl) after 6 h and completely eradicating biofilms after 24 h. In contrast, the coated formulation without porogen and unprocessed CIP showed surviving colonies at 24 h, with reductions of only  $-4.0$  log and  $-2.8$  log at 6 h, respectively. In conclusion, lipid-coated microencapsulation with porogens further improved CIP solubility and efficacy against *P. aeruginosa* biofilms. The combination of coating and porogen created an osmotic micro-pump effect that enhanced drug dissolution, while the microcapsules displayed excellent aerodynamic properties for inhalable dry powder delivery, with a fine particle fraction exceeding that of current commercial inhalation products (20–40%).

**Autores:** Tosta M.M. 1\*; Belén L.H. 2; Zamorano M. 1; Pessoa A. 3; Fariás J. 1\*

**Afiliación:** Engineering, Biotechnology and Applied Biochemistry Laboratory, Department of Chemical Engineering, Faculty of Engineering and Science, Universidad de La Frontera

**Área de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** [m.tosta01@ufromail.cl](mailto:m.tosta01@ufromail.cl)

**Agradecimientos:** -Engineering, Biotechnology, and Applied Biochemistry Laboratory (LIBBA).

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**Socio Patrocinante:** Jorge Fariás Avendaño

### 3. EFFECT OF A POLYPHENOL-RICH MURTILLA EXTRACT ON AN IN VIVO MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

Efecto de un extracto de murtila rico en polifenoles en un modelo de hígado graso no alcohólico in vivo

**Resumen:** Non-alcoholic fatty liver disease (MASLD) is an excessive accumulation of hepatic fat, with an increasing global prevalence and healthcare costs. There are very few pharmacological treatments for MASLD, with lifestyle modifications being the only therapeutic approach. Its pathophysiology is complex, involving mechanisms of de novo lipogenesis, inflammation, and oxidative stress. In this context, we have found murtila (*Ugni molinae*), a Chilean endemic berry with potent antioxidant capacity. We are currently investigating a standardized murtila extract to evaluate its antilipogenic and antioxidant properties in high-fat diet murine models, through the administration of a high-polyphenol murtila extract (M) in a murine model. 26 C57BL/6 strain mice were used for 4 experimental groups: two treated with a high-fat diet (HFD) and two with a control diet (CD) for 12 weeks. One group from each diet was given 200 mg/kg of a lyophilized murtila fruit extract. Histological liver sections were performed and gene expression was evaluated by RT-qPCR. The results showed that histological sections from the HFD+M group had less adipose infiltration compared to the HFD group. A significant increase in GPx was also observed in the HFD+M group compared to the HFD group. In conclusion, the results show that murtila extract has an impact on an MASLD model, providing a natural alternative to handle this condition.

**Autores:** Uribe-Rubilar D.1,2; Orellana J.F. 1; Norambuena U. 1,4; Díaz C. 1; Aravena V.1; Fonfach C.1; Cáceres G. 5; Castillo C.5; Valenzuela-Barra G. 4; García-Díaz D. 2,4; Catalán M. 1

**Afiliación:** 1. Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Independencia 1027, Santiago, Chile 2. Departamento de Nutrición, Facultad de Medicina, Universidad de Chile 3. Instituto de Nutrición y Tecnología de los Alimentos (INTA) Universidad de Chile 4. Facultad de Ciencias Químicas y Farmacéuticas (Faciqyf) Uni

**Área de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** [denisse.uribe@inta.uchile.cl](mailto:denisse.uribe@inta.uchile.cl)

**Agradecimientos:** Proyecto Puente 2023 Mabel Catalán

**Socio Patrocinante:** Dra. Mabel Catalán

**4. SYMBIOTIC FORMULATION CONTAINING MAQUI BERRY, CHEMICAL, ANTIOXIDANT, AND CARDIOPROTECTIVE EVALUATION OF A GLOBAL ETHANOLIC EXTRACT OF PROPOLIS FROM THE CENTRAL ZONE OF CHILE**  
 Fórmula simbiótica con maqui, inulina y probióticos reduce los problemas cognitivos y sinápticos causados por la ketamina en ratones adolescentes.

**Resumen:** Dietary interventions have emerged as promising neuroprotective strategies against drug-induced neurotoxicity in preclinical models. We investigated whether a symbiotic formulation containing maqui berry (*Aristotelia chilensis*) polyphenols, inulin, and probiotics could mitigate ketamine-induced cognitive and synaptic deficits in adolescent mice. Cognitive function was assessed via novel object recognition (NOR) testing, while synaptic plasticity was evaluated through field excitatory postsynaptic potential (fEPSP) recordings in the hippocampal dentate gyrus. Ketamine administration induced significant recognition memory impairments. Notably, symbiotic supplementation partially restored cognitive performance and normalized synaptic responses following high-frequency stimulation, whereas ketamine-only animals exhibited persistent electrophysiological abnormalities. These findings suggest that the maqui-based symbiotic formulation exerts neuroprotective effects by preserving both cognitive function and synaptic plasticity mechanisms. This study provides preliminary evidence supporting the potential of targeted dietary bioactive compounds as therapeutic agents to counteract ketamine-induced neurodevelopmental impairments. Further studies are warranted to elucidate the molecular mechanisms and translational relevance of this intervention.

**Autores:** Vidal-Herrera N1,2,3,4,5,6,7; Álvarez-Villablanca D 2,4,6,7; Ahumada J1,3,5,7; Cerna C 1,3,5,7; Gereduz-Agapito L 1,2,3,5,6,7; Jopia G; Rodríguez G 1,3,5,7; Fuenzalida M 1,3,5,7; Thomas-Valdés S 2, 4, 5, 6, 7

**Afiliación:** 1 Laboratorio Plasticidad Neuronal; 2 Centro de Micro-Bioinnovación; 3 Instituto de Fisiología; 4 Escuela de Nutrición y Dietética; 5 Facultad de Ciencias; 6 Facultad de Farmacia; 7 Universidad de Valparaíso

**Area de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** [nicole.vidal@postgrado.uv.cl](mailto:nicole.vidal@postgrado.uv.cl)

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**Socio Patrocinante:** —

**5. CHEMICAL, ANTIOXIDANT, AND CARDIOPROTECTIVE EVALUATION OF A GLOBAL ETHANOLIC EXTRACT OF PROPOLIS FROM THE CENTRAL ZONE OF CHILE**  
 Evaluación química, antioxidante y cardioprotectora de un extracto etanólico global de propóleo proveniente de la zona central de Chile

**Resumen:** El daño por isquemia y reperfusión (I/R) genera un aumento del estrés oxidativo que agrava la lesión miocárdica, siendo una de las principales causas de disfunción cardíaca (Yellon & Hausenloy, 2007). En la búsqueda de estrategias terapéuticas, los compuestos naturales con actividad antioxidante, como los presentes en el propóleo, han demostrado potencial para mitigar este daño. Se obtuvo un extracto etanólico global (EEG) de propóleo proveniente de Palmilla (Región de O'Higgins, Chile) mediante un proceso de descerado y extracción con etanol (Kalogeropoulos et al., 2009). Se caracterizó su composición química y se evaluó su capacidad antioxidante y efecto cardioprotector. El contenido total de compuestos fenólicos fue de  $22,1 \pm 1,7$  mg/m (equivalentes de ácido gálico), el de flavonoides de  $0,88 \pm 0,8$  mg/m (equivalentes de quercetina) y el de flavanonas y dihidroflavonoles de  $40,7 \pm 4,1$  mg/m (equivalentes de naringenina) (Valenzuela-Barra et al., 2015). Mediante HPLC-DAD y HPLC-MS/MS se identificaron compuestos mayoritarios como pinocebrina, crisina, apigenina, galangina y kaempferol, todos con reconocida actividad antioxidante (Zúñiga-López et al., 2021). Los ensayos FRAP, ORAC-FL y DPPH (Castro et al., 2014) evidenciaron una alta capacidad antioxidante, comparable o superior a la reportada en propóleos de otras regiones del país. En un modelo ex vivo de isquemia/reperfusión en corazones aislados de ratón (sistema de Langendorff) (Zhang et al., 2016), la

perfusión con el EEG (8,9 mg/L) redujo significativamente el tamaño del infarto de  $51,8 \pm 10,4$  % a  $23,3 \pm 5,1$  % respecto al control, confirmando su efecto protector frente al daño oxidativo y tisular. En conclusión, el propóleo de Palmilla presenta un perfil fenólico diverso, alta actividad antioxidante y un efecto cardioprotector significativo, respaldando su potencial como fuente natural de compuestos bioactivos de interés farmacológico.

**Autores:** Felipe Navarrete\* (1, 2, 3, 4), Gabriel Fuentes (5), María Carolina Zúñiga (5), Jaime Riquelme (6), Javier Morales Montecinos (2, 3, 4), Gabriela Valenzuela-Barra (1).

**Afiliación:** 1. Laboratorio de Productos Naturales, Departamento de Química Farmacológica y Toxicológica Facultad de Ciencias Químicas y Farmacéuticas Universidad de Chile. 2. Drug Delivery Laboratory, Departamento de Ciencias y Tecnología Farmacéuticas, Facultad de Ciencias Químicas y Farmacéuticas Universidad de Chile, Chile. 3. Advanced Center for Chronic Diseases (ACCDIS), Chile. 4. Center of New Drugs for

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** [fnavarretebravo@gmail.com](mailto:fnavarretebravo@gmail.com)

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**Socio Patrocinante:** Gabriela Valenzuela Barra

**6. ACTIVATION OF THE AMPK-PGC1A PATHWAY ON CARDIAC FIBROBLASTS AS A NOVEL ANTIFIBROTIC MECHANISM**  
 Activación de la vía AMPK-PGC1 $\alpha$  en fibroblastos cardíacos como nuevo mecanismo antifibrótico

**Resumen:** Cardiovascular diseases are the leading cause of mortality in Chile and around the world. They are characterized by structural and functional alterations of the heart, mainly due to the development of cardiac fibrosis. This occurs as a consequence of the cardiac fibroblasts (CFs) differentiation into cardiac myofibroblasts, which secrete increased amounts of extracellular matrix (ECM). Although cardiac fibrosis is a common factor in cardiovascular diseases, a targeted and effective treatment that can treat or prevent it has not yet been approved. This work aims to demonstrate that activation of the AMPK-PGC1 $\alpha$  pathway is capable of preventing the mitochondrial reprogramming that affects CFs and is responsible for their TGF- $\beta$ 1-induced differentiation, and that this is a potential target for the cardiac fibrosis treatment. CFs isolated from neonatal Sprague-Dawley rats were treated with TGF- $\beta$ 1 and AMPK activators such as AICAR and SLGT-2 inhibitors to measure protein expression of Collagen1A1, PGC-1 $\alpha$ , AMPK, and p-AMPK by Western blot, and gene expression of differentiation markers and mitochondrial modulators by RT-qPCR. Statistical analyses were performed using ANOVA and T-test. The results show that TGF- $\beta$ 1 significantly increased Collagen1A1 levels and decreased PGC-1 $\alpha$  levels at 24 hours, demonstrating mitochondrial reprogramming and CF differentiation. Furthermore, AICAR, an AMPK activator, decreases Collagen1A1 and increases PGC-1 $\alpha$  at the same time point, demonstrating a prevention of differentiation that is also observed in the gene expression of differentiation markers and an increase in mitochondrial modulators. Similar results were obtained when CF were stimulated with 250nM Empagliflozin, an SGLT-2 inhibitor that also activates AMPK. Our findings suggest that activation of the AMPK-PGC1 $\alpha$  pathway prevents TGF- $\beta$ 1-induced CF differentiation, making it a promising therapeutic target for the prevention of cardiac fibrosis.

**Autores:** Carrasco-Aburto, C.1,2, De León-Aravena, V.1,2, Landaeta-Verdejo, J.1,2, Norambuena, U.1,2, Ponce-Farías, J.1,2, Catalán, M.1,2, Vivar, R. 1,2

**Afiliación:** Laboratorio de Farmacología y Mecanismos de Enfermedad, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** [cata.sator@gmail.com](mailto:cata.sator@gmail.com)

**Agradecimientos:** Regular FONDECYT N°1251398 (Vivar, R.)

**Socio Patrocinante:** Raúl Vivar



## 7. PARTIAL SERUM DEPRIVATION OF ENDOTHELIAL CELLS INCREASES EXTRACELLULAR ATP/METABOLITES SECRETION ELICITED BY MECHANICAL STIMULI; ROLE OF PRIMARY CILIAM

Deprivación parcial de suero en células endoteliales aumenta la secreción extracelular de ATP/metabolitos inducida por estímulo mecánico

**Resumen:** Application of a mechanical stimulus to primary cultures of rat mesenteric endothelial cells (EC) induces extracellular ATP secretion. The primary cilium (PC), an organelle that senses extracellular medium movement, prompted us to investigate its role in nucleotide secretion elicited by mechanical stimuli. We examined procedures that modify PC expression; EC were grown under deprivation of fetal bovine serum (FBS) by reducing its content from 20% in controls to 10% or 2% for 48 h. In addition, the effect of 6 h treatment with palmitic (PA) or butyric acid (BU) was also examined following mechanical stimulation and PC formation. Extracellular purines were quantified following chemical derivatization to the corresponding fluorescent ethenopurines followed by HPLC separation. PC cell expression was evaluated through immunofluorescent PC antibodies. Total ATP released to the extracellular media elicited by mechanical stimuli increased 3 min after mechanical stimulation in controls, reducing media FBS to 10%, halved the release observed 3 min after stimulus ( $116 \pm 24$  ( $n = 10$ ) vs  $380 \pm 155$ , ( $n = 6$ ,  $p < 0.05$ ) pmol/mg protein. Extracellular ADP also increased by halving FBS, while AMP was not affected. ADO released increased from the first minute following 2% FBS ( $72 \pm 27$  ( $n = 12$ ) vs  $306 \pm 111$ , ( $n = 8$ ,  $p < 0.01$ ), pmol/mg protein respectively. Treatment with BU reduced ATP released at 1 min, while PA did not modify released ATP. Consistently, 15% ECs grown in 20% FBS presented PC, while ECs grown in 10% FBS, PC increased to 55% and following 2% FBS, over 65% ECs expressed PC. These results suggest and hypothesize that EC PC expression modulates ATP release elicited by mechanical stimulation. (Fondeqip EQM150069, CEDENNA 200001).

**Autores:** Donoso M.V.; Acuña J.; Lagos, P.; Huidobro-Toro J.P.  
**Afiliación:** Pharmacology Laboratory, Faculty of Chemistry and Biology, University of Santiago, Chile.  
**Area de la Farmacología:** Cardiovascular pharmacology  
**Dirección de Correo:** [verodonoso@hotmail.com](mailto:verodonoso@hotmail.com)  
**Agradecimientos:** Fondeqip EQM150069, CEDENNA 200001

**Socio Patrocinante:** Miembro Sociedad

## 8. EFFECTS OF ALOE-EMODIN ON EARLY ATHEROSCLEROSIS IN A ZEBRAFISH LARVAE MODEL INDUCED BY A HIGH CHOLESTEROL DIET.

Efectos de la aloe-emodina sobre la aterosclerosis temprana en un modelo de larvas de pez cebra inducida por una dieta alta en colesterol.

**Resumen:** Atherosclerotic cardiovascular disease is a chronic inflammatory process characterized by the interaction of lipoproteins, immune cells, and other components within the vascular wall, leading to plaque (atheroma). In vivo models of early atherosclerosis allow for a better understanding of the disease's pathogenesis. Zebrafish (*Danio rerio*) fed a cholesterol-rich diet are an effective alternative to murine models, especially for testing bioactive compounds. Aloe-emodin (AE), an anthraquinone present in plants such as *Aloe vera* and *Rheum palmatum* L., has shown promising anti-inflammatory and anti-atherogenic effects. Objective: To evaluate the effect of aloe-emodin on inflammatory cell accumulation and lipid deposition in a zebrafish model fed a high-cholesterol diet. Methods: Sub-toxic AE concentrations will be determined by viability and hepatic assessment assays. Transgenic and non-transgenic zebrafish larvae, exposed to either a high-cholesterol or control diet, will be treated with AE. In vivo parameters such as heart rate, growth, and peri-arterial inflammatory response will be analyzed by fluorescence microscopy. Sudan Black and Red Oil O staining will detect vascular lipid deposits. Biochemical parameters. Results: It is expected that the high-cholesterol diet will induce vascular inflammation, lipid accumulation, and biochemical alterations. AE treatment is anticipated to significantly attenuate these changes. Preliminary assays indicate that 1  $\mu$ M and 2  $\mu$ M AE do not induce mortality or detectable hepatic damage

in hsp70: GFP transgenic zebrafish larvae at 3 days post-fertilization, supporting these as the proposed therapeutic concentrations. In addition, a decrease in the number of immune cell was observe in larvae fed a high fat cholesterol diet treated with Aloe emodin versus those not treated. Conclusion: AE may reduce lipid accumulation and inflammation in early atherosclerosis, representing a potential preventive and therapeutic agent for this condition.

**Autores:** Flores Moreno, Gabriela<sup>1</sup>, Aguayo Tapia Claudio<sup>2</sup>, De la Paz Javiera F3, Fehrmann-Cartes Karen<sup>4</sup>, Acuña Abasalon<sup>5</sup>.  
**Afiliación:** <sup>1</sup>Laboratory of Embryotoxicology and Development-Environment Interaction (LEIDA), Department of Clinical Biochemistry and Immunology, Faculty of Pharmacy, University of Concepción, Chile. <sup>2</sup>Department of Clinical Biochemistry and Immunology, Faculty of Pharmacy, University of Concepción, Chile. <sup>3</sup>Laboratory of Embryotoxicology and Development-Environment Interaction (LEIDA), Faculty of Biological  
**Area de la Farmacología:** Cardiovascular pharmacology  
**Dirección de Correo:** [gfloresm@udec.cl](mailto:gfloresm@udec.cl)  
**Agradecimientos:** To the financing provided by the Military Hospital of the Republic of Nicaragua for my postgraduate studies. Thanks to Dr. Miguel Allende (University of Chile) for donating the genetic line.  
**Socio Patrocinante:** Claudio Aguayo Tapia

## 9. STUDY OF DIZE EFFECT ON THE DEDIFFERENTIATION OF VASCULAR SMOOTH MUSCLE CELLS

Estudio del efecto de DIZE sobre la dediferenciación de células musculares lisas vasculares

**Resumen:** Diminazene acetate (DIZE) has been described as an activator of angiotensin converting enzyme 2 (ACE2) and can exert protective effects in the vasculature. However, whether ACE2 mediates its protective effects has not been fully elucidated. Thus, we sought to assess whether DIZE can prevent the dedifferentiation of vascular smooth muscle cells (VSMCs), as well as ECs under pro-inflammatory conditions and whether ACE2 is expressed and activated in response to DIZE in both cell types. We pre-treated A7r5 and HUVEC cells with DIZE 1 and 10  $\mu$ M for 30 min, followed by treatment for 48 h with PDGF-BB 20 ng/ml in VSMC and TNF- $\alpha$  10 ng/ml in ECs. Protein levels of eNOS, Calponin,  $\alpha$ SMA, SM22 and ACE2 were evaluated by Western Blot. Migration of VSMC was measured under the same treatment conditions, but PDGF-BB was administered with DIZE for 24 h and a wound healing assay was performed. ACE2 was overexpressed in ECs using an adeno virus for 24 h. Enzymatic activity of ACE2 was determined using a commercial kit. Our results show that PDGF-BB can reduce contractile proteins and increase migration of VSMC, but these effects were prevented by DIZE 10  $\mu$ M. Pre-treatment for 30 min with the ACE2 inhibitor MLN-4760 10  $\mu$ M did not prevent the protective effect of DIZE. Furthermore, DIZE 10  $\mu$ M also prevented the loss of eNOS induced by TNF- $\alpha$ . Interestingly, ECs have a minimal protein content of ACE2 and DIZE did not increase the enzymatic activity. Overexpression of ACE2 increased protein content and activity in ECs and DIZE slightly increased its activity. Thus, our results suggest that DIZE may exert part of its protective effects via an ACE2 independent mechanism.

**Autores:** Constanza Rimassa-Taré, Vania Otárola, Jaime Riquelme Meléndez  
**Afiliación:** Laboratorio de Farmacoterapia Cardiovascular  
**Area de la Farmacología:** Cardiovascular pharmacology  
**Dirección de Correo:** [constanza.rimassa@uochile.cl](mailto:constanza.rimassa@uochile.cl)  
**Agradecimientos:** Proyecto Fondecyt 1231576  
**Socio Patrocinante:** Guillermo Díaz



## 10. IN SILICO CHARACTERIZATION OF THE MOLECULAR INTERACTION BETWEEN ANGIOTENSIN-(1-5) AND THE HUMAN AT2 RECEPTOR

Caracterización in silico de la interacción molecular entre la angiotensina-(1-5) y el receptor AT2 humano

**Resumen:** Cardiovascular diseases (CVD) are the leading cause of global mortality, with acute myocardial infarction (AMI) as a critical manifestation. The renin-angiotensin system (RAS) plays a pivotal role in regulating cardiovascular homeostasis. While the canonical ACE/Angiotensin II/AT1 and ACE2/Angiotensin-(1-7)/Mas axes are well-established, the physiological relevance of smaller RAS-derived peptides, remains unexplored. Ang-(1-5) is a pentapeptide formed through ACE-mediated cleavage of Angiotensin-(1-7). Once considered an inactive metabolite, emerging evidence suggests that Ang-(1-5) exerts cardioprotective effects, particularly against ischemia-reperfusion injury. Nonetheless, its molecular mechanisms of action and receptor interactions have yet to be elucidated. Given that AT2 receptor (AT2R) signaling mediates antihypertrophic and antifibrotic effects in the myocardium, the potential binding of Ang-(1-5) to AT2R represents an intriguing avenue for investigation. This study aimed to characterize in silico the molecular interaction between Ang-(1-5) and the human AT2 receptor. The crystal structure of the human AT2R (PDB: 6JOD) was utilized. Ang-(1-5) was modeled de novo using PEP-FOLD3 and energy-minimized via the MMFF94 force field. Molecular docking was executed using both CABS-DOCK and HAWKDOCK servers. Subsequent ligand-receptor interaction analysis was performed with BIOVIA Discovery Studio, and binding free energies were estimated using MM-PBSA calculations. Our bioinformatics analysis revealed that Ang-(1-5) binds effectively to the AT2R, adopting two primary stable conformations. Significantly, one of these conformations is situated within the primary ligand-binding pocket of the receptor. Binding free energy calculations confirmed a thermodynamically favorable interaction ( $K_d = 4.93 \times 10^{-21}$ ). This discovery posits a novel signaling pathway within the RAS, suggesting that the effects of Ang-(1-5) may be mediated through AT2R activation.

**Autores:** Yero-Haber R.B. 1, 2; Sánchez F. 2; Kogan M.J. 2; Lavandero S. 1, 2, 3

**Afiliación:** 1. Laboratory of Molecular Signal Transduction; 2. Advanced Center for Chronic Diseases (ACCDiS), Faculty of Chemical and Pharmaceutical Sciences & Faculty of Medicine, University of Chile, Santiago, Chile; 3. Cardiology Division, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** [rut.yero@ug.uchile.cl](mailto:rut.yero@ug.uchile.cl)

**Agradecimientos:** FONDECYT 1240443

**Socio Patrocinante:** Dr. Sergio Lavandero González

## 11. EFFECT ON GLUCOSE UPTAKE AND LIPID ACCUMULATION OF C2C12 MUSCLE CELLS TREATED WITH PLASMA EXTRACELLULAR VESICLES UNDER INCREASING GLYCEMIC CONDITIONS

efecto en la captación de glucosa y acumulación de lípidos de células musculares C2C12 tratadas con vesículas extracelulares plasmáticas en condiciones crecientes de glicemia

**Resumen:** Type 2 Diabetes Mellitus (T2DM) represents a growing global public health concern. This disease is characterized by chronic hyperglycemia resulting from peripheral insulin resistance and/or impaired insulin secretion. Since diagnosis often occurs at advanced stages, identifying early biomarkers and cellular mechanisms involved in metabolic dysfunction is essential. Extracellular vesicles (EVs) have emerged as key mediators of intercellular communication and regulators of metabolism under various pathophysiological conditions. Although previous studies have shown that EVs derived from T2DM patients can alter hepatic metabolism, their effect on peripheral tissues such as skeletal muscle—the main site of postprandial glucose uptake—remains poorly explored. The aim of this study was to evaluate the effect of plasma EVs, isolated by size exclusion chromatography (SEC) from normoglycemic, prediabetic, and diabetic individuals (classified by HbA1c levels), on the metabolism of differentiated C2C12 muscle cells.

EVs were characterized by nanoparticle tracking analysis (NTA), dynamic light scattering (DLS), flow cytometry, and Western blot. Glucose uptake was assessed using the fluorescent analog 2-NBDG, and lipid accumulation was determined with the BODIPY probe. Results show that EVs exhibit structural and molecular differences according to HbA1c levels. Furthermore, treatment with these EVs modified glucose uptake and lipid accumulation in C2C12 cells in a manner directly related to the degree of glycosylated hemoglobin. The structure and function of plasma EVs are directly influenced by HbA1c levels, affecting the metabolic response of recipient cells. These findings suggest that EVs may serve as functional biomarkers of early metabolic damage in T2DM. Future work will include microRNA, proteomic, and metabolomic analyses to identify the components responsible for these metabolic effects.

**Autores:** Orellana K. 1; Ormazábal V. 2; Valenzuela F. 1; Ormazábal Y. 1; Contreras H. 1

**Afiliación:** 1 Laboratorio Bioter, Departamento de Bioquímica Clínica e Inmunología, Facultad de Farmacia, Universidad de Concepción. 2 Laboratorio de Función y Análisis de Vesículas Extracelulares, Departamento de Farmacología, Facultad de Ciencias Biológicas, Universidad de Concepción

**Area de la Farmacología:** Clinical pharmacology

**Dirección de Correo:** [korellana2020@udec.cl](mailto:korellana2020@udec.cl)

**Agradecimientos:** Laboratorio Bioter Departamento de Bioquímica Clínica e Inmunología Facultad de Farmacia Proyecto FONDECYT iniciación 11109522 y VRID-UDEC 2023000815

**Socio Patrocinante:** Valeska Ormazábal Valladares

## 12. CHARACTERIZATION OF COMMERCIAL CALAFATE PRODUCTS BY UHPLC-DAD-QTOF AND EVALUATION OF THEIR CYTOTOXICITY IN A HUMAN RENAL TUBULAR CELL MODEL

Caracterización de productos comerciales de calafate mediante UHPLC-DAD-QTOF y evaluación de su citotoxicidad en un modelo de células tubulares renales humanas

**Resumen:** Chronic kidney disease (CKD) is characterized by increased oxidative stress, which induces cellular damage, apoptosis, and fibrotic remodeling, contributing to renal function loss and disease progression. The antioxidant capacity of polyphenols present in *Berberis microphylla* suggests a potential protective effect against the development of chronic kidney disease (CKD). The objective of this study was to determine the antioxidant properties and cytotoxicity of commercial calafate products (fresh fruit, dehydrated fruit, and juice) in a human renal proximal tubular epithelial cell model (HRPTEC). For this purpose, a methanolic extraction of polyphenols from calafate-derived products was performed. The bioactive compounds were characterized using UHPLC-DAD-QTOF, antioxidant capacity was determined through FOLIN, ORAC, ABTS, and CUPRAC assays, and cytotoxicity of the extracts was evaluated in HRPTEC cells using the MTT assay. Results were compared according to the serving portions recommended by the WHO (fresh fruit: 200 g; dehydrated fruit: 15 g; juice: 200 mL). The three matrices exhibited diverse polyphenolic profiles, with total concentrations of  $2784.68 \pm 253.61$  mg/portion in fresh fruit extract,  $199.52 \pm 0.94$  mg/portion in dehydrated calafate, and  $121.32 \pm 21.77$  mg/portion in juice. Regarding antioxidant capacity, all matrices displayed activity, with the following ranges: ORAC:  $461.45 \pm 93.33 - 3874.01 \pm 476.19$  mg Trolox eq./portion; CUPRAC:  $826.20 \pm 20.50 - 5795.05 \pm 348.88$  mg Trolox eq./portion; ABTS:  $601.44 \pm 91.31 - 6111.25 \pm 238.95$  mg Trolox eq./portion; and Folin:  $232.70 \pm 4.31 - 2396.64 \pm 43.27$  mg GAE/portion. The MTT assay revealed that none of the products induced cytotoxicity at the tested concentrations, showing cell viability > 90% in all cases. These results suggest Calafate matrices possess significant antioxidant potential and biocompatibility against CKD-associated oxidative damage.

**Autores:** Hermosilla P. 1; Olivares L. 2; Sanchez A. 2; Riquelme S. 3; Nova D. 1; Vidal F. 1; Opazo M. 1; Mardones P. 1

**Afiliación:** 1 METABOCROM Laboratory, Department of Instrumental Analysis, Faculty of Pharmacy, University of Concepción; 2 Department of Clinical Biochemistry, Faculty of Pharmacy, University of Concepción; 3 Technology Development Unit, University of Concepción.

**Area de la Farmacología:** Clinical pharmacology

**Dirección de Correo:** [pahermosilla201@udec.cl](mailto:pahermosilla201@udec.cl)

**Agradecimientos:** FONDECYT regular 1230625

**Socio Patrocinante:** Dra. Claudia Mardones Peña Dr. Jorge Fuentealba.

### 13. THE THYROID AXIS IN THE REGULATION OF GENES ASSOCIATED WITH MOOD DISORDERS: AN IN SILICO AND TRANSLATIONAL APPROACH

#### EL EJE TIROIDEO EN LA REGULACIÓN DE GENES ASOCIADOS A TRASTORNOS del Ánimo: Un Enfoque In Silico y Traslacional.

**Resumen:** While major depressive disorder (MDD) is typically viewed as a treatable condition with a favorable prognosis, recent epidemiological data indicate that 5–15% of affected individuals develop long-term symptoms and experience no sustained recovery. Importantly, thyroid hormones (THs) are key modulators of central nervous system (CNS) function, playing fundamental roles in mood and cognition. Local T3 availability is tightly regulated by selenoprotein iodothyronine deiodinases, which serve as metabolic switches. TH deficiency in the CNS can precipitate neurological alterations. Type 3 deiodinase (DIO3) is vital for hormonal inactivation, converting T4 into inactive rT3 and degrading T3 to T2. Preclinical studies show *Dio3<sup>-/-</sup>* mice exhibit reduced anxiety-like behavior. Correspondingly, clinical data report that patients with recurrent depressive disorder have significantly decreased DIO1 and DIO2 levels, concurrent with elevated DIO3. Our findings in peripheral blood from depressed patients also reveal elevated DIO3 concentrations. However, no reported mechanism currently explains this effect. This study aimed to determine if genes within the thyroid axis network are differentially expressed in postmortem brain samples from depressed individuals. We initially identified 83 genes linking the thyroid axis with mood disorders. Gene Ontology enrichment analysis categorized these genes, highlighting roles in TH generation (6 genes), thyroid gland development (6 genes), TH transport (4 genes), and oxidative stress response (17 genes). We then processed hippocampal microarray data from MDD patients and controls. Differential expression analysis revealed that 13 of the 83 genes significantly changed their levels in patients, suggesting a potential role of these candidates in thyroid axis dysfunction during mood disorders.

**Autores:** Alarcón-Mardones M; Corrales W. A.; Olave F.A.; Palacios-Avenidaño N; Vergara I.C.; López-González C; Vöhringer-Cárdenas P; Norambuena-Oviedo C; Risco-Neira L; Fiedler JL.

**Afiliación:** Neuroplasticity and Neurogenetic Lab, Faculty of Chemical and Pharmaceutical Sciences, University of Chile.

**Area de la Farmacología:** Endocrine pharmacology

**Dirección de Correo:** [matias.alarcon.m@uq.uchile.cl](mailto:matias.alarcon.m@uq.uchile.cl)

**Agradecimientos:** PROYECTO FONDECYT 1230471

**Socio Patrocinante:** Jenny Fiedler Temer

**Autores:** Lorena Rubio-Quiroz 1,2; Catalina Clarke 1; Alejandro Amoroso 3; Priscilla Cortés 3; Gonzalo-Recabarren-Gajardo 4; Andrea Vecchiola 5 & Carlos F. Lagos 1,2.

**Afiliación:** 1Chemical Biology & Drug Discovery Lab, Facultad de Ciencias, Universidad San Sebastián; 2Centro Basal Ciencia & Vida; 3Departamento de Ciencias Biológicas y Químicas, Universidad San Sebastián; 4Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile; 5Departamento de Endocrinología, Facultad de Medicina, Pontificia Universidad Católica de Chile

**Area de la Farmacología:** Endocrine pharmacology

**Dirección de Correo:** [lubio@docente.uss.cl](mailto:lubio@docente.uss.cl)

**Agradecimientos:** FONDECYT REGULAR 1241969, Centro Basal Ciencia & Vida, FB210008.

**Socio Patrocinante:** Dr. Carlos F. Lagos

### 15. EVALUATION OF THE ANTIOXIDANT CAPACITY OF A HYDROALCOHOLIC EXTRACT OF BUDDLEJA GLOBOSA HOPE.

#### Evaluación de la capacidad antioxidante de un extracto hidroalcohólico de Buddleja globosa Hope

**Resumen:** Buddleja globosa Hope (*B. globosa*) is a Chilean medicinal plant traditionally used to treat inflammation and promote wound healing. In this study, the leaves were collected, dried, and extracted using hydroalcohol (EtOH:H<sub>2</sub>O, 70:30) by maceration. The extract was then concentrated, lyophilized, and chemically characterized. The total phenolic content, determined using the Folin-Ciocalteu method, was 119 mg gallic acid equivalents (GAE)/100 g of dry extract. The antioxidant capacity, measured using the ABTS and DPPH assays, reached 126.94 and 71.44 mg ascorbic acid equivalents/g, respectively. The DPPH assay established an IC<sub>50</sub> of 133.50 µg/mL, confirming a strong antioxidant potential. These effects are associated with bioactive metabolites, such as verbascoside, luteolin-7-O-glucoside, and apigenin-7-O-glucoside, which have been previously identified in this species. Considering that oxidative stress contributes to chronic inflammatory diseases, which are among the leading causes of global mortality, these findings highlight the pharmacological relevance of *B. globosa*. This extract is a promising candidate for further studies on natural therapies for inflammation-related disorders

**Autores:** Mena Y.; Chuhuacuira P.; Hormazábal E.; Alvear M.; Salazar L.A.

**Afiliación:** Center of Molecular Biology and Pharmacogenetics, Department of Basic Sciences, Faculty of Medicine, Universidad de La Frontera, Temuco, Chile.

**Area de la Farmacología:** Ethnopharmacology

**Dirección de Correo:** [yikamenalinares@gmail.com](mailto:yikamenalinares@gmail.com)

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**Socio Patrocinante:** Dr. Luis Salazar Navarrete

### 14. MINERALOCORTICOID RECEPTOR ACTIVATION PROMOTES LIPID ACCUMULATION IN HYPERTROPHIC ADIPOCYTES

#### La activación del receptor mineralocorticoide promueve la acumulación de lípidos en adipocitos hipertrofos.

**Resumen:** Adipocyte hypertrophy is a key feature of obesity-associated metabolic dysfunction. Beyond its classical role in electrolyte balance, the mineralocorticoid receptor (MR) is expressed in adipose tissue and has been linked to lipid metabolism and adipogenesis. This study aimed to determine whether MR signaling modulates lipid accumulation and the expression of MR-responsive genes during in vitro adipocyte hypertrophy. Methods. Human SW872 preadipocytes were differentiated using a standard adipogenic cocktail. Hypertrophy was induced by a fatty acid mixture (palmitic:oleic acid, 2:1). On day 9 of differentiation, cells were treated with aldosterone (MR agonist) or MR antagonists—spironolactone (steroidal) and esaxerenone (non-steroidal). On day 10, lipid accumulation was quantified using Oil Red O staining, and MR target and phenotypic marker expression were assessed by RT-qPCR. Results. The fatty acid mixture induced a dose-dependent increase in intracellular lipid accumulation. Aldosterone further potentiated lipid storage in hypertrophic adipocytes, while MR antagonists significantly reduced lipid accumulation and downregulated the expression of adipogenic and hypertrophy-related genes compared with hypertrophic controls ( $p < 0.05$ ). Conclusions. MR activation enhances lipid storage and modulates gene expression during adipocyte hypertrophy, whereas MR blockade using either steroidal or non-steroidal antagonists mitigates these effects. These findings identify MR signaling as a potential pharmacological target to limit adipocyte hypertrophy and its contribution to metabolic dysfunction in obesity.



## 16. SERIAL ETHANOL EXTRACT OF UGNI MOLINAE TURCZ (C.N. MURTILLA) FRUITS AND ITS CARDIOPROTECTIVE AND ANTIOXIDANT EFFECTS IN AN EX-VIVO MYOCARDIAL ISCHEMIA/REPERFUSION MODEL.

Extracto etanólico seriado de frutos de Ugni molinae Turcz (n.v. Murtilla) y su efecto cardioprotector y antioxidante en un modelo de isquemia/reperfusión cardiaca ex-vivo.

**Resumen:** Currently, approximately 50% of pharmaceuticals originate from natural products due to their wide array of bioactive metabolites. Ugni molinae Turcz. (Murtilla) genotype 19.1 is an endemic Chilean shrub with recognized antioxidant activity. This study evaluated the in vitro antioxidant capacity and the potential ex vivo cardioprotective and antioxidant effects of a serialized ethanolic extract of its fruits against acute myocardial infarction (AMI). The extract was characterized by determining its total polyphenol content (TPC) and total flavonoid content (TFC) using Folin-Ciocalteu and AClC3 assays, respectively, while other compounds were identified through HPLC-MS/MS. In-vitro antioxidant activity was assessed via FRAP, DPPH, and ORAC-FL assays. The cardioprotective effect was evaluated in isolated hearts from adult male C57BL/6N mice subjected to global ischemia/reperfusion, measuring infarct size, malondialdehyde levels, and GSH/GSSG ratio. The TPC and TFC were  $14.5 \pm 0.8$  mg gallic acid equivalents (GAE)/g dry extract (DE) and  $2.83 \pm 0.16$  mg quercetin equivalents (QE)/g DE, respectively. HPLC-MS/MS analysis identified compounds such as quercetin 3-O- $\alpha$ -arabinofuranoside, diethyl malate, and citric, malic, and olean-12-en-28-oic acids. The in-vitro antioxidant activity measurements yielded values of  $112.5 \pm 8.5$ ,  $11.4 \pm 2.3$ , and  $158.3 \pm 1.2$   $\mu$ mol Trolox equivalents (TE)/g DE for FRAP, DPPH, and ORAC-FL, respectively. In the ex-vivo ischemia/reperfusion model, the extract significantly reduced infarct size and increased the GSH/GSSG ratio but did not decrease lipid peroxidation compared to the control. These findings highlight genotype 19.1 of Murtilla as a promising natural agent for the treatment of AMI.

**Autores:** Acevedo-Hernández J. 1,2; Finkelstein J.P. 3; Latorre G. 2; Montecinos L. 3; Rimassa C. 2; Sánchez G. 4; Valenzuela V. 1; Riquelme J.A. 2 y Valenzuela-Barra G. 1

**Afilación:** 1- Natural Products Laboratory 2- Cardiovascular Pharmacotherapy Laboratory, Department of Pharmacological and toxicological chemistry, Faculty of Chemical and Pharmaceutical Sciences, University de Chile. 3- Physiology Program 4- Physiopathology Program, Institute of Biomedical Sciences, School of Medicine, Universidad de Chile.

**Area de la Farmacología:** Ethnopharmacology

**Dirección de Correo:** [javier.acevedo.h@ug.uchile.cl](mailto:javier.acevedo.h@ug.uchile.cl)

**Agradecimientos:** Fondecyt 1231576 y Fondecyt de Iniciación 11241273

**Socio Patrocinante:** Gabriela Valenzuela Barra

## 17. CHARACTERIZATION OF BIOACTIVE COMPOUNDS AND ANTIOXIDANT ACTIVITY OF BUDDLEJA GLOBOSA HOPE (MATICO) HYDROALCOHOLIC EXTRACT FOR ORAL MUCOSAL HEALING

Caracterización de compuestos bioactivos y actividad antioxidante del extracto hidroalcohólico de Buddleja globosa hope (matico) con potencial cicatrizante en mucosa oral

**Resumen:** Oral mucosal healing is a complex biological process involving inflammation, cellular proliferation, and extracellular matrix remodeling. Natural compounds with antioxidant and anti-inflammatory properties can modulate these phases, improving tissue regeneration. Buddleja globosa Hope (Matico), a Chilean plant traditionally used for wound healing, shows potential for phytotherapeutic oral tissue repair. To characterize the phytochemical composition and antioxidant capacity of a hydroalcoholic extract of Buddleja globosa, establishing a biochemical foundation for its evaluation in oral mucosal cell models. Leaves were processed to obtain a 70% hydroalcoholic extract. Phytochemical screening was performed, followed by quantification of total phenolic compounds (Folin-Ciocalteu assay). Antioxidant activity was evaluated through DPPH and ABTS radical scavenging assays. The metabolomic profile was determined by LC-MS analysis. The extract revealed the presence of phenylpropanoids, flavonoids (quercetin, luteolin, apigenin), and verbascoside derivatives. Total phenolic content reached 94.6 mg GAE/g at 200 mg/L. Antioxidant assays showed concentration-dependent activity with IC50 values of 254.6 mg/L (DPPH) and 344.7 mg/L (ABTS). The LC-MS profile confirmed the predominance

of phenylpropanoid glycosides and antioxidant flavonoids consistent with wound-healing activity. The hydroalcoholic extract of Buddleja globosa exhibits a strong antioxidant profile and a diverse composition of bioactive molecules with potential for promoting oral mucosal repair. These findings support further in vitro validation using epithelial and fibroblast cell lines to assess proliferative and migratory responses.

**Autores:** Chuhuaicura P.; Alvear M.; Hormazábal E.; Salazar L.A.

**Afilación:** Universidad de La Frontera

**Area de la Farmacología:** Ethnopharmacology

**Dirección de Correo:** [priscila.chuhuaicura@ufrontera.cl](mailto:priscila.chuhuaicura@ufrontera.cl)

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**Socio Patrocinante:** Dr. Luis Salazar Navarrete

## 18. LEMON PECTIN-BASED ENCAPSULATION SYSTEMS FOR THE PROTECTION OF INTESTINAL EPITHELIAL INTEGRITY

Sistemas de Encapsulación a Base de Pectina de Limón para la Protección de la Integridad Epitelial Intestinal

**Resumen:** Introducción y Objetivos La integridad de la barrera epitelial intestinal es crucial para la homeostasis. Su disrupción se asocia con patologías como la enfermedad inflamatoria intestinal (IBD). Las cepas de Lactobacillus plantarum son probióticos prometedores para reforzar esta barrera, pero requieren protección contra las condiciones gastrointestinales. La microencapsulación con pectina de limón, por su biocompatibilidad y capacidad de gelificación, se presenta como una solución. El objetivo fue comparar microesferas de Quitosano/Pectina de limón y Alginato/Pectina de limón, producidas por electro-goteo con pectinas de alto (DM88) y bajo (DM18) grado de metilación, evaluando su impacto en la integridad de la barrera, la cicatrización (wound healing) y la viabilidad de L. plantarum WCFS1. Métodos Se produjeron microesferas mediante electro-goteo con pectinas DM18/DM88 combinadas con alginato o quitosano. Se evaluó la morfología, el tamaño y la viabilidad de L. plantarum WCFS1 encapsulado. El impacto biológico (microesferas vacías y cargadas) se evaluó en monocapas celulares intestinales T84 mediante la medición de la Resistencia Transepitelial (TEER) en tiempo real (ECIS) tras la disrupción con el ionóforo A23187, el análisis de la expresión génica de uniones estrechas (RT-qPCR) y la reparación de heridas (scratch assay). Resultados y Conclusiones Todas las formulaciones mantuvieron la viabilidad de L. plantarum tras la encapsulación. Las microesferas vacías de Quitosano/DM88 (ChitoDM88) retrasaron significativamente la pérdida de TEER, redujeron la secreción de IL-8 e incrementaron la proliferación celular. Cuando se cargaron con L. plantarum (ChitoDM88-Lp), se potenció el efecto protector, elevando la expresión de ZO-1, Occludina y Claudina-1. El sistema ChitoDM88 vacío demostró ser el candidato terapéutico óptimo por su efecto protector superior e inmunomodulador. La composición y el grado de metilación de la pectina son cruciales para determinar la respuesta

**Autores:** Galvez-Jiron F. 1,2,3; Tang X. 1; de Freitas Pedrosa L. 4; Wandersleben T 5; Navia R. 3,5; Acevedo F. 3,7,8; Silva Lagos L.9; de Vos Paul 2.

**Afilación:** 1 Doctorado en Ciencias Mención Biología Celular y Molecular Aplicada, Facultad de Medicina, Universidad de La Frontera, Chile. 2 Centre for Healthy Eating & Food Innovation (HEFI), Maastricht University – campus Venlo, The Netherlands 3 Millennium Nucleus Bioproducts, Genomics and Environmental Microbiology (BioGEM), Chile 4 Department of Food Science and Experimental Nutrition, School of Pharm

**Area de la Farmacología:** Gastrointestinal pharmacology

**Dirección de Correo:** [felipe.galvez.j@gmail.com](mailto:felipe.galvez.j@gmail.com)

**Agradecimientos:** Este trabajo fue apoyado por la beca 21230358 (FG-J) de la Agencia Nacional de Investigación y Desarrollo (ANID)/Doctorado Nacional y por ANID-Milenio-NCN2023\_054. También ha recibido financiación del programa de investigación e innovación Horizonte 2020 de la Unión Europea en virtud del acuerdo de subvención Marie Skłodowska-Curie (N.º 872019).

**Socio Patrocinante:** Dr. Rodrigo Lopez

## 19. PROBIOTIC BASED ON LACTOBACILLUS SP: POSSIBLE TREATMENT FOR VISCERAL PAIN AND DECREASED INTESTINAL PERMEABILITY

Probiótico a base de *Lactobacillus* sp.: posible tratamiento para el dolor visceral y disminución de la permeabilidad intestinal

**Resumen:** El uso de probióticos ha incrementado gracias a las propiedades benéficas que otorgan al huésped, y se buscan nuevas cepas que otorguen beneficios específicos frente a enfermedades, como por ejemplo el síndrome del intestino irritable (SII). El SII es un trastorno crónico del intestino grueso que afecta la calidad de vida, y su síntoma principal el dolor visceral. Dentro de las vías asociadas al dolor se encuentra la señalización purinérgica (P2), y evaluar los efectos de probióticos en esta vía podría dar paso a nuevas terapias. El objetivo de este estudio es determinar el efecto inducido por un probiótico *Lactobacillus* sp en la expresión de mRNA de receptores P2 y evaluar cambios la barrera intestinal mediante registros de resistencia transepitelial (TEER) y saco evertido en células de colon y en un modelo animal de hipersensibilidad visceral. Se evidenció un aumento en la expresión génica de los receptores purinérgicos asociados a dolor visceral P2X2, P2X3 y P2X4 en células Caco-2 y colon y GRD en los animales con hipersensibilidad, la cual vuelve a niveles normales en los animales tratados con el probiótico, mostrando que este ayuda a disminuir la señalización dolorosa. Además, los cambios en la permeabilidad intestinal muestran un aumento en la permeabilidad paracelular y transcelular en los animales con hipersensibilidad, la cual mejora al aumentar la resistencia eléctrica transepitelial en los animales con el tratamiento probiótico. Los datos presentados sugieren por primera vez que este probiótico disminuye la expresión de receptores P2 asociados al dolor y la permeabilidad intestinal en un modelo asociado al SII, lo que daría pie a un nuevo tratamiento del SII.

**Autores:** Rossi G.1, Oyanadel M.2, Valdes P.1, Covarrubias A.1, Sandoval R.3., Bravo J.4, Urriola N.2., Coddou C.1

**Afiliación:** 1 Laboratorio Señalización Purinérgica, Departamento Ciencias Biomédicas, Universidad Católica del Norte, Chile. 2 Laboratorio de microbiología y Parasitología, Departamento Ciencias Biomédicas, Universidad Católica del Norte, Chile. 3 Laboratorio de Neuropatología y productos naturales, Departamento Ciencias Biomédicas, Universidad Católica del Norte, Chile. 4 Laboratorio NeuroGastroBioquímica, I

**Area de la Farmacología:** Gastrointestinal pharmacology

**Dirección de Correo:** [gabriela.rossi@ucn.cl](mailto:gabriela.rossi@ucn.cl)

**Agradecimientos:** Beca doctorado nacional Minuspain

**Socio Patrocinante:** Claudio Coddou

## 20. ENHANCING THERMOSTABILITY AND RECOMBINANT EXPRESSION OF AN ANTI-MICA SINGLE-CHAIN VARIABLE FRAGMENT THROUGH ANTIBODY ENGINEERING

**Mejora de la termoestabilidad y la expresión** recombinante de un fragmento variable de cadena única anti-MICA mediante ingeniería de anticuerpos

**Resumen:** The successful development of therapeutic antibodies requires molecules with high stability and efficient recombinant expression. The anti-MICA single-chain antibody (scFv) used in this study exhibited poor stability and low yield. Here, a rational engineering strategy was applied to enhance its thermostability and expression without compromising affinity or human-likeness. The aim of this study was to improve the structural stability and recombinant expression of an anti-MICA antibody by introducing mutations in the framework region through antibody engineering. The closest germline V gene was identified using IgBLAST. scFv variants were generated carrying reversion mutations to restore germline-like framework residues, additional point mutations at key positions of the heavy chain, and a variable light-chain family migration to the human gene IGKV1-39. The antibody variable region was modeled using Rosetta. Five scFv variants were expressed in *Escherichia coli* SHuffle T7, and production levels were determined by Western blot. The melting temperature was assessed using the Thermofluor assay, and antigen-binding capacity was verified by ELISA. An optimized antibody variant was successfully generated, exhibiting a 72-fold increase in relative expression and a 13 °C increase in melting temperature compared to the parental antibody. Structural modeling analyses and affinity measurements indicated that the antibody's structure was preserved, as the binding affinity remained

within the same order of magnitude as the parental molecule. In conclusion, an improved anti-MICA antibody variant was generated with optimized biophysical properties, making it a promising candidate for therapeutic development. The applied antibody engineering pipeline enabled a rapid and cost-efficient optimization process without compromising antigen affinity or human-likeness. This strategy represents a valuable tool for the development of other antibodies with suboptimal properties.

**Autores:** Nicolás N. 1; Toledo-Stuardo K. 1; Matthies D. J. 1; Cristi N. 1; Jiménez C. 1; Ortega-Mardones A. 1; Campos I. 1; Guerra Y. 1; Garrido M. J. 1; Reyes N. 1; González-Herrera F. 1; Molina M. C. 1.

**Afiliación:** 1 Laboratorio de Anticuerpos Recombinantes e Inmuno-Oncología, Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Santiago, Chile.

**Area de la Farmacología:** Immunopharmacology

**Dirección de Correo:** [nfehring@uq.uchile.cl](mailto:nfehring@uq.uchile.cl)

**Agradecimientos:** FONDECYT Regular N° 1221031

**Socio Patrocinante:** María Carmen Molina

## 21. FLAGELLIN-LIKE PEPTIDES AS TLR5 MODULATORS: FROM COMPUTATIONAL ANALYSIS TO CELLULAR RESPONSE

**Péptidos análogos a flagelina como moduladores de TLR5: desde el análisis computacional a la respuesta celular**

**Resumen:** Flagellin is the primary component of the flagellum in both Gram-positive and Gram-negative bacteria, and it serves as the specific ligand of Toll-like receptor 5 (TLR5). The activation of flagellin induces the expression of proinflammatory cytokines and chemokines. In this work, we studied the *in silico* interactions of *Vibrio anguillarum* flagellin analogs with TLR5 and, *in vitro*, the biological properties of these molecules in the THP-1 monocyte cell line. The results of the protein-protein interactions showed that the recombinant rND1 and the synthetic peptide 518 have favorable binding free energies ( $\Delta G = -14.3$  and  $-13.2$  kcal/mol, respectively) and dissociation constants in the range of  $3.5 \times 10^{-11}$  M for rND1 and  $2 \times 10^{-10}$  M for peptide 518, demonstrating their ability to bind to TLR5. Interface analysis suggests moderate contact surfaces, with a predominance of charged-apolar interactions (rND=29; 518=27) and low polar-polar contributions (rND=6; 518=4), along with lower apolar-apolar hydrophobic contributions in 518 (7) than in rND1 (17). Taken together, these *in silico* data suggest that rND1 activates TLR5 more effectively than 518. To functionally validate these predictions, we assessed THP-1 cell activation after stimulation with flagellin analogs and quantified the transcriptional response by RT-qPCR. We observed that only rND1 promoted a significant increase in the expression of proinflammatory cytokines compared to the unstimulated control, consistent with greater TLR5 activation than that induced by the synthetic peptide. Overall, the *in silico* data and *in vitro* results show that rND1 is a good candidate as a TLR5-targeting immunomodulator. This opens up the possibility of optimizing peptide sequences to increase hydrophobic contacts and/or salt bridges, thereby enhancing affinity and efficacy in modulating TLR5 and subsequently activating immune cells.

**Autores:** Llanquino J; Lagos C; Silva E; González R

**Afiliación:** Centro de Investigación e Innovación en Cáncer (CIIC)/FALP

**Area de la Farmacología:** Immunopharmacology

**Dirección de Correo:** [jesus.llanquino@falp.org](mailto:jesus.llanquino@falp.org)

**Agradecimientos:** Centro de Investigación e Innovación en Cáncer (CIIC)

**Socio Patrocinante:** Dr. Carlos Lagos Arevalo



## 22. ALLELIC VARIABILITY OF MICA MODULATES ITS EXPRESSION IN TUMOR CELL LINES: IMPLICATIONS FOR FUTURE PERSONALIZED THERAPIES

La variabilidad alélica de MICA modula su expresión en líneas celulares tumorales: implicancias para futuras terapias personalizadas

**Resumen:** The MICA gene encodes a highly polymorphic stress-inducible protein recognized by the activating receptor NKG2D on Natural Killer (NK) cells. Allelic differences in MICA can influence both its expression level and its affinity for NKG2D, thereby modulating immune recognition and tumor evasion. Understanding how allelic variability in MICA affects its expression is essential to elucidate its role in tumor immunogenicity and to evaluate its potential as both a biomarker and therapeutic target in immunopharmacology. In this study, three human tumor cell lines -K562 (chronic myelogenous leukemia), Caco-2 (colorectal adenocarcinoma), and HuH-7.5 (hepatocellular carcinoma)- were analyzed to assess the relationship between the MICA genotype and its transcriptional and protein expression. Genotyping was performed by Sanger sequencing, with allele assignment based on HLA databases. MICA mRNA expression was quantified by RT-qPCR, and MICA protein expression was determined by flow cytometry. The results reveal differential MICA expression profiles between cell lines, correlated with their respective allelic variants. Notably, Caco-2 cells exhibited markedly low MICA expression both on the surface and intracellularly, suggesting limited ligand availability for NKG2D engagement. These findings support the hypothesis that MICA allelic diversity determines expression level and, consequently, NKG2D-mediated immune recognition. Altogether, these results highlight MICA as a promising pharmacological target within the MICA-NKG2D axis, susceptible to modulation for enhancing antitumor immune responses. This knowledge provides molecular foundations for the development of personalized immunotherapeutic strategies, contributing to the rational design of drugs and interventions aimed at improving immune recognition efficacy in cancer.

**Autores:** Reyes N. 1, Garrido M. J. 1, González-Herrera F. 1, Toledo-Stuardo K. 1, Molina M. C. 1

**Afiliación:** 1 Laboratorio de Anticuerpos Recombinantes e Inmuno-Oncología, Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile

**Área de la Farmacología:** Immunopharmacology

**Dirección de Correo:** [naiaad.reyes@uq.uchile.cl](mailto:naiaad.reyes@uq.uchile.cl)

**Agradecimientos:** FONDECYT Projects N° 1221031, N° 3240175.

**Socio Patrocinante:** María Carmen Molina Sampayo

## 23. STUDY OF THE POTENTIAL INHIBITORY EFFECT OF NATURAL FLAVONOIDS ON THE PLK-1 ENZYME AS A THERAPEUTIC TARGET FOR ANTITUMOR THERAPY: A MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE APPROACH.

Estudio del potencial efecto inhibitorio de flavonoides naturales sobre la enzima plk-1 como diana terapéutica antitumoral: un enfoque de aprendizaje automático e inteligencia artificial

**Resumen:** The serine/threonine kinase PLK-1 is currently considered an attractive target for the discovery of antineoplastic drugs. This enzyme is closely related to cell division processes and is overexpressed in tumor cells, playing a decisive role in metastasis. For this reason, the study of its inhibitors offers a promising alternative for cancer treatment. In this study, qualitative machine learning and artificial intelligence models were developed to predict the inhibitory activity of the PLK-1 enzyme as therapeutic alternatives against cancer. A database of small molecules obtained from ChEMBL with experimental IC50 values was utilized. First, data preprocessing was performed using cluster analysis to delete outliers, duplicate compounds, and to split the data into training and prediction series, ensuring structural representativeness. The discretization of the response variable was carried out using a piecewise regression method, estimating a breakpoint to form two classes (inhibitors and non-inhibitors). Classification models were obtained through Linear Discriminant Analysis, Support Vector Machines, Artificial Neural Networks, and k-Nearest Neighbors, implemented in STATISTICA software. The individual models show good overall classification percentages, a defined application domain, and good

performance in the external prediction set and cross-validation. Subsequently, the models were assembled, resulting in a Majority Vote Multiclassifier Virtual Screening System, which was used to identify 15 natural flavonoids that are present in the experimental chemical space of the models and have suitable oral bioavailability properties. Finally, these computational strategies can significantly reduce the experimental chemical space to the most promising candidates for further evaluation.

**Autores:** Cañizares-Carmenate Y.1, Hernandez-Rogriguez E. W.1, Aguado-Herrera D. B.2, Diaz-Amador R.1

**Afiliación:** 1 Laboratorio de Bioinformática y Química Computacional, Departamento de Medicina Traslacional, Facultad de Medicina, Universidad Católica del Maule, Talca, Chile.

**Área de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [ycanizares@ucm.cl](mailto:ycanizares@ucm.cl)

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## 24. SYNTHESIS AND CHARACTERIZATION OF PROHIBITIN 2 LIGANDS TO INDUCE PHB2 MEDIATED MITOPHAGY IN SENESCENT CELLS.

Síntesis y caracterización de ligandos de Prohibitina 2 para inducir mitofagia mediada por PHB2 en células senescentes.

**Resumen:** Population aging is closely linked to biological processes such as cellular senescence and mitochondrial dysfunction. As cells age, they lose the ability to eliminate damaged mitochondria (mitophagy), which promotes oxidative stress and alters cellular metabolism. This decrease in mitophagy leads to the accumulation of dysfunctional mitochondria, impairing ATP production and worsening cellular damage. Furthermore, factors such as increased p53 and decreased PINK1 have been observed to inhibit mitophagy, accelerating aging and tissue degeneration. The PHB2-LC3 pathway plays a key role in preserving mitochondrial health and cellular balance. When properly regulated, it allows the cell to adapt to stress and prevent the accumulation of damaged mitochondria, which contributes to maintaining their functionality and favors survival under adverse conditions. This context has motivated research aimed at identifying PHB2 molecular ligands capable of activating mitophagy. In a previous study with compound YL939, the structure of Prohibitin 2 (PHB2) was analysed to identify its binding site, highlighting key residues capable of inducing conformational changes that could lead to the activation of mitophagy. From this defined site, the first four ligands of a total of sixteen proposed were synthesized, and preliminarily characterized, with the aim of modulating the PHB2 pathway in senescent cells. The synthesis reactions of the compounds gave yields of 44.9%, 56.7%, 61.1% and 85.5%. Structural characterization by NMR spectra (<sup>1</sup>H and <sup>13</sup>C) confirmed their correct preparation. The ΔG values obtained by molecular docking ranged between -7.76 kcal/mol and -8.43 kcal/mol, similar to the control YL-939/PHB2 (-7.74 kcal/mol). An MTT assay is currently being carried out to evaluate the cytotoxicity of the compounds in C2C12 cells.

**Autores:** Ferro, W.1, Almarza G.1, Oyaneder, L.1, Espinosa, C.2, del Campo, A.1.

**Afiliación:** 1 Laboratory of Physiology and Cellular Bioenergetics, 2 Bio-Organic Chemistry Laboratory, School of Chemistry and Pharmacy, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile, Santiago de Chile.

**Área de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [williams.ferro@uc.cl](mailto:williams.ferro@uc.cl)

**Agradecimientos:** FONDECYT Project number # 1230428 to AdC.

**Socio Patrocinante:** Dra. Andrea Estefanía del Campo Sfeir



## 25. DETERMINATION OF MOLECULAR CHANGES IN MURINE BRAIN ASSOCIATED WITH ALZHEIMER'S DISEASE USING MASS SPECTROMETRY IMAGING

Determinación de cambios moleculares en cerebro murino asociado a la Enfermedad de Alzheimer utilizando Mass spectrometry imaging

**Resumen:** Alzheimer's disease (AD) is a neurodegenerative pathology characterized by extracellular  $\beta$ -amyloid deposits and intracellular hyperphosphorylated tau accumulation, leading to significant brain alterations. Mass Spectrometry Imaging (MSI) provides spatial molecular information, representing a promising tool to explore metabolic changes linked to neurodegeneration, drug effects, and biomarker discovery. This study aimed to determine molecular changes associated with AD in APP/PS1 murine brains compared with wild-type (WT) C57Bl6j mice. Brain sample preparation for MSI using MALDI-TOF was optimized by evaluating three freezing methods: liquid nitrogen ( $N_2(l)$ ), isopentane, and immersion in  $N_2(l)$  within a box. Coronal brain sections (10  $\mu$ m) were obtained using a cryostat and mounted on MALDI IntelliSlides. Matrix application was performed by sublimation using 2,5-dihydroxybenzoic acid (DHB, positive mode) or 9-aminoacridine (9-AA, negative mode). Serial sections from the same WT and APP/PS1 brains (3 months old) were analyzed in triplicate to assess reproducibility, using DHB as matrix. MSI analyses were performed on a MALDI-TOF autoflex® maX, and data were processed with SCiLS and MetaboAnalyst 6.0 for PCA and volcano plot analyses ( $p < 0.05$ , FC 1.5). Isopentane provided the best cryopreservation. Both matrices enabled molecular imaging in positive and negative modes. PCA revealed distinct spatial metabolic profiles, with significant differences in cortex, hippocampus, thalamus, hypothalamus, and amygdala. In conclusion, the optimized methodology allowed detection of early molecular alterations in AD brains, contributing to biomarker identification and drug evaluation through spatial metabolomics.

**Autores:** Natalia Hernández 1, Ignacio Salinas 2, Catalina Bravo 2, Daniela Nova 2, Sebastián Riquelme 2, Claudia Mardones 2, Andy J Pérez 2, Luis Aguayo 3, Loreto San Martín 1, Jorge Fuentealba 3, Lia Olivares-Caro 1

**Afiliación:** Metabocrom, Department of Clinical Biochemistry, Faculty of Pharmacy, University of Concepción 1, Department of Instrumental Analysis, Faculty of Pharmacy, University of Concepción 2, Department of Physiology, Faculty of Biological Sciences, University of Concepción 3

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [nhernandez2020@udec.cl](mailto:nhernandez2020@udec.cl)

**Agradecimientos:** FONDECYT POSTDOCTORAL PROJECT 3240171, FONDEQUIP AGRM220055, FONDECYT 1230625, CMA BIO-BIO Proyecto PIA-ANID ECM-12.

**Socio Patrocinante:** Dra. Claudia Mardones Dr. Jorge Fuentealba Dra. Lia Olivares Caro

## 26. EVALUATION OF SYNTHETIC ISOFLAVONOIDS AS DUAL INHIBITORS OF 5-LOX/COX-2

Evaluación de isoflavonoides sintéticos como inhibidores duales de 5-LOX/COX-2

**Resumen:** Lipoxygenases (LOXs) and cyclooxygenases (COXs) are key enzymes involved in the inflammatory pathway through the biosynthesis of leukotrienes (LTs) and prostaglandins (PGs), respectively. Their dysregulation has been associated with several pathological conditions, including allergies, cardiovascular diseases, diabetes, and various types of cancer. Isoflavonoids, a class of polyphenolic compounds found in leguminous and soybean plants, exhibit a wide range of biological activities such as antioxidant, anticancer, and anti-inflammatory effects. In this study, a series of synthetic isoflavones (IR) and isoflavanes (HIR) were evaluated for their inhibitory activity against human 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2). The presence and position of the catechol group on the A ring (6,7-dihydroxy versus 7,8-dihydroxy) significantly influenced enzyme inhibition. Modifications on the B ring substituents affected COX-2 selectivity, particularly in IR-202, IR-203, and IR-207, which exhibited  $IC_{50}$  values below 10  $\mu$ M. Furthermore, reduction of the nitro ( $-NO_2$ ) group to an amino ( $-NH_2$ ) group enhanced COX-2 inhibition. Reduction of the C ring, corresponding to isoflavanes, increased 5-LOX inhibition in catechol-containing derivatives (6,7 positions) and generally favored COX-2 inhibition.

**Autores:** Morales, P. 1,2; Mascayano, C. 1 and Vasquez, Y. 2.

**Afiliación:** Laboratorio de Simulación Computacional y Diseño Racional de Fármacos, Facultad de Química y Biología, Universidad Santiago de Chile

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [pilar.morales@usach.cl](mailto:pilar.morales@usach.cl)

**Agradecimientos:** FONDECYT REGULAR 1251364

**Socio Patrocinante:** -

## 27. Design, synthesis and evaluation of extended N- and 3-arylsulfonylindole derivatives as novel multitarget modulators of 5-HT<sub>1A</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors

Diseño, síntesis y evaluación de derivados extendidos de N- y 3-arylsulfonylindol como nuevos moduladores multidiana de los receptores 5-HT<sub>1A</sub>, 5-HT<sub>6</sub> y 5-HT<sub>7</sub>

**Resumen:** Neurodevelopmental disorders (NDDs) are characterized by deficits in cognition, communication, and behavior. Notably, autism spectrum disorder (ASD) is among the most prevalent NDDs, yet no effective pharmacological treatments addressing its core symptoms currently exist<sup>1-3</sup>. Dysregulation of serotonin signaling has been associated with ASD, highlighting serotonergic receptors as promising therapeutic targets. In particular, the 5-HT<sub>1A</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptor subtypes play key roles in neurodevelopmental processes such as synapse formation, neuronal plasticity and neurite outgrowth<sup>4-6</sup>. The extended N-arylsulfonylindole scaffold was exploited with great success by our research group in earlier studies aiming at the obtention of 5-HT<sub>6</sub> receptor antagonists, including the hit compound BHSL-48 (formerly known as PUC-10)<sup>7-10</sup>. Through in silico studies, novel derivatives from the extended arylsulfonylindole family were designed to fit the pharmacophore models of both the 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors. The ligands were then synthesized and subjected to competitive radioligand binding assays. From the eighteen molecules, we identified seven triple modulators with inhibitory constants within the 100 nM range for all three receptors. Among them, BHSL-29 stood out as the most prominent hit ( $K_i$  5-HT<sub>1A</sub> = 2,58nM;  $K_i$  5-HT<sub>6</sub> = 38,5nM;  $K_i$  5-HT<sub>7</sub> = 10,6nM), thus demonstrating the structural family potential as serotonergic multi-target drug candidates.

**Autores:** Rivera Córdova L. 1, Flores Villagra M. 1, Fuentes Cuevas M. J. 1, Rivera-Illanes, D. 1, González Quezada, N. 1; Lagos C. F. 2, Recabarren-Gajardo G. 1,3.

**Afiliación:** 1 Bioactive Heterocycles Synthesis Laboratory (BHSL), Departamento de Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, 2 Chemical Biology & Drug Discovery Lab, Escuela de Química y Farmacia, Facultad de Ciencias, Universidad San Sebastián 3 Centro Interdisciplinario de Neurociencias, Pontificia Universidad Católica de Chile

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [greabarren@uc.cl](mailto:greabarren@uc.cl)

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**Socio Patrocinante:** N/A



## 28. TARGETING BCR-ABL WITH NOVEL PROTACs: SYNTHESIS AND BIOLOGICAL EVALUATION OF 2,6,9-TRISUBSTITUTED PURINE DERIVATIVES FOR CHRONIC MYELOID LEUKEMIA TREATMENT

Apuntando a Bcr-Abl con nuevos PROTACs: Síntesis y evaluación biológica de derivados de purina 2,6,9-trisustituidas para el tratamiento de la leucemia mieloide crónica

**Resumen:** Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm driven by the Bcr-Abl oncoprotein, with an annual incidence of approximately 2 cases per 100,000 people. Since the introduction of imatinib, a tyrosine kinase inhibitor (TKI) targeting Bcr-Abl, the mortality rate of CML has declined from 10–20% to 1–2%. However, currently FDA-approved TKIs such as imatinib and dasatinib often result in drug resistance and severe adverse effects, underscoring the need for safer and more effective therapeutic strategies. To overcome these limitations, proteolysis-targeting chimeras (PROTACs) have emerged as an innovative approach that induces selective Bcr-Abl degradation through the ubiquitin–proteasome system. In this study, seven novel PROTACs were designed and synthesized based on in-house 2,6,9-trisubstituted purine derivatives to recruit the E3 ligase CRBN. Their antiproliferative activity was evaluated in CML-related K562 cells, where compound 3 exhibited the highest potency ( $GI_{50} = 0.54 \mu\text{M}$ ), followed by compound 2 ( $GI_{50} = 1.19 \mu\text{M}$ ). Both compounds showed activity comparable to the reference inhibitor 1 ( $GI_{50} = 0.90 \mu\text{M}$ ) but demonstrated improved selectivity, as they did not inhibit the proliferation of HEK-293T cells lacking Bcr-Abl ( $GI_{50} > 10 \mu\text{M}$ ), whereas compound 1 inhibited HEK-293T growth ( $GI_{50} = 5.50 \mu\text{M}$ ). Moreover, western blot analysis revealed that compound 2 induced Bcr-Abl degradation in K562 cells after 24 h of treatment at  $10 \mu\text{M}$ . Computational studies, including molecular docking, molecular dynamics, and MM/GBSA analyses, provided insights into the structural determinants underlying PROTAC activity. Overall, compounds 2 and 3 emerged as promising leads for further in vitro and in vivo evaluation toward new therapeutic options for CML.

**Autores:** Delgado T. 1; Silva N. I. 1; Kryštof V. 2; Mella J. 3; Salas C. O.\* 1  
**Afilación:** 1. Departamento de Química Orgánica, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Chile. 2. Department of Experimental Biology, Palacký University Olomouc, Czech Republic. 3. Instituto de Química, Facultad de Ciencias, Universidad de Valparaíso, Chile.  
**Area de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** [nsilvas@estudiante.uc.cl](mailto:nsilvas@estudiante.uc.cl)  
**Agradecimientos:** To Agencia Nacional de Investigación y Desarrollo (ANID), Chile, for the PhD fellowship N° 21241377 for N.I.S. Additionally, the authors also wish to acknowledge the support from Fondecyt, Chile (Research Grant N° 1231199).  
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## 29. BERRIES OF LUZURIAGA RADICANS RUIZ & PAV., A CLIMBING SHRUB FROM THE TEMPERATE FOREST OF VALDIVIA, AS A SOURCE OF COMPOUNDS AGAINST CHRONIC DISEASES.

Bayas de Luzuriaga radicans Ruiz & Pav. un arbusto trepador del bosque templado de Valdivia, como fuente de antioxidantes contra enfermedades crónicas

**Resumen:** In recent years, interest in the biological activities of Valdivian Forest endemic berries has grown, yet several species remain understudied. Here, we present the first phytochemical characterization of a hydroalcoholic extract from Luzuriaga radicans Ruiz & Pav. and evaluate its antioxidant potential as well as its ability to inhibit enzymes implicated in chronic non-communicable diseases. Berries collected in Saval Park (Valdivia) were sonicated in an ethanol/water mixture, and analyzed by UHPLC-DAD, HPLC-APCI(+)-MS and UHPLC-ESI(+)-TOF-MS, which revealed multiple carotenoid esters. Quantification by UHPLC-DAD showed a total carotenoid content of  $983.4 \pm 26.3 \text{ mg/kg}$  dry weight, while total phenolics reached  $9.33 \pm 0.01 \text{ mg GAE/g}$  dry fruit. The extract displayed strong radical-scavenging activity against DPPH and ABTS, along with notable ferric-reducing antioxidant power (FRAP). It also inhibited acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) with  $IC_{50}$  values of  $6.90 \pm 0.42 \mu\text{g/mL}$  and  $18.38 \pm 0.48 \mu\text{g/mL}$ , respectively. Complementary molecular docking of key berry constituents supported these enzyme-inhibition results. However, the

extract showed no activity on vascular reactivity in the rat aorta. Together, these findings position *L. radicans* hydroalcoholic extract as a promising natural antioxidant and enzyme inhibitor, with potential applications in phytotherapeutic and nutraceutical formulations targeting chronic diseases.

**Autores:** Simirgiotis M. 1; Cifuentes F. 2 Scharf S. 3; Romero-Parra J. 4; Winterhalter P. 3; Torres-Benitez A. 5; Gök R. 3  
**Afilación:** 1 Instituto de Farmacia, Facultad de Ciencias, Universidad Austral de Chile, Valdivia 5110566, Chile, 2 Laboratorio de Fisiología Experimental, Instituto Antofagasta, Universidad de Antofagasta, Antofagasta 1270300, Chile; 3 Institute of Food Chemistry, TU Braunschweig, Schleinitzstrasse 20,38106 Braunschweig, Germany; 4 Departamento de Química Orgánica y Fisicoquímica, Facultad de Ciencias Químicas  
**Area de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** [mario.simirgiotis@uach.cl](mailto:mario.simirgiotis@uach.cl)  
**Agradecimientos:** we acknowledge fondecyt 1220075, and TU Braunschweig University  
**Socio Patrocinante:** Mario Simirgiotis and Eliana Sanchez

## 30. OPTIMIZATION OF URINE SAMPLE EXTRACTION FOR METABOLOMICS ANALYSIS BY LIQUID CHROMATOGRAPHY COUPLED TO HIGH RESOLUTION MASS SPECTROMETRY IN CHRONIC KIDNEY DISEASE

Optimización de extracción de muestras de orina para análisis metabolómico mediante cromatografía líquida acoplada a espectrometría de masas de alta resolución en Enfermedad Renal Crónica

**Resumen:** Introduction: Chronic kidney disease (CKD) impairs renal function, resulting in progressive damage and a decrease in glomerular filtration rate. Traditional diagnostic approaches rely on markers such as creatinine and estimated glomerular filtration rate. However, these are indicators of late-stage disease. Metabolomics enables the comprehensive analysis of metabolites in biological samples, providing a holistic view of disease-related metabolic alterations. This study aimed to optimize the preparation of urine samples and the subsequent chromatographic analysis coupled with high-resolution mass spectrometry (UHPLC-QTOF/MS) to maximize signal detection for metabolomics analysis. Methodology: Four extraction solvents were evaluated: acetonitrile, water with 0.1% formic acid, methanol, and methanol/methyl tert-butyl ether (97:3, v/v). Extracts were analyzed by UHPLC-QTOF/MS in both positive and negative electrospray ionization modes. Chromatographic separation was performed on a C18 column ( $100 \times 3 \text{ mm}$ ,  $1.7 \mu\text{m}$ ) at  $50^\circ\text{C}$ , using mobile phase A: water with 0.1% formic acid (v/v) and mobile phase B: acetonitrile with 0.1% formic acid (v/v). Two chromatographic methods were tested using the same mobile phases but different initial gradients. The first method employed an initial ratio of 50:50 (A:B), whereas the second used 95:5 (A:B). Chromatographic data were processed using DataAnalysis software to quantify the total number of detected signals for each extraction method under both chromatographic conditions. Results: The chromatographic gradient starting at 95:5 (A:B) yielded a higher number of detected signals compared to the 50:50 (A:B) gradient. Moreover, methanolic urine extracts analyzed under the 95:5 (A:B) gradient exhibited a greater number of signals than those obtained with the other extraction solvents. Conclusion: Therefore, the extraction and chromatographic methods coupled with high-resolution mass spectrometry were optimized for subsequent metabolomic analysis

**Autores:** Vidal F.1, Olivares L.2, Riquelme S.1, Nova D.1, Hermosilla P.1, Opazo M.1, Enos D.3, Mardones C.1  
**Afilación:** 1 Metabocrom Laboratory, Department of Instrumental Analysis, Faculty of Pharmacy, University of Concepción 2 Department of Clinical Biochemistry, Faculty of Pharmacy, University of Concepción 3 Department of Internal Medicine, University of Concepción, Los Angeles Campus, Biobío, Chile  
**Area de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** [vidal2019@udec.cl](mailto:vidal2019@udec.cl)  
**Agradecimientos:** FONDECYT Regular 1230625.  
**Socio Patrocinante:** Dra. Claudia Mardones Peña Dr. Jorge Fuentealba

### 31. NATURAL MODULATORS OF SERT: ANTIDEPRESSANT POTENTIAL OF 1,8-CINEOLE, $\alpha$ -PINENE, AND CAMPHOR FROM ROSEMARY ESSENTIAL OIL

Moduladores naturales del SERT: potencial antidepresivo de 1,8-cineol,  $\alpha$ -pineno y alcanfor del aceite esencial de romero.

**Resumen:** Selective serotonin reuptake inhibitors (SSRIs) are the first-choice drug treatment for major depressive disorders. However, its delayed onset of action and the frequent occurrence of adverse effects limit its clinical efficacy. In the search for safer and better-tolerated alternatives, essential oils obtained from *Rosmarinus officinalis* L. (rosemary) have shown promising neuropharmacological properties. This study explored the molecular interactions of three of the main monoterpenes present in rosemary essential oil – 1,8-cineole,  $\alpha$ -pinene, and camphor – and the human serotonin transporter (hSERT), a key target in the treatment of depression. Using molecular docking techniques using SwissDock, AutoDock Vina, and Maestro (Schrödinger Suite), the binding affinities and interaction profiles of these compounds at the central (S1) and allosteric (S2) sites of the transporter were evaluated. The results showed moderate but slightly higher affinities at the S1 site, suggesting that this would be the main point of interaction, while the interactions detected at S2 could indicate a possible secondary allosteric modulatory role. In addition, in vitro assays are being developed in hSERT-expressing HEK293 cells to quantify the inhibition of the uptake of the false fluorescent neurotransmitter FFN246 and to determine the IC<sub>50</sub> values of each compound. Together, these advances provide relevant molecular information on the interaction of natural monoterpenes with the serotonin transporter and evaluate their potential as complementary agents in the development of new antidepressant therapeutic strategies based on natural products.

**Autores:** Valle C.1; Pino J.A.2; Mella J. 3; Lapier M1

**Afiliación:** 1Laboratorio de Química Medicinal, Facultad de Farmacia, Universidad de Valparaíso. 2Facultad de ciencias de la vida, laboratorio de bioquímica y farmacología molecular, universidad Viña del Mar. 3 Instituto de Química, Facultad de Ciencias, Universidad de Valparaíso

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [carolina.vall@postgrado.uv.cl](mailto:carolina.vall@postgrado.uv.cl)

**Agradecimientos:** Projects: Puente UV 22991 y FIIUVM-CYT-2506

**Socio Patrocinante:** José Antonio Pino Reyes

### 32. PHOTODYNAMIC ACTIVITY OF FITC- AND RITC-FUNCTIONALIZED PAMAM DENDRIMERS AGAINST HeLa CELLS AND *S. aureus*

ACTIVIDAD FOTODINÁMICA DE DENDRÍMEROS PAMAM FUNCIONALIZADOS CON FITC Y RITC CONTRA CÉLULAS HeLa Y *S. Aureus*

**Resumen:** Cancer and antibiotic-resistant bacterial infections require the development of innovative therapeutic strategies. A promising alternative is photodynamic therapy, which uses photosensitizing molecules that, upon light activation, generate reactive oxygen species (ROS) capable of destroying malignant cells and microorganisms. To optimize this approach, this study employed fourth-generation polyamidoamine (PAMAM) dendrimers as versatile nanocarriers functionalized with fluorescein isothiocyanate (FITC) and rhodamine B isothiocyanate (RITC). The objective was to develop and evaluate these nanoconjugates for photodynamic applications against HeLa cervical cancer cells and *Staphylococcus aureus*. The synthesis, confirmed by <sup>1</sup>H NMR, successfully functionalized approximately 11% of surface amines with FITC and 8% with RITC. Photobiological assays showed that PAMAM-FITC, at micromolar concentrations, exhibited strong phototoxic activity against *S. aureus*, producing an inhibition halo of 32.5 mm, comparable to free fluorescein (33 mm). No cytotoxic effects were observed in HeLa cells under either light or dark conditions, suggesting a preferential antibacterial effect. Conversely, PAMAM-RITC displayed phototoxic activity against both microorganisms and tumor cells: inhibition halos of 14 mm (100  $\mu$ M) and 13.5 mm (10  $\mu$ M) were recorded for *S. aureus*, while HeLa cell viability decreased by up to 60% at 10  $\mu$ M upon light exposure. These results indicate that PAMAM-FITC primarily acts through singlet oxygen generation, whereas PAMAM-RITC, despite minimal singlet oxygen production, induces potent light-dependent

cytotoxicity. In conclusion, PAMAM conjugation enhances and stabilizes photosensitizer performance. PAMAM-FITC and PAMAM-RITC emerge as selective, biocompatible candidates for dual anticancer and antibacterial photodynamic therapy, representing a promising and less invasive therapeutic alternative.

**Autores:** Bustos C.1; Sandoval P.1; Baquedano C.1; Zapata V.1; Guzmán L.1; Díaz C.1\*

**Afiliación:** Departamento de Ciencias Químicas, Facultad de Ciencias Exactas, Universidad Andrés Bello, Chile y Departamento de Fisiología, Facultad de Ciencias Biológicas, Universidad de Concepción, Chile.

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** [im.camilabustos@gmail.com](mailto:im.camilabustos@gmail.com)

**Agradecimientos:** The authors acknowledge the financial support of Fondecyt projects No. 11251282 and No. 1241829.

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### 33. ANTITUMOR EFFECTS OF ARSENIC NANOPARTICLES IN ORAL MUCOSA, BREAST AND SKIN CANCER MODELS

Efectos antitumorales de las nanopartículas de arsénico en modelos de cáncer de mucosa oral, mama y piel

**Resumen:** Our research team recently isolated and characterized arsenic nanoparticles (AsNPs) from the anaerobic bacterium *Fusibacter ascotense*, found in Chile's Ascotán Salar. These AsNPs show promising biomedical potential, particularly antitumor activity. We first examined the effects of AsNPs on the human oral squamous carcinoma cell line OECM-1. Resazurin assays (1–100  $\mu$ M) revealed a concentration-dependent decrease in viability, which was not observed in non-tumoral GES-1 cells. This cytotoxic effect was directly associated with apoptosis induction, as demonstrated by Bcl-2 and Bax expression, cleaved caspase-3 detection by Western blot, caspase-3/7 activity by luminometry, and DNA fragmentation by the TUNEL assay. AsNP-treated OECM-1 cells activated both intrinsic and extrinsic apoptotic pathways, accompanied by decreased P-Akt/Akt and P-ERK/ERK ratios and increased PTEN, p53, and Bit-1 expression. These findings indicate that AsNPs trigger anoikis, an anchorage-dependent form of apoptosis. Similarly, in breast cancer-derived 4T-1 cells, AsNPs caused a dose-dependent inhibition of cell viability. Building on these results, we have initiated a new project to evaluate the effects of AsNPs on cell lines derived from skin diseases, including actinic keratosis (AK)—a precancerous condition—squamous cell carcinoma (SCC), and melanoma. Skin diseases linked to prolonged UV radiation exposure have been increasing in recent years, and Chile's Coquimbo Region is among the five regions with extreme UV radiation levels. In summary, arsenic nanoparticles represent a novel and promising strategy for the treatment of various types of cancer. Keyword: Arsenic nanoparticles, Anoikis, Melanoma, OECM-1.

**Autores:** Covarrubias AA.1,2; Cerda D.1; Marin S.3; Demergasso C.3; Coddou C.1

**Afiliación:** 1Laboratorio de Señalización Purinérgica, Departamento de Ciencias Biomédicas, Facultad de Medicina, Universidad Católica del Norte, Coquimbo. 2 Facultad de Ciencias Agropecuarias, Universidad del Alba, La Serena 1700000, Chile. 3 Centro de Biotecnología, "Profesor Alberto Ruiz", Universidad Católica del Norte, Antofagasta, Chile.

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** [alejandra.covarrubias@ucn.cl](mailto:alejandra.covarrubias@ucn.cl)

**Agradecimientos:** FIC-R 2025 Cod BIP 40064890-0 | Investigación Nanocompuestos Terapia y Prevención Cáncer de Piel

**Socio Patrocinante:** Claudio Coddou



#### 34. THE LIPOPHILIC CATION DERIVED FROM GALLIC ACID INDUCES BROWNING AND ANTIOXIDANT EFFECTS IN ADIPOCYTES

El catión lipofílico derivado de ácido gálico induce efectos pardeantes y antioxidantes en adipocitos

**Resumen:** WAT is classified as a reserve tissue; it allows the accumulation of lipids in a process defined as adipogenic, having poor mitochondrial content and a large unilocular lipid droplet. Excess in the mass of WAT is highly correlated with obesity and metabolic disease development. Conversely, BAT and BeigeAT are morphologically and functionally abundant in mitochondria, with numerous multilocular lipid droplets. They can use the stored lipids when necessary, thus metabolizing the content through  $\beta$ -oxidation and lipolysis, generating heat dissipation. Therefore, BAT and BeigeAT play a crucial role in non-shivering thermogenesis. It has been reported that a singular stimulus can transform WAT into BeigeAT, a process classified as browning, which could be induced to regulate obesity through novel pharmacological strategies. Our goal was to study the browning and antioxidant effects of a lipophilic cation derived from gallic acid developed in our laboratory (TPP+C10). To achieve this, the markers PGC1- $\alpha$ , PRDM16, and UCP1 (proteins involved in browning and mitochondrial biogenesis), were evaluated by RT-qPCR using mouse adipose tissue and cell culture samples. Additionally, oxidative stress was assessed in differentiated adipocyte cell cultures using flow cytometry with dichlorofluorescein as dye. Increases in the expression of PGC1- $\alpha$ , PRDM16, and UCP1 were observed when mouse tissues were treated with the TPP+C10, while a decrease in oxidative stress was observed in adipocytes when they were incubated with the cation. These results indicate that TPP+C10 has a browning effect and an antioxidant activity at the level of mitochondrial oxidative stress.

**Autores:** Díaz-Martínez, C.1; Uribe, D.1; Norambuena, U.1; Orellana, J.F.1; Fonfach, C.1; Suárez-Rozas, C.2; Vivar, R.1; Catalán, M.1

**Afiliación:** 1Laboratorio de Farmacología y Mecanismos de Enfermedad, ICBM, Facultad de Medicina, Universidad de Chile; 2Centro de Química Médica, ICIM, Facultad de Medicina, Universidad del Desarrollo.

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** [carla.diaz\\_m@uq.uchile.cl](mailto:carla.diaz_m@uq.uchile.cl)

**Agradecimientos:** Fondecyt Regular 1251859 (Mabel Catalán) Fondecyt Regular 1251398 (Raúl Vivar)

**Socio Patrocinante:** Mabel Catalán

#### 35. ISO-1 INDUCES PI3K PHOSPHORYLATION MEDIATED BY THE $\alpha 7$ -NACHR IN HUMAN ENDOTHELIAL CELLS (HUVEC)

ISO-1 induce la fosforilación de PI3K mediada por el receptor  $\alpha 7$ -nAChR en células endoteliales humanas (HUVEC)

**Resumen:** Angiogenesis is an essential process for tissue growth and repair, whose dysregulation has been associated with various pathologies. Among the molecular pathways involved, the  $\alpha 7$  isoform of non-neuronal nicotinic acetylcholine receptors ( $\alpha 7$ -nAChR) stands out as a pentameric ion channel highly permeable to  $\text{Ca}^{2+}$  that promotes angiogenesis through activation of the phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathway. In our laboratory, we have demonstrated that the isoxazolic nucleus-containing molecule ISO-1 modulates these receptors; however, its effects on angiogenic processes and the PI3K/Akt pathway mediated by  $\alpha 7$ -nAChR remain not fully elucidated. The objective of this study was to evaluate the effect of ISO-1 on the activation of phosphatidylinositol-3-kinase (PI3K) in human umbilical vein endothelial cells (HUVEC), by optimizing the Western blot (WB) protocol for the detection of the phosphorylated form of PI3K (p-PI3K). Optimization included adjustments to incubation time, blocking time, and washing steps. Cells were exposed to ISO-1 (1  $\mu\text{M}$ ), choline ( $\alpha 7$ -nAChR agonist; 10  $\mu\text{M}$ ),  $\alpha$ -bungarotoxin ( $\alpha 7$ -nAChR antagonist; 100 nM), and ISO-1+BTX, and levels of p-PI3K and total PI3K were assessed by WB using specific antibodies. ISO-1 was found to induce PI3K phosphorylation mediated by  $\alpha 7$ -nAChR under optimized WB conditions: 5-minute incubation with the agonist, 120-minute blocking at room temperature, and five 5-minute washes. This effect was evidenced by an increased intensity of the p-PI3K band upon ISO-1 stimulation, similar to that observed with choline, and was markedly reduced by

preincubation with BTX. These findings confirm that the proangiogenic effects of ISO-1 are specifically mediated by PI3K activation through the  $\alpha 7$ -nAChR.

**Autores:** Hernández-Vivanco B. 1,2; Foster S. 1,2; Espinoza H. 1; Cortés-Saavedra MP. 1

**Afiliación:** 1 Vascular Research Laboratory, School of Chemistry and Pharmacy, Faculty of Pharmacy, University of Valparaíso, Valparaíso, 2360102, Chile.; 2 Quilpué Hospital, Quilpué, Chile

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** [bastian.hernandez@uv.cl](mailto:bastian.hernandez@uv.cl)

**Agradecimientos:** None

**Socio Patrocinante:** None

#### 36. RATIONAL DESIGN AND TEA BAG-BASED SOLID-PHASE SYNTHESIS (FMOC) OF ANTIVIRAL PEPTIDES TARGETING THE RNA-DEPENDENT RNA POLYMERASE (RDRP) OF THE INFECTIOUS SALMON ANEMIA VIRUS (ISAV). diseño racional y síntesis en fase sólida (fmoc) con estrategia tea bag de péptidos antivirales dirigidos a la rna polimerasa del isav.

**Resumen:** The infectious Salmon Anemia Virus (ISAV) is a major pathogen affecting the global salmon aquaculture industry, causing significant economic losses. Current control measures, including vaccination and biosecurity protocols, are insufficient to fully prevent outbreaks, highlighting the urgent need for alternative antiviral strategies. Antiviral peptides have emerged as promising candidates due to their specificity, adaptability, and potential for rational design using computational approaches. This study aimed to design, evaluate, and synthesize antiviral peptides targeting the RNA-dependent RNA polymerase (RdRp) of ISAV, a key enzyme for viral replication. The computational workflow included three stages: structural modeling and sequence generation, obtaining consensus sequences of RdRp subunits from 42 ISAV isolates and predicting their 3D structures with AlphaFold, evaluated via SWISSMODEL, interaction analysis and peptide design, analyzing inter-subunit interactions with LigPlot+ and visualizing key residues in VMD to extract peptide fragments; and candidate evaluation, performing docking simulation with HPEPDOCK and estimating binding free energies ( $\Delta G$ , kcal/mol) with PRODIGY to select the most promising peptides. Selected inhibitory peptides (iPeps) were subsequently synthesized by solid-phase peptide synthesis using the Tea Bag strategy, allowing parallel and efficient production of sequences. In silico analyses identified iPeps with strong predicted interactions in conserved regions of the RdRp active site and favorable binding energies. This study demonstrates that the integration of rational bioinformatic design with Tea Bag-based SPPS provides a versatile and efficient pipeline for developing novel antiviral peptides against ISAV. Future work will involve in vitro validation to assess the antiviral activity and therapeutic potential of the synthesized peptides.

**Autores:** Salas E.

**Afiliación:** PUCV

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** [evelyn.salas.o@mail.pucv.cl](mailto:evelyn.salas.o@mail.pucv.cl)

**Agradecimientos:** FONDECYT 1240448

**Socio Patrocinante:** Javier Bravo



### 37. MAR1 RESTORES CARDIAC STRUCTURE AND FUNCTION IN EARLY DIABETIC CARDIOMYOPATHY

**MAR1 RESTAURA LA ESTRUCTURA y la función cardíaca en la cardiomiopatía diabética temprana**

**Resumen:** Introduction: Diabetic cardiomyopathy (DCM) is characterized by chronic hyperglycemia-induced remodeling, including inflammation, cardiomyocyte hypertrophy and death, fibrosis, and systolic/diastolic dysfunction. Specialized pro-resolving mediators (SPMs), derived from omega-3 fatty acids, actively terminate inflammation and promote repair. Maresin 1 (MaR1) is an SPM shown in cardiac injury models to reduce inflammation, favor reparative macrophage phenotypes, limit cell death, and preserve function. Objective: To investigate the cardioprotective actions of MaR1 on cardiac remodeling and macrophage subpopulations in diabetic myocardium. Methods: Diabetes was induced in male C57BL/6 mice by daily intraperitoneal injections of streptozotocin (50 mg/kg) for 5 days. After 4 weeks, animals received MaR1 (4 ng/g, i.p.) or vehicle for 4 weeks. Normoglycemic mice served as controls (n=4–6/group). Cardiac hypertrophy, fibrosis, and cell death were evaluated histologically; cytokine expression by RT-qPCR; function by echocardiography; and leukocyte populations by flow cytometry. Data are mean  $\pm$  SD and analyzed by one-way ANOVA or Kruskal-Wallis. Results: MaR1 reduced cardiac fibrosis (6.8 $\pm$ 0.8% control, 8.2 $\pm$ 2.1% diabetic, 6.2 $\pm$ 1.6% diabetic+MaR1) and cardiomyocyte death (2.0 $\pm$ 0.7%, 6.1 $\pm$ 1.4%, 5.0 $\pm$ 1.5%), while increasing myocyte diameter (13.0 $\pm$ 0.6  $\mu$ m, 23.3 $\pm$ 1.0  $\mu$ m, 34.7 $\pm$ 4.4  $\mu$ m). TNF- $\alpha$  expression decreased (1.0 $\pm$ 0.0, 2.4 $\pm$ 0.6, 1.7 $\pm$ 0.8), whereas IL-4 rose (1.0 $\pm$ 0.0, 1.3 $\pm$ 0.3, 2.3 $\pm$ 0.4). Function improved, with reduced left ventricular diameter (0.7 $\pm$ 0.0 mm, 1.0 $\pm$ 0.0 mm, 0.6 $\pm$ 0.0 mm). MaR1 also restored macrophage balance: Timd4+ macrophages (1.1 $\pm$ 0.1%, 2.0 $\pm$ 0.4%, 1.7 $\pm$ 0.5%) and Timd4- monocytes (13.7 $\pm$ 4.5%, 44.9 $\pm$ 22.0%, 15.0 $\pm$ 9.3%). Conclusions: MaR1 exerts cardioprotective effects in DCM by attenuating fibrosis and cell death, modulating hypertrophy, restoring macrophage composition, and improving cardiac function.

**Autores:** Norambuena-González R.1,2; Morales Muñoz P.1,2; Herrera Vielma F.2,4; Quiñones San Martín M.2,4; Berrocal Navarrete F.2,6; Muñoz Carrasco N.2,5; Marín Sanhueza P.2,6; Ocaris Jiménez M.2,6; Pailahual Oyarzo J.2,6; Andrés A Herrada7; Moore-Carrasco R.3; Zúñiga-Hernández J.2; Daniel R. González2.  
**Afiliación:** Doctorate Program in Biomedical Sciences, Universidad de Talca1. Pharmacology Laboratory, Department of Basic Biomedical Sciences, Faculty of Health Sciences, Universidad de Talca2. Department of Clinical Biochemistry and Immunohematology, Faculty of Health Sciences, Universidad de Talca3. Doctorate in Science Program, mention in Research and Development of Bioactive Products, Institute of Chemist  
**Area de la Farmacología:** Cardiovascular pharmacology  
**Dirección de Correo:** [ramon.norambuena.rng@gmail.com](mailto:ramon.norambuena.rng@gmail.com)  
**Agradecimientos:** National Doctoral Scholarship ANID N°21221512 and Fondecyt Initiation N° 11200258 (PhD Jessica Zúñiga Hernández).  
**Socio Patrocinante:** Dra. Jessica Zúñiga

### 38. STANDARDIZING A MURINE MODEL OF ANXIETY DURING NALOXONE-PRECIPIATED MORPHINE WITHDRAWAL

**Estandarización de un modelo murino de ansiedad durante la abstinencia de morfina precipitada por naloxona**

**Resumen:** Opioid withdrawal induces anxiety that promotes relapse. We aimed to standardize an acute morphine-withdrawal model in mice and to establish a sensitive scheme to quantify anxiety for future pharmacological testing. We treated C57BL/6 mice of both sexes with an escalated morphine regimen (10–80 mg/kg, i.p.) for 6 days (11 total injections) and precipitated withdrawal with naloxone (2 mg/kg, i.p.). We validated withdrawal aversiveness with a conditioned place aversion (CPA) paradigm. We assessed anxiety in two-time windows using the Open Field (OF) and Elevated Plus Maze (EPM): a basal window (24 h for OF and 48 h for EPM after withdrawal) and an acute window (15 min after re-inducing withdrawal with morphine/naloxone to increase sensitivity). The morphine/naloxone regimen produced robust CPA (F(2,44) = 1676.276, p < 0.001), confirming precipitated withdrawal as aversive. We detected a significant effect in females and a non-significant trend in males. In the basal window (24–48 h), we did not observe treatment-related differences in OF or EPM, indicating low

sensitivity at that time. We are implementing an acute re-induction scheme to align measurement with the expected behavioral peak and to confirm detection of induced anxiety. In summary, we standardized a naloxone-precipitated morphine-withdrawal model that induces aversion in C57BL/6 mice. Although the model is robust, accurate anxiety quantification requires assessment in an acute window after re-induction to maximize detection. This protocol could provide a solid methodological basis for screening anxiolytic compounds during opioid withdrawal.

**Autores:** Gárate-Pérez MF1, 2, Renard GM1  
**Afiliación:** Universidad de Santiago de Chile  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [macarena.garate@usach.cl](mailto:macarena.garate@usach.cl)  
**Agradecimientos:** DICYT Regular 022401RG, Universidad de Santiago de Chile.  
**Socio Patrocinante:** Renard GM

### 39. BIOINFORMATIC CHARACTERIZATION OF GLP1-R REVEALS DISTINCT BINDING PROFILES OF ANTIPILEPTIC AND ANTIMIGRAINE AGENTS

**La caracterización bioinformática del receptor GLP1 revela perfiles de unión distintos para agentes antiepilépticos y antimigrañosos.**

**Resumen:** Appetite and body weight regulation are complex physiological processes often disrupted by pharmacological treatments for neurological disorders. Several clinical reports have shown that long-term use of antiepileptic and antimigraine drugs may cause appetite alterations and weight fluctuations (Schmidt & Schachter, 2014). These metabolic side effects represent a significant yet underappreciated clinical concern. The glucagon-like peptide 1 receptor (GLP-1R), widely expressed in metabolic and central nervous system tissues, plays a crucial role in regulating appetite and energy balance (Chen et al., 2009; Zhang et al., 2016). Therefore, exploring how neurological drugs may interact with this receptor could provide molecular insight into their metabolic effects. This study aimed to evaluate, through molecular docking and bioinformatic analysis, the potential binding and modulatory capacity of 35 drugs (25 antiepileptics and 10 antimigraine agents) toward the GLP-1 receptor (GLP1-R). Ligands and receptor were optimized. A large-scale docking study was conducted using AutoDock Vina after protonation correction with PropKa and interaction profiling with PLIP. Antimigraine compounds, particularly dihydroergotamine (–11.283 kcal/mol), ergotamine (–11.247 kcal/mol) and lasmiditan (–9.425 kcal/mol), exhibited stronger hydrophobic and  $\pi$ – $\pi$  stacking stabilization. In comparison, antiepileptics such as phenytoin (–8.788 kcal/mol) and fosphenytoin (–8.670 kcal/mol) showed predominant hydrogen bonding and polar contacts. These findings support a structural rationale by which antimigraine drugs may enhance GLP1-R stabilization and signaling, offering a molecular explanation for the appetite-modulating effects observed clinically.

**Autores:** Hendández-Galán, V.1; Velásquez, V.B.2; Iturriaga-Vázquez, P.1; Sotomayor-Zárate, R.2.  
**Afiliación:** 1. Laboratorio de Farmacología Molecular y Química Medicinal, Depto. Ciencias Químicas y RRNN, Facultad de Ingeniería y Ciencias, Universidad de La Frontera, Temuco. 2. Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso.  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [v.hernandez06@ufromail.cl](mailto:v.hernandez06@ufromail.cl)  
**Agradecimientos:** FONDECYT Grant 124-0688 P.I.-V., FONDECYT Grant 124-0141, and CIDI-UV 01/2024 to R.S.-Z. National Doctoral Scholarship No. 21210569 to Velásquez V.B.  
**Socio Patrocinante:** Patricio Iturriaga Vasquez



#### 40. INFLUENCE OF AROMATIC BROMINATION IN THE EFFECTS OF THE ENTACTOGEN MDMA (3,4-METHYLENEDIOXYMETHAMPHETAMINE, "ECSTASY") ON HELPING BEHAVIOUR IN SPRAGUE-DAWLEY RATS

Influencia de la bromación aromática en los efectos del entactógeno MDMA (3,4-metilendioxi metanfetamina, "Éxtasis") en la conducta de ayuda en ratas Sprague-Dawley

**Resumen:** Empathy-like behaviours (e.g., social interaction and helping behaviour) are expressed in humans and rodents through various prosocial behaviours that may be enhanced by the entactogen MDMA (3,4-methylenedioxyamphetamine, or "Ecstasy"). While MDMA increases social interaction, subtoxic doses of the drug seem to disrupt helping behaviour through an unidentified mechanism. Additionally, the aromatic bromination of MDMA at C(2) abolishes its classical psychomotor/prosocial effects in rats. Nevertheless, its effects on helping behaviour are unknown. In the present work, the effect of a single dose of 2Br-MDMA (5 mg/kg i.p.) on helping behaviour has been studied in rats using a water-trap model developed ad hoc. Male Sprague-Dawley rats housed individually for at least one week were randomly assigned in pairs (one named "helper" and the other named "soaked") and placed separately in a "wet"/"dry" box divided by a transparent, acrylic wall with a circular door to go across the wall. Cycles of twelve 5-minute sessions were conducted on consecutive days. Similar cycles were also conducted after interchanging roles. Helping behaviour was verified when the helper rat opened the door to rescue the soaked rat. The results obtained indicated that 2Br-MDMA could inhibit helping behaviour in naïve rat pairs at the single dose evaluated. This effect seems to persist after interchanging roles in the animals tested, as the corresponding latencies do not diminish along cycle sessions. Therefore, 2Br-MDMA might exhibit a disruptive profile like MDMA on helping behaviour, regardless of the water-trap experience. The data are consistent with the notion that aromatic bromination at C(2) might not modulate the effects of MDMA on the willingness to help in naïve rats and preserves inhibition in formerly soaked animals as well.

**Autores:** Jara-Clen, D. 1,2; Silva-Rodríguez A. 1,2; Sepúlveda-Fernández Y. 1,2; Livacic-Rojas, P. 2; Hernández A. 3; Sáez-Briones, P. 1.  
**Afiliación:** 1 Laboratory of Neuropharmacology and Behaviour, School of Medicine, Faculty of Medical Sciences, Universidad de Santiago de Chile. 2 School of Psychology, Faculty of Humanities, Universidad de Santiago de Chile. 3 Laboratory of Neurobiology, Department of Biology, Faculty of Chemistry and Biology, Universidad de Santiago de Chile.  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [dorvs.jara@usach.cl](mailto:dorvs.jara@usach.cl)  
**Agradecimientos:** FUNDING SUPPORT: DICYT-USACH GRANT 022401SB.  
**Socio Patrocinante:** Patricio Sáez-Briones

#### 41. EFFECTS OF CHRONIC ADMINISTRATION OF THE D2 AGONIST QUINPIROLE ON GRK2 IN THE MESOLIMBIC DOPAMINERGIC SYSTEM OF MICE.

Efecto de la administración crónica del agonista D2 quinpirol sobre GRK2 en el sistema dopaminérgico mesolímbico de ratones

**Resumen:** Dopamine (DA) in the mesolimbic circuit is essential for the execution of motivated behaviors, with dopaminergic neurons originating in the ventral tegmental area (VTA) projecting to the nucleus accumbens (NAc). D1R and D2R receptors, coupled to G proteins, mediate dopaminergic signaling in the direct and indirect striatal pathways, respectively, regulating locomotion and DA release. Chronic administration of quinpirole (QNP), a D2R agonist, induces locomotor sensitization and compulsive-like behaviors; however, the underlying cellular mechanisms remain poorly understood. The kinase GRK2 modulates D2R trafficking and desensitization, but its distribution in the mesolimbic system and its response to repeated D2R activation remain incompletely characterized in mice. This study aimed to determine the distribution and levels of GRK2 in the mesolimbic dopaminergic system of C57BL/6J mice, both under basal conditions and after repeated QNP administration. Immunofluorescence was used to identify GRK2 in dopaminergic neurons of the VTA and substantia nigra compacta (SNc), and target areas the NAc and dorsal striatum (DS). Results showed that GRK2 is highly expressed in dopaminergic neurons and less in other unidentified neurons in the midbrain. In projection areas, GRK2 was

localized in medium spiny neurons (MSNs) and other neuronal types. Interestingly, the levels of GRK2 were higher in the midbrain than in the target areas. Repeated QNP produced an acute inhibitory effect on locomotion but did not alter the distribution or levels of GRK2 in either the mesolimbic or mesostriatal pathways. In conclusion, GRK2 is distributed in mesostriatal and mesolimbic pathways, suggesting a role in dopaminergic neurotransmission. Repeated D2R activation via QNP does not alter GRK2 expression or localization, indicating that the drug's early hypolocomotor effects are not dependent on changes in this kinase.

**Autores:** Moreno R.D.1,2,4, Gatica R. 3, Estela Andrés M. 3, Escobar A.P.1,2,4.  
**Afiliación:** Universidad de Valparaíso  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [robinson.moreno@postgrado.uv.cl](mailto:robinson.moreno@postgrado.uv.cl)  
**Agradecimientos:** Fondecyt iniciación N° 11240331 (APE). Fondecyt postdoctorado 3230573 Centro de Neurobiología y Fisiopatología integrativa (CENFI): CIDI UV\_01\_2024 Núcleo EpiNeuro Estela, Andrés Lab: Neuroepigenética Magister en Ciencias biológicas mención Neurociencias – UV  
**Socio Patrocinante:** Angélica del Pilar Escobar Maldonado.

#### 42. SEXUAL DIMORPHISM IN THE REGULATION OF SOMATOSTATIN INTERNEURONS IN THE HIPPOCAMPUS AND THEIR ROLE IN LEARNING AND MEMORY

Dimorfismo sexual en la regulación de las interneuronas de somatostatina en el hipocampo y su rol en aprendizaje y memoria

**Resumen:** Cognitive impairment is characterized by dysfunction in cognitive functions such as memory and learning. During aging, the population of GABAergic interneurons such as somatostatin (SST), parvalbumin (PV), and calretinin (CLR) is affected. This study evaluated how age and sex modulate these populations in the dentate gyrus (DG) and CA1 region of mice aged 6, 12, 18, and 24 months using immunofluorescence. In females, SST interneurons (SST-INs) increased by 83% at 12 months compared to 6 months in the DG, whereas in males they remained constant in the DG up to 24 months. PV-INs showed a progressive reduction in the CA1 of females; in the CA1 of males, they decreased by 37% at 12 months and then increased by 121% at 18 months, accompanied by a compensatory 113% increase in CLR in the DG at 12 months, while females exhibited a continuous decline in CLR in both DG and CA1. These results indicate that sex differentially influences the dynamics of hippocampal interneurons. SST activity was modulated by injecting viral vectors into the dentate gyrus that, when activated by a ligand, induce chemogenetic stimulation (AAV-hSyn-DIO-hM3D(Gq)-mCherry) or inhibition (AAV-hSyn-DIO-h4MD(Gi)-mCherry) of SST neurons. One month after surgery, intraperitoneal administration of the agonist CB21 was used to evaluate the role of SST-INs in different types of memory. Working memory (T-maze), recognition memory, and spatial memory (Barnes Maze and object location) were assessed. Stimulation of SST-INs in the dentate gyrus revealed opposite effects depending on sex: in males it improved working memory by 56% but reduced spatial memory by 59%, whereas in females it increased spatial memory by 56%. These findings confirm a sex-specific dimorphism in hippocampal interneurons and memory.

**Autores:** Antonia-Muñoz, Antonella Osses-Toledo, Ignacio Negroni and Estibaliz Ampuero  
**Afiliación:** Laboratorio de neurofarmacología del comportamiento, facultad de química y biología, Universidad de Santiago de Chile  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [antonia.munoz.a@usach.cl](mailto:antonia.munoz.a@usach.cl)  
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**Socio Patrocinante:** Dra. Estibaliz Ampuero



#### 43. SEX-BIASED m<sup>6</sup>A-Ψ CROSSTALK REPROGRAMS SYNAPTIC TRANSCRIPTS IN THE RAT DORSAL HIPPOCAMPUS UNDER CHRONIC STRESS

Interacción cruzada de m<sup>6</sup>A-Ψ, sesgada por el sexo, reprograma transcritos sinápticos en el hipocampo dorsal de rata bajo estrés crónico

**Resumen:** Epitranscriptomics—the type- and site-specific chemical modification of RNA—adds a regulatory layer to gene expression analogous to DNA/histone epigenetics, but acting at the RNA level. Among more than 170 RNA marks, N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) is the most abundant mRNA modification in the brain and regulates the processing, stability, localization, and translation. Pseudouridine (Ψ) is widespread across RNA classes, conferring distinct structural and functional properties to these molecules. Because neuronal function depends on precise spatiotemporal control, the nervous system may be sensitive to the dynamics of these marks. We hypothesize that chronic stress reshapes the m<sup>6</sup>A-Ψ landscape in the rat dorsal hippocampus (DH)—a relevant structure for cognitive functions such as memory and learning. To explore this, we used a depressive-like paradigm (chronic restraint stress, 2.5 h per day for 14 days) on adult male and female Sprague-Dawley rats (n=4 per condition and sex) to evaluate stress-induced and sex-biased changes in the DH using Nanopore direct RNA-sequencing (DRS) to assess the m<sup>6</sup>A-Ψ landscape. Our data revealed stress-induced, sex-biased remodeling of m<sup>6</sup>A-Ψ on synaptic transcripts in DH. In females, we observed a prevalent opposite signature (m<sup>6</sup>A↓ / Ψ↑) across receptor–excitability and trafficking modules (e.g., Gria1, Cnr1; endosomal Rab11a/Ehd1/Sort1), extending to plasticity regulators (Camk2b, Mtor). In males, intersections showed mostly concordant shifts (m<sup>6</sup>A↑ / Ψ↑) in vesicle cycling and AMPAR auxiliary genes (Synj2, Shisa7, Cacng8) and ionic homeostasis (Atp1a3), with Slc8a2 as an opposite case (m<sup>6</sup>A↑ / Ψ↓). These patterns converge on three drug-addressable synaptic hubs: AMPAR gating/trafficking, vesicle dynamics, and excitability set-points. Our findings indicate that sex-biased m<sup>6</sup>A-Ψ patterns may reflect RNA-level mechanisms of neuroplasticity under chronic stress, supporting the development of candidate biomarkers and RNA-targeted interventions.

**Autores:** Palacios-Avenidaño N.; Corrales W.A.; Alarcón-Mardones M.; Guarnieri T. A.; Fiedler J.L.

**Afiliación:** Laboratory of Neuroplasticity and Neurogenetics, Department of Biochemistry and Molecular Biology, Faculty of Chemical and Pharmaceutical Science, Universidad de Chile.

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [nicolas.palacios@ug.uchile.cl](mailto:nicolas.palacios@ug.uchile.cl)

**Agradecimientos:** This work was supported by FONDECYT 1230471 (JLF)

**Socio Patrocinante:** Jenny Lucy Fiedler Temer

#### 44. ASTROGLIOSIS-INDUCED NEUROINFLAMMATION AS A MODULATOR OF SYNAPTIC PLASTICITY IN EARLY OBESITY: PHARMACOLOGICAL PROJECTIONS IN THE REGULATION OF HIPPOCAMPAL AMPA AND NMDA RECEPTORS

Neuroinflamación inducida por astrogliosis como modulador de la plasticidad sináptica en obesidad temprana: proyecciones farmacológicas en la regulación de receptores AMPA y NMDA del hipocampo

**Resumen:** Early-life obesity has been linked to hippocampal dysfunction and cognitive deficits during critical developmental stages. Neuroinflammation, characterized by reactive astrogliosis and elevated GFAP expression, is considered a key factor disrupting glutamatergic signaling and synaptic plasticity mechanisms. This study investigated the effects of chronic high-fat diet (HFD) exposure from weaning (postnatal days 21–77) on spatial memory and hippocampal gene expression of glutamate receptor subunits, including GluA1 and GluA2 (AMPA receptors), as well as GluN1, GluN2A, and GluN2B (NMDA receptors), and GFAP in C57BL/6 mice. Behavioral assessments were conducted using the Y-maze and Open Field tests, while gene expression levels were quantified via RT-qPCR in dorsal and ventral hippocampal regions. Results indicated that HFD led to early glial activation and increased expression of glutamatergic receptor subunits in males, suggestive of synaptic overactivation and a potential imbalance in glutamatergic homeostasis. Conversely, HFD females displayed spatial memory impairments without significant molecular alterations, implying

compensatory mechanisms or involvement of extra-hippocampal circuits. These findings highlight a sex-dependent response to early-life obesity and support the hypothesis that astrocyte-mediated neuroinflammation modulates synaptic plasticity through regulation of AMPA and NMDA receptors. Importantly, these results suggest potential pharmacological strategies targeting glutamatergic receptor activity to prevent or alleviate synaptic dysfunction associated with early metabolic stress.

**Autores:** Salazar-Cea, M.; Escobar-Luna, J.; Etcheagaray-González, C.; Dib-Schwelling, T.; Olivares-Barraza R.; Sotomayor-Zárate, R.

**Afiliación:** Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso

**Área de la Farmacología:** Neurofarmacología

**Dirección de correo:** [ramon.sotomayor@uv.cl](mailto:ramon.sotomayor@uv.cl)

**Agradecimientos:** FONDECYT Grant 124-0141 and CIDI-UV 01/2024 to R.S.-Z. National Doctoral Scholarship No. 21230865 to Escobar-Luna, J.

**Socio patrocinate:** Ramón Eduardo Sotomayor Zárate

#### 45. NAPHTYL-PYRROLIDINE DERIVATIVES NOVELS DUAL SERT/NACHR BLOCKERS AND THEIR SWIMMING BEHAVIOR ON ZEBRAFISH USING THE NOVEL TANK DIVING TEST (NTT). Derivados de Naftil-Pirrolidina: nuevos bloqueadores duales de SERT/nAChR y su comportamiento de natación en pez cebra utilizando el Novel Tank Diving Test (NTT).

**Resumen:** Monoaminergic neurotransmitters, such as dopamine, norepinephrine, and serotonin, along with acetylcholine, regulate crucial functions of the central nervous system (CNS). They are responsible for modulating emotions, learning, attention, and motor activity, and are essential regulators of behavior. Serotonin is a key regulator of mood, sleep, and cognition, while dopamine regulates movement and executive functions of the cerebral cortex. Acetylcholine is a crucial chemical mediator in the release of dopamine, and through the activation of nicotinic receptors, it regulates the vesicular release of both dopamine and norepinephrine. nAChRs (nicotinic receptors) are primarily associated with anxiety disorders, attention, and learning. In our laboratory, we have designed novel molecules with dual activity, acting as serotonin transporter blockers and antagonists of the alpha 4, beta 2 subtype of nicotinic acetylcholine receptors (nAChRs). We achieved this by using the naphthyl group of duloxetine and the pyrrolidine portion of nicotine, linked via an ester bond to obtain substances with simultaneous activity against SERT and nAChRs. In this study, we investigated the swimming behavior of zebrafish using the Novel Tank Diving Test to determine if these compounds exhibit anxiolytic activity in this animal model. Our results indicate that NPE exhibits a more pronounced anxiolytic profile than NPM, characterized by a significant decrease in time spent at the bottom of the fish tank and a reduction in latency to the top of the tank. Exploratory activity (transitions) was observed to be reduced for both compounds.

**Autores:** Segura K. 1; Aties C. 1; Iturra A. 1; Vega G. 1; Leal C. 1; Iturriaga-Vásquez P. 1; Fariás A. 2

**Afiliación:** 1.- Universidad de La Frontera; 2.- Universidad de Viña del Mar

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [k.segura01@ufromail.cl](mailto:k.segura01@ufromail.cl)

**Agradecimientos:** Fondecyt Regular 1240688

**Socio Patrocinante:** Patricio Iturriaga Vásquez



#### 46. THE EFFECT OF 5-HT<sub>2A</sub> RECEPTOR INHIBITION ON THE NEUROPLASTIC EFFECTS OF MDMA (3,4-METHYLENEDIOXYMETHAMPHETAMINE) IN THE ANTERIOR CINGULATE CORTEX: POSSIBLE IMPLICATIONS FOR HELPING BEHAVIOUR IN RATS

La inhibición del receptor 5-HT<sub>2A</sub> sobre la neuroplasticidad inducida por MDMA (3,4-metilendioximetanfetamina) en la corteza cingulada anterior: implicaciones en la conducta de ayuda en ratas

**Resumen:** Helping behaviour is an empathy-based prosocial behaviour that may occur in humans and rodents as the result of a combination between the willingness to help with the activation of key central nuclei associated with cognitive capabilities. Indeed, helping behaviour relies on the activity of mirror neurones located in the anterior cingulate cortex (ACC), and some studies have shown that neuroplasticity in the ACC is associated with emotions. Intriguingly, the entactogen MDMA (3,4-methylenedioxymethamphetamine, "Ecstasy") has been reported to disrupt helping behaviour. Nevertheless, the relevance of cognitive functions mediated by the ACC in the execution or remembering of prosocial decisions is not fully understood, and the functional role of serotonin remains unknown. In this work, the effects of the 5-HT<sub>2A</sub> receptor antagonist ketanserin (5µg/0.5µl) on long-term synaptic potentiation (LTP) evoked by MDMA (10 mg/kg) in vivo were evaluated by microinjection in the ipsilateral paraventricular hypothalamic nucleus and contralaterally evoked in the ACC in rats. The animals were anaesthetised, tracheostomised, and placed in a stereotaxic frame under artificial ventilation. Field potentials were evoked in the ACC by electrical stimulation in the contralateral ACC. Transcallosal LTP-like plasticity was elicited by applying two consecutive pulse trains of 100 Hz each at double strength. The results obtained showed that train-stimulation of the contralateral ACC of saline-treated rats produced a long-lasting increase in peak-to-peak amplitude of transcallosal responses. Following MDMA administration, a significant LTP increase could be recorded at the ACC. This effect is inhibited by the 5-HT<sub>2A</sub> antagonist ketanserin. These data confirm that transcallosal LTP is increased by serotonin released in the ACC after MDMA treatment, which might be related to an eventual effect of MDMA on remembering helping behaviour execution.

**Autores:** Silva-Rodríguez A. 1,2; Hernández A. 3; Sepúlveda-Fernández Y. 1,2; Jara-Clen, D. 1,2; Livavic-Rojas, P. 2; Sáez-Briones, P. 1.

**Afilación:** 1 Laboratory of Neuropharmacology and Behaviour, School of Medicine, Faculty of Medical Sciences, Universidad de Santiago de Chile. 2 School of Psychology, Faculty of Humanities, Universidad de Santiago de Chile. 3 Laboratory of Neurobiology, Department of Biology, Faculty of Chemistry and Biology, Universidad de Santiago de Chile.

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [amanda.silva@usach.cl](mailto:amanda.silva@usach.cl)

**Agradecimientos:** FUNDING SUPPORT: DICYT-USACH GRANT 022401SB.

**Socio Patrocinante:** Alejandro Hernández Kunstmann

#### 47. THE ROCK INHIBITOR FASUDIL AND SERTRALINE SHARE MORPHOLOGICAL AND MOLECULAR EFFECTS IN THE HIPPOCAMPUS OF CHRONICALLY STRESSED RATS: EXPLORING COMMON ANTIDEPRESSANT PATHWAYS BY NETWORK PHARMACOLOGY

el inhibidor de rock fasudil y la sertralina comparten efectos morfológicos y moleculares en el hipocampo de ratas crónicamente estresadas: explorando vías antidepresivas comunes mediante farmacología de redes

**Resumen:** Despite the widespread use of selective serotonin reuptake inhibitors like sertraline, the intricate molecular mechanisms underlying major depression and the therapeutic efficacy of these treatments remain not fully elucidated. Building on our preliminary findings, this study investigates the antidepressant effects of fasudil, a Rho-associated protein kinase (ROCK) inhibitor typically utilized as a vasodilator and antispasmodic, and compares its effects with those of sertraline using a chronic restraint stress model in rats. Specifically, we examined the effects of chronic administration on dendritic spine density, key molecular survival pathways, and miRNA levels in the hippocampus. Adult male Sprague-Dawley rats were administered sertraline, fasudil (10 mg/kg/day), or saline over 14 days, with a subset experiencing daily restraint stress. Our findings demonstrate that both sertraline and fasudil

effectively prevented stress-induced reductions in dendritic spine density and miR-138 levels in the rat hippocampus. Additionally, by employing a network pharmacology approach, we explored the converging molecular pathways influenced by both drugs, facilitating the identification of novel molecular targets and pathways implicated in the pathophysiology of depression and its treatment. Pharmacoinformatic analysis revealed common signaling cascades and critical proteins that may potentially underlie the observed pharmacological effects, contributing to a paradigm shift in understanding depression by integrating drug repurposing and network pharmacology, offering valuable insights into the underlying mechanisms of depression and the antidepressant effect from a new network-based paradigm rather than focusing solely on a single protein target.

**Autores:** Gonzalo García-Rojo <sup>1,2</sup>; Ignacio Valenzuela Martínez <sup>3</sup>; Felipe Aguayo <sup>1</sup>;

Mauricio Muñoz-Llanos <sup>1</sup>; David Ramírez <sup>3</sup>; and Jenny L. Fiedler <sup>1</sup>

**Afilación:** <sup>1</sup> Share the first authorship, 1 Laboratory of Neuroplasticity and Neurogenetics, Department of Biochemistry and Molecular Biology, Faculty of Chemical and Pharmaceutical Sciences, Universidad de Chile; 2 Departamento de Química, Facultad de Ciencias, Universidad de La Serena; 3 Departamento de Farmacología, Facultad de Ciencias Biológicas, Universidad de Concepción

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [ignmarinez@udec.cl](mailto:ignmarinez@udec.cl)

**Agradecimientos:** This study was supported by FONDECYT 11241164 (García-Rojo G.), FONDECYT 1230471 (J.L. Fiedler), FONDECYT 1220656 (Ramírez, D.), and DIDULS PR23211213 (García-Rojo G.).

**Socio Patrocinante:** No corresponde.

#### 48. PSILOCIIN TREATMENT MODULATES m<sup>6</sup>A RNA METHYLATION IN CULTURED CORTICAL NEURONS

Tratamiento con psilocina modula las metilaciones m<sup>6</sup>A en RNA de cultivo de neuronas corticales.

**Resumen:** Psychedelic compounds have shown remarkable therapeutic potential in the treatment of various neuropsychiatric disorders. This effect is associated with their ability to induce rapid and sustained effects on neuroplasticity. Among classical psychedelics, psilocybin stands out for having the strongest clinical evidence and for receiving FDA breakthrough therapy designation for treatment-resistant depression. Psilocybin acts as a prodrug, and the effects observed in vivo are attributed to its active metabolite, psilocin. Psilocin acts as an agonist at serotonin 5-HT<sub>2</sub> receptors, with its neuroplastic and therapeutic actions primarily driven by 5-HT<sub>2A</sub> receptor activation in prefrontal cortex pyramidal neurons. Its enduring neuroplastic effects, even after clearance, suggest a lasting impact on gene expression. While transcriptomic and epigenetic changes have been documented, they do not fully explain these long-term effects, indicating a role for additional regulatory mechanisms such as post-transcriptional modifications. To date, the influence of psilocin on post-transcriptional regulation in neurons remains unexplored. N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) is the most prevalent mRNA modification in mammals and is especially abundant in the brain, where it supports neuronal plasticity. In this study, we investigated whether psilocin alters global m<sup>6</sup>A levels in cultured cortical neurons. Psilocin treatment significantly increased m<sup>6</sup>A methylation, accompanied by enhanced nuclear translocation of the methyltransferase METTL3. These findings suggest that m<sup>6</sup>A modifications may contribute to the sustained neuroplastic effects of psilocin.

**Autores:** Gonzales P. I.; Palacios N. A.; Alarcón M. I.; Guarnieri T. A. and Fiedler J. L.

**Afilación:** Laboratorio de neuroplasticidad y neurogenética, Facultad de ciencias químicas y farmacéuticas, Universidad de Chile.

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [pablo.gonzalez\\_mori@ug.uchile.cl](mailto:pablo.gonzalez_mori@ug.uchile.cl)

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**Socio Patrocinante:** Jenny Fiedler.



#### 49. NETWORK PHARMACOLOGY AND THE NEUROPROTECTIVE POTENTIAL OF A CANNABIDIOL-RICH FULL SPECTRUM OIL

Farmacología de redes y el potencial neuroprotector de un aceite de espectro completo rico en cannabidiol

**Resumen:** Cannabis sativa has gained increasing attention for its therapeutic applications, with cannabidiol (CBD) standing out for its potential neuroprotective effects in neurodegenerative diseases. In this study, the chemical composition of a full-spectrum CBD-rich oil (OCBD) was analyzed using HPLC-DAD and HPLC-QTOF-MS/MS, identifying 62 phytocompounds, including 10 quantified phytocannabinoids, with CBD representing 57% of the total content. Lipid and metal profiles were also determined. Cytotoxicity was assessed in PC12 cells using the MTT assay, revealing that OCBD was non-toxic at low concentrations, while higher doses reduced cell viability in a concentration- and time-dependent manner. The optimal working concentration was established at 5 µg/mL. The antioxidant effect of OCBD was confirmed in PC12 cells exposed to H<sub>2</sub>O<sub>2</sub>, where it significantly improved cell viability. Through network pharmacology, 24 protein targets of 20 phytocannabinoids were identified from the ChEMBL database, highlighting CNR1, CNR2, and TRPV1 receptors. A protein-protein interaction network was constructed using STRING, and 524 associated diseases were retrieved through Open Targets and Disease Ontology. A sub-analysis focused on Alzheimer's and Parkinson's diseases revealed key interactions with adrenergic and dopaminergic receptors, as well as enzymes involved in neuroinflammation. Functional enrichment analysis using ShinyGo and Enrichr identified relevant signaling pathways, including GABAergic synapse, retrograde endocannabinoid signaling, and long-term potentiation. Overall, these findings suggest that OCBD may modulate critical neurobiological pathways associated with neurodegeneration, supporting its therapeutic potential as a multi-target neuroprotective agent.

**Autores:** Martínez-García C.1, Borrego-Muñoz P.2, Estuardo F.J.1, Valenzuela-Martínez L.1, Oliares L.3, Pombo Ospina L.M.2, Piñeros L.G.2, Delgado Delgadillo C.2, González J.5, Mardones C.3, Fuentealba J.4, Ramírez R.1.

**Afilación:** 1Departamento de Farmacología, Facultad de Ciencias Biológicas, Universidad de Concepción. 2Centro de Investigación, Fundación Universitaria Juan N. Corpas. 3Departamento de Análisis Instrumental, Facultad de Farmacia, Universidad de Concepción. 4Departamento de Fisiología, Facultad de Ciencias Biológicas, Universidad de Concepción. 5Nutrición y Bioquímica, Pontificia Universidad Javieriana

**Área de la Farmacología:** Neurofarmacología

**Dirección de Correo:** [clamarinez2022@udec.cl](mailto:clamarinez2022@udec.cl)

**Agradecimientos:** Agencia Nacional de Investigación y Desarrollo (ANID) chilena, Fondecyt 1220656, 1230446. Beca de Doctorado Nacional, Año Académico 2024, ANID, Folio N° 2124242.

**Socio Patrocinante:** Dr. David Ramírez Sánchez

#### 50. PHARMACOGENOMICS APPLIED TO 5-FU IN ADVANCED COLORECTAL CANCER: IMPACT OF GENETIC POLYMORPHISMS IN TYMS, DPYD, ABCB1 AND MTHFR ON OVERALL SURVIVAL.

Farmacogenómica aplicada a 5-FU en cáncer colorrectal: impacto de polimorfismos genéticos en TYMS, DPYD, ABCB1 y MTHFR en la sobrevida global.

**Resumen:** Colorectal cancer (CRC) is the second most common malignancy in Chile, frequently diagnosed at advanced stages, with nearly 25% of cases metastatic at onset and a five-year survival rate of 14%. Its treatment typically involves 5-fluorouracil (5-FU)-based regimens. However, both the efficacy and safety profiles of 5-FU vary among patients, partly due to genetic polymorphisms in thymidylate synthase (TYMS) and dihydropyrimidine dehydrogenase (DPYD) genes. Likewise, variants in genes related to glutathione-S-transferases (e.g., GSTP1) and DNA repair pathways have been associated with oxaliplatin response, although findings remain inconsistent across studies. The aim of this study was to identify clinically relevant genetic variants in TYMS, DPYD, MTHFR, and ABCB1 genes and their association with treatment efficacy in Chilean patients with advanced CRC and to integrate these with clinical factors into a predictive survival model for 5-FU-based chemotherapy. In order to that, a retrospective cohort of 126 patients with advanced CRC treated with 5-FU-based regimens was analyzed. Treatment efficacy was assessed using Kaplan-Meier survival curves

and log-rank tests for five-year overall survival (OS), complemented by multivariate regression models. Eleven variants from four genes were evaluated: TYMS (rs45445694, rs151264360, rs2847153), DPYD (rs1801265, rs67376798, rs55886062, rs3918290), ABCB1 (rs1045642, rs1128503), and MTHFR (rs1801131, rs1801133). Decreased OS was observed for TYMS del/del (HR = 1.95), ABCB1 c.3435T>C T/T (HR = 2.74), DPYD rs1801265 C allele (HR = 2.22), MTHFR rs1801131 CC (HR = 2.96), and hepatic metastasis (HR = 2.06) (model p = 0.0001). This study developed preliminary predictive models integrating pharmacogenetic variants in DPYD, TYMS, ABCB1, and MTHFR with clinical variables. These findings support the implementation of pharmacogenetic-guided dosing strategies to optimize 5-FU efficacy in Chilean CRC patients.

**Autores:** Claudio Alarcón 1,2; Audry Escudero 3; Alicia Colombo 4,5; Olga Barajas 6; Nelson M. Varela 1,7; Luis Quiñones 1,2,4,7; Leslie Cerpa 1,5,7.

**Afilación:** 1 Laboratory CQF, Department of Basic and Clinical Oncology, University of Chile. 2 Department of Pharmaceutical Sciences and Technology, Faculty of Chemical and Pharmaceutical Sciences, University of Chile. 3 Faculty of Pharmacy, University of Costa Rica, 4 Biobank of Fluid and Tissues of University of Chile 5 CECAN, Santiago, Chile. 6 HCUCH. 7 RELVAF, Santiago, Chile.

**Área de la Farmacología:** Farmacogenética

**Dirección de Correo:** [claudio.alarcon.c@ug.uchile.cl](mailto:claudio.alarcon.c@ug.uchile.cl)

**Agradecimientos:** FONDECYT Grant N°1211948

**Socio Patrocinante:** Leslie Cerpa

#### 51. DPYD RS1801265 GENETIC AND HAPB3 VARIANTS AS PREDICTORS OF 5-FLUOROURACIL TOXICITY IN CHILEAN COLORECTAL CANCER PATIENTS

Variantes genéticas rs1801265 y HapB3 del gen DPYD como predictores de toxicidad a 5-fluorouracil en pacientes chilenos con cáncer colorrectal

**Resumen:** Background/Objectives: The DPYD gene plays a central role in the metabolism of fluoropyrimidines such as 5-fluorouracil (5-FU), influencing both drug toxicity and therapeutic efficacy. Genetic polymorphisms in DPYD contribute to interindividual variability in dihydropyrimidine dehydrogenase activity and 5-FU elimination, with 10–30% of treated patients developing severe toxicity. However, most pharmacogenomic data derive from European populations, limiting predictive applications across Latin American groups, while additional functionally significant polymorphisms remain unexplored. This study evaluated the DPYD rs1801265 variant and HapB3 haplotype in Chilean colorectal cancer patients undergoing neoadjuvant 5-FU-based chemotherapy. Methods: Genotyping was performed using allele-specific TaqMan® probes. Genotype and allele frequencies were determined by direct counting, and Hardy–Weinberg equilibrium was verified by  $\chi^2$  test. Associations with clinical outcomes were assessed under dominant and recessive models. For rs1801265, overall survival was analyzed through Kaplan–Meier curves and log-rank tests, while hazard ratios (HR) and 95% confidence intervals were estimated using Cox proportional hazards regression adjusted for age, sex, treatment regimen, and metastasis. Toxicity endpoints (neuropathy, digestive and hematologic events) were evaluated by logistic regression. HapB3 haplotype was analyzed using haplotype-based logistic models for recessive effects. Results: Carriers of the rs1801265 C allele showed increased risk of reduced overall survival (HR=1.8; p=0.049) and chemotherapy-induced neuropathy (OR=4.6; p=0.05). A trend toward higher digestive toxicity was also observed. HapB3 displayed a possible association with clinical toxicity under a recessive model. Conclusions: These findings highlight the clinical relevance of DPYD variants in the Chilean population and support their inclusion in pharmacogenetic testing to optimize fluoropyrimidine safety.

**Autores:** Andrea Calquín1, Claudio Alarcón1,2; Alicia Colombo3,4; Olga Barajas5,6; Luis Quiñones1,2,5,7; Leslie Cerpa1,5,7.

**Afilación:** 1 Lab. Chem. Carcinogenesis & Pharmacogenetics (CQF), Dept. Basic & Clinical Oncology, Univ. Chile. 2 Dept. Pharm. Sci. & Tech., Fac. Chem. & Pharm. Sci., Univ. Chile. 4 Biobank of Fluids & Tissues, Univ. Chile. 5 Ctr. Cancer Prev. & Control (CECAN), Santiago, Chile. 6 Clinical Hospital, Univ. Chile. 7 Latin American Network for Clinical Pharmacogenomics (RELVAF), Santiago, Chile.

**Área de la Farmacología:** Farmacogenética

**Dirección de Correo:** [andrea.calquin@ug.uchile.cl](mailto:andrea.calquin@ug.uchile.cl)

**Agradecimientos:** ACKNOWLEDGMENTS AND FUNDING: Proyecto Semilla-CECAN 2025

**Socio Patrocinante:** SPONSORING SOFARCHI MEMBER: Leslie Cerpa

## 52. ASSOCIATION BETWEEN ADVERSE REACTIONS TO FLUOROPYRIMIDINE-BASED CHEMOTHERAPY AND POLYMORPHIC VARIANTS IN GENES ENCODING ENZYMES INVOLVED IN THEIR METABOLISM IN PATIENTS WITH ADVANCED COLORECTAL CANCER

Asociación entre reacciones adversas a tratamientos quimioterapéuticos con fluoropirimidinas y variantes polimórficas en genes codificantes para enzimas implicadas en su metabolización, en pacientes con cáncer colorrectal avanzado.

**Resumen:** Colorectal cancer is a significant public health issue in Chile, with 3,330 deaths reported in 2022. The main chemotherapeutic agents, 5-fluorouracil (5-FU) and capecitabine, are effective but can cause severe adverse drug reactions (ADRs), sometimes leading to hospitalization or death. Although factors such as age, ethnicity, comorbidities, and drug interactions influence treatment response, interindividual variability cannot be fully explained without considering genetic factors. Polymorphisms in the DPYD gene, involved in fluoropyrimidine elimination, are known contributors but are too infrequent to explain all ADRs. Therefore, variants in other metabolic genes such as CES1, CDA, TYMP, UMPS, and TYMS are being studied for their potential association with 5-FU and capecitabine toxicity. This retrospective, observational, case-control study evaluated the association between polymorphic variants in these genes and the development of ADRs in 92 patients with advanced colorectal cancer treated with 5-FU. Samples were genotyped using TaqMan® probes and qPCR. Associations were assessed through univariate linear regression and multivariable logistic regression analyses to construct predictive models. Three genetic variants were significantly associated with ADR risk: the T allele of TYMS (rs2853741) with general ADRs, the AA genotype of CDA (rs10916825) with gastrointestinal ADRs, and the G allele of TYMP (rs11479) with hematological ADRs. Predictive models integrated both genetic and clinical variables, including sex, age, chemotherapy type, cancer stage, and presence of pulmonary metastasis. These findings indicate that specific polymorphisms in genes involved in fluoropyrimidine metabolism may serve as risk biomarkers for adverse reactions to 5-FU-based chemotherapy, representing an initial step toward personalized dosing strategies for patients with advanced colorectal cancer.

**Autores:** Kaempfe-Moreno, G.1; Flores, I.2; Peña, S.1; Finschi, D.1; Barra, S.1; Calfunao, S.1; Colombo, A.5; Donoso, G.4,5; Barajas, O.4,6; Cáceres, D.1; Quiñones, L.1,3,4,7; Varela, N.1,3; Cerpa, L.1,3,4.

**Afiliación:** 1. Laboratory of Chemical Carcinogenesis and Pharmacogenetics (CQF). Department of Basic and Clinical Oncology, University of Chile. 2. Pharmacovigilance and Clinical Pharmacy Unit, Arturo López Pérez Foundation (FALP), Chile. 3. Latin American Network for Implementation and Validation of Clinical Pharmacogenomics Guidelines (RELIVAF), Santiago, Chile. 4. Center for Cancer Prevention and Control (C

**Área de la Farmacología:** Pharmacogenomics

**Dirección de Correo:** [Guikm14@gmail.com](mailto:Guikm14@gmail.com)

**Agradecimientos:** FONDECYT Regular Project N°1211948

**Socio Patrocinante:** Leslie Cerpa

## 53. INFLUENCE OF TYMS AND DPYD PROMOTER HYPERMETHYLATION ON THE SURVIVAL OF ADVANCED COLORECTAL CANCER PATIENTS TREATED WITH 5-FLUOROURACIL-BASED CHEMOTHERAPY: A PILOT STUDY.

Influencia de la hipermetilación de los promotores de TYMS y DPYD en la sobrevida de pacientes con cáncer colorrectal avanzado tratados con 5-fluorouracilo. Estudio piloto.

**Resumen:** Colorectal cancer (CRC) is a highly prevalent disease in Chile. Treatment often includes 5-fluorouracil(5-FU)-based chemotherapy. Dihydropyrimidine dehydrogenase (DPD) is a key enzyme of 5-FU catabolism, while thymidylate synthase (TS) is its main pharmacological target. Variations in the expression of DPD and TS genes (DPYD and TYMS, respectively) are known to affect the efficiency of the treatment and the outcome of the patients. On the other hand, promoter hypermethylation is an epigenetic modification known to suppress gene expression, however, the impact of this mechanism on

both genes, and on the clinical outcome of CRC patients treated with 5-FU is unknown. The aim of this study is to evaluate the relationship between the promoter methylation of TYMS and DPYD and the overall survival of advanced CRC patients treated with 5-FU-based chemotherapy. To achieve this, DNA was extracted from biopsy samples from 80 CRC patients receiving 5-FU-based chemotherapy and the methylation status of the promoter region of DPYD and TYMS was assessed by sodium bisulfite conversion and methylation specific PCR (MSP). The results were associated with clinical variables obtained from patient records. Survival analysis was performed by Kaplan-Meier curves, log-rank test and Cox regression analysis. A significant relationship was observed between the overall survival and the hypermethylation status of TYMS and DPYD, evidencing an association between an hypermethylated state of genes involved in the function and metabolism of 5-FU and an increase in the survival of CRC patients.

**Autores:** Lobos-Castillo M.1; Escudero A.2; Quiñones L.1,3,4,5; Cerpa L.1,3,4.

**Afiliación:** 1. Laboratory of Chemical Carcinogenesis and Pharmacogenetics (CQF). Department of Basic and Clinical Oncology, University of Chile. 2. Faculty of Pharmacy, University of Costa Rica. 3. RELIVAF, Santiago, Chile. 4. CECAN, Santiago, Chile. 5. Department of Pharmaceutical Sciences and Technology, Faculty of Chemical and Pharmaceutical Sciences, University of Chile.

**Área de la Farmacología:** Pharmacogenomics

**Dirección de Correo:** [macarena.lobos@uq.uchile.cl](mailto:macarena.lobos@uq.uchile.cl)

**Agradecimientos:** Proyecto iDOBC 2025.

**Socio Patrocinante:** Leslie Cerpa

### 1. ORGANIC AND ORGANOMETALLIC ANALOGS OF CELECOXIB AND ML-141 ON VIABILITY AND MIGRATION IN HUMAN GASTRIC ADENOCARCINOMA CELLS: POSSIBLE ROLE OF SMALL RHO GTPASES.

Análogos Orgánicos y Organometálicos de Celecoxib y ML-141 en Viabilidad y Migración en Células de Adenocarcinoma Gástrico Humano, posible rol de Rho-GTPasas pequeñas.

**Resumen:** Gastric cancer is a leading cause of mortality in Chile and worldwide, with adenocarcinoma being the most common histological subtype. Its development is associated with inflammatory processes that activate signaling pathways involved in tumor progression. In advanced stages, the proteins CDC42 and RAC1 regulate metastasis, whose overexpression enhances cell migration. Celecoxib (COX-2 inhibitor) and ML-141 (CDC42 inhibitor) are structural analogs that inhibit cell migration. This work evaluated a family of organic and organometallic structural analogs of celecoxib and ML-141 for their effects on cell viability and migration in human gastric adenocarcinoma AGS cells, as well as their potential binding energies to CDC42 and RAC1. Structural modifications, including partial methylation (compound B,  $CC_{50} = 24.57 \pm 1.11 \mu\text{M}$ ; D,  $CC_{50} = 13.90 \pm 1.07 \mu\text{M}$ ) and the incorporation of a ferrocene moiety (compound C,  $CC_{50} = 25.79 \pm 1.85 \mu\text{M}$ ; D,  $CC_{50} = 13.90 \pm 1.07 \mu\text{M}$ ; I,  $CC_{50} = 3.91 \pm 0.14 \mu\text{M}$ ), increased cytotoxicity against AGS cells and significantly inhibited cell migration at low concentrations, particularly molecules A (10  $\mu\text{M}$ ), B (5  $\mu\text{M}$ ), C (5  $\mu\text{M}$ ), and E (10  $\mu\text{M}$ ). These results, along with the favorable binding energy of the compounds near the active sites of CDC42 and RAC1, indicate that these molecules are potential candidates for the development of targeted therapies to inhibit metastasis in gastric cancer. **Keywords:** Gastric cancer, Adenocarcinoma, Metastasis, Cell Migration, Rho GTPases, Rho GTPase Inhibitor, COX-2 Inhibitor, Celecoxib, ML-141, Structural analog.

**Autores:** Leiton, G. 1; Muñoz-Osses M. 2; Mascayano C. 2; Milla L.A.

**Afiliación:** Laboratorio de análisis computacional y diseño racional de fármacos, Universidad de Santiago de Chile

**Area de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** [Gisselle.Leiton@usach.cl](mailto:Gisselle.Leiton@usach.cl)

**Agradecimientos:** Puente DGT 2023-017 Fondecyt Iniciación 11230581 Dicyt Regular 022441MC

**Socio Patrocinante:** Carolina Mascayano Collado

### 2. RATIONAL DESIGN OF PEPTIDES BASED ON THE NL1/NRX1B SYNAPTIC ADHESION COMPLEX

Diseño racional de péptidos basados en el complejo de adhesión sináptica NL1/Nrx1 $\beta$

**Resumen:** One of the most important synaptic adhesion complexes is the NL1/Nrx1 $\beta$  complex, which enables the formation and stabilization of contacts between presynaptic and postsynaptic neurons in the CNS, where NL1 is specifically found in glutamatergic synapses, while Nrx1 $\beta$  stimulates synaptic differentiation and regulates neurotransmitter transfer. Mutations in this protein are associated with autism and neurodevelopmental disorders. Given its high-resolution structure (up to 2.4 Å),. Therefore, this complex is a good candidate for a pharmacological target, and we hypothesize that there are structural elements of this complex that allow the rational design of peptides with affinity for the complex to generate a pharmacological tool to target dendrimers linked to these peptides through a linker. In this work, a structural bioinformatics strategy was applied combining peptide–protein docking (AutoDock Vina and GLIDE), delta G estimation by MM/GBSA, and 150ns MD simulations (Desmond). Using a previously designed peptide (ADEAIVA) as a reference model (Vásquez et al., 2020), its interaction on two predicted binding sites was reassessed, and two complexes (DOCK\_1 and DOCK\_3) were selected for detailed analysis of stability and interaction profiles. The DOCK\_1 complex showed more persistent interactions and a lower average RMSD compared to DOCK\_3. Based on this, 11 peptide variants were generated using in silico mutagenesis, and 10 of them presented more favorable docking

scores and delta G values than DOCK\_1. Moreover, MD simulations of VAR\_2, VAR\_3, and VAR\_7 revealed similar or higher stability, along with longer key interactions with the NL1/Nrx1 $\beta$  protein complex. This study demonstrates the feasibility of rational design of peptides targeting the NL1/Nrx1 $\beta$  complex, integrating structural bioinformatics and MD simulations tools to optimize affinity and stability. The optimized peptides are promising candidates for therapeutic applications based on specific synaptic structures.

**Autores:** Zambrano S. 1; Quintana S. 3; Leonardo Guzmán 1; Jimenez V. 2; Burgos C.F. 3

**Afiliación:** Molecular Neurobiology Laboratory, Department of Physiology, Faculty of Biological Sciences, Universidad de Concepción, Concepción, Chile. 1; Laboratory of Theoretical and Computational Chemistry, Faculty of Exact Sciences, Universidad Andrés Bello, Santiago, Chile. 2; Department of Physiology, Faculty of Biological Sciences, Universidad de Concepción, Concepción, Chile 3 **Area de la Farmacología:** Biopharmaceuticals

**Dirección de Correo:** [joseguzman@udec.cl](mailto:joseguzman@udec.cl)

**Agradecimientos:** FONDECYT REGULAR 1241829

**Socio Patrocinante:** Leonardo Guzmán

### 3. IL-4 AS A PROFIBROTIC MEDIATOR OF CARDIAC FIBROBLAST DIFFERENTIATION THROUGH ROS AND TGF- $\beta$ 1 SIGNALING

IL-4 como mediador profibrótico de la diferenciación de fibroblastos cardíacos a través de la señalización de ROS y TGF- $\beta$ 1

**Resumen:** The differentiation of cardiac fibroblast (CF) is essential in cardiac pathologies. During this process, CFs acquire a secretory phenotype characterized by the production of collagen I, along with enhanced contractile, migratory, and proliferative capacities, which contribute to heart failure. Therefore, understanding the molecular mechanisms involved in this process is fundamental. Cardiac diseases are associated with an inflammatory response characterized by the secretion of pro- and anti-inflammatory cytokines that aim to repair tissue through the regulation of oxidative stress. TGF- $\beta$ 1 is the main cytokine involved in CF differentiation. Nevertheless, other cytokines also participate in fibrotic processes, with IL-4 being notable for its anti-inflammatory and immunomodulatory properties, although its specific effect on CFs remains unclear. To evaluate whether IL-4 requires increased oxidative stress and TGF- $\beta$ 1 signaling to induce CF differentiation. CFs from neonatal Sprague-Dawley rats were stimulated with 10 ng/mL IL-4. Pharmacological inhibitors were added 1 hour prior to stimulation. Western Blot and RT-qPCR were performed to quantify protein levels and mRNA expression of fibrotic and antioxidant markers. Cell proliferation was assessed using crystal violet staining, while migration was evaluated through Transwell assays. Intracellular ROS levels were measured using DCFH-DA, and TGF- $\beta$ 1 synthesis was quantified by ELISA. IL-4 increased the expression of fibrosis-related markers, such as Col1A1 and  $\alpha$ -SMA, while reducing the antioxidant machinery by downregulating FoxO3a and its target genes, catalase and SOD2, thereby elevating ROS levels. Additionally, IL-4 promoted TGF- $\beta$ 1 synthesis and secretion, whereas inhibition of its signaling pathway prevented IL-4-induced changes in fibrotic and oxidative markers in CF. IL-4 induces CF differentiation through TGF- $\beta$ 1, leading to increased oxidative stress. Consequently, IL-4 emerges as a potential profibrotic agent.

**Autores:** Ponce, J.N.; Landaeta, J.; Carrasco, C.; De León, V.; Catalán, M.; Vivar, R.

**Afiliación:** Laboratorio de Farmacología y Mecanismos de Enfermedad, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile.

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** [javieraponce@ug.uchile.cl](mailto:javieraponce@ug.uchile.cl)

**Agradecimientos:** FONDECYT Regular 1251398

**Socio Patrocinante:** Dr. Raúl Vivar



#### 4. EFFECT OF DOXYCYCLINE ON MITOCHONDRIAL QUALITY CONTROL SYSTEM PROTEINS IN NEONATAL RAT CARDIAC FIBROBLASTS

Efecto de doxiciclina sobre proteínas del sistema de control de calidad mitocondrial en fibroblastos cardíacos de rata neonata

**Resumen:** Cardiac fibroblasts (CFs) play a central role in cardiac homeostasis, and their behavior is modulated by metabolic and signaling changes closely linked to mitochondrial function. In addition to their bioenergetic role, mitochondria regulate redox signaling, calcium homeostasis, and the activation of cell survival or death pathways. Their deterioration compromises CF viability and contributes to cardiac dysfunction. In response to stress, this organelle has a mitochondrial quality control system (MQS) designed to preserve mitochondrial functionality and adaptability, including UPRmt, the antioxidant enzyme system, biogenesis, mitophagy, and mitochondrial dynamics. The aim of this research was to evaluate the dose-dependent effects of doxycycline (a protein synthesis inhibitor) on cell viability, UPRmt, biogenesis, and mitophagy in neonatal rat CF. Cells were treated with 5–30 µg/mL doxycycline for 24 h, and cell viability, mitochondrial membrane potential, and the expression of key proteins involved in UPRmt, biogenesis, mitophagy, and apoptosis were analyzed by Western blot and immunofluorescence. The results of the 24-hour treatment show a dose-dependent biphasic response. At 15 µg/mL, doxycycline induced an adaptive response, characterized by activation of the UPRmt (nuclear translocation of ATF5 and increase in CHOP) and an increase in PGC1α. In contrast, the 30 µg/mL dose triggered generalized MQS dysfunction: Although the UPRmt (ATF5) remained active, there was overexpression of CHOP, a drop in Bcl-xl, LONP1, parkin, a decrease in membrane potential, and LDH release, with no changes in PGC1α, suggesting a maladaptive pro-apoptotic response. These findings delineate the transition between adaptation and mitochondrial collapse in CF, providing evidence for the mechanisms linking mitochondrial stress to cellular dysfunction in the heart.

**Autores:** Sebastián Rivas, Víctor Machuca, Guillermo Díaz  
**Afiliación:** Laboratorio de farmacología molecular, universidad de Chile  
**Area de la Farmacología:** Cardiovascular pharmacology  
**Dirección de Correo:** [sebastian.rivas@ug.uchile.cl](mailto:sebastian.rivas@ug.uchile.cl)  
**Agradecimientos:** PROYECTO FONDECYT 1250183  
**Socio Patrocinante:** Dr. Guillermo Díaz Araya

#### 5. THE EFFECT OF VARIABLE STIFFNESS OF MATRICES ON CARDIAC FIBROBLAST CULTURE

1.-Laboratorio de Farmacología Molecular, FaEl efecto de la rigidez variable de las matrices en el cultivo de fibroblastos cardíacos

**Resumen:** Stiffness is a fundamental biomechanical property that varies across tissues. In the healthy heart, it remains between 10 and 15 kPa, while under pathological conditions it can increase to nearly 100 kPa. Cardiac fibroblasts play an essential role in the structural and functional maintenance of the myocardium; however, when faced with mechanical stimuli or stress situations, they can activate and differentiate into myofibroblasts, characterized by the expression of α-SMA and the formation of stress fibers, events closely related to the development of fibrosis. In this study, fibroblasts were cultured on hydrogels with different stiffnesses and composition (8, 10, 64, and 100 kPa; using Acrylamide-bisacrylamide, and dimethylpolysiloxane) to simulate physiological and pathological environments, with the aim of analyzing their cellular response. The stiffness of the extracellular matrix, modulated by acrylamide-bisacrylamide and dimethylpolysiloxane hydrogels, was observed to significantly influence adhesion, morphology, and protein expression. Crystal violet staining revealed notable differences in cell adhesion and morphology depending on the substrate, while immunofluorescence analysis revealed differential expression of α-SMA associated with environmental stiffness. Furthermore, variations in cell morphology and proliferation were detected in Cytosoft® hydrogels (dimethylpolysiloxane) at 8 and 64 kPa. In contrast, doxorubicin treatment reduced cell size and altered the number of senescent cells, demonstrating the influence of the biochemical environment on cell

behavior. These results confirm that microenvironmental stiffness is a key regulator of the functional response of cardiac fibroblasts.

**Autores:** Rivera N.1; Sagredo P.1; Díaz-Araya G.1  
**Afiliación:** 1.-Laboratorio de Farmacología Molecular, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile  
**Area de la Farmacología:** Cardiovascular pharmacology  
**Dirección de Correo:** [pablo.sagredo@ug.chile.cl](mailto:pablo.sagredo@ug.chile.cl)  
**Agradecimientos:** Fondecyt 1250183  
**Socio Patrocinante:** Dr. Guillermo Díaz Araya

#### 6. HYPOTENSIVE AND VASORELAXANT EFFECT OF AQUEOUS EXTRACT OF PANAMANIAN GEISHA COFFEE IN RATS

Efecto hipotensor y vasorelajante del extracto acuoso de café geisha Panameño en ratas

**Resumen:** Panamanian Geisha coffee, internationally recognized for its exceptional sensory attributes, possesses a distinctive phytochemical profile that may confer beneficial cardiovascular effects. However, no biological assessments of this coffee variety have been reported to date. The present study aimed to evaluate the effects of aqueous extract of Geisha coffee (AEGC) on mean arterial pressure (MAP) and heart rate (HR) in anesthetized Sprague–Dawley rats (0.01-30 mcg/Kg). In addition, the vasorelaxant activity of AEGC (500-3000 ug/mL) in isolated aortic rings and its possible mechanism of action using pharmacological inhibitors as L-NAME (NO synthase inhibitor), methylene blue (guanylate cyclase inhibitor), atropine (muscarinic blocker), and indomethacin (cyclooxygenases inhibitor) were investigated. Intravenous administration of AEGC produced a significant reduction in MAP in normotensive rats (maximum decrease: 54.86 ± 2.08 mmHg) with a lightly effect on heart rate (maximum decrease: 4.34 ± 2.44 BPM). AEGC induced concentration-dependent relaxation in both endothelium-intact and endothelium-denuded aortic rings precontracted with phenylephrine (1 µM) (70.84 ± 2.88% vs. 72.62 ± 6.74%), while a weaker relaxation response was observed in rings precontracted with KCl (5.31 ± 2.43% vs. 18.52 ± 4.22%). The vasorelaxant effect of AEGC was attenuated by L-NAME and indomethacin (54.61 ± 7.36% and 63.83 ± 6.63%, respectively), but was unaffected by methylene blue or atropine. This study provides the first evidence of the cardiovascular properties of AEGC, demonstrating significant hypotensive activity in normotensive rats. The vasodilatory action of AEGC likely involves multiple mechanisms mediated through both smooth muscle cells and endothelial pathways.

**Autores:** Caballero K.M. 1,2, Sánchez Martínez H.A.1,2; Vega A. 4; Del Olmo-Fernández E.3; López-Pérez J.L.2,3; Guerrero de León E.2,3; Morán-Pinzón J.A.2,3  
**Afiliación:** 1Programa de Maestría en Ciencias Biomédicas, Universidad de Panamá 2Centro de Investigaciones Psicofarmacológicas, Universidad de Panamá, 3Departamento de Farmacología, Facultad de Medicina, Universidad de Panamá, 4 Centro de Investigación en Recursos Naturales, Universidad Autónoma de Chiriquí, Panamá, 5 Departamento de Ciencias Farmacéuticas, Universidad de Salamanca, España  
**Area de la Farmacología:** Cardiovascular pharmacology  
**Dirección de Correo:** [quererodleon@gmail.com](mailto:quererodleon@gmail.com)  
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**Socio Patrocinante:** Kimberly Caballero



## 7. ROLE OF STATINS AS A POTENTIAL ADJUVANT IN ANTITUMOUR THERAPY WITH KRASG12C INHIBITORS

Rol de las estatinas como potencial coadyuvante en la terapia antitumoral con inhibidores de KRASG12C

**Resumen:** Las estatinas, inhibidores de la HMG-CoA reductasa (HMGCR), enzima limitante de la vía del mevalonato (MVA), han sido estudiadas por sus propiedades anticancerígenas. La HMGCR es regulada por el factor de transcripción SREBP2 y participa en la síntesis de intermediarios esenciales para la correcta localización y funcionamiento de KRAS, codificada por uno de los genes más frecuentemente mutados en el cáncer. En el cáncer de pulmón (CP), la mutación KRASG12C es la más prevalente y se asocia con mal pronóstico y resistencia a terapias convencionales. KRASmut activa constitutivamente vías que sustentan el cáncer (MAPK-AKT). Aunque las terapias dirigidas contra KRASG12C han significado un avance importante, su eficacia clínica se ve limitada por la resistencia adquirida. El objetivo de este estudio fue estudiar la relación entre la MVA y la actividad de KRAS, y evaluar el efecto sinérgico de un inhibidor de KRASG12C y estatinas en células de CP. Los niveles de SREBP2, HMGCR y la actividad de la vía MAPK se analizaron mediante western blot, mientras que la funcionalidad de SREBP2 se estudió mediante un ensayo de gen reportero. Se realizó un ensayo de viabilidad celular con MTT tras los tratamientos combinados de adagrasib-estatinas, y el sinergismo se analizó con el software Combeneft. Se observaron niveles significativos de HMGCR y SREBP2 en células KRASwt (H1299) y KRASG12C (Calu-1 y H358) con respecto a células normales. El ensayo de gen reportero mostró una mayor actividad de SREBP2 tras tratamiento con simvastatina, indicando una activación compensatoria del eje SREBP2-HMGCR. Finalmente, la combinación adagrasib-estatinas mostró sinergismo. Estos resultados sugieren una interacción funcional entre la MVA y KRAS y un potencial efecto coadyuvante de las estatinas en células de CP con KRASG12C

**Autores:** Maestre A.1; Chipon C.1; Diaz F.1; Carillo D.2; Salazar N.2; López-Muñoz R.1  
**Afiliación:** 1.1. Facultad de Ciencias Veterinarias, Instituto de Farmacología y Morfofisiología, Universidad Austral de Chile, Valdivia, Chile.  
**Area de la Farmacología:** Chemotherapy  
**Dirección de Correo:** [rodrigo.lopez@uach.cl](mailto:rodrigo.lopez@uach.cl)  
**Agradecimientos:** Fondecyt 1241400  
**Socio Patrocinante:** Rodrigo Andrés López Muñoz

## 8. NOVEL LIPIDIC NANOPARTICLES FUNCTIONALIZED WITH RGD PEPTIDE AS INNOVATIVE TREATMENT TO INCREASE DRUG DELIVERY AGAINST BREAST CANCER

Nuevas nanopartículas lipídicas funcionalizadas con péptido RGD como tratamiento innovador para aumentar la administración de fármacos contra el cáncer de mama

**Resumen:** Breast cancer (BC) is the leading cause of cancer-related death among women in western countries. BC cells express different levels of integrin family receptors that recognize the Arginine-Glycine-Aspartic Acid (RGD) amino acid sequence in their ligands. Nanomedicine allows to incorporate amphipathic molecules with RGD sequence in colloidal systems at nanometric scale to improve the delivery of drugs to its target cell. Oily core nanoparticles (NPs) can contain drugs with high lipophilicity, allows us to use drugs with deficient biopharmaceutical properties. This study shows the development, characterization and evaluation of a lipid NPs functionalized with an antipathic molecule with RGD sequence to improving the delivery of cytotoxic drugs to BC cells with integrins. Novel lipidic NPs have been developed using emulsification methods. Characterization of particle size and Z potential was determined by dynamic light scattering. Etoposide load and release from NPs were determined by high performance liquid chromatography. NPs were loaded with Nile Red (NR) fluorescent dye and then isolated. Next, the uptake of NR-loaded NPs functionalized with RGD in cells was studied by fluorescence microscopy and flow cytometry and cell viability was determined using Alamar Blue method. Etoposide and NR loaded RGD-NPs have a size of 168 nm, a Z potential of -11 mV and a monomodal polydispersity index. RGD-NPs release 50% of etoposide at

24h. RGD increased the uptake of NPs 2-fold in integrin containing human BC cells. RGD-NPs loaded with etoposide decrease more efficiently BC cell viability. Lipid NPs with the RGD sequence were characterized and showed greater uptake and cytotoxic effect in human BC cells that express integrins. Future studies will allow evaluation of the in vivo efficacy and safety of NPs.

**Autores:** Renato Burgos-Ravanel, Rayen Valdivia-Olivares, Loreto Barrientos, José Vicente Gonzalez-Aramúndiz  
**Afiliación:** Laboratorio de Nanotecnología Farmacéutica Aplicada, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile.  
**Area de la Farmacología:** Chemotherapy  
**Dirección de Correo:** [rburgos@uc.cl](mailto:rburgos@uc.cl)  
**Agradecimientos:** This work was supported by Fondecyt regular 1201482, FONDEQUIP 160041, and Fondecyt postdoctoral 3230568.  
**Socio Patrocinante:** No aplica

## 9. RUTHENIUM(II)-BENZENE THIOSEMICARBAZONE COMPLEXES: COORDINATION MODE INFLUENCE ON BIOLOGICAL INTERACTIONS AND MITOCHONDRIAL ROS-DEPENDENT APOPTOSIS

Complejos de rutenio(II)-benceno con tiosemicarbazona: Influencia del modo de coordinación en interacciones biomoleculares y apoptosis mitocondrial mediada por ROS en células cancerígenas

**Resumen:** Ru(II)-benzene complexes (P1 and P2) were synthesized using a thiosemicarbazone ligand (L1) in two different coordination modes, monodentate S and bidentate N,S, through carefully adjusted reaction conditions. Comprehensive characterization of the complexes was achieved through single crystal X-ray diffraction, revealing a piano-stool geometry around the Ru(II) ion. To evaluate the binding capabilities of the complexes towards CT DNA and BSA, UV-Vis and/or hydrodynamic methods were utilized. Docking studies further validated the intercalative binding mode with DNA, in agreement with the experimental findings, and identified specific BSA amino acids involved in the binding interactions. Based on the results of binding studies, cytotoxicity of the ligands and complexes was appraised in various cancer and normal cell lines alongside the commercial pharmaceuticals. Complexes P1 and P2 displayed a promising activity against MDA-MB-231 [IC<sub>50</sub> = 5.1 (P1) and 3.4 μM (P2)] and PANC-1 [IC<sub>50</sub> = 7.2 (P1) and 4.8 μM (P2)] cancer cells; with the bidentate system (P2) exhibiting a higher activity than its monodentate congener P1, although both of them showed superior activity than the reference drugs. Various bioassays including Western blot analysis revealed the mode of cell death to be apoptosis, which was further concluded to be via the ROS-mediated mitochondrial signaling pathway.

**Autores:** Haribabu J. 1,\*; Monserrat H. M. 1; Maura, O. D. 1; Rocio, P. M. 1  
**Afiliación:** 1Bioinorganic Medicinal Chemistry Laboratory (BMCL), Faculty of Medicine, University of Atacama, Los Carreras 1579, 1532502 Copiapo, Chile  
**Area de la Farmacología:** Chemotherapy  
**Dirección de Correo:** [ebiti.haribabu@uda.cl](mailto:ebiti.haribabu@uda.cl)  
**Agradecimientos:** J. H. thanks the University of Atacama for financial support for this work through the project DIUDA:88231R3.  
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## 10 CO-ENCAPSULATION OF METHOTREXATE AND 6-MERCAPTOPYRINE IN PAMAM-G4 DENDRIMERS: A NANOTECHNOLOGICAL STRATEGY TO OPTIMIZE ACUTE LYMPHOBLASTIC LEUKEMIA THERAPY

Coencapsulación de metotrexato y 6-mercaptopurina en dendrímeros PAMAM-G4: una estrategia nanotecnológica para optimizar la terapia de la leucemia linfoblástica aguda

**Resumen:** La leucemia linfoblástica aguda (LLA) es un cáncer hematológico de alta prevalencia en niños entre 2 y 5 años caracterizado por la proliferación descontrolada de linfoblastos inmaduros en médula ósea, sangre periférica y otros tejidos. El tratamiento convencional emplea antimetabolitos como metotrexato (MTX) y 6-mercaptopurina (6-MP). Ambos se administran en combinación, ya que el MTX mejora la biodisponibilidad de la 6-MP. No obstante, su baja solubilidad acuosa (MTX: 0,171 g/L; 6-MP: 22,5 mg/L) limita la eficacia terapéutica y favorece efectos secundarios. Este estudio aplicó nanotecnología farmacéutica para mejorar las propiedades fisicoquímicas y la liberación de ambos fármacos. Se evaluó el dendrímero poliamidoamina de cuarta generación (PAMAM-G4) como nanotransportador para incrementar la solubilidad y controlar la liberación de MTX y 6-MP, individualmente y en combinación. La encapsulación se realizó por equilibrio de solubilidad, y la liberación se estudió mediante diálisis en condiciones fisiológicas. Las concentraciones se determinaron por espectroscopia UV-Vis y cromatografía líquida de alta resolución (HPLC), tanto para evaluar el incremento de solubilidad como la cinética de liberación. Los datos experimentales de liberación se ajustaron a los modelos cinéticos de orden cero, primer orden, Higuchi y Korsmeyer-Peppas. El PAMAM-G4 aumentó significativamente la solubilidad de ambos fármacos, permitiendo encapsular hasta 19 moles de MTX y 8 moles de 6-MP por mol de dendrímero. Resultados similares se obtuvieron al estudiar ambas drogas en mezcla, demostrando que pueden coencapsularse sin afectar la capacidad de carga. Las formulaciones mostraron una liberación sostenida ajustada al modelo cinético de primer orden. Estos hallazgos respaldan el potencial de los dendrímeros PAMAM como plataforma para la coencapsulación y la liberación controlada de MTX y 6-MP, orientada a terapias más efectivas contra la LLA.

**Autores:** Tapia G. 1; Villagrán C. 2; Morales-Reyes C.F. 3; Barraza L.F. 3  
**Afiliación:** 1. Carrera de Química y Farmacia, Facultad de Ciencias, Universidad San Sebastián, Sede Valdivia; 2.- Carrera de Bachillerato en Ciencias de la Salud, Facultad de Ciencias, Universidad San Sebastián, Sede Valdivia. 3.- Departamento de ciencias biológicas y químicas, Facultad de Ciencias, Universidad San Sebastián, Sede Valdivia **Area de la Farmacología:** Chemotherapy  
**Dirección de Correo:** [gtapia@correo.uss.cl](mailto:gtapia@correo.uss.cl)  
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## 10. SAFETY AND ANALGESIC EFFECT OF HIGH-CONCENTRATION LIDOCAINE/TETRACAINE CREAM IN OLDER ADULTS WITH LOCALIZED NEUROPATHIC PAIN: A PILOT STUDY

Estudio piloto: Seguridad y efecto analgésico de una crema con alta concentración de lidocaína-tetracaína, en adultos mayores con dolor neuropático localizado.

**Resumen:** Background: Neuropathic pain in older adults remains challenging due to polypharmacy and comorbidities. High-concentration topical anesthetics may offer local pain relief with minimal systemic risk. Methods: Twenty patients ( $\geq 60$  years) with localized neuropathic pain received a topical lidocaine 23%/tetracaine 7% cream (10 g/200 cm<sup>2</sup>) twice daily for 48 hours. Pain was assessed with the Numeric Rating Scale (NRS) pre- and post-treatment. Plasma lidocaine concentrations were measured; adverse events were recorded. Results: Mean age was 69.7 years; 50% female. All plasma lidocaine levels remained  $< 2$  mcg/mL. Pain reduction: 30% achieved complete relief;  $> 50\%$  had  $\geq 50\%$  NRS reduction. Only one mild local irritation was observed; no systemic toxicity. Conclusions: Short-term application of high-concentration lidocaine/tetracaine cream appears safe and effective in older adults with refractory localized neuropathic pain. Larger randomized trials are warranted.

**Autores:** Iturra P.A.1; León P.J.2; Solari S.3; Elgueta M.F.2

**Afiliación:** 1. Programa de Farmacología y Toxicología. Facultad de Medicina. Pontificia Universidad Católica de Chile. 2. División de Anestesiología. Facultad de Medicina. Pontificia Universidad Católica de Chile. 3. Departamento de Laboratorios Clínicos. Facultad de Medicina. Pontificia Universidad Católica de Chile

**Area de la Farmacología:** Clinical pharmacology

**Dirección de Correo:** [paiturram@uc.cl](mailto:paiturram@uc.cl)

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**Socio Patrocinante:** No aplica

## 11. INFLUENCE OF GUT MICROBIOTA IN NEUROMOTOR COMMUNICATION FOLLOWING COMPRESSIVE SPINAL CORD INJURY

Influencia de la microbiota intestinal en la comunicación neuromotora después de una lesión medular compresiva

**Resumen:** Introduction: Degenerative Cervical Myelopathy (DCM) is a progressive compression of the spinal cord that disrupts neural signaling between motoneurons and skeletal muscles, prevalent in the elderly population. Despite advances, the cellular and molecular mechanisms of neuromotor dysfunction in DCM, including the potential role of gut microbiota (GM) dysbiosis, remain unclear. This study investigated whether GM-based supplementation could mitigate neuromotor impairment in a DCM model. Materials and Methods: DCM was induced in mice by implanting an aromatic polyether material that simulates chronic compression at C5-C6. Three months post-implantation, sensorimotor function was assessed in control, DCM, and DCM mice supplemented with GM every other day for two months. Pathological changes in cervical motoneurons, their target muscles (supraspinatus and biceps brachii), and neuromuscular junctions (NMJs) were evaluated by immunohistochemistry. Results: At three months of compression, DCM mice showed a significant decrease in locomotor activity and strength compared to controls. Notably, GM supplementation delayed motor decline. Histopathological analysis revealed a disruption of the cervical spinal cord architecture in the DCM group, which was preserved by GM supplementation. At the neuromuscular level, DCM mice exhibited a reduced endplate surface area correlated with smaller presynaptic axon terminals in the supraspinatus muscle. Conversely, the biceps brachii showed an increased cross-sectional area in the DCM mouse model. Importantly, the GM supplementation of DCM mice maintained these muscle parameters at control levels, preventing these pathological changes. Discussion: These findings suggest that fecal microbiota supplementation from age-matched healthy mice preserves the structural integrity of motoneuron-muscle communication, thereby maintaining upper extremity motor function in DCM.

**Autores:** Jorge Ojeda<sup>1,2</sup>, Antonia Mora<sup>1</sup>, Daleska Tenelema<sup>1</sup>, Mayra Vergara<sup>2</sup>, Pia M Vidal<sup>2</sup>.

**Afiliación:** Facultad de Odontología<sup>1</sup>, Sede Concepción, Universidad San Sebastián; Neuroimmunology and Developmental Neurobiology Unit<sup>2</sup>, Biomedical Science Research Laboratory, Basic Sciences Department, Faculty of Medicine, Universidad Católica de la Santísima Concepción, Concepción, Chile. **Area de la Farmacología:** Clinical pharmacology

**Dirección de Correo:** [jorge.ojeda@uss.cl](mailto:jorge.ojeda@uss.cl)

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**Socio Patrocinante:** Lorena Armijo Weingart



## 12. MS/MS BASED BIOACTIVE METABOLITES IDENTIFICATION FROM CARALLUMA TUBERCVLATA AND THEIR ANTIOXIDANT AND ANTI-BREAST CANCER ACTIVITIES

Identificación de metabolitos bioactivos de *Caralluma tuberculata* basada en MS/MS y sus actividades antioxidantes y anticáncer de mama

**Resumen:** *Caralluma tuberculata*, a medicinal and edible plant from the Apocynaceae family, has been traditionally used in folk medicine in several countries, including Pakistan, India South Arabia, among other. In Pakistan it is used as antidiabetic and anticancer vegetable. The aim of this study was to identify the bioactive compounds from the shoots, of *Caralluma tuberculata* by using HPLC and LC-ESI MS/MS based analysis. The HPLC chromatograms of *Caralluma tuberculata* extract revealed a diverse phytochemical composition, including flavonoids, phenolic compounds, and pregnane glycosides, with major bioactive peaks between 45-to-80-minute elution time. The heatmap analysis further highlights the complexity of metabolites, emphasizing the extract potential for antioxidant and anti-breast cancer applications. The LC-MS analysis of *Caralluma tuberculata* methanolic extract revealed a diverse range of secondary metabolites, with major peaks at elution times at 17.20 and 22.50 minutes, suggesting abundant bioactive compounds like flavonoids, terpenoids, or saponins. LC-ESI MS/MS analysis identified 70 phytochemicals in *Caralluma tuberculata* methanolic extract, including organic acids, amino acid derivatives, phenolic compounds, flavonoids, alkaloids, and other bioactive organic constituents. The methanolic extract of *Caralluma tuberculata* exhibited significant cytotoxicity against MDA-MB-231 breast cancer cells, reducing its viability by 50%, while showing milder effects on healthy breast MCF-12F cells (a 20% reduction), highlighting its potential as a selective anticancer agent. The antioxidative potential of the *Caralluma tuberculata* extract at 200 and 400 µg/mL concentrations was assessed through various tests and exhibited pronounced scavenging potential in reducing power, ABTS + free radical scavenging, hydrogen peroxide formation inhibition and hydroxyl radical scavenging potential, respectively. The outcomes of the study were exceptional and hold promising implications for f

**Autores:** Ayesha Siddiqi, Juan Pedro Luna Arias

**Afiliación:** Cinvestav, IPN Mexico city

**Area de la Farmacología:** Ethnopharmacology

**Dirección de Correo:** [ali.amir@cinvestav.mx](mailto:ali.amir@cinvestav.mx)

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**Socio Patrocinante:** i am doctorate student

## 13. COFFEE AND MORINGA EXTRACTS SHOW DIFFERENTIAL HEPATOPROTECTIVE EFFECTS AGAINST ETHANOL-INDUCED CYTOTOXICITY IN HEPG2 CELLS

Los extractos de café y moringa muestran efectos hepatoprotectores diferenciales contra la citotoxicidad inducida por etanol en células HepG2

**Resumen:** In recent years, no FDA-approved pharmacological therapies exist for alcohol-associated liver disease (ALD), prompting patients to explore natural products. Coffee (*Coffea arabica* L.) and moringa (*Moringa oleifera* Lam.), traditionally consumed for nutritional and medicinal benefits, have shown hepatoprotective potential in preclinical models via antioxidant and anti-inflammatory mechanisms; however, hepatic pathophysiology is complex. As the central metabolic organ, the liver exhibits compensatory responses that can alter metabolic flux and potentially exacerbate injury. HepG2 cells were treated with 50% ethanolic coffee extract or 80% methanolic moringa extract (6.25–100 µg/mL), alone or combined, under two protocols: 24 h co-treatment with ethanol (EtOH) or 4 h extract pretreatment followed by EtOH exposure. Cell viability was assessed by MTS assay (co-treatment and pretreatment), and membrane integrity was evaluated via propidium iodide (PI) uptake by flow cytometry (co-treatment only). Low-dose coffee (6.25 µg/mL) attenuated EtOH-induced viability loss in both protocols but failed to preserve membrane integrity during co-treatment. Moringa extract offered no protection and exacerbated cytotoxicity, while moringa-rich combinations showed synergistic damage. These results highlight mechanistic divergence: coffee's viability benefit likely involves

metabolic or mitochondrial pathways rather than membrane stabilization. The findings underscore that protection against some xenobiotics may not extend to ethanol toxicity. Multi-parametric assessment (MTS + PI) is essential, as single-endpoint analyses risk incomplete or misleading conclusions regarding safety and therapeutic potential. Thorough phytochemical interaction studies are critical for defining natural products' role in hepatoprotection.

**Autores:** Cortés-De Guzmán, K. 1; Méndez Alcaman, L. A. 2; Catalán, M. 3; Rivera-Meza, M. 1; Valenzuela – Barra, G. 1

**Afiliación:** 1. Departamento de Química Farmacológica y Toxicológica Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile; 2. Clínica Alemana; 3. Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile

**Area de la Farmacología:** Ethnopharmacology

**Dirección de Correo:** [kevin.cortes@ug.uchile.cl](mailto:kevin.cortes@ug.uchile.cl)

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**Socio Patrocinante:** Gabriela Valenzuela – Barra.

## 14. CHEMICAL CHARACTERIZATION AND EVALUATION OF THE IN VITRO ANTIOXIDANT AND ANTI-INFLAMMATORY CAPACITY OF ETHANOLIC EXTRACTS OF LEAVES AND FLOWERS OF FUCHSIA MAGELLANICA LAM.

Caracterización química y evaluación de la capacidad antioxidante y antiinflamatoria in vitro de los extractos etanólicos de hojas y flores de *Fuchsia magellanica* Lam.

**Resumen:** Traditional medicine uses plants with therapeutic properties based on compounds known as secondary metabolites, including flavonoids and phenolic acids, recognized for their antioxidant and anti-inflammatory properties. *Fuchsia magellanica* Lam., a shrub native to Chile and used in Mapuche medicine as a diuretic, emmenagogue, and wound healing agent. The chemical composition of *F. magellanica* leaves has been documented, with flavonoids such as quercetin and kaempferol, and phenolic acids such as gallic acid found. Various types of anthocyanins have been reported in its flowers. Furthermore, plant material obtained outside of Chile was verified for its antioxidant, antimicrobial, wound healing, and antispasmodic activity. In the study, serial extractions were performed on plant material collected in the Valparaíso region of Chile. Using HPLC-MS, the ethanolic extract of flowers was found to contain mainly quinic, malic, and gallic acids, while the leaf extract contained mainly quercetin glycosides and gallic acid. ORAC-FI assays showed high antioxidant capacity in both extracts: leaves (1800 eq Trolox/g ext. s.) and flowers (1200 eq Trolox/g ext. s.). Anti-inflammatory activity was evaluated in LPS-stimulated human fibroblasts (HFF-1). It was observed that the ethanolic extract of flowers, at 100 µg/mL, significantly inhibited the phosphorylation of the transcription factor NF-κB. In contrast, the leaf extract did not show significant inhibition. This work provides relevant evidence on the antioxidant activity and, for the first time, on the anti-inflammatory activity of *F. magellanica*, supporting its traditional use and establishing a basis for future in vivo studies exploring its regulated therapeutic potential.

**Autores:** Norambuena-Jopia U.; Ruiz L.; Cáceres M.; Quintana M.; Carrasco C.; Catalán M.; Valenzuela G.

**Afiliación:** Departamento de Química Farmacológica y Toxicológica, Facultad de Ciencias Químicas y Farmacéuticas (Faciqyf) Universidad de Chile. + Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Independencia 1027, Santiago, Chile

**Area de la Farmacología:** Ethnopharmacology

**Dirección de Correo:** [ulises.norambuena@ug.uchile.cl](mailto:ulises.norambuena@ug.uchile.cl)

**Agradecimientos:** Fondecyt de Iniciación a la Investigación 11241273

**Socio Patrocinante:** Gabriela Valenzuela Barra.



### 15. EFFECTS OF TIME RESTRICTED FEEDING (TRF) ON MACROPHAGE PHENOTYPE, ITS IMPACT ON SKELETAL MUSCLE BIOENERGETICS AND FUNCTION IN OBESE MICE

efectos de la alimentación con restricción temporal (art) sobre el fenotipo de macrófagos, su impacto en la bioenergética y la función del músculo esquelético en ratones obesos

**Resumen:** Sarcopenia is the loss of muscle mass and function caused by obesity or aging. In aged mice and in obesity there is an imbalance in macrophage phenotypes, often with increased proportion of M1 (glycolytic metabolism and pro-inflammation) to M2 (oxidative metabolism and anti-inflammatory) macrophages subtypes. These data suggest that an M1/M2 imbalance in muscle could drive sarcopenia in obesity. Our preliminary data showed that TRF reduces sarcopenia in aged mice. Determine whether obesity increases M1 to M2 macrophages in skeletal muscle, and if this correlates with altered muscle function and bioenergetics; and whether this effect can be rescued by TRF. Macrophages were isolated from skeletal muscle from control and high-fat diet (HFD) mice subjected to TRF (no food access during light phase) or ad libitum. Macrophage number and phenotype were assessed by flow cytometry. Levels of proteins related to bioenergetics were analyzed by Western Blot. Body weight, muscle strength, maximum running speed were measured. Statistical analyses included three-way repeated measured ANOVA for physiological data, and two-way ANOVA for Western blot and flow cytometry analyses. HFD increased body weight gain compared to control-fed mice without a significant effect of TRF. However, TRF prevented the decline in maximum running speed observed in HFD mice. Macrophage infiltration into skeletal muscle was not different between groups, and HFD showed increased CD86 (M1) and CD206 (M2), while CD163(M2) decreased. HFD-fed mice showed decreased levels of mitochondrial complexes III, and increased complex I, which was reversed by TRF. TRF in HFD-fed mice preserved physiological performance and prevented speed loss. HFD promoted an intermediate phenotype in skeletal muscle-resident macrophages. TRF partially reversed HFD-induced metabolic changes, notably the increase in complex I.

**Autores:** Briones-Manríquez F. 1,4; Ibarra-Barahona I. 1; Almarza G. 1; Araya M.J. 2,3; Luz-Crawford P. 2,3; Pérez-Leighton C. 4; del Campo A. 1.  
**Afiliación:** Laboratorio de Fisiología y Bioenergética Celular, Escuela de Química y Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile  
**Area de la Farmacología:** Immunopharmacology  
**Dirección de Correo:** [fernanda.briones@uc.cl](mailto:fernanda.briones@uc.cl)  
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**Socio Patrocinante:** Andrea del Campo Sfeir

### 16. PRODUCTION AND CHARACTERIZATION OF A NOVEL RECOMBINANT BIESPECIFIC ANTIBODY WITH SPECIFIC RECOGNITION OF ITS TARGET

Producción y caracterización de un nuevo anticuerpo biespecifico recombinante con reconocimiento específico de su diana

**Resumen:** Bispecific antibodies (bsAbs) represent one of the most significant innovations in next-generation biologic therapies. In recent years, there has been a significant increase in the development and approval of therapeutic bsAbs, highlighting their growing impact in immuno-oncology and personalized medicine. Their ability to simultaneously recognize two different epitopes/antigens, allows modulation of multiple biological pathways, recruit immune effectors, or enhanced therapeutic specificity toward complex targets. However, bsAbs development poses major challenges in molecular engineering and expression, particularly ensuring correct chains pairing and maintaining structural and functional stability. In this work, a CrossMab-based design was employed, introducing specific amino acid substitutions in the heavy chain to promote selective pairing between distinct heavy chains. Additionally, targeted mutations were incorporated into the CH1 and CL constant domains of one antibody arm to ensure correct heavy-light chain assembly. The bsAb was transiently expressed in the ExpiCHO system and purified using a single step of protein G affinity chromatography, achieving a purity level greater than 95%. Structural integrity was confirmed by SDS-PAGE and Western blot, while ELISA

demonstrated specific, concentration-dependent binding to its target. This work strengthens national capabilities in protein engineering and contributes to the development of local platforms for bispecific antibody production.

**Autores:** Garrido M. J. 1; Fehring N. 1; Toledo-Stuardo K. 1; Matthies D. J. 1; González-Herrera F. 1; Campos I. 1; Guerra Y. 1; Molina M. C. 1  
**Afiliación:** 1. Laboratorio de Anticuerpos Recombinantes e Inmuno-Oncología, Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Santiago, Chile.  
**Area de la Farmacología:** Immunopharmacology  
**Dirección de Correo:** [kotegarrido16@gmail.com](mailto:kotegarrido16@gmail.com)  
**Agradecimientos:** FONDECYT Project N° 1221031  
**Socio Patrocinante:** .

### 17. ANTITUMOR MECHANISMS TRIGGERED BY A NOVEL FULLY HUMAN ANTIBODY TARGETING THE MICA PROTEIN

Mecanismos antitumorales inducidos por un nuevo anticuerpo completamente humano dirigido contra la proteína MICA

**Resumen:** Monoclonal antibodies have emerged as a cornerstone in cancer immunotherapy due to their capacity to selectively recognize tumor-associated antigens and recruit immune effector cells through their crystallizable fragment (Fc). Once bound to the target, Fc-Fcγ receptor interactions on immune cells trigger antibody-dependent effector mechanisms such as cellular cytotoxicity (ADCC) and phagocytosis (ADCP), which contribute to the elimination of malignant cells. The stress-induced protein MICA is broadly expressed on tumor cell surfaces, representing an attractive target for antibody-based therapies. This study aimed to characterize the antitumor mechanisms mediated by a novel fully human IgG1 anti-MICA antibody in different MICA-expressing cell lines. NK cell-enriched PBMCs from healthy donors were co-cultured with K562 target cells in the presence of anti-MICA, isotype control, or vehicle (PBS). ADCC was analyzed by measuring NK cell degranulation (CD107a expression) and IFN-γ secretion using flow cytometry. To evaluate ADCP, U937 monocytic cells stably expressing GFP were differentiated into macrophages with PMA. Human gastric epithelial GES1 cells, labeled with TFL4 and expressing MICA, were co-incubated with macrophages under similar treatment conditions, and phagocytic uptake was assessed by flow cytometry and confocal microscopy. Our results revealed that anti-MICA significantly increased CD107a expression and IFN-γ production in NK cells compared with controls. Moreover, macrophages exhibited enhanced phagocytosis of GES1 cells in the presence of anti-MICA. Altogether, these findings demonstrate that the fully human anti-MICA IgG1 antibody promotes both ADCC and ADCP, highlighting its potential as an immunotherapeutic candidate against MICA-expressing tumors.

**Autores:** González-Herrera F. 1; Toledo-Stuardo K. 1; Guerra Y. 1; Garrido M.J. 1; Campos I. 1; Díaz C. 1; Matthies D. 1; Fehring N. 1; Reyes, N. 1; Tello, S. 1; Ribeiro C. 1; Molina M.C. 1  
**Afiliación:** Laboratorio de Anticuerpos Recombinantes e Inmuno-Oncología, Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Santiago, Chile.  
**Area de la Farmacología:** Immunopharmacology  
**Dirección de Correo:** [fabiola.gonzalez@uq.uchile.cl](mailto:fabiola.gonzalez@uq.uchile.cl)  
**Agradecimientos:** FONDECYT Projects N° 1221031, N° 3240175, and N° 3230454.  
**Socio Patrocinante:** María Carmen Molina Sampayo.

**18. Trisubstituted pyridines and pyrimidines designed as ligands for the adenosine A2A receptor and the histamine H3 receptor. A novel approach for the treatment of triple-negative breast cancer.**

Piridinas y pirimidinas trisustituídas diseñadas como ligandos del receptor adenosínico A2A y del receptor de histamina H3. Un nuevo enfoque para el tratamiento del cáncer de mama triple negativo.

**Resumen:** Triple-negative breast cancer (TNBC) is recognized as one of the most biologically and clinically aggressive breast cancer subtypes. It is characterized by a high rate of cellular proliferation, metastasis, a high recurrence rate, decreased survival, and presents a poor prognosis. TNBC is defined as one type of breast cancer that does not express estrogen, progesterone, or human epidermal growth factor 2 receptors, which is why the search for alternatives for its treatment is still an important area of study. The adenosine A2A receptor (A2AR) has been recognized as an important immunological checkpoint in tumor progression. Therefore, the use of antagonists would allow the activation of cells of the immune system, promoting the elimination of tumor cells. On the other hand, several studies have reported the involvement of the histamine H3 receptor (H3R) in cell proliferation and has been associated with a poor prognosis and shorter survival in patients with TNBC. Thus, antagonizing the H3R would provide a new strategy for addressing the treatment of this type of cancer. This work proposes the design of new trisubstituted pyridine and pyrimidine derivatives which contain the structural requirements to antagonize both the A2AR and the H3R. The development of these dual antagonists could provide a new approach in the search for promising alternatives for the (immuno)therapy of triple-negative breast cancer. Our research group has already successfully synthesized and characterized seven derivatives, and we are awaiting the first results of their biological activity, that is, their affinity for both receptors and their effect on cell viability in the TNBC cell line: MDA-MB-231.

**Autores:** Jesús Díaz-Venegas; Christian Espinosa-Bustos  
**Afiliación:** Laboratorio de Química Bio-Orgánica (LabQBO), Escuela de Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile.  
**Area de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** [jdiaz9@uc.cl](mailto:jdiaz9@uc.cl)  
**Agradecimientos:** Fondo Ciencia Básica DIPOG N°39175004-301-81, Facultad de Química y de Farmacia UC.  
**Socio Patrocinante:** Christian Espinosa Bustos

**19. METABOLITES WITH EXTREMELY POTENT ANTIOXIDANT PROPERTIES ARE GENERATED UPON EXPOSURE OF QUERCETIN AND KAEMPFEROL TO GASTRIC FLUID**  
GENERACIÓN DE METABOLITOS CON EXTREMADAMENTE ALTA POTENCIA ANTIOXIDANTE TRAS LA EXPOSICIÓN DE QUERCETINA Y KAEMPFEROL A FLUIDO GÁSTRICO

**Resumen:** Recently, we demonstrated that the oxidation of the flavonols quercetin (Que) or kaempferol (Kae) gives rise to the formation of a type of metabolites (benzoylbenzofuranones, BZF) whose intracellular antioxidant potency is, paradoxically, 1,000- and 5,000-fold greater than that of their precursors, respectively. Considering that Que and Kae occur in edible plants, we evaluated the formation of BZF-Que and BZF-Kae after their exposure to nitrous acid (NA), an oxidant molecule that naturally occurs in human gastric fluid. Disappearance of Que and Kae and appearance of their corresponding BZFs were monitored (HPLC-DAD) during their exposure to NA. The influence of increasing concentrations of these flavonols on the formation of their corresponding BZFs was explored, and the effect of flavonoids that do not form BZFs (such as catechins) on BZF-Que formation was investigated. Results indicate that the formation of both BZFs is concentration- and time-dependently. The joint incubation of Que and Kae with NA led to a further increase of their disappearance, with no greater formation of their corresponding BZFs. Interestingly, the combined exposure of Que and epicatechin to NA resulted not only in their greater disappearance but also in a considerably greater formation of BZF-Que. The present results reveal that the presence of NA in gastric fluid constitute a chemical environment capable of inducing the oxidation of Que and Kae, leading to the formation of their respective BZFs. In view of the considerably

greater antioxidant properties of these metabolites, we propose that their formation in gastric fluid would result in a substantial increase in its antioxidant capacity, having therefore potential implications on the antioxidant status of the gastrointestinal epithelial cells.

**Autores:** Fuentes J.1; Nina N.2; Schmeda-Hirschmann G.3; Speisky H.1  
**Afiliación:** 1. Laboratory of Antioxidants, Nutrition and Food Technology Institute, University of Chile. 2. Universidad Mayor de San Andrés, Instituto de Investigaciones Fármaco Bioquímicas, La Paz, Bolivia. 3. Laboratorio de Química de Productos Naturales, Instituto de Química de Recursos Naturales, Campus Lircay, Universidad de Talca.  
**Area de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** [ifuentes@inta.uchile.cl](mailto:ifuentes@inta.uchile.cl)  
**Agradecimientos:** FONDECYT 1250088  
**Socio Patrocinante:** NO APLICABLE

**20. SYNTHESIS AND STUDY OF THE PHYSICO-CHEMICAL AND BIOLOGICAL PROPERTIES OF NEW INDOLE DERIVATIVES**

Síntesis y estudio de las propiedades fisicoquímicas y biológicas de nuevos derivados de indol

**Resumen:** Chagas disease remains a neglected global health burden, with current treatments—nifurtimox and benznidazole—proving ineffective in the chronic stage and exhibiting high toxicity. Addressing this critical need, this study focused on the synthesis of six novel indole derivatives, designed as structural analogues of nifurtimox, with the primary goal of discovering compounds that are both more active and less toxic. The central hypothesis posits that the mechanism of action involves the selective generation of oxidative stress within the parasite. Electrochemical and in situ EPR (Electron Paramagnetic Resonance) studies substantiated this mechanism by confirming the formation of a nitroanion radical upon reduction, suggesting that the trypanocidal activity is mediated by the formation of reactive free radicals. Furthermore, cruzipain, an enzyme vital for *T. cruzi* survival and host cell infectivity, was selected as a key pharmacological target for inhibition. In the initial in vitro assays, compound 3 demonstrated the most promising profile, exhibiting superior trypanocidal activity (IC<sub>50</sub> = 75 ± 3 μM) alongside a significantly lower cytotoxicity against mammalian cells (IC<sub>50</sub> > 100 μM). The subsequent mechanistic study on compound 3 involves evaluating ROS (Reactive Oxygen Species) generation within the parasite environment and assessing its potential enzymatic inhibition against cruzipain and trypanothione reductase. To bridge the gap between in vitro findings and the in vivo environment, the most active compound will finally be tested in complex 3D cardiac spheroid models infected with *T. cruzi*, with the anticipation that its trypanocidal efficacy will be sustained or even enhanced in this more physiologically relevant tissue model.

**Autores:** Pozo-Martínez J.1,2; Costales J. 2; Moncada M 3; Lapier M 1.  
**Afiliación:** 1Laboratorio de Química Medicinal, Facultad de Farmacia, Universidad de Valparaíso, Chile. 2 Centro de Investigación para la Salud en América Latina, Pontificia Universidad Católica del Ecuador, Quito, Ecuador. 3 Instituto Universitario de Investigación y Desarrollo Tecnológico, Universidad Tecnológica Metropolitana, Chile  
**Area de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** [michel.lapier@uv.cl](mailto:michel.lapier@uv.cl)  
**Agradecimientos:** Proyecto Fondecyt 3230385, Puente UV 22991 .  
**Socio Patrocinante:** Mabel Catalan



## 21. SYNTHESIS AND EVALUATION OF COUMARIN DERIVATIVES FUSED WITH TRIPHENYLPHOSPHINE CATIONS FOR USE AS POTENTIAL ANTI-CANCER AGENTS.

Síntesis y evaluación de derivados de cumarina fusionados con cationes de trifenilfosfina como posibles agentes anticancerígenos

**Resumen:** Cancer is one of the world's leading causes of death, accounting for one in six fatalities. It is characterised by the uncontrolled proliferation of abnormal cells that can invade tissues and spread to other parts of the body. Current treatments include surgery, radiotherapy and chemotherapy. The latter is the most widely used, but it has limitations, such as severe adverse effects, damage to healthy cells and therapeutic resistance. In this context, new therapeutic strategies that are more effective and selective are needed. Bioactive molecules derived from natural sources are a promising alternative in this regard. Coumarins, in particular, have generated interest due to their anti-cancer properties, which could target tumour cells specifically, thereby reducing side effects. Coumarins act by inhibiting cyclin-dependent kinases (CDKs), regulating apoptotic proteins and interfering with efflux pumps, thereby reducing drug resistance. On the other hand, lipophilic triphenylphosphine cations (TPP<sup>+</sup>) show high affinity for hyperpolarised mitochondria in malignant cells, accumulating selectively in them [3]. Our group has previously worked with TPP<sup>+</sup> in the neurodegenerative context, observing cytotoxicity in tumour cells [4]. For this reason, in this study we synthesised six compounds (3a-f) fused with coumarin-TPP<sup>+</sup> with different spacer lengths to enhance antiproliferative activity and evaluate their effect on cell viability and mitochondrial potential. This strategy seeks to offer an innovative approach to the development of more effective and selective oncological drugs. To date, we have evaluated the cell viability of compound 3f on triple-negative breast cancer cells MDA-MB-231, obtaining an IC<sub>50</sub> = 1.6 µM, which is equipotent to the drug doxorubicin.

**Autores:** Osses-Mendoza, P.1, Almarza, G.1, del Campo, A.1, Espinosa-Bustos, C.1  
**Afiliación:** 1 Bio-Organic Chemistry Laboratory, School of Chemistry and Pharmacy, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile, Santiago de Chile.  
**Área de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** [paula.osses@uc.cl](mailto:paula.osses@uc.cl)  
**Agradecimientos:**

**Socio Patrocinante:** Dr. Christian Espinosa-Bustos.

## 22. NOVEL SUBSTITUTED 7-AZAINDOLE DERIVATIVES AS MULTI-TARGET MODULATORS OF 5-HT<sub>1A</sub>, 5-HT<sub>6</sub> AND 5-HT<sub>7</sub> RECEPTORS.

Nuevos derivados de 7-azaindol sustituidos como moduladores multidiana de los receptores 5-HT<sub>1A</sub>, 5-HT<sub>6</sub> y 5-HT<sub>7</sub>.

**Resumen:** Neurodevelopmental disorders (NDDs) are a multifaceted group of mental conditions which are characterized by cognitive deficits and behavioral impairment, with autism spectrum disorder (ASD) being among the most prevalent. Despite the high prevalence, lack of pharmacological treatment aiming at the core symptoms of ASD remains an issue. Serotonin signaling has been shown to be impaired both in humans and animal models, hence serotonin receptor modulation has been proposed as a pharmacological strategy for ASD. The 5-HT<sub>1A</sub> receptor plays a role in social behavior, synapse maturation, and other brain-development functions. The 5-HT<sub>6</sub> receptor interacts with the mTOR pathway of autophagy, known to be related to neurodevelopmental mechanisms<sup>3</sup>. The 5-HT<sub>7</sub> receptor agonism has shown to rescue repetitive stereotypic behavior in an autistic-like animal model. Previously, we established and validated our design methodology for the obtention of high affinity 5-HT<sub>6</sub> receptor antagonists, with a subsequent 3D-QSAR model. Among the designed molecules, BHSL-48 (formerly known as PUC-10), has demonstrated autophagy induction via mTOR signalling pathway inhibition. Based on the merging of known pharmacophore models of the 5-HT<sub>6</sub>, 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors, a series of molecules was designed and subsequently synthesized. From radioligand binding competition assays we have identified BHSL-6 as a novel high affinity triple modulator (K<sub>i</sub> 5-HT<sub>1A</sub> = 45,4nM; K<sub>i</sub> 5-HT<sub>6</sub> =

42,3nM; K<sub>i</sub> 5-HT<sub>7</sub> = 76,1nM), as well as several dual and single serotonin receptor ligands from the substituted 7-azaindole family. Overall, these findings highlight the 7-azaindole core as a promising scaffold for 5-HT receptor modulation.

**Autores:** Madrid F. 1; Rojas D. 1; Rivera-Illanes, D. 1; Lagos, C. F. 2; Recabarren-Gajardo 1, 3.

**Afiliación:** 1 Bioactive Heterocycles Synthesis Laboratory (BHSL), Departamento de Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile; 2 Chemical Biology & Drug Discovery Lab, Escuela de Química y Farmacia, Facultad de Medicina y Ciencia, Universidad San Sebastián; 3 Centro Interdisciplinario de Neurociencias, Pontificia Universidad Católica de Chile

**Área de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [darivera4@uc.cl](mailto:darivera4@uc.cl)

**Agradecimientos:** The authors would like to thank ANID for the granted funds Proyecto Fondecyt Regular N°1241192.

**Socio Patrocinante:** N/A

## 23. COMPUTATIONAL DESIGN, SYNTHESIS, AND BIOLOGICAL ASSESSMENT OF NEW SULFONAMIDES AS POSITIVE ALLOSTERIC MODULATORS OF THE PHOSPHORYLATED α<sub>3</sub> GLYCINE RECEPTOR

Diseño computacional, síntesis y evaluación biológica de nuevas sulfonamidas como moduladores alostéricos positivos del receptor de glicina α<sub>3</sub> fosforilado

**Resumen:** Chronic pain is a major therapeutic challenge due to its high prevalence and complexity, linked to synaptic disinhibition processes in the spinal cord. In this context, the α<sub>3</sub> glycine receptor (GlyRα<sub>3</sub>), particularly in its phosphorylated form at serine 346 (S346), has emerged as a crucial molecular target. PKA-mediated phosphorylation decreases glycinergic currents, enhancing pain sensitivity. This study focuses on the rational design of sulfonamides with tetrahydroquinoline (THQ) rings as positive allosteric modulators (PAMs) able to restore the phosphorylated GlyRα<sub>3</sub> function. Using molecular modeling tools and molecular dynamics simulations, compounds with high affinity and conformational stability in the allosteric site of GlyRα<sub>3</sub> were identified. The derivatives JL-02 and CO2-1 were chosen for their favorable energy profiles and specific interactions with key receptor residues. Subsequently, four compounds were synthesized, yielding between 32% and 97%, which are currently undergoing electrophysiological evaluation in cell models expressing both wild-type GlyRα<sub>3</sub> and the phosphomimetic S346E mutant. Preliminary functional results obtained with these molecules suggest divergent effects between the wild-type receptor and the phosphomimetic receptor (S346E). Whole-cell recordings showed inhibitory effects (40% inhibition of glycine currents at 10 µM) on the wild-type receptor. In contrast, phosphomimetic receptors showed an approximately 100% increase in glycine-activated currents at 10 µM. Based on these preliminary results, we propose that this multidisciplinary approach, which integrates computational chemistry, organic synthesis, and functional evaluation, represents an innovative strategy for the treatment of chronic pain.

**Autores:** Laura Sánchez-Aros. 1; Laura Pacheco Paternina. 1; Jessica Valero-Rojas. 1; Claudia Martínez-García. 1; Efraín Polo-Cuadrado. 2; Jhon López 3; Paul Soto 4; Gustavo Moraga-Cid 4; David Ramírez 1.

**Afiliación:** Universidad de Concepción

**Área de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** [laurasanchezaros@gmail.com](mailto:laurasanchezaros@gmail.com)

**Agradecimientos:** Acknowledgments: Fondecyt Regular Project 1220656 (DR) and 1251488 (GMC).

**Socio Patrocinante:** Dr. David Ramírez

#### 24. DECIPHERING THE TRANSACTIVATION MECHANISM BETWEEN THE PURINERGIC RECEPTOR P2Y2 AND HER2 IN GASTRIC CANCER

Descifrando el mecanismo de transactivación entre el receptor purinérgico P2Y2 y HER2 en cáncer gástrico

**Resumen:** Gastric cancer (GC) ranks among the most prevalent malignancies in Chile. Within current therapeutic approaches, HER2-targeted agents hold particular clinical relevance. Epidermal growth factor receptors (EGFR) can be indirectly activated by G protein-coupled receptors (GPCRs) through a process known as transactivation. Emerging evidence suggests that purinergic GPCRs can transactivate EGFR, positioning them as novel and promising pharmacological targets in GC. This study investigates the role of P2Y2R/HER2 transactivation in GC cell lines and primary cultures. Quantitative PCR (qPCR) assays were conducted on GC cell lines and patient-derived biopsies to assess P2Y2R and HER2 expression. Results from GC cell lines indicate a potential functional interaction between these receptors. Upon stimulation with UTP, both cell lines and primary cultures exhibited a concentration-dependent increase in proliferation. Lapatinib-mediated inhibition significantly reduced proliferation in AGS cells, confirming the functional relevance of this signaling axis. Immunodetection of phosphorylated EGFR and AKT in AGS cells treated with UTP for 6 hours further validated P2Y2/EGFR transactivation. Moreover, HER2 and P2Y2R expression levels were markedly elevated in GC samples compared to healthy gastric mucosa. These findings provide the first evidence of P2Y2/HER2 transactivation in GC and underscore its potential as a therapeutic target for future clinical interventions.

**Autores:** Cerda D. 1, 2; Covarrubias A.A.1,2,3; Reyna-Jeldes D.1,2; Coddou C.1,2.  
**Afiliación:** 1 Departamento de Ciencias Biomédicas, Facultad de Medicina, Universidad Católica del Norte 2 Núcleo para el estudio del cáncer a nivel básico, aplicado y clínico, Universidad Católica del Norte 3 Facultad de Ciencias Agropecuarias, Universidad del Alba, La Serena 1700000, Chile  
**Área de la Farmacología:** Molecular pharmacology  
**Dirección de Correo:** [daniela.cerda.barraza@gmail.com](mailto:daniela.cerda.barraza@gmail.com)  
**Agradecimientos:** Fondecyt Regular COD 1251487  
**Socio Patrocinante:** Dr. Claudio Coddou Alvarez

#### 25. STRUCTURAL MODELING AND FUNCTIONAL ANALYSIS OF CYSTEINE RESIDUES IN THE HUMAN VITAMIN C TRANSPORTER SVCT2

Modelamiento estructural y análisis funcional de los residuos de cisteína en el transportador humano de vitamina C SVCT2.

**Resumen:** The sodium-dependent vitamin C transporter 2 (SVCT2) mediates ascorbic acid (AA) uptake across human tissues, playing a crucial role in antioxidant defense and cellular redox homeostasis. Despite its physiological importance, the structural determinants underlying SVCT2 function remain poorly understood. Using homology modeling based on mSVCT1, we generated a structural model of human SVCT2 (hSVCT2) and examined the contribution of its 14 cysteine residues to transport activity and stability. HEK-293 cells expressing wild-type or cysteine-to-serine mutants were analyzed under reducing (DTT) and alkylating (NEM, PCMB) conditions, and AA uptake kinetics were evaluated. Alkylation of cysteines completely inhibited AA transport by decreasing  $V_{max}$  without altering  $K_m$  or sodium cooperativity, indicating that cysteine integrity is essential for catalytic efficiency but not for substrate affinity or sodium binding. Five residues, C113, C129, C160, C187, and C401, were identified as critical for transport activity, while membrane localization remained unaffected, suggesting a role in conformational dynamics rather than trafficking. Structural modeling predicts a potential disulfide bond between C129 and C187, and highlights C113 as essential for maintaining the AA-binding site near H109. This study provides the first systematic evaluation of cysteine residues in hSVCT2, revealing their importance in transporter kinetics, structural stability, and redox regulation. These findings advance our understanding of vitamin C homeostasis and support the potential of

SVCT2 as a pharmacological target in oxidative stress-related diseases and cancer.

**Autores:** Gatica M. A.; Burgos C. F.; Aylwin C. F.; Muñoz A. A.; Sweet K. S.; Rivas C. I.  
**Afiliación:** Enzymology Laboratory, Department of Biochemistry and Molecular Biology, Faculty of Biological Sciences, University of Concepción  
**Área de la Farmacología:** Molecular pharmacology  
**Dirección de Correo:** [marcgatica@udec.cl](mailto:marcgatica@udec.cl)  
**Agradecimientos:** VRID-UDEC No. 2022000435-INI; 1140429 ANID-FONDECYT; 1201496 ANID-FONDECYT  
**Socio Patrocinante:** .

#### 26. SPATIOTEMPORAL MAPPING OF PAMAM DENDRIMER COLOCALIZATION WITH SUBCELLULAR STRUCTURES

Mapeo espacio temporal de la colocalización de dendrímeros con estructuras subcelulares

**Resumen:** Polyamidoamine (PAMAM) dendrimers are synthetic nanoparticles with significant potential for drug delivery. A key feature is their ability to be internalized by cells. Therefore, a detailed mapping of their intracellular trafficking is critical for their rational development. However, their precise subcellular localization remains poorly characterized. This work aims to define the spatial and temporal association of PAMAM dendrimers with specific organelles. The experimental approach utilized fluorescein isothiocyanate-labeled PAMAM dendrimers (PAMAM-FITC) in conjunction with immunofluorescence for distinct cellular components: Clathrin (endocytic vesicles), Calnexin (endoplasmic reticulum), Tom20 (mitochondria), and Lamp1 (lysosomes). The fluorescence signals were captured by confocal microscopy. HEK293 cells were exposed to PAMAM-FITC for 15 minutes and, after washing, were analyzed at 0, 4, and 18 hours post-incubation. Colocalization was analyzed using Manders' coefficient at a 150 nm resolution. A steady decrease in cellular PAMAM fluorescence was observed, suggesting possible exocytosis or degradative clearance. The association with Clathrin decreased over time, from a Manders' coefficient of  $0.327 \pm 0.018$  at 0 hours to  $0.224 \pm 0.014$  at 18 hours. In contrast, colocalization with the endoplasmic reticulum and mitochondria peaked transiently at 4 hours ( $0.320 \pm 0.0155$  and  $0.359 \pm 0.023$ , respectively) before declining by the 18-hour mark. The most pronounced trend was the continuous and strong accumulation in lysosomes, where colocalization increased markedly from  $0.090 \pm 0.007$  at 0 hours to  $0.257 \pm 0.012$  at 4 hours, and further to  $0.457 \pm 0.018$  at 18 hours. Thus, this study successfully delineates specific and dynamic trafficking pathways for PAMAM dendrimers inside cells. The transient interaction with the endoplasmic reticulum and mitochondria contrasts with the progressive accumulation in lysosomes.

**Autores:** Rojas, E.1, Cifuentes, D.1, Díaz, C.2, Guzmán, L.1  
**Afiliación:** 1. Laboratorio de Neurobiología Molecular, Departamento de Fisiología, Universidad de Concepción; 2. Departamento de Ciencias Químicas, Facultad de Ciencias Exactas, Universidad Andrés Bello  
**Área de la Farmacología:** Molecular pharmacology  
**Dirección de Correo:** [joseguzman@udec.cl](mailto:joseguzman@udec.cl)  
**Agradecimientos:** FONDECYT 1241829 FONDECYT 11251282  
**Socio Patrocinante:** .



## 27. A FLUORESCENT-BASED METHOD TO ASSESS THE ACTIVITY OF THE HUMAN SODIUM COUPLED CITRATE TRANSPORTER

Un método basado en fluorescencia para evaluar la actividad del transportador de citrato acoplado al sodio humano

**Resumen:** The human sodium-coupled citrate transporter (hNaCT/SLC13A5) has emerged as a promising pharmacological target due to its involvement in metabolic syndrome and SLC13A5-related neurodevelopmental disorders. While isotopic tracers remain the reference method for evaluating citrate transport, their requirement for specialized equipment and regulatory approval limits broad implementation in pharmacological studies. Here, we present a fluorescence-based high-throughput screening (HTS) platform that enables functional evaluation of hNaCT in live mammalian cells. The assay is based on the co-expression of hNaCT and the genetically encoded citrate sensor Citron1, allowing real-time monitoring of intracellular citrate dynamics. To assess the performance of the system, we examined previously characterized gain- and loss-of-function hNaCT variants, confirming that the fluorescence signal accurately reflected their reported transport capacities. We further demonstrated that the assay reliably detects pharmacological modulation of hNaCT activity through before-and-after measurements using specific inhibitors and activators. These inhibitors were used as reference compounds to validate the suitability of the assay for systematic drug screening. Building on these validations, the method was adapted to a 96-well HTS format, achieving Z'-factor values above 0.6 and confirming its robustness for drug-screening applications. This fluorescence-based approach provides a sensitive, quantitative, and reproducible framework for evaluating hNaCT modulation in live cells and establishes a solid foundation for future drug discovery efforts targeting this transporter. This strategy could be readily adapted to other metabolite transporters for which genetically encoded fluorescent sensors are available.

**Autores:** Carcamo-Lemus N. 1; Bernier A. 1; Oporto-Ortega I. 1, 2; Sandoval PY 1, 3  
**Afiliación:** 1 Centro de Estudios Científicos; 2 Universidad Austral de Chile; 3 Universidad San Sebastián  
**Área de la Farmacología:** Molecular pharmacology  
**Dirección de Correo:** [pamela.sandoval@uss.cl](mailto:pamela.sandoval@uss.cl)  
**Agradecimientos:** This work was funded partly by USS-FIN-23-FAPE-03 (PYS), FONDECYT project #11190584 (PYS), and FONDECYT project # 1230145 (LFB)  
**Socio Patrocinante:** María Angélica Hidalgo

## 28. EFFECT OF A NOVEL NITROGEN-BASED LIPOPHILIC CATION DERIVED FROM GALLIC ACID (GA-C10-ISOQ) ON BROWNING IN ADIPOCYTES IN VITRO.

Efecto de un nuevo catión lipofílico basado en nitrógeno derivado del ácido gálico (GA-C10-ISOQ) sobre el pardeamiento en adipocitos in vitro

**Resumen:** Obesity is a global public health issue and Chile is one of the most affected countries. This condition promotes chronic diseases and has driven the search for novel therapies targeting white adipose tissue, which can induce browning through UCP1 and PGC-1 $\alpha$ , enhancing thermogenesis and mitochondrial biogenesis. Polyphenols have shown potential in this process, although their limited bioavailability remains a major limitation. One strategy to overcome this limitation has been their conjugation with lipophilic cations such as triphenylphosphonium (TPP $^{+}$ ), which, despite positive effects in animal models, is associated with toxicity risks, motivating the development of alternative nitrogen-based cationic carriers. The aim of this study was to evaluate the effect of the gallic acid-derived cation GA-C10-ISOQ on adipocyte browning in vitro. Differentiated 3T3-L1 adipocytes were treated for 24 h with 10, 25, 50, and 100  $\mu$ M GA-C10-ISOQ, and the gene (*ucp1*, *pgc-1 $\alpha$* , *prdm16*, and *cidea*) and protein (UCP1, PGC-1 $\alpha$ , PRDM16) expression of browning-associated markers were assessed. Data were analyzed by one-way ANOVA followed by Dunnett's post hoc test ( $p < 0.05$ ). Results on gene expression showed that GA-C10-ISOQ significantly increased *ucp1* expression at all tested concentrations. For *pgc-1 $\alpha$* , significant effects

were observed at 10 and 50  $\mu$ M, whereas *prdm16* and *cidea* were significantly upregulated at 50  $\mu$ M and at 50 and 100  $\mu$ M, respectively, compared to control. At the protein level, UCP1 and PGC-1 $\alpha$  expression were significantly elevated across all concentrations, while PRDM16 showed an increasing trend at 50  $\mu$ M ( $p = 0.0605$ ). These findings demonstrate a browning effect of GA-C10-ISOQ and highlight its potential as a promising candidate for future in vivo studies in obesity models and as a possible modulator of energy metabolism.

**Autores:** Orellana JF. 1; Suárez-Rozas C. 2; García-Díaz D. 4; Catalán M. 1; Olmedo I. 3.  
**Afiliación:** 1: Núcleo Interdisciplinario de Farmacología e Inmunología, ICBM, Facultad de Medicina, U. de Chile; 2: Centro de Química Médica, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina, U. del Desarrollo; 3: Núcleo Interdisciplinario de Fisiología, Biofísica y Fisiopatología, ICBM, Facultad de Medicina, U. de Chile; 4: Departamento de Nutrición, Facultad de Medicina, U. de Chile  
**Área de la Farmacología:** Molecular pharmacology  
**Correo:** [juan.orellanacornejo@gmail.com](mailto:juan.orellanacornejo@gmail.com), **Agradecimientos:** Agradecimientos a la ANID Fondecyt Dra. Olmedo 2024 (Fondecyt N° 1240954) y Dra. Catalán 2025 (Fondecyt N° 1251859). Además, por la Beca Doctorado Nacional (ANID N° 21240246) y Beneficio Complementario – Gastos Operacionales del Proyecto de Tesis Doctoral (ANID N° 242250268) adjudicados por Orellana JF el año 2024 y 2025, respectivamente.  
**Socio Patrocinante:** Mabel Catalán Díaz.

## 29. DIFFERENTIAL MODULATION OF THE MITOCHONDRIAL UNFOLDED PROTEIN RESPONSE (UPR<sup>mt</sup>) IN MEF CELLS KNOCK OUT FOR MITOFUSIN 1 AND MITOFUSIN 2

Modulación diferencial de la respuesta de proteínas desplegadas mitocondriales (UPR<sup>mt</sup>) en células MEF con delección de mitofusina 1 y mitofusina 2

**Resumen:** Mitochondrial morphology is more than just structural; it functions as a dynamic regulator of cellular stress and metabolic homeostasis. Mitofusins 1 and 2 (MFN1/2) mediate outer membrane fusion, a process essential for maintaining mitochondrial integrity. However, only MFN2 facilitates communication with the endoplasmic reticulum (ER). The loss of these proteins disrupts mitochondrial dynamics and may impair stress signaling pathways, including the mitochondrial unfolded protein response (UPR<sup>mt</sup>), an adaptive mechanism that restores proteostasis and limits cellular stress. This study aims to investigate how the lack of each MFN isoform modulates UPR<sup>mt</sup> activation and to elucidate how this adaptive pathway compensates for structural defects and contributes to proteostatic homeostasis. Mouse embryonic fibroblast (MEF) WT, MFN1-KO and MFN2-KO cells were cultured under standard conditions. MFN1/MFN2 immunoblots validated knockouts, while UPR<sup>mt</sup> markers (LONP1, HSP60, HSP90, CLPP, ATF5) were analyzed by Western Blot and RT-qPCR. Our findings indicate that gene and protein expression analyses demonstrated that MFN1 and MFN2 deletions differentially modulate UPR<sup>mt</sup> signaling. MFN1 deficiency triggered the upregulation of stress-responsive chaperones and proteases, consistent with adaptive activation of the UPR<sup>mt</sup>, while MFN2-KO cells showed downregulation of UPR<sup>mt</sup> markers and MFN1. The loss of MFN2, but not MFN1, disrupts this interaction, impairing stress signaling and reducing adaptive capacity. Thus, MFN2 emerges as a central coordinator of mitochondrial stress signaling homeostasis. Altogether the findings suggest that appropriate mitochondrial-ER communication is crucial for efficient UPR<sup>mt</sup> activation.

**Autores:** Pesce L. M. 1; Briones-Manríquez F. G. 1; Almarza G. 1; del Campo A. E. 1  
**Afiliación:** Laboratory of Physiology and Cellular Bioenergetics, School of Chemistry and Pharmacy, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile  
**Área de la Farmacología:** Molecular pharmacology  
**Dirección de Correo:** [luciana.pesce@uc.cl](mailto:luciana.pesce@uc.cl)  
**Agradecimientos:** FONDECYT 1230428 to AdC, Dr. María Isabel Hernández Alvarez for kindly donating the MEF KO cell lines.  
**Socio Patrocinante:** Dr. Andrea Estefanía del Campo Steir

### 30. MARESIN 1 EXERTS HEPATOPROTECTIVE, ANTI-INFLAMMATORY AND ANTIOXIDANT EFFECTS IN AN EXPERIMENTAL MODEL OF MAFLD/DM2 IN SPRAGUE-DAWLEY RATS BY MODULATING THE NUCLEAR RECEPTORS ROR $\alpha$ , PPAR $\alpha$ AND PPAR $\gamma$

Maresina 1 ejerce efectos hepatoprotectores, antiinflamatorios y antioxidantes en un modelo experimental de MAFLD/DM2 en ratas Sprague-Dawley mediante la modulación de los receptores nucleares ROR $\alpha$ , PPAR $\alpha$  y PPAR $\gamma$

**Resumen:** Metabolic dysfunction-associated fatty liver disease (MAFLD) is one of the leading causes of hepatic morbidity, affecting 35% of the adult population, with a prevalence ranging from 17 % to 46 % worldwide, closely linked to type 2 diabetes mellitus (DM2). This study evaluated the hepatoprotective and metabolic modulatory potential of the pro-resolving lipid mediator Maresin-1 (MaR1), a derivative of docosahexaenoic acid (DHA, an omega-3 fatty acid), in a MAFLD/DM2 experimental model in Sprague-Dawley rats. Animals were divided into four groups: Control, MAFLD/DM2, MaR1, and MAFLD/DM2+MaR1. MaR1 administration (4 ng/mg for 4 weeks) improved insulin sensitivity and reduced serum cholesterol, triglycerides, and transaminase levels, partially restoring hepatic function. Histological analysis revealed that MaR1 administration significantly decreases fibrosis (collagen type I), steatosis, and hepatic inflammation, while preserving tissue architecture. At the molecular level, MaR1 promoted nuclear translocation and upregulation of the nuclear receptors ROR $\alpha$ , PPAR $\alpha$ , and PPAR $\gamma$ , which are key regulators of lipid metabolism and energy homeostasis. Moreover, MaR1 attenuated the activation of the proinflammatory transcription factor NF- $\kappa$ B, reducing the expression of IL-1 $\beta$  and IL-18, while increasing the expression of anti-inflammatory cytokines such as IL-10 and IL-4. In parallel, activation of the NRF2/SOD1 antioxidant pathway and a reduction in protein carbonylation were generated by MaR1, indicating strong protection against oxidative stress. Finally, MaR1 normalized the expression of TGF- $\beta$ , BMAL1, and SREBP1C, modulating fibrosis and lipogenesis processes. Collectively, these findings demonstrate that MaR1 exerts a broad hepatoprotective effect by regulating metabolic, inflammatory, and oxidative pathways, supporting its potential as a therapeutic modulator in MAFLD associated with DM2.

**Autores:** Quiñones San Martín M. 1,2; Herrera Vielma F. 1,2; Norambuena-González R. 1,3; Marín-Sanhueza P. 1; Ocaris Jiménez M. 1; Gonzáles D.R 1; Perera-Sardiña Y. 1; Zúñiga-Hernández J. 1.

**Afiliación:** 1. Lab of Pharmacology and Physiology, Department of Basic Biomedical Sciences, Faculty of Health Sciences, University of Talca. 2. Doctorate in Science Program, mention in Research and Development of Bioactive Products, Institute of Chemistry of Natural Resources, University of Talca. 3. Doctorate in Biomedical Sciences Program, Faculty of Health Sciences, University of Talca. **Área de la Farmacología:** Molecular pharmacology.

**Correo:** [mquinones@utalca.cl](mailto:mquinones@utalca.cl). **Agradecimientos:** Acknowledgments: ANID national doctoral scholarship N° 21220031 (MQSM); Project INGE210025 University of Talca (JZH); and Project FOVI230100 (DGR).

**Socio Patrocinante:** Dra. Jessica Zúñiga Hernández

### 31. A PUTATIVE ENDOCANNABINOID BINDING SITE ON THE GLYCINE RECEPTOR INVOLVING TM4 AND INTRACELLULAR RESIDUES

POTENCIAL SITIO DE UNIÓN PARA ENDOCANABINOIDES EN EL RECEPTOR DE GLICINA COMPUESTO RESIDUOS DE TM4 Y DEL DOMINIO INTRACELULAR

**Resumen:** Cannabinoid ligands are a family of diverse bioactive compounds mostly targeting G protein coupled cannabinoid receptors. Nevertheless, many cannabinoids have been also characterized as ion channel modulators. Experimental evidence has described that inhibitory glycine receptors (GlyRs) are modulated by phytocannabinoids (PCs) and endocannabinoids (ECs), including the PCs  $\Delta$ 9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and the EC anandamide (AEA). A recent study has provided the first structures of GlyRs-THC complexes, revealing a novel allosteric site. Conversely, the EC binding sites on GlyRs still remain undefined. Using electrophysiology, mutagenesis and bioinformatics, we outline a putative EC binding site majorly associated with TM4 residues. Mutated GlyRs with impaired PC sensitivity (W239F and F395A) showed a significantly reduced sensitivity to AEA and NA-Gly, two ECs having hydroxylated or

acidic groups. On the other hand, non-conservative substitutions of the TM4-associated K385 residue decreased the potentiation induced by AEA and NA-Gly. Interestingly, while the charge-reversal mutation K385E enabled the GlyR potentiation by the basic EC virodhamine, substitutions on K385 did not alter the potentiation elicited by CBD. Structural predictions suggest that K385 and F395 plays a dual role in the EC binding to a site majorly located on the TM4 domain, in close vicinity to the intracellular side. Collectively, our findings suggest that a residue network located around TM4 configures an EC acceptor site on GlyRs. Our data suggest that the molecular determinants for the modulation of GlyRs by PCs and ECs involve diverse, but in part interdependent, key residues. Further insights on GlyR modulation by cannabinoid ligands may provide unrecognized molecular sites and mechanisms for allosteric control, which can be useful for the design of novel modulators.

**Autores:** Marileo A.M.; Millar-Obreque C.; Salgado-Martínez B.; Acevedo-Zapata N.; Castro P.A.; Moraga-Cid G.; Aguayo L.G.; Burgos C.F.; Yévenes G.E.

**Afiliación:** Department of Physiology, Faculty of Biological Sciences, University of Concepcion, Chile

**Área de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** [GYEVENES@UDEC.CL](mailto:GYEVENES@UDEC.CL)

**Agradecimientos:** Supported by ANID-FONDECYT 1250856

**Socio Patrocinante:** Gonzalo YEVENES

### 32. ESSENTIAL OIL FROM ACANTHOLIPPIA DESERTICOLA (RICA-RICA) MODULATES HIPPOCAMPAL GABAERGIC TRANSMISSION IN MICE

El aceite esencial de *Acantholippia deserticola* (rica-rica) modula la transmisión gabaérgica en el hipocampo de ratones.

**Resumen:** Rica-rica (*Acantholippia deserticola*), a medicinal and aromatic plant endemic to Chile's Andean highlands, is traditionally consumed as an herbal infusion by indigenous communities to treat various illnesses. Despite its widespread use and reported bioactive properties, including antioxidant, anti-inflammatory, anxiolytic, and stimulant effects, the neurobiological mechanisms underlying these effects remain unexplored. Natural products remain a rich source of neuroactive molecules that modulate neuronal excitability and synaptic transmission. Rica-rica oil consists primarily of (~90%) of thujones, bicyclic monoterpenes structurally similar to constituents of *Artemisia absinthium* (wormwood), which exhibit psychoactive properties and are known to interact with GABA receptors. Here, we investigated the neurophysiological effects of an essential oil derived from *A. deserticola*. Using whole-cell patch-clamp recordings in acute hippocampal slices from a mouse model, we found that the oil robustly suppressed GABAergic synaptic transmission in CA1 pyramidal neurons. Bath application of the oil reduced the amplitude of evoked inhibitory postsynaptic currents (eIPSCs), decreased both the frequency and amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs), and increased the paired-pulse ratio (PPR). These findings are consistent with combined presynaptic and postsynaptic mechanisms of action. These findings identify rica-rica oil as a promising source of bioactive compounds capable of modulating inhibitory tone within hippocampal microcircuits. Given that dysregulated GABAergic signaling is implicated in various neuropsychiatric conditions, including anxiety and depressive disorders. These results underscore the potential relevance of rica-rica oil for understanding and potentially treating neuropsychiatric disorders.

**Autores:** Ahumada J. 2,3; Morel P. 1; Vera W., 1 and Fuenzalida M. 2,3

**Afiliación:** 1-Laboratorio de Química de Metabolitos Bioactivos, Escuela de Química y Farmacia, Facultad de Farmacia, Universidad de Valparaíso; 2-Laboratorio de Plasticidad Neuronal, Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso; 3-Millennium Nucleus of Neuroepigenetics and Plasticity, Universidad Andrés Bello, Santiago.

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [juan.ahumada@uv.cl](mailto:juan.ahumada@uv.cl)

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**Socio Patrocinante:** No aplica



### 33. DETERMINATION OF PHENYTOIN IN SERUM BY LIQUID CHROMATOGRAPHY AND A PORTABLE DEVICE DETERMINACIÓN DE FENITOÍNA EN SUERO MEDIANTE CROMATOGRFÍA LÍQUIDA Y UN DISPOSITIVO PORTÁTIL

**Resumen:** Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures. Its management relies mainly on anticonvulsant drugs such as phenytoin (PHE), which requires strict therapeutic monitoring due to its narrow therapeutic range and nonlinear pharmacokinetics. Current monitoring methods, including chromatographic and immunoassay techniques, demand specialized equipment, trained personnel, and long processing times. In this work, a portable Point of Care Testing (POCT) prototype based on an electrochemical sensor was developed for PHE quantification in serum, comparing its results against liquid chromatography as the reference method. Chromatographic analysis were performed using a C-18 column and a water/acetonitrile mobile phase at a flow rate of 1 mL·min<sup>-1</sup>, with UV detection at 235 nm for PHE and 195 nm for the internal standard, bromazepam. Electrochemical measurements were carried out with a CHI660c potentiostat using gold-modified screen-printed electrodes. Optimal conditions were determined through cyclic voltammetry (-0.4 to 1.1 V), evaluating pH values from 7 to 13. The POCT device integrates an ESP32 microcontroller with Bluetooth BLE connectivity, an amperometric circuit, battery power supply, all housed in a 3D-printed case. Such microcontroller was linked to an Android app, allowing patient management, real-time data acquisition, concentration visualization, and access to historical records. A calibration curve obtained at 0.4 V and pH 12.7 (NaOH 50 mM) exhibited linearity between 20 and 160 µg/mL. The chromatographic method was validated according to the FDA Bioanalytical Method Validation Guidance, meeting all acceptance criteria. Under optimized conditions, PHE quantification using the developed POCT device showed a linear range of 20-150 µg/mL with a correlation coefficient of R<sup>2</sup> = 0.996. Finally, the developed POCT device can measure the target PHE concentrations.

**Autores:** De Diego M. 1; Mundaca R. 1; Pino E. 2; Godoy R. 1  
**Afiliación:** 1. Departamento de Farmacia, Facultad de Farmacia, Universidad de Concepción. 2. Departamento de Ingeniería Eléctrica, Facultad de Ingeniería, Universidad de Concepción.  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [mdediego@udec.cl](mailto:mdediego@udec.cl)  
**Agradecimientos:** Proyecto de Investigación VRID N° 2023000929INT, Investigación Interdisciplinaria, Dirección de Investigación, Universidad de Concepción.  
**Socio Patrocinante:** Ninguno

### 34. METHODOLOGICAL STANDARDIZATION OF DUAL-COLOR FIBER PHOTOMETRY FOR IN VIVO MONITORING OF CALCIUM AND DOPAMINE DYNAMICS IN THE MOUSE NUCLEUS ACCUMBENS DURING FOOD REWARD

Estandarización Metodológica de la Fotometría de Fibra Bicromática para el Monitoreo In Vivo de la Dinámica de Calcio y Dopamina en el Núcleo Accumbens de Ratón Durante la Recompensa Alimentaria

**Resumen:** In vivo monitoring of synaptic activity within reward-related circuits is crucial for elucidating the neurobiological mechanisms underlying hedonic feeding. Fiber photometry enables real-time measurement of neuronal population dynamics through genetically encoded sensors. This study aims to establish a standardized methodological protocol for dual-color fiber photometry to concurrently assess calcium-dependent neuronal activity and dopaminergic signaling within the nucleus accumbens (NAc) during exposure to a food reward. Adult C57BL/6 mice were implanted with optical fibers targeting the NAc and injected with adeno-associated viral vectors encoding GCaMP8f and RdLight1, under neuron- and dopaminergic-specific promoters, respectively. Following recovery, animals were exposed to a palatable high-sugar, high-fat stimulus (Mantecol). Fluorescence signals were recorded using synchronized excitation sources and emission filters. Signal preprocessing involved motion artifact correction, offset subtraction, and ΔF/F normalization. Preliminary findings demonstrated synchronized calcium and dopamine transients in the NAc during food approach and consumption, indicative of increased dopaminergic activity

associated with reward processing. The developed protocol offers a reproducible framework for investigating reward-induced synaptic dynamics in vivo. Future applications may include adaptation of this methodology to examine glucagon-like peptide-1 (GLP-1) mediated activity within the lateral septum during food reward, thereby providing insights into hormonal modulation of hedonic circuits and identifying potential targets for pharmacological interventions in obesity.

**Autores:** Etcheagaray-González, C.; Dib-Schwelling, T.; Sotomayor-Zárate, R.  
**Afiliación:** Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [ramon.sotomayor@uv.cl](mailto:ramon.sotomayor@uv.cl)  
**Agradecimientos:** FONDECYT Grant 124-0141 and CIDI-UV 01/2024 to R.S-Z.  
**Socio Patrocinante:** Ramón Eduardo Sotomayor Zárate

### 35. IN VITRO EVALUATION OF NOVEL MODULATORS OF HP2X2 AND HP2X4 RECEPTORS IDENTIFIED THROUGH IN SILICO SCREENING.

Evaluación in vitro de nuevos moduladores de receptores hP2X2 y hP2X4 identificados a través ensayos in silico

**Resumen:** Purinergic P2X receptors (P2XRs) are ligand-gated ion channels activated by ATP and composed of seven subunits capable of forming homo or heterotrimers. P2XRs play key roles in several neurological disorders, including Alzheimer's disease, in which overexpression of P2X2, P2X4, and P2X7 has been reported. Despite advances in understanding their structure and function, only a few specific modulators have been identified to date. Before the recently published cryo-EM structures of human P2X2 and P2X4 (hP2X2 and hP2X4), we generated homology models for these receptors based on the zebrafish P2X4 (zP2X4) structure and performed large-scale protein-ligand docking simulations using over one million compounds from the MolPort database. For in silico screening, interaction grids were positioned at the ATP binding site identified through multiple sequence alignments with zP2X4 and rat P2X2. From this analysis, eleven candidate molecules were selected for in vitro testing based on docking scores and predicted binding free energies comparable to ATP. Here, we report the electrophysiological evaluation of these candidates using ATP-evoked currents in recombinant hP2X2 and hP2X4 receptors. All compounds were tested at a concentration of 100 µM. Five molecules presented solubility issues that prevented reliable analysis, while four displayed promising modulatory effects: C4 acted as an inhibitor of both receptors, C10 potentiated both, whereas C2 and C5 exhibited receptor-specific actions. These results validate our in silico screening strategy as an effective approach to identify novel modulators of purinergic receptors and reveal promising candidates for further characterization in neuronal models relevant to neurodegenerative diseases.

**Autores:** Godoy P. A.1; Rubilar N.2, Ramírez-Molina O.2, Díaz Gómez C.3, Burgos C. F.1  
**Afiliación:** 1. Laboratorio de Neuromodulación, Departamento de Fisiología, Universidad de Concepción, Chile. 2. Laboratorio de Screening de Compuestos Neuroactivos, Departamento de Fisiología, Universidad de Concepción, Chile. 3. Departamento de Ciencias Químicas, Facultad de Ciencias Exactas, Universidad Andrés Bello, Concepción, Chile  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [pamegodoyr@gmail.com](mailto:pamegodoyr@gmail.com)  
**Agradecimientos:** ANID FONDECYT Postdoctorado 3230515 to GPA, ANID FONDECYT 11221211 to BCF  
**Socio Patrocinante:** ----.



### 36. LPS ACTIVATION DOWNREGULATED REELIN SIGNALING PATHWAYS IN BV2 MICROGLIAL CELLS.

La activación con LPS reduce la señalización de reelina en células microgliales BV2

**Resumen:** Neuroinflamación, caracterizada por la activación de microglia residente, es un componente crítico de enfermedades neurodegenerativas. Reelin, una glicoproteína extracelular esencial para el desarrollo neuronal y la plasticidad sináptica, también juega un papel neuroprotector en el cerebro adulto. Evidencia reciente sugiere que su participación en la neurodegeneración es compleja, ya que puede tanto exacerbar mecanismos patogénicos como modular respuestas gliales. La microglia es conocida por expresar Reelin y sus receptores, sugiriendo un papel regulador potencial en la respuesta inflamatoria. La vía de señalización de Reelin canónica involucra la unión a sus receptores (ApoER2/VLDLR), conduciendo a la fosforilación de la proteína adaptadora Disabled-1 (pDab1) y a la activación downstream de varias quinasas, incluyendo a ERK1/2 y CREB. Investigamos el efecto de lipopolisacárido (LPS)-inducida inflamación de células microgliales BV2 sobre la intensidad de fluorescencia de Reelin, su receptor ApoER2, y el estado de fosforilación de componentes de señalización clave downstream: pCREB, pDab1, y pERK1/2. Células microgliales BV2 fueron tratadas con 100 ng/mL LPS por 24 horas para inducir un fenotipo pro-inflamatorio. Los niveles de Reelin, ApoER2, pCREB, pDab1, y pERK1/2 fueron medidos usando intensidad de inmunofluorescencia. LPS estimulación mostró una reducción en los niveles de expresión de Reelin y su receptor ApoER2 comparado con células control no estimuladas. Concurrentemente, los niveles de fluorescencia de componentes fosforilados de señalización pDab1, pCREB, y pERK1/2 exhibieron una tendencia consistente de reducción tras el tratamiento con LPS. Estos resultados sugieren que la activación inducida por LPS promueve una regulación concurrente y a la baja de la vía de señalización de Reelin/ApoER2 y sus efectores (pDab1, pCREB, y pERK1/2). Estos resultados sugieren una pérdida potencial de la función moduladora de la vía bajo condiciones inflamatorias, alineándose con reportes de desregulación de Reelin en patologías neurodegenerativas.

**Autores:** Daniela Gomez 1, Amanda Gutiérrez Riffó1, Antonia Muñoz 1, David Ramírez2, Paula Santana 3, Violeta Chang4, Estibaliz M. Ampuero  
**Afiliación:** Laboratorio de Neurofarmacología, Facultad de Química y Biología, Universidad de Santiago de Chile  
**Área de la Farmacología:** Neurofarmacología  
**Dirección de Correo:** [estibaliz.ampuero@usach.cl](mailto:estibaliz.ampuero@usach.cl)  
**Agradecimientos:** Vinculab 25-6, Vinculab 25-7, Dicyt Asociativo 022243ALL, USACH  
**Socio Patrocinante:** Leonel Rojo

### 37. PUC-10, A MODULATOR OF SEROTONIN RECEPTORS, AS A NOVEL THERAPEUTIC APPROACH FOR AUTISM-LIKE PHENOTYPES IN A ZEBRAFISH LARVAE MODEL INDUCED BY VALPROIC ACID

PUC-10, un modulador de los receptores de serotonina, como nuevo enfoque terapéutico para fenotipos similares al autismo en un modelo de larvas de pez cebra inducido por ácido valproico.

**Resumen:** El Trastorno del Espectro Autista (TEA) es una condición neurodesarrollativa que afecta a aproximadamente el 1% de los niños en todo el mundo, según la Organización Mundial de la Salud (OMS). Los síntomas principales incluyen déficits en la interacción social y comportamientos restrictivos y repetitivos, a menudo acompañados por comorbilidades. Los tratamientos farmacológicos actuales permanecen limitados, ya que los mecanismos subyacentes del TEA aún no están completamente entendidos. Entre los dianas terapéuticas emergentes se encuentran los receptores de serotonina, una familia de proteínas involucradas en la regulación del desarrollo neuronal y la homeostasis. Estudios previos han demostrado que el antagonismo del receptor de serotonina isoforma 6 mejora la interacción social y reduce los comportamientos repetitivos en modelos de autismo-like en roedores, mientras que los agonistas de las isoformas 1A y 7 mejoran el comportamiento social. Basado en esta evidencia, nuestro grupo de investigación identificó moléculas nuevas que actúan como ligandos triples para estas isoformas de receptores y estudios preliminares *in vitro* demostraron buena viabilidad celular e incremento de autofagia en grupos tratados. Ensayos de unión fueron realizados *in vitro* usando competencia por receptores de serotonina isoformas 1A, 6, y 7. PUC-10

exhibió una fuerte afinidad de unión, con constantes de inhibición ( $K_i$ ) de 30.6, 5.16, y 60.5 nM, respectivamente. Para evaluar este compuesto, empleamos un modelo de autismo inducido en larvas de pez cebra con ácido valproico (VPA). Las larvas fueron expuestas a VPA, seguidas por el tratamiento con 10 o 20  $\mu$ M de PUC-10. El fenotipo de autismo-like fue reproducido exitosamente bajo nuestras condiciones. Sin embargo, PUC-10 no afectó significativamente la interacción social o el comportamiento en campo abierto. Notablemente, mejoró el desempeño locomotor, restaurando este parámetro en los grupos tratados a niveles de control (18.41 mm, 20.62 mm, y 25.30 mm respectivamente versus 7.87 mm en VPA;  $p \leq 0.0219$ ). En resumen, PUC-10 no redujo la distancia inter-individual pero mejoró la actividad locomotora, sugiriendo un efecto modulador sobre dominios motores que warrants investigación adicional.

**Autores:** González-Quezada N. 1; Rivera-Illanes D. 1; Egaña J. T. 1; Recabarren-Gajardo G 2,3. **Afiliación:** 1. Tissue Engineering and Regeneration Laboratory, Institute of Biological and Medical Engineering, Faculty of Engineering, Pontificia Universidad Católica de Chile; 2. Bioactive Heterocycles Synthesis Laboratory, School of Pharmacy, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile; 3. Interdisciplinary Center for Neuroscience, Pontificia Universidad Católica de Chile  
**Área de la Farmacología:** Neurofarmacología  
**Dirección de Correo:** [ngonzalezquezada@alumni.uc.cl](mailto:ngonzalezquezada@alumni.uc.cl)  
**Agradecimientos:** Fondecyt Regular 1241192  
**Socio Patrocinante:** N/A

### 38. ENGINEERING STABLE PEG-PLA NANOPARTICLES FOR EFFECTIVE NUCLEIC ACID DELIVERY TO THE BRAIN

Ingeniería de nanopartículas estables de PEG-PLA para una entrega eficaz de ácidos nucleicos al cerebro

**Resumen:** Recientemente, varios ácidos nucleicos (NAs), incluyendo microRNAs, han sido reportados para mostrar potencial terapéutico en modelos animales de enfermedades del sistema nervioso central (SNC). Sin embargo, las rutas de administración convencionales no permiten eficientemente el tránsito a través de la barrera hematoencefálica. Este estudio buscó desarrollar nanopartículas poliméricas (NPs) cargadas con NAs para su entrega al cerebro. Los materiales y métodos NPs fueron sintetizados usando PEG y PLA copolímeros (mPEG-PLA) a través de un método de emulsión doble y cargadas con NAs modelo. Caracterizamos NPs cargadas con NAs (NP-mPEG-PLA-NA) en términos de diámetro hidrodinámico (HD), índice de polidispersidad (Pdl), potencial zeta (ZP), y estabilidad. HD, Pdl, y ZP fueron medidos por Dynamic Light Scattering (DLS). La concentración de NPs fue cuantificada por Nanoparticle Tracking Analysis (NTA), y la morfología visualizada por Scanning Transmission Electron Microscopy (STEM). La citotoxicidad fue evaluada en células neuronales HT-22 del hipocampo usando ensayo MTT. La eficiencia de encapsulación fue corroborada por electroforesis en gel de agarosa. Los NPs exhibieron un HD promedio de  $165 \pm 10$  nm, un Pdl de 0.21–0.32, y un ZP de  $-30$  a  $-25$  mV, indicando buena estabilidad coloidal. NP-mPEG-PLA-NA permaneció estable por al menos cuatro semanas a  $4^\circ\text{C}$  con variaciones mínimas. Ensayos de citotoxicidad en células HT-22 mostraron que la viabilidad permaneció por encima del 97% tras 24 h de exposición a  $100 \mu\text{g/mL}$ . Estos resultados indican que las NPs tienen una distribución de tamaño estrecha y exhiben una fuerte repulsión electrostática, reduciendo su tendencia a agregarse. Importantly, no ejercieron efecto significativo sobre la viabilidad de las células HT-22 a las concentraciones probadas, respaldando la biocompatibilidad. Sus propiedades fisicoquímicas las hacen candidatas prometedoras para la entrega al cerebro con aplicaciones en modelos de enfermedades del SNC. Estudios *in vivo* serán necesarios para confirmar la biodistribución y la eficacia terapéutica.

**Autores:** Tatiana A. Guarnieri1,2,3,4, Nicolás Palacios1, Javier O. Morales2,3,4 and Jenny L. Fiedler1  
**Afiliación:** Laboratory of Neuroplasticity and Neurogenetics, Ciencias Químicas y Farmacéuticas, Universidad de Chile.  
**Área de la Farmacología:** Neurofarmacología  
**Dirección de Correo:** [iguarnieri@ug.uchile.cl](mailto:iguarnieri@ug.uchile.cl)  
**Agradecimientos:** This work was supported by ANID Scholarship 21230789, FONDECYT 1230471, FONDECYT 1231154 and Anillo ACT240058.  
**Socio Patrocinante:** J. Fiedler.



### 39. A INTERFERENCE PEPTIDE OF REELIN SIGNALING AMELIORATES NEUROINFLAMMATION IN VITRO

La interferencia en la señalización de Reelina con un péptido reduce la neuroinflamación in vitro

**Resumen:** The extracellular matrix (ECM) plays a crucial role in restricting plasticity by limiting axonal and dendritic growth and preventing synaptic reactivation. Components of the ECM, such as Reelin, are essential for synaptic maturation, learning, and memory. Reelin is secreted by GABAergic interneurons and regulates synaptic maturation by signaling through the ApoER2 receptor, which promotes the maturation of glutamatergic synapses by binding to NMDA receptors. Previous studies have shown that interference with Reelin signaling—using an antibody to neutralize Reelin—reactivates dendritogenesis and shifts synapses toward a more immature, plastic phenotype in both in vitro and in vivo models. This suggests that modulation of ECM can reactivate neural plasticity. To further explore this concept, we designed a peptide named RA01 to interfere with Reelin signaling and promote neuronal plasticity in mature neurons. We determined the optimal concentration of RA01 for binding Reelin through in vitro assays. Primary cultures of mature cortical neurons (20 days in vitro) were incubated for one hour with the peptide at a concentration of 200 nM to analyze its effects on Reelin signaling, synaptic composition, and morphology. Immunofluorescence analysis of treated neurons revealed that RA01 administration interferes with Reelin signaling pathways, evidenced by decreased fluorescence intensity of phosphorylated Dab1 (p-Dab1), phosphorylated CREB (p-CREB), and Erk1/2. In addition we observed that RA01 treatment reduced the levels of neuroinflammatory markers such as TGFB and IF beta in vitro.

**Autores:** Amanda Gutiérrez Riffó1, Daniela Gomez 1, Antonia Muñoz 1, David Ramirez2, Paula Santana 3, Violeta Chang4, Estibaliz M. Ampuero  
**Afiliación:** Laboratorio de Neurofarmacología del Comportamiento, Facultad de Química y Biología, Universidad de Santiago de Chile  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [estibaliz.ampuero@usach.cl](mailto:estibaliz.ampuero@usach.cl)  
**Agradecimientos:** Vinculab 25-6, Vinculab 25-7, Dicyt Asociativo 022243ALL, USACH  
**Socio Patrocinante:** Leonel Rojo

### 40. SPATIAL DISTRIBUTION AND NICOTINE-DEPENDENT MODULATION OF AChR(α4)-DAT INTERACTIONS IN THE ZEBRAFISH BRAIN

Distribución espacial y modulación dependiente de la nicotina de las interacciones AChR(α4)-DAT en el cerebro del pez cebra

**Resumen:** Neuroregeneration plays a crucial role in the formation, consolidation, and retrieval of memory, being fundamental for restoring cognitive functions impaired by aging or neurodegenerative disorders. Recent studies have demonstrated that adult hippocampal neurogenesis is associated with memory consolidation, and its stimulation can reverse cognitive deficits in Alzheimer's disease models. In this context, our research employs the zebrafish (*Danio rerio*) as an experimental model to investigate the molecular mechanisms underlying learning and memory, using pharmacological modulators of the cholinergic and dopaminergic systems, such as nicotine. In previous work, we demonstrated that nicotine enhances memory performance in zebrafish and that, in rats, there is a protein-protein interaction between nicotinic α4β2 receptors (AChR) and the dopamine transporter (DAT), with a higher density of these complexes in neuroregenerative brain regions. In the present study, we used the Proximity Ligation Assay (PLA in situ) technique to analyze the distribution and modulation of AChR(α4)-DAT complexes in the zebrafish brain following nicotine administration. Our results reveal a specific spatial distribution of these interactions, with a dose-dependent increase in telencephalic regions involved in memory, particularly in the ventral area (Vv). These findings suggest that nicotine enhances the formation of AChR(α4)-DAT complexes in brain regions associated with memory processes and neuroregeneration.

**Autores:** Martínez-Durán L.M.; Pérez L.; Atiés R.C.; Leal C.; Borroto-Escuela D.O.; Iturriaga-Vásquez P.  
**Afiliación:** Molecular Pharmacology and Medicinal Chemistry Lab, Facultad de Ingeniería y

Ciencias, Universidad de la Frontera.

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [luxmart.du@gmail.com](mailto:luxmart.du@gmail.com)

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**Socio Patrocinante:** Patricio Iturriaga Vásquez.

### 41. DENDRIMERS FUNCTIONALIZED WITH PEPTIDES TARGETING THE β-NEUREXIN/NEUROLIGIN-1 COMPLEX

Dendrimeros funcionalizados con péptidos dirigidos al complejo β-Neurexin/Neuroigin-1

**Resumen:** Introduction: Central nervous system (CNS) diseases involve the loss of neuronal structure and function. Pharmacological therapies for these disorders face major limitations due to adverse effects from low drug-target specificity. Current research focuses on developing therapies that specifically target the tissues or cells directly affected by the pathology. Dendrimers are nanoscale structures capable of encapsulating or conjugating therapeutic molecules, positioning them as a promising tool to overcome pharmacological limitations. Targeted delivery using these nanostructures represents an innovative therapeutic strategy. However, their behavior in the CNS remains poorly explored. Given that this region is affected by several neurological disorders, neuronal communication constitutes a potential pharmacological target. Synapses represent a type of neuron-to-neuron communication, in which synaptic adhesion complexes such as the β-Neurexin/Neuroigin-1 (Nrx-NL) complex are key. This study proposes that dendrimers conjugated with specific peptides can target Nrx-NL complex, enabling selective association with synaptic structures. Methods: Transfection: HEK-293 cells were transfected with a plasmid encoding Neuroigin-1 (NL1), using Lipofectamine 2000. Western blot: Primary antibodies were mouse anti-HA and anti-GAPDH, followed by HRP-conjugated antibody. Immunocytochemistry: Transfected cells were incubated with the peptide and then incubated with mouse anti-HA primary antibody and Cy3 antibody. Images were obtained using a confocal microscope. Results: Confocal images revealed NL1 distribution mainly at the cell periphery. Peptide incubation produced a moderately intense staining pattern in peripheral regions. Colocalization analysis demonstrated a Mander's coefficient value of 0,63. This suggests association between NL1 and the peptides designed. Discussion: These findings support future evaluation of dendrimer-peptide conjugates for targeted CNS drug delivery.

**Autores:** Martínez I. 1, Zambrano S. 1; Guzmán J. 1

**Afiliación:** Molecular Neurobiology Laboratory, Department of Physiology, Faculty of Biological Sciences, Universidad de Concepción, Concepción, Chile.

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [joseguzman@udec.cl](mailto:joseguzman@udec.cl)

**Agradecimientos:** Acknowledgements: FONDECYT 1241829

**Socio Patrocinante:** Dr. José Leonardo Guzmán



#### 42. STUDYING THE ROLE OF DOPAMINE D2-SIGNALING IN SYNAPTIC PLASTICITY AND REVERSAL LEARNING.

Caracterizando el rol de señalización de dopamina D2 en plasticidad sináptica y aprendizaje reverso

**Resumen:** Reversal Learning (RL) is the process of learning to inhibit previously rewarded actions, allowing us to study the flexibility required to adapt to an ever-changing environment. This complex ability depends on multiple brain areas, with the hippocampus synaptic plasticity being crucial for RL. Previous studies demonstrated that manipulations of dopamine (DA) signalling impair RL. Interestingly, chronic administration of QNP, a D2R agonist, impairs RL in mice and rats, indicating that D2R function is essential for the synaptic plasticity underlying RL. This leaves the role of D2R-signaling regulate hippocampal synaptic plasticity and RL remains unclear. Here, we analysed the effects of acute and chronic receptor activation via QNP and relating them to synaptic plasticity and RL. Isolate excitatory field potential (fEPSP) was performed in the presence of bicuculline, and QNP was bath-applied while high-frequency stimulation was applied. Our preliminary results showed that acute activation of D2R attenuates excitatory synaptic plasticity. Currently, we are administering QNP chronically to mice to study the effects on RL and synaptic plasticity.

**Autores:** Moya-Guerrero J.1, Moya P.R.2, Chávez A.E.3, Escobar A.P. 2,4.  
**Afiliación:** 1. Magister en Ciencias Biológicas mención Neurociencias, Universidad de Valparaíso; 2. Instituto de Fisiología, Universidad de Valparaíso; 3. Instituto de Neurociencias, Universidad de Valparaíso; 4. Centro de Neurobiología y Fisiopatología Integrativa, Universidad de Valparaíso.  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [javier.moya@postgrado.uv.cl](mailto:javier.moya@postgrado.uv.cl)  
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**Socio Patrocinante:** Angélica P. Escobar, Ph.D.

#### 43. STUDY OF A BEHAVIORAL PROFILE OF NICOTINIC RECEPTOR (NACHR) AGONISTS AND ANTAGONISTS IN AN IN VIVO ZEBRAFISH MODEL.

Estudio del perfil conductual de agonistas y antagonistas del receptor nicotínico (nAChR) en un modelo in vivo de pez cebra.

**Resumen:** Zebrafish (*Danio rerio*) is a valuable model in neuropharmacology because of its simple handling and low cost. Several paradigms can be associated with complex behaviors in zebrafish, including the Novel Tank Diving Test (NTT), which is linked to exploratory activity, stress, and anxiety. Additionally, there is a conditioning place preference (CPP), which, as in mammals, is associated with addiction. This study evaluated the behavioral effects of agonists (nicotine, cytosine, and ethanol) and an antagonist (erysodine) of nicotinic acetylcholine receptors (nAChRs), using the Novel Tank Test (NTT) and Conditioned Place Preference (CPP) paradigm. In the NTT, fish were exposed to nicotine, cytosine, and erysodine at concentrations of 50 and 100 mg/L, and ethanol at concentrations of 0.5%, 0.75%, and 1.0% (v/v). The results showed dose-dependent modulation; high concentrations of cytosine and erysodine increase the bottom dwelling. Nicotine exhibited a biphasic effect (low doses decrease the bottom dwelling, and high doses increase the bottom dwelling), ethanol increased the bottom dwelling at low concentrations, an effect that was reduced at higher doses. Furthermore, ethanol at 300 mg/L induced a conditioned preference for CPP paradigm. These findings confirmed the utility of zebrafish and suggested the potential of nAChRs as therapeutic targets.

**Autores:** Pérez L.; Farias-Cea A.; Aties C.; Martínez L.; Leal C.; Iturriaga-Vázquez P.  
**Afiliación:** 1. Laboratorio de Farmacología Molecular y Química Medicinal, Depto. Ciencias Químicas y RRNN, Facultad de Ingeniería y Ciencias, Universidad de La Frontera, Temuco.  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [lisandraperez0118@gmail.com](mailto:lisandraperez0118@gmail.com)  
**Agradecimientos:** Fondecyt Regular 1240688  
**Socio Patrocinante:** Patricio Iturriaga Vasquez

#### 44. EVALUATION OF THE ANTI-INFLAMMATORY EFFECT OF THE F15 FRACTION OF SHILAJIT ANDINO IN A MURINE MODEL OF LIPOPOLYSACCHARIDE-INDUCED NEUROINFLAMMATION.

Evaluación del efecto antiinflamatorio de la fracción F15 de Shilajit Andino en un modelo murino de neuroinflamación inducido por lipopolisacárido.

**Resumen:** Neuroinflammation has been described as a key detrimental factor in neurodegenerative disorders such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, all of which currently have no cure. In the search for new therapeutic targets, our laboratory has extensively studied Andean Shilajit, a natural complex found in the Andes Mountains of northern Chile. A recent clinical study from our group demonstrated that Andean Shilajit improves neuropsychiatric parameters evaluated through the NPI index. Based on these findings, purified fractions of the Shilajit complex were analyzed. Fraction F15, obtained through chemical extraction, showed anti-inflammatory properties in cellular models of neuroinflammation. In this work, we evaluated the in vivo effect of fraction F15 in a murine model of neuroinflammation induced by intracerebroventricular (icv) injection of lipopolysaccharide (LPS). The treatment with F15 completely restored performance in working memory in the Y-maze test, reaching values similar to the Sham group (~10% higher than LPS + Veh). A similar effect was observed in the novel object recognition test, indicating recovery of recognition memory. Immunofluorescence analysis revealed that F15 treatment reduced by approximately 50% the number of IBA-1-positive cells in hippocampal subregions such as the dentate gyrus, CA1, and CA3. These findings suggest that fraction F15 exerts neuroprotective and anti-inflammatory effects, improving cognitive performance and reducing microglial activation in vivo. Further studies are warranted to explore the therapeutic potential of Andean Shilajit and its active fractions as natural anti-inflammatory agents for neurodegenerative diseases.

Pizarro Fernanda 1; Wong-Guerra M. 1; Ampuero Estibaliz 2; Maccioni Ricardo B.; Pizarro Ignacio S. 4; Ortiz Fernando C. 4; Rojo Leonel E 1.  
**Afiliación:** Universidad de Santiago de Chile  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [fernanda.pizarro.h@usach.cl](mailto:fernanda.pizarro.h@usach.cl)  
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#### 45. SEX- AND SOCIAL ISOLATION-DEPENDENT EFFECTS ON MESOCORTICOLIMBIC NEUROTRANSMISSION AND RISK-TAKING BEHAVIOR DURING ADOLESCENCE

Efectos dependientes del sexo y del aislamiento social sobre la neurotransmisión mesocorticolímbica y la conducta de toma de riesgos durante la adolescencia

**Resumen:** Depression and anxiety are highly prevalent psychiatric disorders whose incidence increases during adolescence, a developmental stage marked by intense neural plasticity and sensitivity to environmental influences. During this period, social interactions are essential for emotional and cognitive maturation. Social isolation (SI) constitutes a psychoemotional stressor that interferes with neurodevelopment and induces long-lasting alterations, often exhibiting sex-dependent effects. Such differences may arise from the organizational actions of sex hormones during critical periods of brain development. This study aimed to assess whether sex and rearing conditions differentially modulate neurotransmitter systems involved in emotional regulation and stress responses, as well as anxiety- and depression-like behaviors. Male and female rats were reared socially or subjected to isolation between postnatal days (PND) 21 and 54 and gonadectomized after the pubertal surge (PND 45). Between PND 50 and 54, one group underwent behavioral testing, while in another, dopamine (DA), serotonin (5-HT) and their metabolites, glutamate (Glu), and GABA tissue levels were quantified by HPLC in the medial prefrontal cortex (PFCm), dorsal hippocampus (dHIP), and nucleus accumbens (NAc). Results revealed significant effects of sex and rearing on monoaminergic and aminoacidergic neurotransmission. SI reduced DA levels and turnover, increased serotonergic turnover, and elevated the Glu/GABA ratio, particularly in females. Behaviorally, SI animals exhibited enhanced exploratory and risk-taking behavior in the plus maze and open field tests and reduced immobility in the forced swim test. Together, these findings indicate that adolescent SI disrupts neurochemical homeostasis and promotes a more disinhibited behavioral phenotype, supporting the view that sex, pubertal hormones, and social environment interact to shape mesocorticolimbic circuits underlying emotional and motivational regulation.

**Autores:** Toselli A. P. 1; Bahamonde T. 4; Cáceres-Vergara D. 4; Gárate-Pérez M. F. 4; Sanhueza C. 4; Rivarola M. A. 1,2; Mir F. R. 1,3; Renard M. G. 4. **Afiliación:** 1 Laboratorio de Neuroendocrinología Comportamental, FCEfyN, UNC, Argentina; 2 INICSA, Instituto de Investigaciones en Ciencias de la Salud, CONICET, Facultad de Ciencias Médicas, UNC, Argentina; 3 Cátedra de Fisiología Animal, DACEfyN, UNLAR Argentina; 4 USACH, Facultad de Ciencias Médicas, Escuela de Medicina, Centro de Investigación Biomédica y Aplicada (CIBAP), Chile  
**Area de la Farmacología:** Neuropharmacology  
**Correo:** [ana.paula.toselli@mi.unc.edu.ar](mailto:ana.paula.toselli@mi.unc.edu.ar) **Agradecimientos:** – Beca Interna Doctoral CONICET 2023-2028 – PICT-2021-1-INV1-00719. Director del Proyecto MIR, F. Además contamos con los – PIP 2021-2023. CONICET. Directora del Proyecto Rivarola, A. – IW-3412838504 – 2024 Neuroscience Capacity Accelerator for Mental Health (NCAMH) program, International Brain Research Organization (IBRO). Directora del Proyecto Rivarola, A. **Socio Patrocinante:** Renard Georgina M.

#### 46. TARGETING THE P75 NEUROTROPHIN RECEPTOR: A PHARMACOLOGICAL STRATEGY TO REDUCE CHRONIC INFLAMMATORY PAIN SENSITIVITY

Inhibición del receptor de neurotrofinas p75: estrategia farmacológica para reducir la sensibilidad asociada al dolor crónico inflamatorio.

**Resumen:** Introduction: Chronic inflammatory pain (CIP) involves complex neuroplastic mechanisms in the spinal cord, where neurotrophin signaling modulates nociceptive sensitivity. However, the role of the p75 neurotrophin receptor (p75NTR) in chronic inflammatory pain remains poorly understood. Here, we characterize the p75NTR inhibition during chronic inflammatory pain. Materials and Methods: CIP was induced in mice by intraplantar injection of Complete Freund's Adjuvant (CFA). p75NTR expression was analyzed by qPCR, western blot, and confocal microscopy. Pharmacological inhibition was performed by oral administration of LM11A-31 (50 mg/kg) for 14 days. Behavioral assessments included thermal, mechanical, and cold sensitivity tests. Cytokines were quantified by ELISA. In a deeper analysis, p75NTR expression was depleted in primary spinal, sensory, and cortical neurons using CRISPR-shRNAp75 and CAS9 virus, measured by immunostaining and qPCR. Results: CFA injection induced a significant

upregulation of p75NTR expression in the spinal dorsal horn, whereas levels of its neurotrophin ligands remained unchanged. LM11A-31 treatment significantly reduced mechanical allodynia and thermal hypersensitivity without altering cold sensitivity. p75NTR inhibition also decreased p-JNK and c-Fos immunoreactivity in spinal and brain regions, indicating reduced synaptic activity, while systemic pro- and anti-inflammatory cytokines remained unmodified. Moreover, viral-mediated knockdown of p75NTR shows a higher infection efficiency in spinal, sensory, and cortical neurons. Discussion: These findings identify p75NTR as a critical mediator of central sensitization in chronic inflammatory pain. Pharmacological inhibition of p75NTR mitigates nociceptive hypersensitivity, positioning this receptor as a promising therapeutic target for chronic inflammatory pain.

**Autores:** Camila Uribe-Martínez1,2, Sofia Recabarren1,2, Rocío Muñoz1,2, Bernardita Salgado-Martínez1,2, Anggelo Sazo1,2, Marcela Pedraza-Cortés3,4, Claudio Catrupay1,2, Raúl Lagos-Ailón2,6, Marcela Mondaca2,6, Andrés Villarroel2,6, Fernando J Bustos3,4, Roberto Elizondo2,6, Karina Oyarce2,5, Caroll J Beltrán2,7,8, Patricio Castro1,2, Gonzalo Yévenes1,2, Viviana Pérez1,2\*. (\*[viviperez@udec.cl](mailto:viviperez@udec.cl)). **Afiliación:** 1 Department of Physiology, 2 University of Concepción, 3 Institute of Biomedical Science, University Andres Bello, Santiago, Chile. 4 (EpiNeuro), Santiago, Chile. 5 Departamento de Bioquímica Clínica e Inmunología. 6 Departamento de Biología Celular. 7Clinical Biochemistry and Immunology Department. 8Medicine Faculty, Universidad de Chile.. **Area de la Farmacología:** Neuropharmacology  
**Correo:** [viviperez@udec.cl](mailto:viviperez@udec.cl) **Agradecimientos:** Acknowledgements: ANID-MILENIO NCN2023\_32 (FB), FONDECYT 1250955 (FB), 1241214 (RE), 1231596 (CB), 1231038 (PC), 1250856 (GY) and 11240814 (VP). **Socio Patrocinante:** Gonzalo Yévenes Viviana Pérez

#### 47. IMPACT OF SWEETENER CONSUMPTION ON HIPPOCAMPAL FUNCTION AND MEMORY FLEXIBILITY

Impacto del Consumo de Edulcorantes en la Función Hipocámpal y la Flexibilidad de Memoria

**Resumen:** Adolescence is a critical period for hippocampal development, during which the brain is highly vulnerable to external factors, including dietary components. This period coincides with a surge in non-caloric sweetener (NCS) consumption among adolescents, driven by sugar-reduction policies and their widespread presence in processed foods. However, the long-term impact of NCS on brain function is poorly understood. In this study, we evaluated both synaptic plasticity in the hippocampus and cognition. To test this, male and female mice were given sucralose throughout adolescence and into adulthood. Spatial learning and cognitive flexibility were assessed in the Barnes maze. Synaptic function in hippocampal CA1 was examined via electrophysiological recordings of theta-burst stimulation (TBS)-induced long-term potentiation (LTP) and pharmacologically induced, group I mGluR-dependent long-term depression (LTD). Behavioral results showed that sucralose-exposed mice exhibited intact spatial learning and memory. However, electrophysiological recordings demonstrated a significant impairment in LTP and deficient DHPG-induced LTD. These synaptic deficits persisted into adulthood despite the absence of overt behavioral changes. These findings suggest that adolescent sucralose exposure results in a lasting dissociation between compromised synaptic plasticity and preserved behavior in standard tests. This highlights a latent vulnerability of the developing hippocampus to NCS and emphasizes the need to re-evaluate their neurological safety and the importance of considering NCS consumption during critical periods of brain development.

**Autores:** Villarroel-Donoso C. 1,2; Vidal N. 1,4; Cerna C. 1,4; Ahumada J. 1,5; Rodríguez G. 1; Thomas S. 3; Fuenzalida M. 1,5

**Afiliación:** 1Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso. 2Programa de Magister Ciencias Biológicas Mención Neurociencias, Facultad de Ciencias, Universidad de Valparaíso. 3Escuela de Nutrición y Dietética, Universidad de Valparaíso, Valparaíso, Chile. 4Programa de Doctorado en Ciencias Mención Neurociencias, Facultad

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [constanza.villarroel@postgrado.uv.cl](mailto:constanza.villarroel@postgrado.uv.cl)

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#### 48. AUT1 RESCUES FAST-SPIKING DEFICITS IN HIPPOCAMPAL PARVALBUMIN INTERNEURONS AFTER EPILEPSY ONSET

aut1 rescata los déficits de disparo rápido en interneuronas parvalbúmina del hipocampo después del inicio de la epilepsia

##### Resumen:

Parvalbumin-positive interneurons (PV-INs) maintain excitatory–inhibitory balance in hippocampal circuits, and their impaired firing capacity contributes to epileptogenesis. While PV-IN dysfunction in epilepsy is well-established, the intrinsic excitability mechanisms underlying reduced firing and potential therapeutic interventions remain poorly understood. Using PV-Cre::Ai9 transgenic mice, we induced chemical kindling with pentylenetetrazol (PTZ; 35 mg/kg i.p., 8–12 injections every 48h) until generalized seizures emerged. Whole-cell patch-clamp recordings from CA1 PV-INs revealed paradoxical firing deficits in PTZ-treated animals: despite depolarized resting membrane potentials, neurons exhibited reduced firing frequency and depolarized action potential thresholds, indicating compromised spike initiation. Furthermore, PTZ-treated PV-INs displayed slowed action potential repolarization and enhanced afterhyperpolarization amplitudes—signatures of potassium channel dysfunction. Given that Kv3.1 channels mediate the rapid repolarization essential for PV-IN fast-spiking phenotypes, we tested whether pharmacological enhancement could rescue firing deficits. Bath application of AUT1 (12.5  $\mu$ M), a Kv3.1-positive modulator, restored firing frequency in PTZ-treated PV-INs to control levels and further enhanced firing in naïve neurons. These results demonstrate that Kv3.1 enhancement can recover PV-IN fast-spiking capability after epilepsy establishment, not merely during preventive stages. Targeting Kv3.1 channels may represent a novel therapeutic strategy to restore inhibitory network function in established epilepsy.

**Autores:** Aguilar F.; Guiffa F.; Van Buuren S.; Ahumada J.; Fuenzalida M.  
**Afiliación:** Laboratorio de plasticidad neuronal, centro de Fisiología, universidad de Valparaíso  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [freddy.aguilar@postgrado.uv.cl](mailto:freddy.aguilar@postgrado.uv.cl)  
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#### 49. PRECLINICAL EVALUATION OF CHRONIC PSILOLOCIN MICRODOSING AS A POTENTIAL TREATMENT FOR FIBROMYALGIA-LIKE PAIN

Evaluación preclínica de microdosis crónica de psilocina como tratamiento potencial para el dolor similar a fibromialgia

**Resumen:** Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread musculoskeletal pain of unknown origin and without identifiable injury. Currently, there is no specific diagnostic test or effective treatment for FM. It is classified as nociplastic pain, arising from altered nociceptive modulation. Patients with FM exhibit impaired Diffuse Noxious Inhibitory Controls (DNIC), indicating dysfunction in descending pain pathways. Serotonin (5-HT), through its 5-HT<sub>3</sub> and 5-HT<sub>7</sub> receptors, plays a key role in this modulation by activating GABAergic interneurons in the spinal cord and inducing analgesia. Psilocin, the active metabolite of psilocybin found in Psilocybe mushrooms, is a 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>7</sub> receptor agonist with potential analgesic effects; however, its hallucinogenic properties limit its clinical use. This study evaluated whether chronic administration of psilocin microdoses could alleviate fibromyalgia-like pain in rats subjected to neonatal limited bedding (NLB), a model that reproduces pain and behavioral alterations resembling FM. Adult NLB rats received daily psilocin microdoses (0.3 mg/kg) for 10 days. Treated animals showed a progressive increase in paw withdrawal thresholds (Randall–Selitto test), reaching 225 ± 12 g/cm<sup>2</sup> by day 4 in females and 362 ± 11 g/cm<sup>2</sup> by day 6 in males, with effects persisting for at least 20 days post-treatment. Psilocin also reduced anxiety-like behavior in the elevated plus maze without affecting body weight or causing adverse effects. These findings suggest that chronic

microdosing with psilocin produces long-lasting analgesic and anxiolytic effects, supporting its potential as a novel therapeutic approach for fibromyalgia.

**Autores:** Osses A. 1; Muñoz A. 1; Onetto N. 2; Ampuero E. 1; Ortiz F. 1; Pelissier T. 2; Hernández A. 2; Martínez D. 3; Retamal J. 1; Constandil L. 1.  
**Afiliación:** 1.- Unidad de Psicofarmacología, Facultad de Química y Biología, Universidad de Santiago de Chile 2.- Laboratorio de Neurobiología, Facultad de Química y Biología, Universidad de Santiago de Chile 3.- NativeX SpA  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [luis.constandil@usach.cl](mailto:luis.constandil@usach.cl)  
**Agradecimientos:** Proyecto Fondecyt 1231042  
**Socio Patrocinante:** Luis Constandil

#### 50. MARESIN-1 AND DHA: PRO-RESOLVING AGENTS THAT ATTENUATE CARDIAC FIBROSIS SECONDARY TO LIVER INJURY

Maresina-1 y DHA: agentes pro-resolutivos atenúan la fibrosis cardíaca secundaria a una lesión hepática.

**Resumen:** Hepatic fibrosis is a major cause of global mortality because it triggers fibrogenic and proinflammatory processes that lead to progressive loss of liver function and disruption of metabolic homeostasis, detoxification, and immune responses, producing systemic effects on the heart, kidney, and metabolism. Chronic liver disease is associated with cardiac fibrosis, which promotes myocardial stiffening, diastolic dysfunction, and eventual heart failure, making control of inflammation and myocardial remodeling. Maresin 1 (MaR1), a pro-resolving mediator derived from DHA (an omega-3 fatty acid), has been shown in experimental models to reduce structural remodeling and post-infarction ventricular arrhythmias, and thus is proposed as a promising therapeutic alternative. In this context, the present study aimed to evaluate the antifibrotic effect of DHA (375 mg) and its derivative MaR1 (4 ng/g) on cardiac tissue in a rat model of hepatic fibrosis. Hepatic fibrosis was induced by intraperitoneal injection of diethylnitrosamine (DEN) in male Sprague-Dawley rats, which were subsequently treated with MaR1 and DHA for four weeks. Morphological analysis using hematoxylin-eosin (H&E) staining revealed normal cell size and orderly myocyte organization in the groups treated with the omega-3–derived lipid mediators. Cardiac fibrosis was assessed by Picrosirius Red staining and immunohistochemistry for collagen I and  $\alpha$ -SMA, showing that MaR1 and DHA administration attenuated ventricular structural remodeling. Together, the results demonstrate that MaR1 and DHA exert a protective effect on cardiac tissue in the setting of liver-injury–induced fibrosis, reducing structural remodeling and collagen deposition. These findings support the therapeutic potential of omega-3–derived lipid mediators as antifibrotic and pro-resolving agents capable of modulating systemic inflammatory responses and preserving the functional and structural integrity of the myocardium.

**Autores:** Gabriela Moya Moya<sup>1,2</sup>, Matías Quiñones San Martín<sup>1,3</sup>, Francisca Herrera Vielma<sup>1,3</sup>, Ramón Norambuena-González<sup>1,4</sup>, Daniel R. González<sup>1</sup> and Jessica Zúñiga-Hernández<sup>1</sup>.  
**Afiliación:** 1. Lab of Pharmacology and Physiology, Department of Basic Biomedical Sciences, Faculty of Health Sciences, University of Talca. 2. Master in Biomedical Sciences Program, Faculty of Health Sciences, University of Talca. 3. Doctorate in Science Program, mention in Research and Development of Bioactive Products, Institute of Chemistry of Natural Resources, University of Talca. 4. Doctorate in Biome  
**Área de la Farmacología:** Pharmacokinetics / drug metabolism  
**Dirección de Correo:** [gabriela.moya@utalca.cl](mailto:gabriela.moya@utalca.cl)  
**Agradecimientos:** Proyecto interno de académicas Facultad Cs de la Salud 01-2024, Universidad de Talca  
**Socio Patrocinante:** Jessica Zúñiga Hernández.



**51. PLASMA METABOLOME ALTERATIONS ASSOCIATED WITH OXIDATIVE STRESS IN AGED MICE UNDER A POLYPHENOL-RICH DIET (BERBERIS MICROPHYLLA G. FORST) AND REGULAR AEROBIC EXERCISE, DETERMINED BY LC-QTOF-MS**  
cambios en el metaboloma plasmático asociados al estrés oxidativo en ratones envejecidos suplementados con calafate y sometidos a ejercicio aeróbico regular, determinados mediante lc-qtof-ms

**Resumen:** Aging is characterized by a sustained increase in oxidative stress and disruption of redox homeostasis, affecting key metabolic pathways such as bile acid and phospholipid metabolism. This study evaluated the impact of regular aerobic exercise and a polyphenol-rich diet on oxidative stress modulation and plasma metabolome remodeling in aged C57BL/6 mice. Animals were subjected for nine weeks to a polyphenol-rich diet and/or regular aerobic exercise. Plasma samples were analyzed using UHPLC-DAD-QTOF-MS/MS with a multimodal chromatographic approach (polar, semipolar, and apolar separations). Data were processed through the GNPS platform for molecular networking and pathway mapping. The results revealed a significant decrease in conjugated bile acids, particularly taurocholic acid, whose accumulation has been associated with inflammation and redox imbalance. In addition, changes were observed in phosphatidylcholines (PC 18:0/18:2 and PC 16:0/18:1) related to lipid peroxidation and membrane integrity. These modulations correlated with lower oxidative activity in plasma and peripheral tissues. These results indicate that moderate exercise combined with a polyphenol-rich diet promotes a coordinated modulation of bile acid and phospholipid metabolism, contributing to the maintenance of systemic redox balance during aging.

**Autores:** Daniela Nova-Baza<sup>1</sup>, Lia Olivares-Carao<sup>1</sup>, Sebastián Riquelme<sup>1</sup>, Carolina Castillo<sup>2</sup>, Luis Bustamante<sup>1</sup>, Jorge Fuentealba<sup>2</sup>, Claudia Mardones<sup>\*1</sup>

**Afiliación:** <sup>1</sup>Facultad de Farmacia, Universidad de Concepción; <sup>2</sup>Facultad de Ciencias Biológicas, Universidad de Concepción

**Area de la Farmacología:** Pharmacokinetics / drug metabolism

**Dirección de Correo:** [Cmardone@udec.cl](mailto:Cmardone@udec.cl)

**Agradecimientos:** FONDECYT 1230625 FONDECYT EQM 170023

**Socio Patrocinante:** –

## **52. MTOR ACTIVATION AFFECTS ADENOSINERGIC TONE IN EXPERIMENTAL DIABETIC NEPHROPATHY**

La activación de mTOR afecta el tono de adenosina en la nefropatía diabética

**Resumen:** Introduction: The maintenance of homeostatic extracellular adenosine levels in the kidney is mediated by insulin, which promotes nucleoside uptake through the Equilibrative Nucleoside Transporter 2 (ENT2). However, insulin action on ENT2 activity is impaired in diabetic nephropathy (DN). mTOR is a master regulator of cellular metabolism and is overactivated in DN. We aimed to determine how mTOR activity affects adenosine homeostasis in the kidney. Materials and Methods: A human immortalized podocyte cell line was used to evaluate the effects of mTOR activation by TGF- $\beta$  (5 ng/mL) or inhibition with rapamycin (500 ng/mL). Purified glomeruli from control and streptozotocin-induced diabetic rats were used to assess the effects of mTOR inhibition on adenosine levels. Extracellular adenosine was quantified after derivatization with chloroacetaldehyde using HPLC. Plasma membrane distribution of ENT2 was analyzed by surface biotinylation. Results: Insulin promoted ENT2 activity and decreased extracellular adenosine levels in podocytes. This effect was blunted by mTOR activation using TGF- $\beta$  but restored by rapamycin. We found that rapamycin rescued the insulin-induced translocation of ENT2 to the plasma membrane in podocytes. In glomeruli from diabetic rats the extracellular adenosine levels were elevated compared with controls. Insulin reduced extracellular adenosine in control glomeruli but failed to do so in diabetic glomeruli. Notably, rapamycin treatment restored insulin responsiveness in diabetic glomeruli. Discussion: mTOR overactivation plays a key role in podocyte insulin resistance and the loss of adenosine homeostasis in diabetic nephropathy.

**Autores:** Lester I. 1; Moscol D. 1; Oyarzún C. 1; San Martín R. 1

**Afiliación:** Molecular Pathology Laboratory, Biochemistry and Microbiology Institute, Science

## **53. VALPROATE ACID IN EMBRYONIC DEVELOPMENT, AN ANIMAL MODEL OF AUTISM, ALTERS THE RELATIONSHIP BETWEEN SOCIABILITY AND BIOLOGICAL MOTION PERCEPTION IN MICE**

Acido Valproico en el desarrollo embrionario, un modelo animal de autismo, altera la relación entre la sociabilidad y la percepción del movimiento biológico en ratones.

**Resumen:** The anticonvulsant and mood stabilizer Valproate acid (VPA) use during pregnancy has been relate to autism in human. Multilevel differences in neural connectivity have been described in the autistic brain affecting various neural networks and, in particular the social interaction network, which involves perceptual, affective, motor, and cognitive aspects of social relevance. A crucial subfunction within the social network is the “theory of mind” (ToM), which corresponds to attributing mental states and intentions to others in order to understand their behavior and respond appropriately. ToM depends on basic perceptual elements for its construction like biological movement perception (BMP). Currently is unknown whether the alteration in biological motion perception (BMP) is prior to, or concomitant, with the alteration in sociability. To assess the effect of prenatal VPA in the relationship between BMP and sociability at an early stage of development, we injected VPA in pregnant mice (500 mg/kg i.p) at E12.5 and conducted three-chamber social test (TS-3C), followed by a BPM test at postnatal day 21. Control mice showed preference for spending more time in the social area than in the non-social area ( $p=0.0366$ , ANOVA), while VPA-treated mice lost this preference ( $p=0.7761$ ). Additionally, in the control animals, we found a positive correlation between sociability index and PMB ( $r^2 = 0.7382$ ;  $p = 0.0063$ , linear regression), while in VPA group this correlation was lost ( $r^2 = 0.1930$ ;  $p = 0.2761$ ). These results show that embryonic VPA prime brain wiring conducting to a decoupling between perceptual and executive components of the social network. This result may be relevant to understand why VPA, or others neuropharmacological molecules, may induce autism acting in embryonic development.

**Autores:** Villagra C<sup>1</sup>, Vivero F<sup>1</sup>, Albornoz A<sup>1</sup>, Morgado-Gallardo K<sup>1,2</sup>, Aliaga E<sup>1,2</sup>. **Afiliación:**

1. Laboratorio de Neurociencia. Escuela de Tecnología Médica. Facultad de Ciencias de la Salud. Universidad Católica del Maule.

2. Centro de Investigación en Neuropsicología y Neurociencias Cognitivas (CINPSI-Neurocog). Facultad de Ciencias de la Salud. Universidad Católica del Maule.

3. Departamento de Psicología. Facultad de Ciencias de la Salud. Universidad Católica del Maule. **Area de la Farmacología:** neuropharmacology

**Dirección de Correo:** [ps.carla.villagra@gmail.com](mailto:ps.carla.villagra@gmail.com) **Agradecimientos:** Financiamiento:

proyectos UCM-IN-22224 y UCM-IN-23218 **Socio Patrocinante:** N/A

#### 54. UNRAVELING THE ROLE OF THE MINERALOCORTICOID RECEPTOR IN ALDOSTERONE-INDUCED UNFOLDED PROTEIN RESPONSE IN HEPG2 AND HEK293 CELLS

Desentrañando el papel del receptor mineralocorticoide en la respuesta a proteínas mal plegadas inducida por Aldosterona en células HepG2 y HEK293

**Resumen:** Aldosterone, a mineralocorticoid hormone vital for electrolyte balance, has been increasingly associated with cellular stress responses in non-classical target tissues. This study examines the role of the mineralocorticoid receptor (MR) in mediating aldosterone's effects on the unfolded protein response (UPR), a crucial cellular stress signaling pathway that influences cell fate decisions, in hepatic (HepG2) and epithelial (HEK293) cells. We concentrated primarily on the IRE1 and PERK branches of the UPR pathway. We employed cellular reporter assays to examine cultures exposed to aldosterone, with or without steroidal and non-steroidal MR antagonists, evaluating the activation of fluorescent reporters linked to the IRE1 and PERK signaling pathways, which are key indicators of UPR activation. Findings demonstrate that aldosterone activates specific UPR pathways contingent on cell type, including a PERK-mediated stress response that may lead to cellular damage with prolonged exposure. The extent of MR involvement in UPR activation may elucidate the non-classical effects of aldosterone, offering insights into its possible significance in the development of renal and hepatic stress-related diseases. Targeting UPR pathways stimulated by aldosterone may provide novel therapeutic strategies for addressing mineralocorticoid-induced cellular stress in these tissues.

**Autores:** Alejandro Amoroso A 1, Priscilla Cortés 1, Martina Luna 4, Lorena Rubio-Quiroz 2,3, Andrea Vecchiola 5 & Carlos F. Lagos 2,3

**Afiliación:** 1Departamento de Ciencias Biológicas y Químicas, Facultad de Ciencias, Universidad San Sebastián; 2 Chemical Biology & Drug Discovery Lab, Facultad de Ciencias, Universidad San Sebastián; 3 Centro Basal Ciencia & Vida, Fundación Ciencia; 4 Escuela de Bioquímica, Facultad de Ciencias; 5 Departamento de Endocrinología, Facultad de Medicina, Pontificia Universidad Católica de Chile

**Area de la Farmacología:** Endocrine pharmacology

**Dirección de Correo:** alejandro.amoros@uss.cl

**Agradecimientos:** FONDECYT REGULAR 1241969, Centro Basal Ciencia & Vida, FB210008,

**Socio Patrocinante:** Dr. Carlos F. Lagos

## 1. EFFECTS OF CBD EXPOSURE DURING NEURULATION ON CARDIAC DEVELOPMENT

Efectos de la exposición a CBD durante la Neurulación en el desarrollo cardíaco

**Resumen:** Cannabis sativa produces several phytocannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), molecules of great interest due to their neuromodulatory effects and broad consumption. CBD acts pharmacologically via receptors of the endocannabinoid system (eCBs) CB1 and CB2 and other proteins (endocannabinoidome), including the PPARg. This receptor has been described as participating in cardiac development, promoting the differentiation of precursors from early stages of embryonic development, such as neurulation (stages 12.5-20). With this background, an alteration in PPARg-mediated signaling would have an impact on cardiovascular development. This investigation evaluated the functional and morphological cardiac effects of CBD exposure during neurulation in the chordate *Xenopus laevis*. Embryos were exposed to increasing concentrations of CBD during neurulation, and its effects were evaluated at the tadpole stage (stage 45). Cardiac function was analyzed by comparative analysis of contraction frequencies; heart morphology was assessed through anatomical measurements of histological sections; and cardiac gene expression was evaluated by RTqPCR. The results showed a significant decrease in heart rate in embryos treated with CBD from concentrations of 3µM ( $142 \pm 1.1$  vs.  $137 \pm 1.3^*$ ). This effect was also observed in embryos treated with a PPARg antagonist SR16832 ( $134 \pm 0.9^*$ ). Higher CBD concentrations (100 µM) significantly increased heart size, especially in the atrium ( $164 \pm 8.9$  vs.  $204 \pm 9.3^*$  µm). RTqPCR results showed differential expression of the TBX5 and ACTC genes, suggesting possible alterations in cardiac tissue differentiation and maturation. This work demonstrates that CBD exposure during neurulation may have significant effects on functional and morphological cardiac development, possibly through PPARg, with relevant implications in the use of cannabinoids during pregnancy.

**Autores:** Oñate D.1,4; Osorio C.1,4; Valdenegro S.1,4; Valdivia G.1; Catrupay C.1; Gutiérrez I.1; Yévenes G.2,3; Sepúlveda F.3; Vejar C.4; Grez P.4; Escudero C.5; León J.6; Castro P.A.1,3\*

**Afiliación:** 1Laboratorio para el Desarrollo Neural, LAND, 2Departamento de Fisiología, 3Magister en Neurobiología, Facultad de Ciencias Biológicas; 4Departamento de Tecnología Médica, Facultad de Medicina, Universidad de Concepción. 5Departamento de Ciencias Básicas, Facultad de Ciencias; 6Departamento de Enfermería, Facultad de Ciencias de la Salud, Universidad del BioBio. \*pacastro@udec.cl

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** pacastro@udec.cl

**Agradecimientos:** FONDECYT 1231038

## 2. EMPAGLIFLOZIN COUNTERACTS TNFA-INDUCED INFLAMMATION VIA AMP-ACTIVATED PROTEIN KINASE (AMPK) ACTIVATION IN CARDIAC FIBROBLASTS.

Empagliflozina contrarresta la inflamación inducida por TNFα a través de la activación de la proteína quinasa activada por AMP (AMPK) en fibroblastos cardíacos.

**Resumen:** Cardiac fibroblasts (CFs) play a central role in maintaining cardiac tissue homeostasis by synthesizing a variety of extracellular matrix (ECM) proteins. Nowadays, several clinical studies indicate a gradual rise in patients with cardiac fibrosis, which is linked to pathological states (e.g., chronic inflammation) that drive the differentiation of CFs to myofibroblasts, thereby contributing to irreversible cardiac damage. Pro-inflammatory cytokines, such as TNF-α, have been demonstrated to promote this effect through the increased synthesis of inflammatory proteins VCAM-1, ICAM-1, among other cytokine mediators. Earlier investigations, conducted in adipose tissue and cardiomyocytes, have revealed that activation of AMPK by Empagliflozin (EMPA), a SGLT2 inhibitor, confers a protective effect by reducing TNF-α-induced inflammation and promoting energy metabolism. Meanwhile, Compound C abolishes AMPK activity. To date, the existence of a relationship between AMPK and chronic inflammation

in CFs remains unclear. Therefore, the aim of our research was to investigate whether AMPK activation by SGLT-2 inhibition exerts anti-inflammatory activity in CFs. Primary CFs from neonatal Sprague-Dawley rats (2-4 days old) were stimulated with TNF-α and treated with EMPA and Compound C, activating and inhibiting AMPK, respectively. We demonstrated that EMPA treatment activated AMPK in TNF-α-stimulated CF cells, downregulating both protein and mRNA expression levels of inflammatory mediators such as VCAM-1, ICAM-1, TNF-α, IL-1β, and MCP1. Surprisingly, SGLT2 expression remained unchanged under these experimental conditions. Nevertheless, the anti-inflammatory effects of EMPA were reversed by Compound C, confirming that AMPK activation is required for this protective mechanism. Finally, our results showed that EMPA activates AMPK, thereby eliciting a novel AMPK-dependent anti-inflammatory effect against TNF-α-induced inflammation.

**Autores:** De León-Aravena, V.1,2, Carrasco-Aburto, C.1,2, Landaeta-Verdejo, J.1,2, Ponce-Farías, J.1,2, Catalán, M.1,2, Vivar, R.1,2. **Afiliación:** (1) Laboratory of Pharmacology and Disease Mechanism, Pharmacology and Immunology Program, University of Chile, Independencia 1027, Santiago, Chile. (2) Biomedical Science Institute, Faculty of Medicine, University of Chile, Santiago, Chile

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** victordeleonaravena20@gmail.com

**Agradecimientos:** Regular FONDECYT N° 1251398 (Vivar, R.)

**Socio Patrocinante:** Raúl Vivar

## 3. PROTECTIVE EFFECTS OF DOXYCYCLINE AGAINST ANGIOTENSIN II-INDUCED CARDIAC FIBROSIS: POSSIBLE INVOLVEMENT OF THE MITOCHONDRIAL UNFOLDED PROTEIN RESPONSE (UPRmt)

Efectos Protectores de Doxiciclina Frente a la Fibrosis Cardíaca Inducida por Angiotensina II: Posible Participación de la Respuesta Mitocondrial a Proteínas Mal Plegadas (UPRmt)

**Resumen:** Introduction. Angiotensin II induces cardiac fibrosis and pathological remodeling, ultimately leading to heart failure. UPRmt has emerged as a potential therapeutic target for cardiac fibrosis. Doxycycline, an FDA-approved antibiotic, has been identified as an inducer of UPRmt. However, it remains unclear whether doxycycline-induced UPRmt activation exerts protective effects against angiotensin II-mediated cardiac injury. Methodology. Male C57BL/6N mice were treated with doxycycline (6 mg/kg/day, IP) for six days and subsequently subjected to an angiotensin II infusion (1,5 mg/kg/day, osmotic mini-pumps) for 14 days. Arterial blood pressure was measured, and cardiac function was evaluated by echocardiography. Cardiac tissue was collected to assess cardiac hypertrophy and fibrosis. Cardiac fibrosis was analyzed by Sirius Red staining and cardiomyocyte hypertrophy was evaluated using WGA staining. Expression of UPRmt markers, including ATF5, HSP60, LONP1 and SOD2, was determined by Western Blot. Results. Doxycycline treatment induced UPRmt in cardiac tissue, as evidenced by increased levels of ATF5, HSP60, LONP1 and SOD2. Pretreatment with doxycycline conferred protection against angiotensin II-induced cardiac injury, demonstrated by reduced left ventricular wall thickening, decreased cardiomyocyte hypertrophy, and attenuated cardiac hypertrophy and fibrosis. However, doxycycline did not prevent angiotensin II-induced arterial hypertension. Conclusion. Doxycycline induces UPRmt in cardiac tissue and provides protection against angiotensin II-induced cardiac hypertrophy and fibrosis, although it does not prevent hypertension. These findings suggest that UPRmt activation may contribute to the cardioprotective effects of doxycycline and highlight its potential as a therapeutic strategy for cardiac remodeling.

**Autores:** Machuca-Escobar, Víctor; Rivas, S.; Rimassa-Taré C.; Díaz-Araya, G.

**Afiliación:** Molecular Pharmacology Laboratory, Department of Pharmacological and Toxicological Chemistry, Faculty of Chemical and Pharmaceutical Sciences, University of Chile

**Area de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** victor.machuca@ug.uchile.cl

**Agradecimientos:** Fondecyt 1250183 – Díaz-Araya, Guillermo.

**Socio Patrocinante:** Guillermo Díaz Araya



#### 4. TOXICOLOGICAL AND PHARMACOLOGICAL EVALUATION OF BENZIMIDAZOLE DERIVATIVES IN ARTEMIA SALINA AND SPRAGUE-DAWLEY RATS

Evaluación toxicológica y farmacológica de derivados de benzimidazol en Artemia salina y ratas Sprague-Dawley

**Resumen:** The benzimidazole (BZ) scaffold constitutes as a crucial structural core in the design and development of therapeutically significant agents with clinical relevance. This study aimed to evaluate the pharmacological activity of eight BZ derivatives, selected based on preliminary toxicity data. A sequential screening protocol was employed, beginning with a toxicity assessment using the Artemia salina bioassay. Compounds exhibiting lower toxicity were subjected to functional assays. Vasorelaxant effects were assessed by constructing concentration–response curves ( $1 \times 10^{-8}$  M– $1 \times 10^{-4}$  M) in rat aortic rings precontracted with phenylephrine ( $1 \times 10^{-6}$  M) or KCl (80 mM). Subsequently, the activity on smooth muscle was determined in rat ileum and bladder preparations by generating concentration–response curves to carbachol ( $1 \times 10^{-10}$  M– $1 \times 10^{-4}$  M). From the Artemia salina screen, BZ-26 and BZ-35 were identified as lead candidates for pharmacological evaluation. In isolated rat aortic rings, BZ-26 and BZ-35 induced maximal vasodilation of  $82.6 \pm 6.4\%$  and  $70.9 \pm 5.6\%$  (mean  $\pm$  SEM), respectively, comparable to the acetylcholine control ( $91.6 \pm 0.9\%$ ). Both compounds also demonstrated inhibitory effects on carbachol-induced contractions in smooth muscle tissues. In bladder preparations, contractions were reduced by  $81.7 \pm 8.1\%$  (BZ-26) and  $64.7 \pm 8.1\%$  (BZ-35), while in the ileum, contractions were diminished by  $85.1 \pm 6.7\%$  (BZ-26) and  $77.9 \pm 6.7\%$  (BZ-35). This inhibitory activity was comparable to that of verapamil. BZ-26 and BZ-35 thus emerge as promising lead compounds with vasorelaxant and spasmodic properties comparable to acetylcholine and verapamil. These findings warrant the need for further research to clarify their underlying mechanisms of action and explore their potential as therapeutic options for cardiovascular and smooth muscle–related disorders.

**Autores:** Sánchez-Martínez H.A.1\*; Morán-Pinzón J.A.1,2; Del Olmo-Fernández E.3; Alejo-Armijo A.3; López-Pérez J.L.1,3; Guerrero De León E.1,2.

**Afiliación:** 1Centro de Investigaciones Psicofarmacológicas, Universidad de Panamá, Panamá 2Departamento de Farmacología, Facultad de Medicina, Universidad de Panamá, Panamá. 3Departamento de Ciencias Farmacéuticas, Área de Química Farmacéutica, Facultad de Farmacia, CIETUS, IBSAL, Campus Miguel de Unamuno, Universidad de Salamanca, 37007-Salamanca, España.

**Área de la Farmacología:** Cardiovascular pharmacology

**Dirección de Correo:** hugo.sanchez02@up.ac.pa

**Agradecimientos:** – Secretaría Nacional de Ciencia y Tecnología, Panamá (APY-NI-2024A-24) – Vicerrectoría de Investigación y Postgrado, UP (CUFI-2023-CS-EP-002) – Estela Guerrero De León, SNI

**Socio Patrocinante:** NA

#### 5. PARALLEL VIRTUAL SCREENING OF NUCLEAR HORMONE RECEPTORS TO IDENTIFY SELECTIVE NONSTEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS

Cribado virtual paralelo sobre receptores nucleares de hormonas para identificar antagonistas selectivos no esteroideos de receptores mineralocorticoides

**Resumen:** Nuclear hormone receptors (NHRs) such as the mineralocorticoid (MR), glucocorticoid (GR), progesterone (PR), and androgen (AR) receptors share highly conserved ligand-binding domains, leading to cross-reactivity and off-target effects among first-generation MR antagonists (e.g., spironolactone). Leveraging available NHR crystal structures enables target-parallel virtual screening strategies to identify MR-selective nonsteroidal antagonists with improved safety profiles. Methods. Crystal structures of MR (PDB 3VHV), GR (3H52), PR (3ZRA), and AR (1Z95) were curated and aligned in ChimeraX for receptor grid generation. A commercial compound library (M-Cule; 6.56 million molecules) was processed using OMEGA to generate multi-conformer databases, followed by parallel docking with FRED/Chemgauss4. The top 6,500 scoring molecules per receptor were retained. After de-duplication and cross-target filtering, compounds exhibiting high MR affinity and low GR/PR/AR binding scores were prioritized. Final candidates underwent binding-mode inspection, in silico ADME/Tox evaluation, and tractability analysis. Results. The workflow reduced 6.56 million initial entries to 6,500 docking hits per receptor.

Cross-target filtering yielded 30 nonsteroidal compounds showing MR-preferential binding and minimal affinity toward GR, PR, and AR. Predicted binding poses revealed MR-specific interactions with key pocket residues, while ADME/Tox properties remained within acceptable drug-like parameters. Conclusions. This target-parallel virtual screening approach efficiently enriches for selective MR antagonists by exploiting the structural diversity among NHRs. The resulting 30 compounds represent tractable leads for experimental validation and medicinal chemistry optimization toward safer and more selective MR blockade.

**Autores:** Camila Manquel-Leal 1; Lorena Rubio-Quiroz 1,2; Alejandro Amoroso 3; Priscilla Cortés 3; Andrea Vecchiola 4; Gonzalo-Recabarren-Gajardo 5 & Carlos F. Lagos 1,2

**Afiliación:** 1Escuela de Química y Farmacia, Facultad de Ciencias, Universidad San Sebastián; 2Centro Basal Ciencia & Vida; 3Departamento de Ciencias Biológicas y Químicas, Universidad San Sebastián; 4Departamento de Endocrinología, Escuela de Medicina Pontificia Universidad Católica de Chile. 5Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile

**Área de la Farmacología:** Endocrine pharmacology

**Dirección de Correo:** cmanquell@correo.uss.cl

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**Socio Patrocinante:** Dr. Carlos F. Lagos

#### 6. DOXYCYCLINE AS A MODULATOR OF THE MITOCHONDRIAL UPR: EFFECTS ON SENEESCENCE-RELATED MYOGENIC DIFFERENTIATION AND SKELETAL MUSCLE IN OLDER MICE

Doxiciclina como modulador de la UPR mitocondrial: Efectos sobre la diferenciación miogénica relacionada con la senescencia y el músculo esquelético en ratones envejecidos

**Resumen:** Aging is accompanied by a progressive decline in skeletal muscle mass and strength, a condition known as sarcopenia. Mitochondria play a central role in muscle physiology, generating energy for contraction and maintaining proteostasis through the mitochondrial unfolded protein response (UPRmt). However, the effectiveness of this mechanism decreases with age, reducing mitochondrial capacity to respond to stressors like chronic inflammation and reactive oxygen species (ROS), contributing to sarcopenia. This research aims to study the protective and restorative effects of doxycycline (a tetracycline that has been reported as an inducer of UPRmt) on muscle cells and aged skeletal muscle. Mice aged 3 months, 20 months, and 20 months treated orally with doxycycline were evaluated for body and muscle weight. In parallel, C2C12 myoblast-derived cells were subjected to nutritional stress in the presence of doxycycline. Senescence was induced through extended passaging, and differentiation-related parameters including size, morphology and nuclear alignment, as well as mitochondrial network morphology were evaluated using fluorescence microscopy. UPRmt-associated proteins were measured by Western blot in both models. Our results show that in vitro, doxycycline induces the UPRmt, protecting cells from nutritional stress, and improved nuclear alignment. Senescent cells showed significant restoration of their nuclear alignment and mitochondrial network. In vivo, aged mice treated with doxycycline displayed increased body and muscle mass. Overall, the findings suggest that doxycycline exerts a restorative effect on the senescent phenotype in both models.

**Authors:** Arias, P.1, Almarza, G.1, & del Campo, A.1

**Affiliation:** 1 Laboratory of Physiology and Cellular Bioenergetics, School of Chemistry and Pharmacy, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile, Santiago, Chile. **Pharmacology area:** Molecular Pharmacology

**Email Address:** pa.arias2001@uc.cl

**Acknowledgments:** FONDECYT 1230428 to AdC, Dr. Cheril Tapia Rojas for kindly donating the mice.

**Sponsor:** Dr. Andrea Estefanía del Campo Sfeir

## 7. SHAPE- AND ELECTROSTATIC-BASED VIRTUAL SCREENING IDENTIFIES POTENTIAL NOVEL MINERALOCORTICOID RECEPTOR ANTAGONISTS

El cribado virtual basado en la forma y electrostática identifica potenciales nuevos antagonistas del receptor mineralocorticoide

**Resumen:** Mineralocorticoid receptor (MR) antagonists are valuable in the treatment of cardiorenal diseases, yet the discovery of new nonsteroidal chemotypes remains a major challenge. Ligand-centric approaches that integrate 3D shape and electrostatic similarity offer a promising route for “lead-hopping” identification of novel scaffolds with conserved pharmacophoric features of known antagonists. Methods. Using a previously reported MR antagonist conformation, we applied ensemble docking to generate a plausible binding pose for finerenone, a potent and selective nonsteroidal MR antagonist. A shape-based query derived from this pose was validated against 2,368 decoys (ROC AUC = 0.80). An in-house ultra-large library (~100 million compounds), integrating public and commercial sources, was screened with ROCS, retaining the top 1% by Tanimoto Combo score. The resulting subset (~1 million molecules) was rescored in EON to assess electrostatic similarity based on pre-aligned potential maps. From the highest-ranked hits, 100 candidates were prioritized by binding-mode plausibility, in silico ADME/Tox, and commercial availability. Functional validation included qRT-PCR assays for MR-responsive genes and cytotoxicity evaluation in HEK293 cells. Results. The finerenone-based query showed robust early enrichment (ROC AUC = 0.80), confirming model reliability. The combined ROCS→EON cascade efficiently reduced the initial 100 million entries to 100 purchasable candidates. Among them, two compounds displayed MR antagonistic activity comparable to eplerenone and finerenone in cell-based assays, without detectable cytotoxicity. Conclusions. A scalable shape-then-electrostatics virtual screening workflow enables efficient exploration of ultra-large chemical space for novel MR antagonists. The identified candidates demonstrate promising in vitro activity and drug-like properties, supporting this approach as a tractable strategy for ligand-centric MR drug discovery.

**Autores:** Carlos F. Lagos 1,2; Gonzalo-Recabarren-Gajardo 3; Alejandro Amoroso 4; Priscilla Cortés 4; Lorena Rubio-Quiroz 1,2 & Andrea Vecchiola 5.

**Afilación:** 1Chemical Biology & Drug Discovery Lab, Facultad de Ciencias, Universidad San Sebastián; 2Centro Basal Ciencia & Vida; 3Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile; 4Departamento de Ciencias Biológicas y Químicas, Universidad San Sebastián; 5Departamento de Endocrinología, Facultad de Medicina, Pontificia Universidad Católica de Chile.

**Area de la Farmacología:** Endocrine pharmacology

**Dirección de Correo:** carlos.lagos@uss.cl

**Agradecimientos:** FONDECYT Regular 1241969; Centro Basal Ciencia & Vida (FB210008); Powered@NLHPC (CCSS210001); ChemAxon & OpenEye Scientific academic software licenses.

**Socio Patrocinante:** Dr. Carlos F. Lagos

## 8. FUNCTIONALIZED GOLD NANOSPHERES AS IMMUNOPHARMACOLOGICAL TOOLS TO REINFORCE ANTIBODY-MEDIATED PHAGOCYTOSIS VIA MICA TARGETING

Nanosferas de oro funcionalizadas como herramientas inmunofarmacológicas para reforzar la fagocitosis mediada por anticuerpos a través del reconocimiento de MICA

**Resumen:** Gold nanoparticles (AuNPs) offer exceptional physicochemical stability, biocompatibility, and surface versatility, making them ideal platforms for biomedical applications. Functionalization of AuNPs with monoclonal antibodies can improve therapeutic targeting and immune modulation. In this study, we employed a cooperative adsorption approach to functionalize AuNPs with a novel anti-MICA antibody, aiming to promote macrophage-mediated phagocytosis of MICA-expressing epithelial cells. Objective: To develop and characterize an anti-MICA functionalized gold nanosystem capable of enhancing antibody-dependent phagocytosis in an in vitro gastric epithelial cell model. Methods: Spherical AuNPs (40 nm) were synthesized by the seed-growth method and functionalized with anti-MICA antibodies through cooperative adsorption. Conjugation was evaluated by UV-Vis spectroscopy, zeta potential, and hydrodynamic diameter analysis. Indirect quantification of bound antibodies was performed by ELISA of the supernatant, followed by BSA blocking to

improve colloidal stability. The nanosystem was assessed by SERS to confirm protein corona composition. Biocompatibility was tested in GES-1 and U937 cells via MTS assay. Phagocytosis was quantified using Cytation V imaging and colocalization analysis. Results: The nanosized structure displayed a plasmonic red shift and increased hydrodynamic diameter, confirming successful conjugation. Indirect quantification estimated 90 antibodies per nanoparticle. SERS spectra verified the coexistence of antibody and BSA. The nanosystem was biocompatible and significantly increased macrophage phagocytosis of MICA-expressing GES-1 cells compared with controls. Conclusions: Cooperative adsorption enables efficient, stable, and functional antibody immobilization on AuNPs. The resulting nanosystem enhances immune effector interactions, representing a promising nanobiotechnological platform. Acknowledgments: FONDECYT Project N° 1221031 & Beca ANID 21221729.

**Autores:** Campos I. 1, 2; Riveros A. 2; Gonzalez-Herrera F. 1; Toledo K. 1, 3; Guerra Y. 1; Garrido M. J. 1; Fehring N. 1; Donoso O. 2; Gonzalez-Olivares M. 1; Hermoso M. 3; Kogan M. 2; Molina M. C. 1.

**Afilación:** 1. Laboratorio de Anticuerpos Recombinantes e Inmuno-Oncología, Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile; 2. Laboratorio de Nanomedicina y Nanoteranóstica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile; 3. Gastroenterology and Hepatology Department, University Medical Center Groningen

**Area de la Farmacología:** Immunopharmacology

**Dirección de Correo:** ivo.campos@ug.uchile.cl

**Agradecimientos:** FONDECYT Project N° 1221031. Beca ANID doctorado nacional 21221729

**Socio Patrocinante:**

## 9. CHARACTERIZATION OF BONE MARROW-DERIVED MACROPHAGES AND THEIR MITOCHONDRIAL FUNCTION IN MICE WITH OBESITY

Caracterización de macrófagos derivados de médula ósea y su función mitocondrial en ratones con obesidad

**Resumen:** Obesity leads to excessive fat accumulation and low-grade chronic inflammation. The expansion of adipose tissue induces cellular stress, promoting the infiltration and differentiation of pro-inflammatory macrophages (M1) that exacerbate systemic inflammation and associated metabolic disorders. The aim of this study was to characterize how obesity impacts macrophage polarization and mitochondrial function in bone marrow-derived macrophages (BMDMs). Experiments were conducted using control and high-fat diet (HFD) mice. Body weight, white adipose tissue and liver weight were measured. Bone marrow-derived macrophages (BMDMs) were obtained and stimulated with lipopolysaccharide (LPS) and characterized by flow cytometry. To assess the M1 phenotype, the surface markers used were CD86 and MHC-II whereas for the anti-inflammatory phenotype (M2) CD206 and CD163 were used. Mitochondrial potential and mass were also evaluated using tetramethylrhodamine (TMRM) and Mitotracker Green (MTG), respectively. Our results show trends towards alterations in macrophage polarization of BMDMs from control and HFD mice. In addition, HFD macrophages showed no alterations in mitochondrial function. Our results suggest that obesity could play a role in the phenotype and mitochondrial function of BMDMs and so, it should be studied extensively in other models.

**Autores:** Grau-Grass A.1; Briones-Manríquez F.1; Ibarra I.1; Araya M.J.2,3; Luz-Crawford P.2,3; Almaraz G.1; del Campo A.1

**Afilación:** 1 Laboratory of Physiology and Cellular Bioenergetics, School of Chemistry and Pharmacy, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile. 2 Laboratory of Cellular and Molecular Immunology, Center for Biomedical Research and Innovation, Faculty of Medicine, Universidad de Los Andes. 3 IMPACT, Center of Interventional Medicine for Precision and Advanced Cellular Therapy.

**Area de la Farmacología:** Immunopharmacology

**Dirección de Correo:** amanda.grau@uc.cl

**Agradecimientos:** FONDECYT 1230428 to AdC

**Socio Patrocinante:** Dr. Andrea Estefanía del Campo Sfeir



## 10. IL-37 ATTENUATES INFLAMMATION IN A 3D HUMAN INTESTINAL ORGANOID MODEL OF INFLAMMATORY BOWEL DISEASE (IBD)

IL-37 atenúa la inflamación en un modelo de organoides intestinales humanos de enfermedad inflamatoria intestinal (EII)

**Resumen:** Introduction: Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are characterized by an increased presence of proinflammatory cytokines (such as IL-8, IL-18 and TNF- $\alpha$ ) that contribute to mucosal damage and increased epithelial permeability. IL-37 is an anti-inflammatory cytokine that acts via SIGIRR and IL-18R1 receptors to regulate inflammation. However, the role of the IL-37/SIGIRR axis in inflammatory bowel disease (IBD) remains poorly understood. Aim: To evaluate the immunomodulatory potential of IL-37 in both 2D and 3D models of inflamed human intestinal organoids. Methods: Human intestinal organoids were generated from the colonic tissue of healthy volunteers and cultured for 15 days. The organoids were then exposed to pro-inflammatory cytokines for either 6 or 24 hours, with or without the addition of recombinant IL-37. IL-6 and TNF transcripts were quantified by qPCR and IL-18 protein in the culture medium was quantified by ELISA. In a 2D model, Caco-2 monolayers were used to evaluate the epithelial barrier's function under inflammatory conditions, with transepithelial electrical resistance (TEER) serving as the readout. Results: IL-37 reduced IL-6 and TNF transcript levels, as well as IL-18 protein levels, in an inflamed model of human intestinal organoids. Furthermore, inflammation induced by cytokines decreased SIGIRR receptor expression in intestinal organoids. IL-37 protects against inflammatory cytokine-induced damage to epithelial permeability in a 2D model using inflamed Caco-2 cells. Conclusions: IL-37 reduces the production of inflammatory cytokines in inflamed organoid models, thereby attenuating intestinal inflammation. It also protects against damage to epithelial permeability in a 2D model of CACO-2 cells. AGRADECIMIENTOS: FONDECYT Postdoctorado ANID 3230454, FONDECYT N° 1220702, 1221031 y FONDEF ID23i10018, ECOS220024.

**Autores:** Toledo-Stuardo K.1,3; López V.1; Dubois-Camacho K.2; Parada-Venegas D.2; Liu M.3; Álvarez V.1; Delgado F. 1; Tello S.1; Astorga J.1, Ortega A.1; González F.1; Ribeiro C. 1; Nico-Faber K. 2; Quera R.3; Molina M.C.1; Hermoso M.A.2  
**Afiliación:** 1 Núcleo Interdisciplinario de Farmacología e Inmunología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile. 2 Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen. 3 Programa de Enfermedad Inflamatoria Intestinal, Clínica Universidad de los Andes, Universidad de los Andes  
**Área de la Farmacología:** Immunopharmacology  
**Dirección de Correo:** karen.toledo.stuardo@gmail.com  
**Agradecimientos:** AGRADECIMIENTOS: FONDECYT Postdoctorado ANID 3230454, FONDECYT N° 1220702, 1221031 y FONDEF ID23i10018, ECOS220024.  
**Socio Patrocinante:** No aplica

## 11. ROLE OF THE DHA/RVD1 PATHWAY AS A POTENTIAL ANTI-INFLAMMATORY STRATEGY IN BOVINE ENDOMETRIAL CELLS

Rol de la vía DHA/RvD1 como potencial estrategia antiinflamatoria en células de endometrio bovino

**Resumen:** The bovine endometrium in the postpartum period is exposed to bacterial lipopolysaccharides (LPS) and damage-associated molecular patterns such as adenosine triphosphate (ATP). These stimuli activate intracellular signaling pathways, including NF- $\kappa$ B, ERK1/2, and Akt, which amplify the inflammatory response. The omega-3 fatty acid DHA (docosahexaenoic acid) is a precursor for the synthesis of resolvins D (RvD), a specialized pro-resolving mediator; however, its effect on endometrial cells has not been studied. In this study, we evaluated whether DHA and RvD1 can reduce the activation of inflammatory pathways in bovine endometrial (BEND) cells. BEND cells were treated with inhibitors of RvD1 synthesis, DHA, or RvD1, and stimulated with LPS or ATP. The production of interleukin (IL)-6, IL-8, and RvD1 was analyzed by ELISA, while ERK1/2 and Akt phosphorylation and p65 NF- $\kappa$ B activation were assessed by immunoblotting. It was observed that DHA (50  $\mu$ M) induced RvD1 production in BEND cells, and the inhibition of the 15-lipoxygenase enzyme reduced this effect. LPS did not modify DHA-induced RvD1 production. DHA decreased IL-6 production but increased IL-8 production induced by LPS. RvD1 significantly reduced LPS-induced

IL-6 and IL-8 release. DHA decreased the LPS-induced ERK1/2 and Akt phosphorylation, and partially reduced ATP-induced phosphorylation. RvD1 did not modify ERK1/2 or Akt phosphorylation. Neither DHA nor RvD1 affected NF- $\kappa$ B activation. In conclusion, DHA induces RvD1 production, decreases IL-6 production, and reduces ERK1/2 and Akt phosphorylation. In addition, RvD1 reduces IL-6 and IL-8 production in endometrial cells.

**Autores:** Moya M.; Sánchez G.; Gutiérrez N.; Hidalgo M.A.  
**Afiliación:** Laboratory of Immunometabolism, Institute of Pharmacology and Morphophysiology, Faculty of Veterinary Sciences, Universidad Austral de Chile  
**Área de la Farmacología:** Immunopharmacology  
**Dirección de Correo:** mauricio.moya@alumnos.uach.cl  
**Agradecimientos:** FONDECYT 1200905  
**Socio Patrocinante:** PhD. María Angélica Hidalgo MSc. Rafael Burgos

## 12. PHARMACOLOGICAL EVALUATION OF THE DRIMANE SESQUITERPENES ISOTADEONAL AND POLYGODIAL FROM DRIMYS WINTERI AS MODULATORS OF THE NF- $\kappa$ B PATHWAY

Evaluación farmacológica de los sesquiterpenos drimanos isotadeonal y polygodial de *Drimys winteri* como moduladores de la vía NF- $\kappa$ B

**Resumen:** Los productos naturales constituyen una fuente relevante de compuestos bioactivos con potencial terapéutico. En este estudio se evaluó la actividad antiinflamatoria de los sesquiterpenos drimanos isotadeonal y polygodial, aislados del árbol chileno *Drimys winteri*. Isotadeonal, obtenido por epimerización de polygodial en medio básico ( $\text{Na}_2\text{CO}_3$ , 60% de rendimiento), mostró una inhibición más potente de la vía NF- $\kappa$ B en células THP-1 y microgliales HMC-3 estimuladas con LPS (100 ng/mL). A concentraciones de 10  $\mu$ M, isotadeonal redujo significativamente la fosforilación de I $\kappa$ B- $\alpha$  y la actividad SEAP en un 71,4% ( $p < 0.001$ ), superando la actividad de polygodial (56,9% a 25  $\mu$ M) y de los controles positivos quercetina y CAPE. Los análisis in silico evidenciaron una mayor afinidad teórica de isotadeonal por IKK $\beta$  (-7.12 kcal/mol), junto con alta permeabilidad a la barrera hematoencefálica y cumplimiento de la regla de Lipinski. Estos resultados destacan a isotadeonal como un modulador natural de NF- $\kappa$ B con potencial farmacológico en el desarrollo de agentes antiinflamatorios de origen vegetal.

**Autores:** Marín, V.1; Villegas, C. 2; Ogundele, A. 1; Cabrera-Pardo, J. 3,4; Schmidt, B. 5; Paz, C. 1; and Burgos, V. 6.  
**Afiliación:** 1 Laboratory of Natural Products & Drug Discovery, Center CEBIM, Department of Basic Sciences, Faculty of Medicine, Universidad de La Frontera, Temuco 4780000, Chile; victor.marinmossi.bq@gmail.com (V.M.); vicshow2001@gmail.com (A.V.O.) 2 Departamento de Ciencias Biológicas y Químicas, Facultad de Recursos Naturales, Universidad Católica de Temuco, Rudecindo Ortega, Temuco 4780000, Chile; ceciv42@  
**Área de la Farmacología:** Medicinal chemistry  
**Dirección de Correo:** vburos7@santotomas.cl  
**Agradecimientos:** ANID Chile, grant number Fondecyt Regular 1220831, Fondecyt Postdoctoral 3220305, National Scholarship ANID 21210835, and ANID Fondecyt EQM 220161  
**Socio Patrocinante:** Viviana Burgos



### 13. EVALUATION OF PAMAM DENDRIMERS AS NANOCARRIERS OF P2X RECEPTOR MODULATORS: EFFECTS ON SOLUBILITY AND CYTOTOXICITY

Evaluación de dendrímeros PAMAM como nanotransportadores de moléculas moduladoras de receptores P2X: efectos sobre solubilidad y citotoxicidad

**Resumen:** Alzheimer's disease is characterized by the accumulation of  $\beta$ -amyloid peptide, which triggers neuroinflammation and intracellular calcium imbalance. Purinergic P2X receptors (P2X7, P2X4, and P2X2) represent potential therapeutic targets due to their role in calcium influx. In a previous study, molecules potentially modulating P2X2 and P2X4 receptors were identified through large-scale docking of chemical libraries; however, the poor solubility of some candidates had so far prevented their experimental characterization. To overcome this limitation, we investigated the ability of PAMAM dendrimers (PAMAM-OH, PAMAM-NH<sub>2</sub>, and PAMAM-PEG) to form supramolecular complexes with these compounds. Complex formation was characterized by UV-Visible spectroscopy using the Higuchi-Connors method under physiological pH conditions. Biocompatibility was assessed through 24-hour viability assays in HEK-293 cells, comparing insoluble modulator suspensions with their respective dendrimer complexes. PAMAM-NH<sub>2</sub> exhibited the highest capacity to solubilize the docking-identified candidates, showing a direct correlation between dendrimer concentration and solubility. The complexes replicated the cytotoxicity profile of the individual dendrimers, with PAMAM-NH<sub>2</sub> being the most cytotoxic at high concentrations. Free modulator suspensions did not exhibit cytotoxicity, consistent with their expected pharmacological profile as specific receptor modulators. At concentrations below 10  $\mu$ M, PAMAM-NH<sub>2</sub> complexes maintained adequate cell viability, indicating acceptable biocompatibility. This study overcomes a key limitation in the experimental evaluation of P2XR modulators by enabling their solubilization and preliminary biological testing. The formation of PAMAM-NH<sub>2</sub> complexes at concentrations below 10  $\mu$ M represents a viable strategy for future functional assays on P2X receptor activity, contributing to the development of potential therapeutic applications for Alzheimer's disease.

**Autores:** Coronado N.1; Fernández R.1; Torres M.1; Valdebenito D.1; Bustos C.2; Ramirez G.3; Godoy P.A.3; Díaz C.2

**Afiliación:** 1. Departamento de Tecnología Médica, Facultad de Medicina, Universidad Andrés Bello. 2. Departamento de Ciencias Químicas, Facultad de Ciencias Exactas, Universidad Andrés Bello. 3. Departamento de Fisiología, Facultad de Ciencias Biológicas, Universidad de Concepción.

**Area de la Farmacología:** Medicinal chemistry  
Dirección de Correo: n.coronadosierpe@uandresbello.edu

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**Socio Patrocinante:** NA

### 14. AMINOALKOXYCHALCONES AS HISTAMINE H3 RECEPTOR LIGANDS AND ACETYLCHOLINESTERASE INHIBITORS

Aminoalcoxichalconas como ligandos del receptor de histamina H3 e inhibidores de la enzima acetilcolinesterasa

**Resumen:** El receptor H3R de histamina 3 es ampliamente reconocido como un valioso blanco farmacológico para el tratamiento de enfermedades neurodegenerativas. Existe un creciente conjunto de datos farmacológicos que demuestran el potencial de los antagonistas/agonistas inversos del H3R en el tratamiento de la enfermedad de Alzheimer (EA). 1 Por otra parte, la hipótesis colinérgica ha sentado las bases de la mayoría de las estrategias terapéuticas y enfoques para el desarrollo de fármacos contra la EA, incluidos los inhibidores de la acetilcolinesterasa. 2 En este sentido, la literatura ha descrito ligandos duales AChE/H3R. Este enfoque de ligandos dirigidos a múltiples dianas (MTDL) puede lograr un nivel más específico de mejora cognitiva a través de la neurotransmisión colinérgica, que un inhibidor de la AChE o un antagonista del H3R por sí solos. 3-5 A la luz de la urgente necesidad de nuevos tratamientos para la EA y teniendo en cuenta la naturaleza multifactorial de la enfermedad, en el presente estudio mostramos el diseño, síntesis y evaluación de una serie de aminoalcoxichalcona para su posible uso en el tratamiento de la EA destinadas a interactuar con y la acetilcolinesterasa. Algunos de estos compuestos presentaron gran afinidad por el H3R Ki <100 nM e IC50

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**Autores:** Espinosa-Bustos C. 1; Diaz J. 1; Osses P. 1; Salas C. 1; Gutiérrez M. 2; Stark H. 3  
**Afiliación:** 1. Laboratorio de Química Bio-Orgánica, Facultad de Química y Farmacia, Pontificia Universidad Católica de Chile, 2. Laboratorio de Síntesis Orgánica, Instituto de Química de Recursos Naturales Universidad de Talca, Chile, 3. Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Germany

**Area de la Farmacología:** Medicinal chemistry  
Dirección de Correo: ccespino@uc.cl

**Agradecimientos:** VRI-PUC Puente-2024-10 y Fondo de apoyo a la investigación Ciencia Básica DIPOG 39175004-301-81

**Socio Patrocinante:** Christian Espinosa

### 15. ARYLDIAMINE-1,4-NAPHTHOQUINONES AS A POTENTIALS DUAL INHIBITION OF HUMAN COX-2/5-LOX

Ardilidamino-1,4-naftoquinonas como potenciales inhibidores duales de la COX-2/5-LOX humana

**Resumen:** This study explored biochemical processes and metabolites associated with the inflammatory response, focusing on the design and evaluation of novel synthetic derivatives with dual inhibition against COX-2 and 5-LOX, key enzymes involved in the biosynthesis of prostaglandins (PGs) and leukotrienes (LTs), respectively. Naphthoquinones have emerged as promising scaffolds due to their redox-cycling ability and broad biological activities, including antitumor and anti-inflammatory effects. Based on this, new derivatives containing the amino-1,4-naphthoquinone pharmacophore were evaluated as potential dual COX-2/5-LOX inhibitors. A combined in silico and in vitro approach was applied. Arylamino-naphthoquinones (2a, 2b, and 2c) were synthesized via aromatic nucleophilic substitution reactions and structurally characterized mainly by NMR (<sup>1</sup>H, <sup>13</sup>C, HSQC, HMBC) and FT-IR spectroscopy. Docking studies revealed high binding affinity toward the COX-2 catalytic site and a preferential orientation within the allosteric pocket of 5-LOX, exhibiting comparable binding energies to those of the control inhibitors celecoxib and AKBA, respectively. Key amino acid residues, Arg120 and Tyr385 in COX-2, as well as Arg101 and Asp166 in 5-LOX, were found to stabilize the ligands through hydrogen bonding and hydrophobic interactions, contributing to the observed inhibitory potency. Compounds 2b and 2c, and to a lesser extent 2a, displayed potent 5-LOX inhibition with IC<sub>50</sub> values of 1.71, 5.19, and 93.71  $\mu$ M, respectively. In this context, the incorporation of aromatic substituents in the new derivatives, such as a phenyl ring, enhanced structural resemblance to AKBA and improved their binding performance. Finally, regarding COX-2 inhibition, compound 2b exhibited an IC<sub>50</sub> value of 138  $\mu$ M, superior to those of 2a and 2c, which showed values above 250  $\mu$ M.

**Autores:** Rebolledo M.1,2; Mascayano C.1; Ibacache J.2; Morales P.2

**Afiliación:** Laboratorio de Simulación Computacional y Diseño racional de fármacos, Facultad de Química y Biología, Universidad de Santiago de Chile.

**Area de la Farmacología:** Medicinal chemistry  
Dirección de Correo: maria.rebolledo.c@usach.cl

**Agradecimientos:** DICYT Project No. 022141IR. Proyecto Fondecyt Regular 1251364

**Socio Patrocinante:** NA



## 16. METABOLOMIC PROFILE AND IN SILICO PHARMACOLOGICAL EVALUATION OF THE ANTARCTIC LICHEN LEPTOGIUM PUBERULUM HUE

Perfil metabolómico y evaluación farmacológica in silico del líquen antártico *Leptogium puberulum* Hue

**Resumen:** Lichens represent an underexplored reservoir of structurally unique secondary metabolites with significant pharmacological potential. This study employed a combined LC-MS and computational approach to characterize the specialized metabolome of the Antarctic lichen *Leptogium puberulum* and evaluate the drug-like properties of its constituents. LC-MS analysis revealed a diverse chemical composition, including lipids (tetrahydroxy and pentahydroxy fatty acids), aromatic compounds (weddelolactone, vaccaihein A), and glycosides (gleditischiaside A). Several long-chain hydroxylated fatty acids, such as 9,10,12,13,14-pentahydroxytetraacosanoic acid (PHTA), 9,10,12,13-tetrahydroxydocosanoic acid (THDA), 9,10,12,13-tetrahydroxyheneicosanoic acid (THHA), and 9,10,12,13-tetrahydroxyheneicosanoic acid (THTA), met the Lipinski and Veber rules. Toxicity profiling using ProTox-3.0 and OSIRIS indicated low risks for most metabolites. Critical exceptions included weddelolactone, flagged for potential mutagenicity and reproductive toxicity, and azelaic and benzoic acids, which showed irritation risks. Bioactivity prediction via SWISS Target Predictor identified the four hydroxylated fatty acids as potential ligands for the prostanoid EP2 receptor (PTGER2), a target in inflammatory pathways. Molecular docking simulations using AutoDock-Vina substantiated this, demonstrating strong binding affinities ( $\Delta G = -7.0$  to  $-7.6$  kcal/mol) comparable to the reference inhibitor ( $\Delta G = -8.0$  kcal/mol). This integrated workflow underscores the chemical richness of *Leptogium puberulum* and identifies specific polyhydroxylated fatty acids as promising hit compounds targeting the PTGER2 receptor. Their potent binding and predicted drug-likeness warrant further investigation into their development as novel anti-inflammatory leads, highlighting the value of merging metabolomics with in silico screening for natural product drug discovery.

**Autores:** Torres-Benitez A.1; Sandoval-Vargas J.1; Ortega-Valencia E.2; Ley-Martinez J.E.2; Simirgiotis M.3

**Afiliación:** 1. Carrera de Química y Farmacia, Facultad de Ciencias, Universidad San Sebastián, Valdivia, Chile; 2. Tecnológico Nacional de México, Instituto Tecnológico Superior de Xalapa, Sección 5ª Reserva Territorial S/N Col. Santa Bárbara, Xalapa-Enriquez, Veracruz, Mexico; 3. Instituto de Farmacia, Facultad de Ciencias, Universidad Austral de Chile, Campus Isla Teja, Valdivia, Chile

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** alfredo.torres@uss.cl

**Agradecimientos:** Fondecyt Regular 1220075; INACH RG\_06\_24; Programa Antártico Colombiano 11EAC-CV-006

**Socio Patrocinante:** No aplica

## 17. STRATEGIES FOR CHOLINESTERASE INHIBITION AND NMDA/AMPA RECEPTOR MODULATION: RATIONAL DESIGN OF TETRAHYDROQUINOLINE-RACETAM DERIVATIVES

Estrategias para la inhibición de colinesterasas y la modulación de receptores nmda/ampa: diseño racional de derivados de tetrahydroquinolina-racetam

### Resumen:

Novel multi-target agents are urgently sought for neurodegenerative diseases. This study reports the rational design and computational screening of novel tetrahydroquinoline derivatives bearing the racetam (pyrrolidone) pharmacophore, hypothesized to be accessible via aza-Diels-Alder reactions. Initial computational screening utilized molecular docking to evaluate the binding affinity of simulated products to key therapeutic targets: Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE), and subunits of the AMPA glutamatergic receptor. Compounds of high predicted pharmacological interest were selected based on optimal predicted binding affinities and favorable interactions across the targeted enzyme and receptor models. The most promising candidates will undergo advanced computational characterization using Molecular Dynamics (MD) simulations with cholinesterases and both AMPA/NMDA receptors and additional potential targets based on known Structure-Activity Relationship (Sar). This integrated approach will lead to the

chemical synthesis and in vitro validation of anticholinesterase activity for the most potent compounds.

**Autores:** Chávez I.1; Vallejos G.1; Romero J.2; Muñoz M.1; Simirgiotis M.3; Sánchez E.3

**Afiliación:** 1. Laboratory of Catalysis and Molecular Structure, Faculty of Sciences, Universidad Austral de Chile; 2. Department of Organic and Physical Chemistry, Faculty of Chemical and Pharmaceutical Sciences, Universidad de Chile; 3. Institute of Pharmacy, Faculty of Sciences, Universidad Austral de Chile

**Area de la Farmacología:** Medicinal chemistry

**Dirección de Correo:** isaac.chavez@alumnos.uach.cl

**Agradecimientos:** None to be disclosed.

**Socio Patrocinante:** Eliana Sánchez Montoya

## 18. EFFECT OF THE B1R AGONIST ON THE LEVELS OF LEKTI AND KALLIKREIN-RELATED PEPTIDASE KLK8 IN HUMAN KERATINOCYTES

Efecto del agonista de RB1 sobre los niveles de LEKTI y de la peptidasa KLK8 relacionada con caliceína en queratinocitos humanos

### Resumen:

Kinin-Kallikrein System modulates essential functions on the skin, including differentiation of keratinocytes and angiogenesis. Kinin peptides are formed during inflammation by the action of tissue kallikrein (KLK1) on kininogens. Kinins activate two G protein-coupled receptors, B1R and B2R, which mediate key events in tissue repair, depending on the cell type. In normal skin, B1R expression is low; however, its levels increase in the inflammatory milieu. KLK1 is part of a large family of serine proteases related to kallikreins (KLKs), comprising 15 members (KLK1-KLK15). In skin, these cascades initiate a proteolytic cascade that generates active proteases, including KLK8, which has a role in skin homeostasis and participates in the late phase of wound healing. This cascade is primarily regulated by an endogenous inhibitor, lymphoepithelial Kazal-type-related inhibitor (LEKTI). Despite the known link between kinins and kallikreins, B1R's role in regulating their expression remains unexplored. Our main objective has been to determine the effect of a B1R agonist on the protein levels of LEKTI and KLK8 in keratinocyte cells. The HaCaT keratinocyte cell line was stimulated with Lys-Des[Arg9]-bradykinin (LDBK), a selective B1R agonist. Protein levels were assessed by western blotting and immunocytochemistry. HaCaT cells were treated with 10 nM LDBK for 6 to 48 hours to evaluate LEKTI and KLK8 levels. Western blot and immunocytochemistry showed that 10 nM for 6 hours decreased LEKTI levels, whereas KLK8 levels increased after 24 hours. This effect was blocked by pretreating with a specific B1R antagonist. These results suggest a regulatory interaction among B1R signaling, LEKTI inhibition, and KLK8 activity that may play a role in the wound-healing process.

**Autores:** Arias M.2; Muñoz D.1; Ehrenfeld P.3,6; Figueroa C.D.3,6; Salazar L.4; Ávila P.2; Matus C.E.1,4,5.

**Afiliación:** Cell Biology and immunology Laboratory, Department of Basic Sciences, Faculty of Medicine, Universidad de La Frontera 1. Cell Biology and immunology Laboratory, Faculty of Agricultural and Environmental Sciences, Universidad de La Frontera 2. Laboratory of cellular pathology, Institute of Anatomy, Histology and Pathology, Faculty of Medicine, Universidad Austral de Chile 3. Center of Molecular Bio

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** m.arias15@ufromail.cl

**Agradecimientos:** Acknowledgments: Supported by grant N° DI24-0100 from Universidad de La Frontera, Temuco, Chile.

**Socio Patrocinante:** No

## 19. FUNCTIONAL CHARACTERIZATION OF NAPHTHYLPYRROLIDINE ESTERS AS BLOCKERS OF THE SEROTONIN TRANSPORTER (SERT)

Caracterización funcional de ésteres de nafilpirrolidina como bloqueadores del transportador de serotonina (SERT)

### Resumen:

The serotonin transporter (SERT) is a high-affinity transmembrane protein responsible for the reuptake of serotonin (5-HT) from the synaptic cleft and regulating central serotonergic tone. Its blockade is a key pharmacological mechanism in the treatment of mood and anxiety disorders. This study aimed to characterize two novel ligands with dual activity against SERT and the nAChR  $\alpha 4\beta 2$ . These molecules, identified as NPM and NPE, were designed by linking the naphthyl group of duloxetine and the pyrrolidine group of nicotine via an ester bond. HEK293 cells stably transfected with human SERT (HEK-SERT) were used, and the uptake of the fluorescent analog FFN246 was quantified by epifluorescence microscopy and spectrophotometry (Ex 388 nm / Em 434 nm). Fluoxetine was used as the standard reference blocker. Both compounds were evaluated at concentrations of 1, 5, 10, 25, 50, and 100  $\mu\text{M}$ . A concentration-dependent inhibition of both ligands was observed. The NPM exhibited better SERT blockade than the NPE, with IC<sub>50</sub> values for SERT of 2.54  $\mu\text{M}$  and 4.71  $\mu\text{M}$ , respectively. This indicates that chain extension in the NPE compound resulted in a nearly twofold decrease in blocking activity compared to the NPM. Binding experiments using [<sup>3</sup>H]-paroxetine and docking energies at the transporter binding site confirm that the inhibition mechanism is competitive at the orthosteric site of SERT, analogous to that observed with selective serotonin transporter inhibitors. In conclusion, naphthylpyrrolidine esters act as functional inhibitors of SERT, reducing serotonin reuptake in a dose-dependent manner. The efficacy of the NPM compound suggests that minor structural variations can significantly modulate activity at the transporter.

**Autores:** Atiés Pérez R.C1, Valle Loyola C2, Reyes J.P2, Segura K1, Hernandez-Galán V1, Velásquez Pineda V3, Sotomayor-Zárate R3, Iturriaga Vázquez P1

**Afiliación:** Departamento de Ciencias Químicas y Recursos Naturales, Facultad de Ingeniería y Ciencias

**Área de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** atiescary93@gmail.com

**Agradecimientos:** Fondecyt 1240688, Beca ANID 21240481

**Socio Patrocinante:** Patricio Iturriaga

## 20. FLUORESCENCE-BASED ASSAY FOR FUNCTIONAL AND PHARMACOLOGICAL PROFILING OF MCT4

Ensayo basado en fluorescencia para la caracterización funcional e identificación de inhibidores para MCT4

**Resumen:** Metabolic transporters orchestrate the exchange of key metabolites that sustain cellular energetics and represent emerging pharmacological targets in cancer and metabolic disease. With the increasing restrictions on animal experimentation, there is a growing need for reliable cell-based platforms to evaluate transporter activity and identify selective inhibitors. We established a fluorescence-based experimental framework that integrates genetically encoded indicators with cell-based assays to enable the functional assessment of a carrier activity. As proof of concept, the strategy was demonstrated using the monocarboxylate transporter MCT4, a key carrier that is upregulated in glycolytic and hypoxic tumors. The strategy begins with the calibration of a fluorescent indicator to define its dynamic range and responsiveness, followed by co-expression with MCT4 to monitor fluorescence changes associated with transport in living cells. Stable HEK293 lines expressing both constructs provided a reproducible model to assess MCT4-mediated monocarboxylate fluxes under physiological and inhibitory conditions. Systematic optimization of assay parameters, including signal stability, temperature sensitivity, and inter-well variation, resulted in a robust fluorescence platform suitable for high-throughput screening (HTS), characterized by high reproducibility and assay quality (mean Z'-factor =  $0.78 \pm 0.12$ ). The readout reliably detected MCT4-specific

inhibition by reference compounds such as syrosingopine, demonstrating its utility for functional screening and pharmacological profiling. Altogether, this work establishes an integrated experimental strategy from metabolic sensor validation to inhibitor detection, providing a scalable framework for HTS-based discovery and characterization of modulators of metabolite transport in live-cell systems.

**Autores:** Cárcamo-Lemus N. 1; Trecaman V. 2; Sandoval PY. 1,2

**Afiliación:** 1. Centro de Estudios Científicos. 2. Escuela de Medicina, Facultad de Medicina, Universidad San Sebastián

**Área de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** pamel.sandoval@uss.cl

**Agradecimientos:** USS-FIN-23-FAPE-03 (PYS), FONDECYT project #11190584 (PYS), and FONDECYT project # 1230145 (LFB)

**Socio Patrocinante:** María Angelica Hidalgo

## 21. GELSEMIUM ALKALOIDS AS NOVEL SMALL-MOLECULE MODULATORS OF TRANSGLUTAMINASE 2 WITH NEUROPROTECTIVE POTENTIAL

Alcaloides de gelsemium como nuevos moduladores de la transglutaminasa 2 con potencial neuroprotector

**Resumen:** Transglutaminase 2 (TG2) is a calcium-dependent enzyme that catalyzes the cross-linking of proteins and peptides. Recent studies have associated the inhibition of its cross-linking activity with neuroprotective effects, characterized by a decrease in the aggregation of amyloidogenic peptides such as  $\beta$ -amyloid ( $A\beta$ ), which is classically implicated in the pathogenesis of Alzheimer's disease (AD). In parallel, gelsemine, a natural indole alkaloid present in species of the Gelsemium genus, has been shown to exert neuroprotective effects against  $A\beta$  oligomers. However, the molecular targets and underlying mechanisms of the neuroprotective actions of gelsemine are still unclear. Here, we employed computational, biochemical, and electrophysiological approaches to explore the mechanisms underlying the neuroprotective effects of the alkaloid in cellular models of AD. Biochemical and bioinformatic analyses revealed that gelsemine inhibits TG2 enzymatic activity, likely through interactions with residues within its catalytic pocket. We observed that the alkaloid modulated the TG2-mediated aggregation process of  $A\beta$ , thereby reducing the formation of neurotoxic oligomers and preserving neuronal function. Ongoing biochemical experiments indicate that additional Gelsemium alkaloids reduce TG2 activity in a concentration-dependent manner. Collectively, our findings establish TG2 as a previously unrecognized molecular target of gelsemine and highlight the potential of Gelsemium-derived alkaloids as neuroprotective agents. Since currently known TG2 modulators are mainly peptide-based molecules, further studies on Gelsemium compounds may lead to the identification of new classes of small-molecule TG2 modulators with potential as therapeutics against  $A\beta$  toxicity and AD.

**Autores:** Marileo A.M.\*; Panes-Fernández J.\*; Espinoza-Rubilar N.1; Salgado-Martínez B.A.; Gaete-Riquelme K.; Moraga-Cid G.; Castro P.A.; Burgos C.F.; Fuentealba J.; Yévenes G.E.

**Afiliación:** Department of Physiology, Faculty of Biological Sciences, University of Concepcion, Chile

**Área de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** anamarileo@udec.cl

**Agradecimientos:** This research was funded by ANID-FONDECYT 1211082 and ANID-FONDECYT 1250856 (to G.E.Y.), as well as ANID-FONDECYT 1251488 (to G.M.-C), ANID-FONDECYT 1231038 (to P.A.C.), and ANID-FONDECYT 11221211 (to C.F.B.). N.E., and K.G. were supported by ANID doctoral fellowships (21241542, 21251365). B.E. S.-M. and K.G.-R were supported by the University of Concepcion through Graduate School Fellowships (MSc program in Neurobiology). The authors also thank J. Gonzalez and I. Cid for their outstanding technical assistance.

**Socio Patrocinante:** Gonzalo Yévenes, PhD.



## 22. SILENCING OF THE MITOCHONDRIAL VITAMIN C TRANSPORTER (MITSVCT2) INCREASES OXIDATIVE STRESS AND REDUCES CELL VIABILITY IN TRIPLE-NEGATIVE BREAST CANCER CELLS

El silenciamiento del transportador mitocondrial de vitamina C (mitSVCT2) aumenta el estrés oxidativo y reduce la viabilidad celular en células de cáncer de mama triple negativo.

### Resumen:

The sodium-dependent vitamin C transporter 2 (SVCT2) enables the cellular uptake of ascorbic acid, contributing to the regulation of redox balance. In cancer cells, SVCT2 has been reported to exhibit intracellular localization, particularly in mitochondria (mitSVCT2), whose role has not yet been fully characterized. The aim of this study was to evaluate the effect of mitSVCT2 silencing on cell viability and reactive oxygen species (ROS) production in an in vitro model of triple-negative breast cancer (MDA-MB-468 cells). To this end, a stable knockdown model was generated using lentiviral transduction of shRNA, resulting in approximately 50% reduction in mitSVCT2 expression. Functional assays showed a significant decrease in cell growth rate and a significant increase in metabolic activity in shSVCT2 cells compared with the control (shCTRL). These results were determined by trypan blue exclusion and MTT assays. Pretreatment with physiological concentrations of ascorbic acid increased metabolic activity in shCTRL cells but not in shSVCT2, demonstrating the dependency on the transporter for the protective effect of ascorbic acid. Using fluorescent probes, a significant increase in both total and mitochondrial ROS levels was observed in shSVCT2 cells compared to shCTRL. Together, these findings indicate that mitSVCT2 actively participates in the regulation of metabolism and redox homeostasis, and that its silencing induces an oxidative imbalance that compromises cell viability in triple-negative breast cancer cells.

**Autores:** Miranda V. P. 1; Alarcón C. 1; Arriagada S. 1; Coralia I. Rivas 1

**Afiliación:** Laboratory of Antioxidants and Cancer, Department of Pathophysiology, Faculty of Biological Sciences, University of Concepción

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** vmiranda2019@udec.cl

**Agradecimientos:** FONDECYT 1201496

**Socio Patrocinante:** Coralia I. Rivas

## 23. COMPARISON OF DERMAL FIBROBLAST- AND ADIPOSE DERIVED MESENCHYMAL STEM CELL SECRETOMES IN REGULATING RAT DERMAL FIBROBLAST FUNCTIONS

Comparación de los secretomas de fibroblastos dérmicos y de células madre mesenquimales derivadas de tejido adiposo en la regulación de las funciones de los fibroblastos dérmicos de rata.

**Resumen:** Introduction: Chronic wounds are characterized by impaired healing, persistent inflammation, and high recurrence rates. Mesenchymal stem cells (MSCs) exert therapeutic effects mainly through their secretome, a complex mixture of bioactive molecules that modulate tissue repair and regeneration. However, the regenerative potential of the fibroblast-derived secretome remains less investigated. Objective: To compare the effects of secretomes from dermal fibroblasts and adipose-derived mesenchymal stem cells (AD-MSCs) on proliferation, viability, migration, and extracellular matrix (ECM)-related gene expression in rat dermal fibroblasts. Methods: Secretomes were obtained from rat dermal fibroblasts and AD-MSCs cultured in monolayer. Total protein content was quantified by Qubit, and fibroblasts were treated with 0, 10, 100, or 1000 ng/mL. Viability and proliferation were determined using resazurin and CyQUANT assays. Migration was assessed by scratch assay at 0, 6, and 24 h. Gene expression of VEGF, collagen type I (COL1), and collagen type III (COL3) was analyzed by qRT-PCR. Statistical analyses included one-way ANOVA and Welch's t-test, with  $p < 0.05$  considered significant. Results: The AD-MSC secretome significantly enhanced fibroblast migration, showing the greatest effect at 100 ng/mL, whereas the fibroblast-derived secretome produced minimal changes. Neither treatment showed cytotoxic effects. Gene expression analysis indicated that the AD-MSC secretome tended to upregulate VEGF, COL1, and COL3, albeit with interexperimental variability, while the fibroblast secretome induced only modest alterations. Conclusion: The AD-MSC secretome demonstrated superior regenerative potential compared to the fibroblast secretome, particularly in promoting cell migration and

modulating ECM-related genes. These results support its potential application as a paracrine-based therapeutic strategy for wound healing and emphasize the value of comparative studies to refine secretome-based

**Autores:** Montenegro Y. 1,2,3,4; Tapia A. 2,3,4; Ceriani R. 1,3,4

**Afiliación:** Laboratorio de Innovación Terapéutica y Diagnóstico Molecular, Escuela de Química y Farmacia, Facultad de Farmacia, Universidad de Valparaíso

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** yarela.montenegro@estudiantes.uv.cl

**Agradecimientos:** SIA85220025 and FONDECYT 11250842

**Socio Patrocinante:** Andrea Tapia Bustos

## 24. NETWORK PHARMACOLOGY AND MOLECULAR DOCKING APPROACHES PREDICT CHILEAN ENDEMIC PLANT FLAVONOIDS AS MULTI-TARGET ANTI-FIBROTIC CANDIDATES WITH SUPERIOR CARDIOVASCULAR PROFILE TO NINTEDANIB

Enfoques de farmacología de redes y de acoplamiento molecular predicen flavonoides de plantas endémicas chilenas como candidatos anti-fibróticos multi-diana con perfil cardiovascular superior a nintedanib

**Resumen:** Idiopathic pulmonary fibrosis (IPF) remains a progressive and fatal disease with limited therapeutic options. Current FDA-approved treatments, nintedanib and pirfenidone, demonstrate modest efficacy and significant cardiovascular toxicity, resulting in 10-16% treatment discontinuation. We hypothesized that flavonoids from Chilean endemic plants (*Aristolelia chilensis*, *Berberis microphylla*, *Ugni molinae*) with documented ethnomedicinal anti-inflammatory properties could provide safer multi-target alternatives. Through integrated computational workflow, we evaluated six bioactive flavonoids via drug-likeness profiling (RDKit v2023.03), inverse target prediction (SwissTargetPrediction, STITCH v5.0), network topology analysis (STRING v12.0, CytoHubba), functional enrichment (Enrichr-KEGG 2021), molecular docking (Glide XP v2023-4), and cardiotoxicity prediction (pkCSM). Nintedanib was processed identically as benchmark control. All flavonoids exhibited favorable drug-like properties (100% Lipinski compliance) and engaged 12 IPF-relevant targets, including master regulators of fibrogenesis (TGFB1, SMAD2/3), inflammation (NLRP3, NF-kappa-B1, IL-6, TNF-alpha), and tissue remodeling (COL1A1, ACTA2, MMP9). Network analysis revealed statistically significant protein-protein interaction enrichment (28 edges, clustering coefficient 0.61, p-value 0.0023) with convergence on five hub proteins (TGFB1, SMAD3, NLRP3, NFKB1, IL6). Functional annotation confirmed mechanistic alignment with TGF-beta signaling (hsa04350, FDR 0.0089), NLRP3 inflammasome (hsa04621, FDR 0.021), and NF-kappa-B pathways (hsa04064, FDR 0.038). Docking demonstrated comparable binding affinities: quercetin-TGFB1 (-8.9 kcal/mol), luteolin-NLRP3 (-8.2 kcal/mol), catechin-SMAD3 (-7.8 kcal/mol) versus nintedanib (-8.5 to -9.1 kcal/mol). Critically, 67% of flavonoids exhibited low hERG liability versus nintedanib's moderate cardiotoxic profile.

**Autores:** Yunier Perera-Sardiña 1, Eduardo Solís-Céspedes 2, Yudith Cañizares-Carmenate 2, Daniel Gonzales-Reinoso 1

**Afiliación:** 1. Departamento de Ciencias Básicas Biomédicas, Facultad de Ciencias de la Salud, Universidad de Talca, Chile. 2. Departamento de Medicina Traslacional, Facultad de Medicina, Universidad Católica del Maule, Chile.

**Area de la Farmacología:** Molecular pharmacology

**Dirección de Correo:** yunier.perera@utalca.cl

**Agradecimientos:** Department of Basic Biomedical Sciences, Faculty of Health Sciences, Universidad de Talca, Talca, 3460000, Chile

**Socio Patrocinante:** Jessica Zuñiga Hernandez

## 25. COMPARATIVE MOLECULAR SIMULATION OF VASOPRESSIN (V1A, V1B), AND OXYTOCIN (OXTR) RECEPTORS FOR THE IDENTIFICATION OF COMPOUNDS WITH POLYPHARMACOLOGICAL POTENTIAL

Simulación molecular comparativa de los receptores de vasopresina (V1a, V1b), y oxitocina (OXTR) para la identificación de compuestos con potencial polifarmacológico

### Resumen:

The long development times of novel drugs motivate the use of computational strategies to guide the early identification of therapeutic compounds. This study presents a comparative molecular simulation approach of the vasopressin receptors V1A and V1B, together with the oxytocin receptor (OXTR), aimed to identify drugs capable of fitting their binding sites and to explore potential polypharmacological profiles among these G protein-coupled receptors. The three selected proteins (V1A and V1B from AlphaFold3; OXTR crystal structure) were prepared using the Protein Preparation Wizard from the Schrödinger 2024-3 suite. Hydrogen atoms were added, protonation states were assigned using PropKa at pH 7.4 ± 0.2, and energy minimization was performed with a 0.3 Å RMSD convergence criterion. A virtual screening upon the three receptors was performed using a database consisting of 3458 molecules derived from ChEMBL v32, curated by the Ramírez' Lab group. Ligands were prepared using LigPrep under the same pH conditions applied to the proteins. Molecular docking studies were conducted with Glide in both Standard Precision (SP) and Extra Precision (XP) modes, generating one pose per ligand. The top-ranked XP poses were subjected to MM-GBSA free energy calculations using the Prime module, allowing flexibility of residues within 5 Å of each ligand. In the case of OXTR, an additional MM-GBSA calculation was performed using the co-crystallized ligand pose as a comparative control. Preliminary results revealed several compounds exhibiting high binding affinity either for each receptor, or combinations of two or three of them. These results highlight potential selective or promiscuous candidates for drug repurposing. This integrated modeling approach suggests new opportunities for the rational design of multitarget ligand-based therapies.

**Autores:** Cantillana-Ramírez N. 1\* ; Palacios-Toledo C. 1\* ; Valenzuela-Hormázabal P. 2; Renard G. M. 3; Ramírez D. 2; Reyes-Parada M. 3. \*Both authors contributed equally  
**Afiliación:** Ingeniería Civil Biomédica, Facultad de Ingeniería, Universidad de Santiago de Chile 1. Departamento de Farmacología, Facultad de Ciencias Biológicas, Universidad de Concepción, Concepción 2. Centro de Investigación Biomédica Aplicada, Escuela de Medicina, Facultad de Ciencias Médicas, Universidad de Santiago de Chile 3.  
**Área de la Farmacología:** Molecular pharmacology  
**Dirección de Correo:** nicole.cantillana.r@usach.cl  
**Agradecimientos:** Supported by FONDECYT Grant 1220656 (DR), DICYT (USACH) Grants 022401RG (GMR) and 022401RP (MR-P).  
**Socio Patrocinante:** Georgina María Renard

## 26. RILUZOLE MODULATES ETHANOL CONSUMPTION AND AVERSION IN MOUSE MODELS OF ALCOHOL USE DISORDER

El riluzol modula el consumo y la aversión a etanol en modelos de ratón del trastorno por consumo de alcohol

### Resumen:

Alcohol use disorder (AUD) is a major global public health issue, characterized by compulsive alcohol intake and chronic relapses. It has been proposed that individuals with AUD exhibit hyperglutamatergic dysregulation in reward-related brain regions. This disruption promotes neuronal hyperexcitability and increases relapse vulnerability. Riluzole, an FDA-approved glutamatergic inhibitor, may restore glutamate homeostasis and reduce ethanol relapse. We investigated the effect of riluzole on alcohol consumption using complementary mouse models. In mice that voluntarily consumed alcohol, modeling early-stage AUD, repeated riluzole administration (4 g/kg) in mice during withdrawal did not reduce relapse drinking in either sex. To test riluzole in a model more representative of the brain alterations of chronic AUD, we employed a chronic + binge protocol. Male and female mice were exposed to a 5% ethanol liquid diet as their sole fluid and food source for 10 days, followed by a 5 g/kg ethanol gavage. This protocol initially induced ethanol aversion, requiring repeated forced exposure cycles to restore voluntary intake to approximately 5 g/kg. During subsequent withdrawal, riluzole (4

mg/kg) was administered daily. In female mice, vehicle-treated controls showed a marked reduction in ethanol preference, reflecting reinstatement of ethanol aversion, whereas riluzole-treated maintained prior consumption levels. No changes were observed in male mice. These findings suggest that riluzole can alter the behavioral expression of ethanol aversion in mice, which can result in an unexpected increase in voluntary consumption. The results highlight the need for diverse experimental models that capture the behavioral and pharmacological complexity, such as their brain glutamatergic state, underlying different stages of alcohol dependence to represent the diversity of AUD patients.

**Autores:** Aguirre-Muñoz F.; Gonzalez-Madrid A.; Berrios-Cárcano P.  
**Afiliación:** Centro de Medicina Regenerativa, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina, Universidad del Desarrollo  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** maria.aguirre@udd.cl  
**Agradecimientos:** This work was supported by Fondecyt 11240471. The authors would like to thank our collaborators from the Center for Regenerative Medicine, University of Desarrollo, and Kaina Herrera for her technical assistance.  
**Socio Patrocinante:** Dr. Pablo Berrios Cárcano

## 27. DISCOVERY OF NOVEL SMALL MOLECULES TARGETING INSECTICIDE-RESISTANT GABA RDL RECEPTORS VIA VIRTUAL SCREENING AND PROTEIN-LIGAND DOCKING

Descubrimiento de nuevas moléculas pequeñas dirigidas a receptores GABA Rdl resistentes a insecticidas mediante cribado virtual y acoplamiento proteína-ligando.

**Resumen:** Gamma-aminobutyric acid type A receptors (GABAARs) are pentameric ligand-gated ion channels controlling neuronal excitability. In insects, the GABA Rdl subtype is the primary target of most GABAergic insecticides, particularly type IA non-competitive antagonists, which block the pore. Resistance typically arises from the A302S mutation in the TM2 domain, a critical pore-forming region. Despite the diversity of available insecticide classes, the discovery of novel compounds with higher selectivity, improved efficacy, and reduced toxicity remains a major challenge. In this study, we employed a computational approach to identify new candidate molecules capable of binding the GABA Rdl A302S receptor at the NCA-IA site. 93 reference structures were retrieved from PubChem, grouped into four insecticide classes (cyclodienes, DDT-derivatives, PCCAs, and phenylpyrazoles). In addition, two compound subsets were downloaded from the MolPort database: a natural products library (426,787 molecules) and a screening library (4,686,582 molecules). All compounds were prepared and evaluated for their ADMET properties. Pharmacophore models were generated and validated based on the four reference insecticide classes, emphasizing key hydrophobic, aromatic, and hydrogen-bonding features. Subsequently, ligand-based virtual screening was performed using three phenylpyrazole-derived pharmacophores against MolPort subsets, yielding the top 1,000 ranked compounds per model (6,000 molecules). Protein-ligand docking with the homomeric GABA Rdl A302S model identified candidates with improved docking score (DS) and deltaG bind compared to fipronil (DS=-4.959, deltaG bind=-36.53 kcal/mol), with the top molecule reaching DS=-11.96 and deltaG bind=-66.41 kcal/mol. Altogether, the combination of structural, functional, and computational approaches enabled the identification of promising small molecules with potential negative modulatory activity on GABA Rdl receptors.

**Autores:** Doderer L.; Millar-Obreque C.; Castro M.; Salgado-Martínez B.; Godoy P.A., Yévenes G.E.; Burgos C.F.  
**Afiliación:** Departamento de Fisiología, Facultad Ciencias Biológicas, Universidad de Concepción  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** luisdoderer2016@udec.cl  
**Agradecimientos:** Supported by ANID-FONDECYT 11221211 (CFB), ANID-FONDECYT 1250856 (GEY), ANID FONDECYT Postdoctoral 3230515 (PAG)  
**Socio Patrocinante:** Gonzalo Yévenes C.



## 28. SEX-DEPENDENT POSITIVE REGULATION OF GLP-1R/GIPR IN THE HIPPOCAMPUS AND SPECIFIC MONOAMINERGIC ALTERATIONS OF THE MESOCORTICOLIMBIC SYSTEM IN A DIET-INDUCED OBESITY MODEL

Regulación positiva dependiente del sexo de GLP-1R/GIPR en el hipocampo y alteraciones monoaminérgicas específicas del sistema mesocorticolímbico en un modelo de obesidad inducido por dieta

**Resumen:** Obesity induces neuroendocrine adaptations that remodel neural circuits regulating feeding and reward. We investigated the impact of early diet-induced obesity (DIO) on central incretin receptor expression and monoaminergic signaling across septo-hippocampal and mesolimbic networks in male and female C57BL/6 mice. Animals were fed a high-fat diet (HFD) from weaning to early adulthood (postnatal day 76). HFD produced a metabolic phenotype characterized by increased body mass, hyperglycemia, and enlarged gonadal, retroperitoneal, and brown adipose depots. Behavioral assessment (Open-Field, Y-maze) revealed no overall impairments in locomotion or spatial performance. However, HFD females exhibited reduced entries into the novel arm of the Y-maze without changes in time spent, consistent with diminished novelty-directed exploration absent overt mnemonic deficits. RT-qPCR analysis revealed sex-specific regulation of incretin receptors (Gipr and Glp1r) were upregulated in dorsal and ventral hippocampus of HFD males but remained unchanged in HFD females, indicating a diet-dependent, sex-specific transcriptional response. In contrast, Gipr and Glp1r expression in lateral septum did not differ between groups. Neurochemical profiling demonstrated nucleus-specific monoaminergic alterations. In nucleus accumbens, dopamine and its metabolite DOPAC displayed sex-dependent differences, whereas serotonin concentrations showed a diet effect and 5-HIAA exhibited no consistent pattern. In prefrontal cortex, DOPAC was reduced in HFD males relative to male controls, and control males exhibited higher DOPAC than control females, revealing both diet effects and baseline sex differences. Collectively, these data indicate that early DIO precipitates sex-dependent alterations in incretin receptor expression and monoaminergic signaling within septo-hippocampal and mesolimbic circuits.

**Autores:** Escobar-Luna, J.; Salazar-Cea, M.; Etchegaray-González, C.; Dib-Schwelling, T.; Ibacache-Álvarez, J.; Olivares-Barraza, R.; Sotomayor-Zárate, R.

**Afiliación:** Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso. **Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [ramon.sotomayor@uv.cl](mailto:ramon.sotomayor@uv.cl)

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**Socio Patrocinante:** Ramón Eduardo Sotomayor Zárate.

## 29. TET2 AS AN EPIGENETIC MEDIATOR OF $\beta$ -AMYLOID-INDUCED MICROGLIAL INFLAMMATORY RESPONSE MODULATED BY 4-OCTYL ITACONATE IN ALZHEIMER'S DISEASE

"TET2 como mediador epigenético de la respuesta inflamatoria microglial inducida por  $\beta$ -amiloides y modulada por 4 octilo itaconato"

**Resumen:** Background: Alzheimer's Disease (AD) is characterized by  $\beta$ -amyloid (A $\beta$ ) plaque accumulation and sustained microglial neuroinflammation. Microglial activation induces metabolic reprogramming that favors a pro-inflammatory phenotype, resulting in the accumulation of the immunometabolite succinate. Succinate potentiates inflammation, partly by stabilizing HIF-1 $\alpha$ . This metabolic state influences epigenetic mechanisms involving the TET2 enzyme, which is  $\alpha$ -ketoglutarate ( $\alpha$ -KG)-dependent and catalyzes the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). TET2 thus emerges as a central node integrating metabolic and epigenetic signals with the potential to modulate microglial inflammatory response in AD. Hypothesis and Methodology: We hypothesize that TET2 promotes a pro-inflammatory state in A $\beta$ -activated BV2 microglia, which is counteracted by 4-octyl itaconate (4-OI). Preliminary "setting" experiments utilized the murine BV2 microglial line stimulated with synthetic A $\beta$ 1-42 oligomers (Bachem). Techniques included RT-qPCR (for TET2, GLUT1) and Western Blot (for NF $\kappa$ B, HKII). Results: The setting phase confirmed basal TET2 expression and its detection following stimulation with synthetic A $\beta$ 1-42 oligomers. Trends were detected toward an increase in glycolytic markers (HKII, GLUT1). These initial assays address the in vitro model for studying TET2 expression.

Future work will focus on synthetic A $\beta$ 1-42 oligomers (Bachem) and the enrichment of 5hmC in promoters of proinflammatory genes (such as IL1- $\beta$ , IL-6, TNF- $\alpha$  and NOS2). Conclusion: These preliminary data confirm BV2 cell reactivity and the early regulation of TET2 and key metabolic pathways in response to amyloidogenic stimuli. 4-OI is positioned as a promising therapeutic candidate to modulate microglia-mediated neuroinflammation in AD, potentially by restoring TET2 activity and influencing the microglial epigenome.

**Autores:** Espindola L. 1,3; Mella A.1,3; López E. 1,3; Inestrosa N.5; Lavandero S. 1,2,3,4.

**Afiliación:** 1Departamento de Bioquímica y Biología Molecular, Facultad Ciencias Químicas y Farmacéuticas, Universidad de Chile. 2Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile. 3Advanced Center for Chronic Diseases, ACCDiS, Universidad de Chile. 4Cardiology Division, University of Texas Southwestern Medical Center, Dallas, USA. 5Centre of Excellence in Biomedicine of Magal

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [liliana.espindola@uq.uchile.cl](mailto:liliana.espindola@uq.uchile.cl)

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**Socio Patrocinante:** -

## 30. ANGIOGENIC-LIKE EFFECT OF ACUTE FLUOXETINE AND ETHANOL IN THE PLANARIAN (DUGESIA) MODEL USING THE PLANARIAN LIGHT/DARK TEST (PLDT)

Efecto ansiogénico de altas dosis de fluoxetina y etanol en el modelo de planaria (*Dugesia*) mediante la prueba de Luz/Oscuridad con Planarias (PLDT).

**Resumen:** The search for alternative animal models for neuropharmacological evaluation is essential. Planaria (*Dugesia* sp.) is emerging as a robust animal model due to its centralized nervous system, with the presence of serotonergic, dopaminergic, and GABAergic neurons, and its high regenerative capacity, supported by the presence of pluripotent stem cells (neoblasts) capable of differentiating into new neuronal cells. Considering that *Dugesia* species exhibit negative phototaxis, and this behavior is considered a defensive response, helping them avoid predators and damaging UV radiation in their natural habitat, this behavior allows for the study of complex behavioral responses, such as the anxiety-like effects, using the Planarian Light/Dark Test (PLDT), where a longer stay on the light side is related to a lower anxiety-like effect, and a shorter stay on the light side is correlated with an anxiety-like inducing state. In this study, ethanol was used at doses of 1%, 1.5%, and 2%, observing that at higher doses, the time spent on the light side was shorter, with an anxiogenic effect that increased with increasing dose, which may be related to serotonergic and GABAergic neurotransmission. In addition, similar tests were conducted with acute fluoxetine exposure (1 $\mu$ M), observing a significant decrease in the time spent in the light compartment, suggesting an anxiogenic effect rather than the anxiolytic effect attributed to this drug.

**Autores:** Fariás-Cea, A. 1,2; Hödar-Salazar, 3; Vargas, A. 1; Schmauck, S. 1; Verdejo-Coll, R. 1; Navarrete, C. 1; Maldonado, M. 1; Godoy, M. 1; Pedraza, B. 1; Valle, C. 1; Pino, J. A. 1

**Afiliación:** 1. Laboratorio de Bioquímica y Farmacología Molecular, Escuela de Ciencias, Facultad de Ciencias de la Vida, Universidad Viña del Mar, Chile; 2. Escuela de Educación, Facultad de Ciencias Jurídicas, Sociales y de la Educación, Universidad Viña del Mar, Chile; 3. Departamento de Procesos Diagnósticos y Evaluación, Fac. de Ciencias de la Salud, Universidad Católica de Temuco, Temuco, Chile

**Área de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [amaury.farias@uvm.cl](mailto:amaury.farias@uvm.cl)

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**Socio Patrocinante:** Amaury Alejandro Fariás Cea and José Antonio Pino Reyes



### 31. EFFECT OF INTRANASAL VASOPRESSIN ON EXTINCTION AND RELAPSE INDUCED BY AMPHETAMINE AND ITS RELATION TO DOPAMINERGIC DYNAMICS IN THE NUCLEUS ACCUMBENS

Efecto de la vasopresina intranasal sobre la extinción y recaída inducida por anfetamina y su relación con la dinámica dopaminérgica en el núcleo accumbens

**Resumen:** Psychostimulant addiction represents a major public health concern, characterized by compulsive drug-seeking behavior and relapse phenomena associated with neurobiological alterations in reward circuits (Koob & Volkow, 2016). Among the modulatory systems involved, vasopressin (AVP) has been relatively underexplored, despite its role in regulating motivation, attachment, and stress responses, as well as its recently reported involvement in addictive behavior (Gárate-Pérez et al., 2024; Wronikowska-Denysiuk et al., 2023). Moreover, AVP exhibits functional sex differences (Albers, 2015; Fattore et al., 2008). In this study, we evaluated the effect of intranasal administration of AVP at different doses (20 and 40 µg) on extinction and relapse in an amphetamine-induced conditioned place preference (CPP) model. At the behavioral level, results showed preference acquisition in all groups, with no significant extinction observed following AVP 20 µg treatment, whereas the 40 µg dose showed a trend toward partial extinction, suggesting possible dose-dependent mechanisms. Neurochemical analysis of rats treated with AVP 20 µg revealed no significant changes in nucleus accumbens (Nac) glutamate or GABA tissue levels. However, increases in dopamine (DA) and a decrease in its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) were observed. These findings suggest that AVP may modulate presynaptic dopaminergic dynamics by reducing DA release or turnover, favoring its intracellular accumulation, which could contribute to the resistance to extinction observed.

**Autores:** González-Ortega C.1, Cáceres-Vergara D.1, Bahamonde T.1, Fuentes A.1, Sanhueza C.1, Reyes-Parada M.1, Sotomayor-Zárate R.2, Renard G.M.1  
**Afiliación:** 1. CIBAP, Escuela de Medicina, Facultad de Ciencias Médicas, Universidad de Santiago de Chile 2. Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile.  
**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [cristian.gonzalez.o@usach.cl](mailto:cristian.gonzalez.o@usach.cl)  
**Agradecimientos:** Acknowledgment: DICYT Regular N° 022401RG, VRIIC, Universidad de Santiago de Chile  
**Socio Patrocinante:** Dra. Georgina Renard

### 32. MODULATION OF KV3 POTASSIUM CHANNELS RESTORES FIRING DEFICITS IN PARVALBUMIN INTERNEURONS AFTER ADOLESCENT KETAMINE EXPOSURE.

La modulación de los canales de potasio Kv3 restaura los déficits de disparo en interneuronas parvalbúmina tras la exposición a ketamina durante la adolescencia

**Resumen:** Background: Adolescent NMDA receptor (NMDAR) hypofunction disrupts prefrontal cortical maturation and is linked to schizophrenia. Although it reduces parvalbumin (PV) interneuron density and expression, its impact on PV interneuron (PV-IN) intrinsic excitability remains unclear. We hypothesized that adolescent NMDAR hypofunction causes lasting PV-IN firing deficits contributing to adult medial prefrontal cortex (mPFC) dysfunction. Methods: Adolescent mice (postnatal days 45–51) received subanesthetic ketamine, and whole-cell recordings were performed from mPFC PV-INs in adulthood. We assessed intrinsic excitability, synaptic properties, and action potential (AP) kinetics, and tested rescue by AUT-1, a positive Kv3 potassium channel modulator. Results: • PV-INs exhibited impaired sustained high-frequency firing during prolonged stimulation, despite intact passive membrane and baseline firing properties. • Inhibitory synaptic input onto PV-INs (sIPSC frequency and amplitude) was unaltered. • Excitatory synaptic drive was enhanced, as evidenced by increased sEPSC frequency without changes in amplitude. • Administration of AUT-1, a Kv3 channel modulator, restored sustained firing and normalized action potential kinetics. Conclusion: Adolescent NMDAR hypofunction induces lasting PV interneuron excitability deficits, disrupting excitatory–inhibitory balance in the adult mPFC. Kv3 channel modulation by AUT-1 effectively restores firing dynamics, identifying a mechanistic target for rescuing cortical circuit function in schizophrenia and related disorders.

**Autores:** Guiffa, F.<sup>1</sup>; van Buuren, S.<sup>1</sup>; Aguilar, F.<sup>1</sup>; Fuenzalida, M.<sup>2,3</sup>

**Afiliación:** <sup>1</sup> Programa de Doctorado en Ciencias, mención Neurociencia, Universidad de Valparaíso, Valparaíso, Chile. <sup>2</sup> Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile. <sup>3</sup> Millennium Nucleus of Neuroepigenetics and Plasticity (EpiNeuro), Chile.

**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [felipe.guiffa@postgrado.uv.cl](mailto:felipe.guiffa@postgrado.uv.cl)

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**Socio Patrocinante:** NO.

### 33. EFFECTS OF EXPOSURE TO A HIGH-FAT AND SUCROSE DIET ON MU-OPIOID RECEPTOR LEVELS IN THE MESOCORTICOLIMBIC CIRCUIT OF MALE AND FEMALE RATS

Efectos de la exposición de una dieta alta en grasa y sacarosa sobre los niveles del receptor mu opioide en el circuito mesocorticolímbico de ratas de ambos sexos

**Resumen:** Currently, obesity is recognized as a global pandemic linked to dysregulation of brain systems controlling feeding behavior—those responding to metabolic need and to reward stimuli, known respectively as homeostatic and hedonic controls. The mesocorticolimbic circuit, central to hedonic regulation of food intake, includes neurons in the ventral tegmental area (VTA) that release dopamine to the nucleus accumbens (Nac) and prefrontal cortex (PFC), regions activated by rewarding stimuli such as drugs, sex, and food. Chronic exposure to hyperpalatable diets has been shown to downregulate dopaminergic neurotransmission. This circuit is also modulated by the endogenous opioid system, composed of opioid ligands and their receptors. Among them, the mu-opioid receptor (MOR) plays a major role in feeding behavior. Evidence suggests that high-fat, high-sugar diets reduce MOR expression at the messenger RNA (mRNA) level, reinforcing maladaptive eating patterns. However, most studies have focused on mRNA detection in male rodents, neglecting protein-level analysis and potential sex differences. In this study, we evaluated the effects of an obesogenic diet on MOR protein levels in the mesocorticolimbic circuit of male and female rats. No significant changes were detected in males, suggesting that exposure duration may be crucial for receptor modulation. Conversely, females exhibited a specific reduction of MOR in the PFC, indicating a potential loss of inhibitory and executive control over feeding behavior. These findings contribute novel evidence of sex-dependent regulation of MOR within the mesocorticolimbic circuit under conditions of diet-induced obesity.

**Autores:** Ibacache-Álvarez, J.; Velásquez, V.B.; Sotomayor-Zárate, R.

**Afiliación:** Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso

**Área de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [ramon.sotomayor@uv.cl](mailto:ramon.sotomayor@uv.cl)

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**Socio Patrocinante:** Ramón Eduardo Sotomayor Zárate.



### 34. DIALYSIS OF INTRACELLULAR A $\beta$ INCREASES EXCITABILITY AND AMPAR-MEDIATED TRANSMISSION IN D1+ NEURONS OF THE NUCLEUS ACCUMBENS

Diálisis de A $\beta$  intracelular incrementa la excitabilidad y transmisión mediada por AMPAR en neuronas D1+ del núcleo accumbens

**Resumen:** Alzheimer's disease (AD) is a neurodegenerative disease that affects brain regions such as the cortex and hippocampus. In advanced stages, it leads to severe cognitive impairment primarily associated with extracellular accumulation of beta-amyloid peptide (A $\beta$ ) and the formation of neurofibrillary tangles. However, growing evidence suggests that intracellular A $\beta$  (iA $\beta$ ) accumulation precedes the appearance of extracellular plaques and may play a crucial role in the early stages of pathogenesis. Interestingly, non-cognitive symptoms observed in early stages of AD have been linked to dysfunctions in basal nuclei, including the nucleus accumbens (nAc). Previous work from our laboratory showed presence of iA $\beta$  in accumbal neurons of 6-month-old APP/PS1 mice, a stage considered pre-symptomatic in this model, associated with increased neuronal excitability. Additionally, we previously observed that AMPA receptor-mediated transmission is augmented in cultured neurons from nAc. Nevertheless, the acute cellular effects of iA $\beta$  on accumbal neurons remain unexplored. In this study, we examined the effect of acute iA $\beta$  application on accumbal neurons using brain slices whole-cell patch-clamp recordings. We found that perfusion of iA $\beta$  rapidly increased the excitability of neurons expressing dopamine receptor 1 (D1+) Moreover, it selectively enhanced AMPAR-mediated excitatory transmission in D1+ but not in D1- neurons, suggesting a neuronal subtype-specific vulnerability and potential impairment of D1R-dependent signaling pathways. Together, these findings provide evidence that acute iA $\beta$  modulates both intrinsic excitability and excitatory synaptic transmission in the nAc. This supports the idea that iA $\beta$  accumulation contributes to accumbal dysfunction and may underlie the non-cognitive symptoms observed in early stages of AD.

**Autores:** Meza I. 1; Rifo-Lepe N. 1; Zambrano H. 1; González - Sanmiguel J. 1; Aguayo LG 1.  
**Afiliación:** 1. Laboratorio de Neurofisiología, Facultad de Ciencias Biológicas, Universidad de Concepción.

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [isaias.mezav@gmail.com](mailto:isaias.mezav@gmail.com)

**Agradecimientos:** FONDECYT 1221080

**Socio Patrocinante:** Luis Gerardo Aguayo Hernández

### 35. EFFECT OF SEX DIFFERENCES ON OLIGODENDROCYTE AND MYELIN DAMAGE INDUCED BY A PERINATAL ASPHYXIA MODEL IN WISTAR RATS

Efecto de las diferencias sexuales sobre la alteración de la mielinización inducida por un modelo de Asfisia Perinatal en ratas Wistar

**Resumen:** Introduction: Perinatal asphyxia (PA) is an obstetric complication that compromises neonatal oxygenation, leading to hypoxemia, hypercapnia, and acidosis. These events trigger oxidative stress, excitotoxicity, and neuroinflammation, resulting in hypoxic-ischemic encephalopathy (HIE), a major cause of neonatal mortality and neurological disability. Myelin, composed mainly of lipids and proteins such as Myelin-Associated Glycoprotein (MAG), is essential for axon-oligodendrocyte communication. In rats, postnatal day 7 (P7) represents a critical period of oligodendrocyte maturation and gliogenesis, making them particularly vulnerable to hypoxia. Objective: To determine whether sex differences influence the damage to mature oligodendrocytes and myelin induced by PA in Wistar rats at P7. Methodology: PA was induced by uterine immersion in water at 37 °C for 21 min, followed by resuscitation and clinical evaluation using an Apgar-like scale. Control and asphyctic pups were euthanized at P7, and coronal telencephalic sections were processed for immunofluorescence. Analyses were performed in the periventricular zone (PVZ), external capsule (EC), and corpus callosum (CC). Quantified parameters included the proportion of MAG<sup>+</sup>/DAPI cells, OL density per area, and MAG fluorescence intensity. Statistical analyses used Student's t-test, one-way ANOVA, or Mann-Whitney test ( $p < 0.05$ ), considering sex as a biological variable. Results: Asphyctic animals showed a significant reduction in the proportion of MAG<sup>+</sup> OLs compared to controls. No significant changes were observed

in overall OL density. MAG fluorescence intensity remained stable, except for trends toward reduction in EC and PVZ. These alterations appeared more pronounced in males, though not statistically significant. Conclusion: Perinatal asphyxia alters oligodendrocytes and telencephalic myelination, reducing MAG<sup>+</sup> cells with tendencies toward sex-related differences. A reduction of MAG<sup>+</sup> cells was confirmed in AS group.

**Autores:** Peña V. 1, 2, 3, 5; Neira S. 1, 2, 3, 5; Maripillán J. 2, 3; Ceriani R. 2, 3, 5; Morales P. 4; Herrera-Marschitz M. 4; Tapia-Bustos A. 1, 3, 4, 5. **Afiliación:** Laboratorio de Medicina Hipóxico-Isquémica, Escuela de Química y farmacia, Facultad de Farmacia, Universidad de Valparaíso.

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [valentina.pena@estudiantes.uv.cl](mailto:valentina.pena@estudiantes.uv.cl)

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**Socio Patrocinante:** Andrea Tapia Bustos.

### 36. EFFECTS OF GPR110 ACTIVATION ON THE MORPHOLOGICAL PROPERTIES OF SPINAL AND SENSORY NEURONS

Efectos de la activación del receptor GPR110 en propiedades morfológicas de neuronas espinales y sensoriales

**Resumen:** GPR110 is a G protein-coupled receptor (GPCR) activated by synaptamide (SYN), an endogenous derivative of docosahexaenoic acid (DHA). Previous studies have shown that SYN promotes neurite outgrowth in cortical neurons, suggesting a trophic role across the nervous system. However, the expression and function of GPR110 in the spinal cord and dorsal root ganglion (DRG), two key regions involved in nociceptive processing, remain unexplored. Moreover, despite its pharmacological potential as a target for novel neurotherapeutics, no synthetic GPR110 modulators have been reported. Here, we evaluate the expression of GPR110 in spinal and sensory neurons, to evaluate the cellular effects of its activation by SYN. In parallel, we performed an in silico screening to identify potential GPR110-interacting molecules among FDA-approved compounds. Using RT-qPCR and western blot, we detected both mRNA and protein expression of GPR110 in spinal and DRG preparations. Immunocytochemistry combined with confocal microscopy revealed that SYN application elicited a significant neurotrophic response, enhancing neurite outgrowth in both spinal (40 $\pm$ 6.48% over control,  $n = 38$ , 500 nM) and DRG neurons (101 $\pm$ 14.5% over control,  $n = 30$ , 1000 nM). Our in silico analyses identified octreotide acetate, vinblastine, and nefazodone, three drugs with known GPCR-modulating activity, as potential ligands capable of stably interacting with the orthosteric site of GPR110, exhibiting binding energies and RMSD values comparable to those of SYN. Collectively, these findings extend the known expression profile of GPR110 beyond the brain and highlight its functional significance in spinal and sensory neurons. We propose that activation of GPR110 by small molecules or repurposed drugs may represent a promising strategy for the development of innovative therapies targeting disorders of the spinal and sensory nervous systems.

**Autores:** Salgado-Martínez, B.; Gaete-Riquelme, K.; Contreras, O.V.; Sazo, A.; Marileo, A.M., Pérez, V.; Burgos, C.F.; Yévenes, G.E.

**Afiliación:** Department of Physiology, Faculty of Biological Sciences, University of Concepcion, Chile.

**Area de la Farmacología:** Neuropharmacology

**Dirección de Correo:** [besalgado2018@udec.cl](mailto:besalgado2018@udec.cl)

**Agradecimientos:** ANID-FONDECYT 1250856, ANID-FONDECYT 11240814.

**Socio Patrocinante:** Gonzalo Yévenes



### 37. NEUROPROTECTIVE EFFECTS OF COPAO EXTRACTS IN A MODEL OF PARKINSON'S DISEASE.

Efectos neuroprotectores de extractos de copao en un modelo de enfermedad de parkinson.

**Resumen:** La enfermedad de Parkinson implica la degeneración progresiva de neuronas dopaminérgicas en la sustancia negra por disfunción mitocondrial, estrés oxidativo y agregación de alfa-sinucleína. La pérdida de dopamina altera los circuitos ganglionares, generando síntomas motores. El tratamiento farmacológico incluye levodopa, agonistas dopaminérgicos, inhibidores de MAO-B y COMT, que buscan restaurar la señal dopaminérgica. Como alternativas, algunos productos naturales, como extractos ricos en antioxidantes (té verde, cúrcuma, resveratrol) y coenzima Q10, se investigan por su potencial neuroprotector; sin embargo, su eficacia clínica es limitada y deben considerarse solo como complementos bajo supervisión profesional para optimizar el manejo global del paciente afectado. Un fruto proveniente de cactáceas, o el copao, fruto del cactus silvestre *Eulychinia acida*, especie endémica del norte de nuestro país, posee múltiples características nutricionales que lo hacen interesante desde el punto de vista biomédico para llevar a cabo investigaciones en distintos ámbitos. Por tanto, se estudiaron los efectos de extractos de copao en ratas a las que se les indujo la Enfermedad de Parkinson usando 6-OHDA en el contenido de neuronas dopaminérgicas en la SN y estudios de marcha. Se encontró que los extractos de copao previenen la muerte celular de células dopaminérgicas de la SN y revierte los déficits motores asociados a la inyección de 6-OHDA en un 55%. Estos resultados sugieren efectos neuroprotectores de extractos de Copao en la Enfermedad de Parkinson

**Autores:** Rossi G. 1, Ortega L. 1, Carmona A. 2, Sandoval R. 1  
**Afiliación:** Laboratory of neurophology and Natural Products, Department of biomedical Sciences, Faculty of Medicine, Universidad Católica del Norte  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [rsandoval@ucn.cl](mailto:rsandoval@ucn.cl)  
**Agradecimientos:** FIC-R BIP-40041044-0  
**Socio Patrocinante:** NA

### 38. EFFECT OF CHEMOGENETIC INHIBITION OF DOPAMINERGIC NEURONS ON D2R FUNCTION AND LEVELS IN THE MOUSE NUCLEUS ACCUMBENS

Efecto de la inhibición quimiogénica de las neuronas dopaminérgicas sobre la función y los niveles de D2R en el núcleo accumbens del ratón

**Resumen:** Repeated administration of quinpirole (QNP), a D2 receptor agonist, induces compulsive behaviors and locomotor sensitization in rats, evidenced by a sustained increase in motor activity. QNP-induced sensitization involves the mesolimbic dopaminergic system, comprising dopaminergic neurons in the ventral tegmental area (VTA) projecting to the nucleus accumbens (NAc). QNP activates D2 receptors (D2R) on indirect medium spiny neurons, promoting locomotion, and on dopaminergic neurons, reducing dopamine release. Microdialysis and fast-scan cyclic voltammetry (FSCV) studies show reduced basal dopamine levels after QNP treatment compared with saline-treated controls, raising the question of whether D2-mediated dopaminergic inhibition is required for the development of locomotor sensitization. To address this, mesolimbic dopaminergic neurons were chronically inhibited using DREADD hM4Di in TH-Cre mice, then treated with the DREADD agonist compound 21 (C-21) for 5 days, followed by QNP for 9 consecutive days. Locomotion was assessed after each injection. In contrast to rats, QNP-treated mice did not develop locomotor sensitization, nor did C-21-pretreated animals; however, the latter group exhibited an increased inhibitory effect following the first dose of QNP, followed by an increase in locomotion. C-21 Western blot analysis of D2R in the NAc revealed no significant differences between groups; however, preliminary results of FSCV show increased presynaptic inhibitory effect of D2 receptors on dopamine release in the NAc. These results indicate that chronic dopaminergic inhibition alone does not reproduce the locomotor sensitization phenotype induced by QNP but reveals a sensitization of D2 receptor presynaptic autoinhibitory function. Future

approaches combining chemogenetic modulation with QNP administration could reveal stronger interactions between these mechanisms and clarify their relationship with OCD-like behaviors.

**Autores:** Urrea-Jara N.<sup>1,2,3</sup>, Solís J.F.<sup>1,3</sup>, Moreno R.<sup>1,3</sup>, Meza R.C.<sup>4</sup>, Moya P.R.<sup>4,5</sup>, Sotomayor-Zárate R.<sup>4,6</sup>, Escobar A.P.<sup>1,3,4,6</sup>  
**Afiliación:** Neurofisiopatología, Centro de neurobiología y fisiopatología integrativa, Facultad de Ciencias, Universidad de Valparaíso  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [nelson.urrea@postgrado.uv.cl](mailto:nelson.urrea@postgrado.uv.cl)  
**Agradecimientos:** CENFI, DIUV-CI 01/2024 -C-Estrés, DIUV CIDI 03/2024; Nucleo Milenio NCN 2023\_32 (EpiNeuro); INICI-UV, UVA 2299; and Ideas Mujer 2.0 INGE210003 to Escobar A.P. -FONDECYT Grants Iniciación#11240331 (APE); Regular: 1231012 (PRM) and 1240141 to (RSZ) -SIA Project 85240137 (RCM)  
**Socio Patrocinante:** Angelica Escobar

### 39. ENHANCED VOLTAGE-ACTIVATED SODIUM CURRENTS IN NEURONS OF THE NUCLEUS ACCUMBENS IN THE APP/PS1 MICE

Aumento de corrientes de sodio voltaje-activadas en neuronas del núcleo accumbens del ratón APP/PS1

**Resumen:** Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive impairment of cognitive functions such as memory and learning, along with non-cognitive symptoms. Recent evidence suggests that mood alterations and loss of motivation may represent early manifestations of the disease. These symptoms are associated with dysfunction in deep brain regions involved in reward processing, like the nucleus accumbens. Previous studies have found an increased excitability of accumbal neurons in transgenic model APP/PS1 at 6 months, although the underlying mechanisms remain unclear. Additionally, alterations in hippocampal and cortical neuron excitability have been associated with changes in the function of voltage-gated sodium channels in the Tg2576 mice. However, these ion channels have not been investigated in accumbal neurons in the context of AD. The aim of the present study was to analyze voltage-gated sodium currents in nucleus accumbens neurons using an in-vitro APP/PS1 model of AD. A voltage-clamp protocol was standardized to record sodium currents in APP/PS1 and control neurons at 10 and 15 days in-vitro (DIV). We measured peak current amplitude and density, calculated as the maximum current divided by the membrane capacitance. Statistical analysis was performed using an unpaired t-test in GraphPad Prism. The mean current density at -20 mV (10 DIV) was  $-21.8 \pm 3.2$  pA/pF in APP/PS1 neurons and  $-13.65 \pm 4.2$  pA/pF in controls ( $p > 0.05$ ). At 10 DIV, the values were  $-27.3 \pm 3.9$  and  $-13.5 \pm 2.4$  pA/pF ( $p < 0.05$ ) in APP/PS1 and controls neurons, respectively. These findings reveal a significant increase in sodium channel function in APP/PS1 accumbal neurons at 15 DIV, highlighting altered intrinsic excitability as a potential early physiological signature and therapeutic target in AD.

**Autores:** Zambrano H. M.1; Meza I.1; Saavedra P.1; Riffo N. 1; Aguayo L. A.1  
**Afiliación:** 1 Laboratory of Neurophysiology, Department of Physiology, Faculty of Biological Sciences, University of Concepción  
**Area de la Farmacología:** Neuropharmacology  
**Dirección de Correo:** [hezambrano2020@udec.cl](mailto:hezambrano2020@udec.cl)  
**Agradecimientos:** FONDECYT 1221080  
**Socio Patrocinante:** Luis Gerardo Aguayo Hernández

#### 40. COST-EFFECTIVENESS ANALYSIS OF PLATFARMA SOFTWARE TO PREVENT PRM IN APS VALDIVIA

Análisis de costo-efectividad de software PlatFarma para prevenir PRM en APS Valdivia

##### Resumen:

**Introduction:** Drug-related problems (DRPs) generate preventable emergencies and hospitalizations that overburden the Chilean healthcare system. Pharmacovigilance clinical support softwares are digital tools that help healthcare professionals identify interactions and adverse effects and optimize treatments to improve patient safety. In this context, PlatFarma integrates clinical and analytical alerts to support safe prescribing for patients with chronic conditions. **Objective:** To conduct a cost-effectiveness analysis of implementing the pharmacovigilance software "PlatFarma" compared to the current practice (status quo) in municipal primary healthcare centers (PHC) in the Valdivia commune, from a public health system perspective over two years, to prevent DRP-related hospitalizations (DRP-RH). **Methodology:** Cost-effectiveness analysis using a decision tree (TreeAge Pro®). **Population:** 9.605 chronic patients ≥60 years of age from the municipal PHC. **Costs:** software use training, implementation, and operation (personnel, hardware, backup, and audits) plus hospitalization costs for DRPs. **Effectiveness:** probabilities and reductions in hospitalizations based on clinical trials of electronic decision support in polypharmacy. **Primary outcome:** Incremental cost-effectiveness ratio (ICER) (cost per DRP-RH avoided). **Univariate sensitivity analysis** was performed. **Results:** The intervention was more effective and less costly, with savings of CLP\$4.175.004 per DRP-RH avoided in the intervention group compared to the status quo. The intervention was more effective and less costly, ranking as the dominant strategy based on the ICER calculation, with savings of CLP\$4.175.004 per DRP-RH avoided. **Sensitivity analyses** confirmed the robustness of the results. **Conclusions:** PlatFarma is a cost-effective alternative for the healthcare system, reducing DRP-RH in chronic primary care patients. These findings support its implementation at scale.

**Autores:** García E.1; Münzemayer M.2; Jerez R. 3; Vera A.1

**Afiliación:** 1. Escuela de Medicina, Facultad de Medicina, Universidad Austral de Chile 2. Instituto de Salud Pública, Facultad de Medicina, Universidad Austral de Chile 3. Escuela de Ingeniería Civil Industrial, Facultad de Ciencias de la Ingeniería, Universidad Austral de Chile

**Área de la Farmacología:** Pharmaco-economics

**Dirección de Correo:** [esanchez@uach.cl](mailto:esanchez@uach.cl)

**Agradecimientos:** InES I + D 2021 UACH INID 210009; DESAM-Valdivia, Equipo de Informática del Núcleo HASFa

**Socio Patrocinante:** Eliana Sánchez Montoya

#### 41. TREND IN PSYCHOTROPIC DRUG CONSUMPTION IN CHILE AND ADHERENCE TO PHARMACOTHERAPY IN GES PATIENTS WITH MENTAL HEALTH DISORDERS

Tendencia de consumo de psicotrópicos en Chile y adherencia a la farmacoterapia en pacientes GES por enfermedades de salud mental

**Resumen:** **Introduction:** Psychotropic drugs are essential for managing mental health disorders. Between 2018 and 2022, the mental illness covered by Chile's GES program included major depression, bipolar disorder, and schizophrenia. However, there is limited evidence on consumption trends of these drugs, and no national reports based on community pharmacy data. **Aim:** To evaluate the levels and trends in psychotropic medication consumption dispensed in community pharmacies in Chile between 2018 and 2022. **Methodology:** A cross-sectional study was conducted using IQVIA community pharmacy databases, covering 93% of the retail market and serving 28% of the population. Annual sales were converted into Defined Daily Doses per 1,000 inhabitants per day (DDD/1,000 inhabitants/day or DHD), following WHO standards. Market share and annual cost per DDD in US dollars were also analyzed. **Results:** Overall psychotropic consumption rose by 62%, from 180 to 291 DHD. Antidepressant use increased by 74%, dominated by selective serotonin reuptake inhibitors (SSRIs, 84%), particularly sertraline (46%) and escitalopram (43%). Sleep inducers and sedative antipsychotics grew by 140% and 99%, respectively. Clonazepam was the most consumed psychotropic (72% of benzodiazepine use), followed by sertraline. Antidepressants accounted

for the largest market share (56%), followed by benzodiazepines (15%) and Z-drugs (12%). The cost per DDD decreased for most drug groups, except benzodiazepines. **Conclusion:** From 2018 to 2022, psychotropic medication consumption in Chile increased by over 60%, mainly driven by antidepressants and sedatives. These findings suggest expanded therapeutic access and possibly greater recognition of mental health needs. However, the lack of information regarding prescription quality and rational use highlights the need for strengthened monitoring and stewardship to ensure safe and effective pharmacotherapy in the Chilean population.

**Autores:** Leal-Pineda S. 1,2; Gutiérrez-Cáceres C. 1; Espinoza-Muñoz S. 1; Cerpa L. 3,4; Martínez M. 1

**Afiliación:** 1.Department of Pharmaceutical Sciences and Technology, Faculty of Chemical and Pharmaceutical Sciences, University of Chile. 2.Department of Pharmacy, Faculty of Pharmaceutical and Food Sciences, University of Antofagasta. 3.Laboratory of Chemical Carcinogenesis and Pharmacogenetics (CCF), Department of Basic and Clinical Oncology, University of Chile. 4.RELIVAF – Santiago, Chile.

**Área de la Farmacología:** Pharmacoepidemiology

**Dirección de Correo:** [sofia.leal@udea.edu.co](mailto:sofia.leal@udea.edu.co)

**Agradecimientos:** We thank the Salcobrand pharmacy chain for providing the data needed to conduct the analyses.

**Socio Patrocinante:** Leslie Cerpa

#### 42. REAL-WORLD DATA ON PHARMACOTHERAPY AND MONITORING IN OLDER ADULTS WITH HYPERTENSION AND/OR DYSLIPIDEMIA FROM PRIMARY CARE IN VALDIVIA, CHILE.

Datos del mundo real sobre farmacoterapia y monitoreo en adultos mayores con hipertensión y/o dislipidemia, procedentes de la atención primaria de Valdivia, Chile

**Resumen:** **Introduction:** Population aging is a global trend that is also evident in Chile, where the proportion of older adults continues to rise. This demographic shift contributes to a growing burden of non-communicable chronic diseases (NCDs). Managing these conditions in older adults presents an ongoing public health challenge, particularly at the primary care level. **Methodology:** Using real-world data (RWD) provided by the Municipal Health Department of Valdivia, we analyzed anonymized clinical records of patients aged 65 and older with a diagnosis of arterial hypertension and/or dyslipidemia between 2017 and 2022. **Pharmacotherapeutic characterization** was performed using RStudio and Microsoft Excel 365, addressing five key areas: polypharmacy (defined as the use of ≥5 medications), anticholinergic burden (AB), diagnostic coexistence, compliance with clinical monitoring, and proportion of clinically compensated patients. The study was approved by the Ethics Committee of the Los Ríos Health Service. **Results:** The study included 11,716 patients, 63.7% of whom were women. Polypharmacy was observed in 32.1% of patients. Most prescriptions (83.7%) had no anticholinergic burden, while 13.9% were classified as high. Frequent coexisting diagnoses included diabetes, hypothyroidism, and osteoarthritis. Monitoring compliance was observed in only 33.2% of patients. Clinical compensation—defined as achieving recommended targets for blood pressure (<140/90 mmHg) and/or total cholesterol (<200 mg/dL), depending on diagnosis—was reached by just 19.8% of patients. Among those classified as high cardiovascular risk, compensation rates were particularly low. **Conclusions:** The use of local clinical data offered valuable insights into the therapeutic complexity of older adults in primary care. These findings highlight the need to strengthen strategies for effective NCD management at the primary care level.

**Autores:** Arroyo-Vargas K. 1, 3; Lagos-Morales X. 2, 3; Sánchez-Montoya E. 2, 3

**Afiliación:** 1 Escuela de Química y Farmacia, Facultad de Ciencias Universidad Austral de Chile 2 Instituto de Farmacia, Facultad de Ciencias Universidad Austral de Chile 3 Núcleo de Innovación HASFa: Herramientas Avanzadas para la Seguridad en la Farmacoterapia-UACH.

**Área de la Farmacología:** Pharmacoepidemiology

**Dirección de Correo:** [esanchez@uach.cl](mailto:esanchez@uach.cl)

**Agradecimientos:** InES I + D 2021 UACH INID 210009; DESAM-Valdivia, Equipo de Informática del Núcleo HASFa-UACH.

**Socio Patrocinante:** Eliana Sánchez Montoya

#### 43. DEVELOPMENT OF EARLY-WARNING CRITERIA FOR POTENTIALLY INAPPROPRIATE PRESCRIPTIONS IN ADULTS UNDER 60 USING REAL-WORLD DATA AND THE OBSFARMA PHARMACOVIGILANCE PLATFORM IN VALDIVIA

Desarrollo de criterios de alerta temprana para prescripciones potencialmente inapropiadas en adultos menores de 60 años utilizando datos del mundo real y la plataforma de farmacovigilancia OBSFarma en Valdivia

**Resumen:** Pharmacovigilance has traditionally been developed for the geriatric population, creating a critical gap in the detection of pharmacotherapeutic risks among individuals under 60 years old with early-onset chronic diseases such as asthma, diabetes and hypertension. Since Chile's aging population is projected to have 32% of its people aged 60 or older by 2050, it is essential to identify potentially inappropriate medications (PIMs) and prescribing cascades at an early stage, as their timely detection can prevent the progression toward polypharmacy and complications associated with aging. However, the healthcare system still maintains a reactive approach, focused on managing consequences rather than preventing risks. This study aims to develop pharmaceutical alert criteria applicable to non-geriatric populations by integrating scientific evidence with real-world data (RWD) provided by the DESAM-Valdivia (2017–2022). A systematic literature review was conducted following the PRISMA model and considering pharmacovigilance alerts issued by the Public Health Institute of Chile (ISP). The quantification of PIP was performed using OBSFarma, a pharmacovigilance web platform developed by the HASFa-UACH research group, in order to test its functionality in the automated detection of risky prescriptions. The most relevant findings included prolonged use of benzodiazepines and proton pump inhibitors, cumulative glucocorticoid exposure  $\geq 1$  g/year, the omeprazole–benzodiazepine interaction, and high cumulative doses of hydrochlorothiazide associated with skin cancer. Additionally, sustained use of salbutamol without concomitant inhaled corticosteroids was observed, contrary to GEMA guidelines. It is concluded that adapting explicit pharmacovigilance criteria to adults with early-onset chronic diseases is both feasible and urgent. OBSFarma demonstrated strong potential to enhance therapeutic safety and promote a preventive approach to pharmacovigilance within the primary health care.

**Autores:** Sáez Gallegos S. 1, 6; Cifuentes B. 2, 6; Corbalán Pösel J. 3, 6; Veas Castillo L. 4, 6; Sánchez Montoya E. 5, 6.

**Afiliación:** 1. Escuela de Química y Farmacia, Fac. de Ciencias, Universidad Austral de Chile (UACH). 2. Escuela de Ing. Civil Informática, Fac. de Cs. de la Ingeniería, UACH. 3. Inst. de Salud Pública, Fac. de Medicina, UACH. 4. Inst. de Informática, Fac. de Cs. de la Ingeniería, UACH. 5. Inst. de Farmacia, Fac. de Ciencias, UACH. 6. Núcleo de innovación HASFa, UACH.

**Area de la Farmacología:** Pharmacoepidemiology

**Dirección de Correo:** [esanchez@uach.cl](mailto:esanchez@uach.cl)

**Agradecimientos:** InES I + D 2021 UACH INID 210009 para Núcleo HASFa: Herramientas Avanzadas para la Seguridad en la Farmacoterapia; Departamento de Salud Municipal (DESAM)-Valdivia.

**Socio Patrocinante:** Eliana Sánchez Montoya

#### 44. ANTIMICROBIAL PRESCRIPTION PATTERNS IN PRIMARY HEALTH CARE IN VALDIVIA (CHILE) USING THE OBSFARMA PHARMACOVIGILANCE WEB PLATFORM- A RETROSPECTIVE ANALYSIS OF 2017–2022.

Patrones de prescripción de antimicrobianos en atención primaria de salud en Valdivia (Chile) utilizando la plataforma web de farmacovigilancia OBSFarma: un análisis retrospectivo de 2017 a 2022.

##### Resumen:

**Introduction:** Antimicrobial resistance (AMR) is a significant global and national public health threat. In Chile, approximately 70% of antimicrobials are prescribed at the Primary Health Care (PHC) level, and up to 40% of these prescriptions may be inappropriate. In response, the Ministry of Health of Chile has promoted the Antimicrobial Stewardship Program (PROA) and the Technical Guidance for the Use of Antibiotics in Community-Acquired Infections (2021); however, their territorial impact remains to be evaluated. **Methodology:** A retrospective descriptive analysis of antimicrobial prescriptions was conducted in PHC dependent of DESAM-Valdivia for the 2017–2022 period. Information

obtained was evaluated using the software OBSFarma, a pharmacovigilance observatory developed by the healthcare innovation hub HASFa-UACH. Prescription appropriateness was assessed against MINSAL clinical guidelines and Beers Criteria for older adults. Results: Inappropriate use of cefuroxime (classified under the Watch group in the WHO AWaRe) was identified in urinary tract infections among women aged 0–44 years (N=4). The use of ceftriaxone displayed a high proportion of inappropriate prescriptions: 68% in 2019, 67.3% in 2020, 62% in 2021, and 78% in 2022, coinciding with the implementation of the Technical Guidance. Amoxicillin/clavulanic acid was most frequently prescribed between May and July, mainly for acute bronchitis (J20), a condition that does not require antibiotic therapy. In accordance with Beers Criteria, only one fluoroquinolone (ciprofloxacin) prescription was recorded in patients over 65 years of age. Conclusion: The use of OBSFarma enabled the visualization of historical prescribing patterns and potential deviations from national guidelines. Ongoing territorial analyses will serve to assess the impact of PROA policies and guide future interventions in primary healthcare.

**Autores:** Sepúlveda-Solis C. 1, 6; Cifuentes-Peña B. 2, 6; Corbalán Pössel J. 3, 6; Veas-Catillo L. 4, 6; Sánchez-Montoya E. 5, 6.

**Afiliación:** 1. Esc. de Química y Farmacia, Fac. de Ciencias, U. Austral de Chile (UACH). 2. Esc. de Ing. Civil Informática, Fac. de Cs. de la Ingeniería, (UACH). 3. Inst. de Salud Pública, Fac. de Medicina, (UACH). 4. Inst. de Informática, Fac. de Cs. de la Ingeniería, (UACH). 5. Inst. de Farmacia, Fac. de Ciencias, (UACH). 6. Núcleo HASFa-UACH. **Area de la Farmacología:** Pharmacoepidemiology. **Correo:** [esanchez@uach.cl](mailto:esanchez@uach.cl).

**Agradecimientos:** InES I + D 2021 UACH INID 210009; Departamento de Salud Municipal (DESAM)-Valdivia, Equipo de Informática del Núcleo de innovación HASFa Herramientas Avanzadas para la Seguridad en la Farmacoterapia, Universidad Austral de Chile.

**Socio Patrocinante:** Eliana Sánchez Montoya

#### 45. PRO-RESOLVING EFFECT OF MARESIN 1 ON THE NLRP3 INFLAMMASOME IN HEPATIC DAMAGE INDUCED BY DIABETES

Efecto proresolutivo de Maresina-1 sobre el inflammasoma NLRP3 en daño hepático por diabetes

**Resumen:** Metabolic dysfunction-associated fatty liver disease (MAFLD) is currently the most prevalent liver disease worldwide, and its incidence increases significantly in the presence of metabolic disorders such as type 2 diabetes mellitus (T2DM). Both conditions are linked to the development of chronic inflammation, in which the NLRP3 inflammasome has been implicated as a key mediator of pathological progression. Recently, it has been proposed that the active resolution of inflammation may be mediated by endogenous compounds derived from omega-3 fatty acids, such as Maresin-1 (MaR1), which exhibits potent pro-resolving and anti-inflammatory properties. In this context, the aim of this study was to evaluate the hepatoprotective action of MaR1 through the inhibition of the NLRP3 pathway in liver tissue using a murine model of metabolic damage induced by T2DM. Male Sprague-Dawley rats were fed with a high-fat diet to induce metabolic damage and received streptozotocin (STZ, 50 mg/kg) to trigger T2DM. Subsequently, MaR1 (4 ng/g) was i.p. administered, and the gene and protein expression of key components of the NLRP3 pathway were assessed. MaR1 treatment significantly reduced the expression of NLRP3, TLR4, IL-1 $\beta$ , IL-18, and Gasdermin D, both at the transcriptional and protein levels. Moreover, a decrease in NF- $\kappa$ B activation and an increase in anti-inflammatory markers were observed, suggesting a general pro-resolving effect. These findings indicate that MaR1 exerts a hepatoprotective effect by modulating chronic inflammation mediated by NLRP3 in a model of hepatic injury induced by T2DM.

**Autores:** Marín-Sanhueza P. 1, 2; Berrocal-Navarrete F. 1, 4; Muñoz-Carrasco N. 1, 3; Quiñones-San Martín M. 1, 5; Zúñiga-Hernández J. 1

**Afiliación:** 1. Laboratory of pharmacology and Physiology, Faculty of Health Sciences, University of Talca, Av. Lircay s/n, Talca 3460000, Chile. 2. Institute of Biological Sciences, School of Biochemistry, University of Talca, Av. Lircay 3 School of Biotechnology Engineering, Faculty of Agricultural and Forestry Sciences, Universidad Católica del Maule, Av. San Miguel 3605, Talca, Chile. 4. Doctoral Program in

**Area de la Farmacología:** Pharmacokinetics / drug metabolism

**Dirección de Correo:** [pmarin19@alumnos.utalca.cl](mailto:pmarin19@alumnos.utalca.cl)

**Agradecimientos:** Proyecto beca ANID N°21220031 (Matías Quiñones San Martín)

**Socio Patrocinante:** Jessica Zúñiga Hernández

#### 46. Acute effects of consumption of polyphenol-rich food on plasma antioxidant capacity in healthy young adults

Efectos agudos del consumo de alimentos ricos en polifenoles sobre la capacidad antioxidante del plasma en adultos jóvenes sanos

##### Resumen:

**Introducción:** Dietary polyphenols are bioactive compounds with antioxidant and potential metabolic benefits. Calafate, an endemic berry from southern Chile, is a natural source rich in anthocyanins and phenolic acids. This study aimed to evaluate changes in plasma antioxidant capacity after the acute consumption of a polyphenol-rich food derived from calafate. **Methodology:** A functional food was developed using Calafate-derived foods, characterized by ultra-high-performance liquid chromatography coupled to diode array detection and quadrupole time-of-flight mass spectrometry (UHPLC-DAD-QTOF). Its antioxidant capacity was determined through Folin–Ciocalteu, CUPRAC, and ORAC assays, showing values of  $2289.78 \pm 42.10$  mg gallic acid equivalents (GAE)/L,  $5792.91 \pm 138.31$  mg Trolox equivalents (TE)/L, and  $6519.46 \pm 152.12$  mg TE/L, respectively. In a pilot study, healthy young men (20–30 years) consumed the product following an overnight fast. Blood samples were collected at baseline and at 0.5, 1-, 2-, and 4-hours post-consumption to determine plasma antioxidant capacity and glucose concentrations. **Results:** Although no statistically significant changes were observed, results showed a consistent trend toward increased plasma antioxidant capacity two hours after intake. This tendency aligns with the expected absorption kinetics of dietary polyphenols but may have been masked by high interindividual variability. The postprandial glucose curve remained stable, suggesting that the product does not acutely affect glycemic homeostasis. **Conclusion:** These findings support the potential of Calafate-derived foods as natural sources of bioactive polyphenols and their application in developing functional foods aimed at improving antioxidant status.

**Autores:** Opazo M. 1-2; Nova D. 1; Olivares L.3; Hermosilla P.1 ; Vidal F. 1; Bustamante L. 1; Radjkovic C.3 ; Mardones C.1

**Afiliación:** 1 Metabocrom Laboratory, Department of Instrumental Analysis, Faculty of Pharmacy, University of Concepción 2 MSc(c) in Clinical Biochemistry and Immunology, Department of Clinical Biochemistry, Faculty of Pharmacy, University of Concepción 3 Department of Clinical Biochemistry, Faculty of Pharmacy, University of Concepción

**Area de la Farmacología:** Pharmacokinetics / drug metabolism

**Dirección de Correo:** [maopazo2019@udec.cl](mailto:maopazo2019@udec.cl)

**Agradecimientos:** FONDECYT REGULAR N° 1230625

**Socio Patrocinante:** Dra. Claudia Mardones Peña Dr. Jorge Fuentealba Arcos

#### 47. ADENOSINE A2B RECEPTOR ANTAGONISM SENSITIZES GLIOBLASTOMA STEM-LIKE CELLS TO CHEMOTHERAPY BY MODULATING MESENCHYMAL TRANSITION

El antagonismo del Receptor de Adenosina A2B sensibiliza a las "Glioblastoma Stem-like Cells" a la quimioterapia mediante la modulación de la transición mesenquimal

**Resumen:** Glioblastoma (GB) is the most common and aggressive primary malignant brain tumor in adults, characterized by a high mortality rate attributed to its pronounced resistance to therapeutic interventions. This aggressiveness and therapeutic resistance are linked to a population of cells known as Glioblastoma Stem-like Cells (GSCs), which can be classified into two cellular subtypes: proneural (PN-GSCs, CD133<sup>+</sup>) and mesenchymal (MES-GSCs, CD44<sup>+</sup>). The proneural-to-mesenchymal transition (PMT) plays a crucial role in tumor progression and chemoresistance. In GB, high levels of extracellular adenosine (ADO) are generated, particularly in hypoxic regions, leading to activation of the low-affinity adenosine A2B receptor (A2BAR). This activation promotes PMT progression and enhances the aggressive phenotype of GSCs. Pharmacological antagonism of A2BAR represents a potential strategy to modulate this transition and improve therapeutic responses. We hypothesize that selective A2BAR antagonism under hypoxic conditions negatively regulates mesenchymal markers in GSCs, thereby promoting sensitization to temozolomide (TMZ) treatment. **Methods:** GSCs were treated with the selective A2BAR antagonist (LBT1) under normoxic and hypoxic conditions. Gene expression was evaluated at 8, 24, and 48 hours by RT-qPCR, whereas protein levels were analyzed at 48 hours by Western blot. Cell viability was assessed

after 48 hours of treatment with LBT1 (500nM) and temozolomide (TMZ, 400μM) under normoxic and hypoxic conditions. **Results:** A2BAR antagonism reduced SNAI1 mRNA levels under normoxia and hypoxia and increased CD133, while decreasing CD44 protein levels relative to normoxic control. Moreover, LBT1 chemosensitized GSCs to TMZ treatment. **Conclusions:** A2BAR antagonism under hypoxic conditions, reduces expression of MES phenotype markers and suggests a shift toward less aggressive PN phenotype, emerging as a promising therapeutic strategy to address malignant PMT in GSCs by promoting TMZ chemosensitization.

**Autores:** Álvarez F.1,2; Villagrán V.1.; Venegas F.1,2; Silva P.1,2; San Martín R.3., Cuevas A.1,2.; Quezada C.1,2

**Afiliación:** 1. Laboratorio de Biología Tumoral, Facultad de Ciencias, Universidad Austral de Chile. 2. Instituto Milenio de Inmunología e Inmunoterapia, Universidad Austral de Chile (IMI). 3. Laboratorio de Patología molecular, Facultad de Ciencias, Universidad Austral de Chile.

**Area de la Farmacología:** Chemotherapy

**Dirección de Correo:** [alexei.cuevas.zhbankova@alumnos.uach.cl](mailto:alexei.cuevas.zhbankova@alumnos.uach.cl)

**Agradecimientos:** FONDECYT Postdoctorado 3240689 (AC) and FONDECYT Regular 1241275 (CQ) and ICM-ANID, ICN2021\_045 (CQ) IMI.

**Socio Patrocinante:** Dr. Rodrigo Lopez Muñoz (UACH)

#### 48. SIMVASTATIN POTENTIATES THE EFFECT OF THE INHIBITOR MRTX1133 IN TUMOR CELLS CARRYING THE KRAS-G12D MUTATION

Simvastatina potencia el efecto del inhibidor MRTX1133 en células tumorales portadoras de la mutación KRAS-G12D

**Resumen:** La mutación KRAS-G12D es una de las mutaciones driver más frecuentes en cáncer de páncreas y pulmón, asociada a mal pronóstico y resistencia terapéutica. Esta mutación activa de forma constitutiva vías de señalización pro-oncogénicas, como MAPK/ERK, que promueven la proliferación y supervivencia celular. Aunque se han desarrollado inhibidores específicos de KRAS-G12D, su eficacia clínica se ve limitada por la resistencia adquirida de las células tumorales. Las estatinas, inhibidores de la 3-hidroxi-3-metilglutaril-CoA reductasa (HMGCR), bloquean la vía del mevalonato (MVA), reduciendo metabolitos esenciales para la prenilación de proteínas RAS (incluyendo KRAS), proceso necesario para su anclaje y función en la membrana plasmática, modulando así la señalización oncogénica de KRAS. El objetivo de este trabajo es evaluar el efecto sinérgico entre un inhibidor de KRAS-G12D (MRTX1133) y un inhibidor de HMGCR (Simvastatina) en líneas celulares SK-LU-1, PANC-1 y SW1990 portadoras de KRAS-G12D. Los niveles de p-ERK se analizaron mediante Western blot, la viabilidad celular mediante el ensayo de reducción de MTT, y el sinergismo farmacológico con los programas Combeneffit y SynergyFinder. El tratamiento con MRTX1133 redujo los niveles de p-ERK, los cuales se recuperaron a las 24 horas; esta recuperación fue retrasada por simvastatina. Por su parte, simvastatina muestra un leve efecto sobre la fosforilación de ERK. En cultivos en monocapa, simvastatina disminuyó la viabilidad celular y mostró un efecto sinérgico con MRTX1133. Los resultados sugieren que Simvastatina potencia la actividad antitumoral del inhibidor MRTX1133 en células con KRAS-G12D, posiblemente al interferir con la prenilación de KRAS y mantener su señalización inactiva.

**Autores:** Francisco Diaz-Lazcano1, Carina Chipon1, Alberto Maestre1, Rodrigo López-Muñoz1

**Afiliación:** Instituto de Farmacología y Morfofisiología

**Area de la Farmacología:** Chemotherapy

**Dirección de Correo:** [francisco.diaz01@alumnos.uach.cl](mailto:francisco.diaz01@alumnos.uach.cl)

**Agradecimientos:** FONDECYT 1241400

**Socio Patrocinante:** Rodrigo Lopez Muñoz

#### 49. ACETYLCHOLINESTERASE SUBSTRATE ANALYSIS FOR IMPROVE THE ORGANOPHOSPHATE DETECTION IN AN OUT-OF-THE-LAB SYSTEM

Análisis de sustratos de la acetilcolinesterasa para la mejora de dispositivos de detección de organofosforados en sistemas out-of-the lab

**Resumen:** Chronic exposure to organophosphate pesticides remains a serious concern in agricultural areas, especially where access to rapid, on-site diagnostic tools is limited. Motivated by this challenge, we developed and tested a portable paper-based colorimetric system designed to detect acetylcholinesterase (AChE) activity, which serves as an indirect biomarker of exposure. The main goal was to fine-tune experimental conditions to improve the device's sensitivity, focusing on three key variables: reaction time, plasma volume, and substrate concentration. Experiments were carried out using LF-1 strips embedded with increased concentrations of the acetylcholine chloride substrate, and human plasma samples—both activated and inactivated—were applied in volumes between 2 and 10  $\mu$ L. The reaction was visualized using the colorimetric technique of bromothymol blue stain, which allowed clear differentiation between samples with normal and reduced AChE enzymatic activity. Color changes were consistent and visible to the naked eye, and further confirmed under microscopy. To support objective interpretation, a portable RGB reader was integrated into the system, enabling quantification of color intensity in the reaction zone. Field validation with human samples confirmed the system's usability in "out-of-the-lab" settings. The combination of simple materials, reproducible results, and digital readout makes this approach a promising tool for epidemiological surveillance and early detection of organophosphate poisoning in vulnerable communities. Overall, this work contributes to the development of low-cost biomedical technologies that are easy to use, adaptable to variable environmental conditions, and capable of bridging the gap between laboratory diagnostics and real-world needs.

**Autores:** Fernanda Berrocal-Navarrete<sup>1,2</sup>; Paz Marín Sanhueza<sup>1,3</sup>; Carlos Zambrá, Jessica Zúñiga-Hernández<sup>1</sup>

**Afiliación:** 1 Laboratory of Pharmacology and Physiology, Faculty of Health Sciences, University of Talca. 2 Doctorate in Biomedical Sciences Program, Faculty of Health Sciences, University of Talca. 3 Institute of Biological Sciences, School of Biochemistry, University of Talca. 4 Laboratory of Process Engineering, Faculty of Engineering, University of Talca

**Area de la Farmacología:** Toxicology

**Dirección de Correo:** [nanda.berrocal19992@gmail.com](mailto:nanda.berrocal19992@gmail.com)

**Agradecimientos:** Project FondecyT2410045.

**Socio Patrocinante:** Jessica Zúñiga Hernández

#### 50. USING IN VIVO ASSAYS AND METABOLOMICS IN ZEBRAFISH TO DETECT SPECIFIC TOXICITY AND POTENTIAL BIOMARKERS OF EXPOSURE TO LIPOPHILIC MARINE BIOTOXINS.

Ensayos in vivo y metabolómica en pez cebra para la detección de toxicidad específica y posibles biomarcadores de exposición a toxinas marinas lipofílicas.

##### Resumen:

Natural and artificial pollutants put at risk human and ecosystem health. Increment of harmful algal blooms (HABs) is a major public health concern due to risk of intoxication and diseases associated to repeated exposure. In Chile, main toxins in HABs are Paralytic and Diarrhetic Shellfish Poisons (DSP). DSP are lipophilic toxins including Okadaic acid (OA) and, Dinophysistoxins. Other commonly co-extracted toxins are associated to hepatotoxicity, cardiotoxicity, and immunotoxicity: Pectenotoxins (PTX) and Yessotoxins (YTX). Detect and identify these lipophilic marine toxins (LMTs) is challenging due to high cost of analytical methods and the lack of specificity and bioethical concerns about the mouse-bioassay. Zebrafish (*Danio rerio*) bioassays can be valuable tools to detect biotoxins since can reveal in vivo effect profiles of molecules. We investigated the larval and embryonic responses to three LMTs: OA, PTX2-b, and YTX-c to detect specific effects previously associated with these toxins and their modes of action (MOAs) in cells

and mammals. Our results indicate that these LMTs produced changes in lipid droplet size and increases leukocytes in the liver region. YTX, which is cardiotoxic in mammals, significantly altered cardiac and vascular parameters in embryos; OA that is neurotoxic induced developmental neuromotor and neural tube alterations; while PTX that depolymerize microfilaments, may be affecting neutrophil cells migration in a controlled tissue damage model. Additionally, the metabolome of whole larvae was analyzed to identify potential biomarkers of exposure using this alternative model. Changes in the metabolome were detected by analyzing both hydrophobic and hydrophilic fractions. Data obtained from our UHPLC-QTOF-based analysis revealed alterations in specific molecules associated with sphingolipid and retinoic acid metabolism, among others, with distinct profiles for each toxin.

**Autores:** De la Paz Javiera F. 1, Olivares-Caro L. 2, Roa- Ulloa S. 1, Gonzalez A. 1, Fuentealba P. 3, Zambrano N3, Mardones c.4, Bustamante L., Yáñez-Bailey P.1,3, Llanos-Rivera A.3.

**Afiliación:** Laboratory of Embryotoxicology and Development-Environment Interaction (LEIDA), Department of Cell Biology, Faculty of Biological Sciences, University of Concepción, Chile.

**Area de la Farmacología:** Toxicology

**Dirección de Correo:** [idelapaz@udec.cl](mailto:idelapaz@udec.cl)

**Agradecimientos:** FONDEF-Idea ID20110078 and VRID 2024001145ini.

**Socio Patrocinante:** Patricio Ilturriaga (UFRO)

#### 51. DETERMINATION OF ALTERNARIA SPP. MYCOTOXINS IN PLANT-BASED PRODUCTS BY LC-ESI-MS/MS: ANALYTICAL TOOL FOR HUMAN EXPOSURE AND TOXICOKINETIC STUDIES

Determinación de micotoxinas de *Alternaria* spp. en productos vegetales mediante LC-ESI-MS/MS: Herramienta analítica para estudios de exposición humana.

**Resumen:** *Alternaria* species produce secondary metabolites known as mycotoxins, with recognized carcinogenic, mutagenic, and cytotoxic effects capable of disrupting key cellular pathways and metabolic processes. Their presence in plant-based products consumed by humans represents a potential health risk and highlights the need for reliable analytical tools for studies of human exposure and toxicological assessment. Among the most relevant mycotoxins are tenuazonic acid (TeA), alternariol (AOH), alternariol monomethyl ether (AME), and tentoxin (TEN), whose chronic exposure may contribute to oxidative stress, genetic damage, and enzymatic alterations. This study aimed to develop and validate a liquid chromatography-tandem mass spectrometry (LC-ESI-QqQ-MS/MS) method for the simultaneous determination of TeA, AOH, AME, and TEN in various plant matrices. The method provides a robust analytical tool suitable for investigations of exposure, toxicokinetics, and metabolism of these mycotoxins. Samples were extracted and purified using liquid-liquid extraction prior to instrumental analysis. Chromatographic separation was performed on a Kinetex column (150 mm  $\times$  4.6 mm, 5  $\mu$ m) with a flow rate of 0.5 mL/min. Detection was carried out in multiple reaction monitoring (MRM) mode optimized for each mycotoxin: TeA (m/z 198.1  $\rightarrow$  125.1, 15 V), AOH (m/z 257.0  $\rightarrow$  213.0, 23 V), AME (m/z 271.1  $\rightarrow$  256.0, 23 V), and TEN (m/z 413.2  $\rightarrow$  141.2, 25 V). The method demonstrated excellent linearity ( $R^2 \geq 0.99$ ), high sensitivity, and reproducibility, allowing simultaneous detection of all four mycotoxins in the analyzed samples. In conclusion, this LC-MS/MS method is a reliable and sensitive analytical tool for the determination of *Alternaria* mycotoxins, with potential applications in studies of human exposure, toxicokinetics, and metabolism, supporting risk assessment related to natural fungal contaminants.

**Autores:** Ríos-Gajardo G. 1; Brandell-Rojas L. 1; Gómez-Pereira P. 1; Pavón-Pérez J. 1

**Afiliación:** Interdisciplinary Mycotoxin Research Laboratory (IMRL), Department of Food Science and Technology, Faculty of Pharmacy, University of Concepción, Chile

**Area de la Farmacología:** Toxicology

**Dirección de Correo:** [grios@udec.cl](mailto:grios@udec.cl)

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**Socio Patrocinante:** --



**52. BETA-HYDROXYBUTYRATE REDUCES THE Staphylococcus aureus-TRIGGERED OVEREXPRESSION OF COX-2 AND TNF-ALPHA, BUT NOT IL-8, IN NEUTROPHILS ISOLATED FROM METABOLICALLY HEALTHY POSTPARTUM DAIRY COWS**  
β-hidroxibutirato reduce la sobreexpresión de COX-2 y TNF-alfa, pero no de IL-8, gatillada por Staphylococcus aureus en neutrófilos aislados de vacas lecheras postparto metabólicamente sanas

**Resumen:** During the postpartum period and early lactation, dairy cows often experience a negative energy balance, which leads to the mobilization of body fat and hyperketonemia. This condition, known as ketosis, has been linked to intramammary infections due to dysfunction in neutrophils. We hypothesize that beta-hydroxybutyrate (B-OHB)-the primary ketone body present in the blood of ketotic cows-may influence the expression of key immunoinflammatory markers during the challenge with the mammary pathogen Staphylococcus aureus (S. aureus). To investigate this, we studied 12 clinically healthy Holstein Friesian cows, between 14 and 42 days postpartum, with B-OHB blood levels below 0.8 mM, somatic cell counts (SCC) in milk below 130,000 cells/mL, and unit-forming colony (UFC) counts in milk below 30,000 UFC/mL. Neutrophils were isolated from jugular blood and preincubated with 2.5- and 5.0-mM B-OHB before being stimulated with S. aureus (MOI = 10) for 2 h. The S. aureus challenge increased the mRNA expression and protein levels of IL-8, COX-2, and TNF-alpha; however, it did not induce the overexpression of IL-1beta or IL-6. Interestingly, preincubation with B-OHB decreased the expression and protein levels of COX-2 and TNF-alpha, but did not affect IL-8. Additionally, B-OHB did not impact the protein levels of I-kappa-B-alpha. These results suggest that S. aureus triggers a differential overexpression of immunoinflammatory factors in bovine neutrophils, and that B-OHB may impair this production independently of the NF-kappa-B pathway.

**Autores:** Durán, D.; Vidal, C.; Henríquez, C.; Burgos, R. A.; Pantoja, D.; Morán, G.; Quiroga, J.  
**Afiliación:** Laboratorio de Inmunometabolismo, Instituto de Farmacología y Morfofisiología, Facultad de Ciencias Veterinarias, Universidad Austral de Chile  
**Area de la Farmacología:** Veterinary pharmacology  
**Dirección de Correo:** [john.quiroga@uach.cl](mailto:john.quiroga@uach.cl)  
**Agradecimientos:** Postdoctoral FONDECYT 3230482; FONDECYT 1250695  
**Socio Patrocinante:** Rafael Agustín Burgos Aguilera

**53. BETA-HYDROXYBUTYRATE DISRUPTS Staphylococcus aureus-INDUCED METABOLIC AND OXIDATIVE RESPONSES IN NEUTROPHILS ISOLATED FROM METABOLICALLY HEALTHY POSTPARTUM DAIRY COWS**

Beta-hidroxibutirato perturba la respuesta metabólica y oxidativa inducida por Staphylococcus aureus en neutrófilos aislados de vacas lecheras postparto metabólicamente sanas

**Resumen:** During early lactation, high-producing dairy cows experience a negative energy balance, leading to fat mobilization and hyperketonemia. This condition (ketosis) has been linked to mastitis due to neutrophil dysfunction. Since neutrophils primarily depend on glycolysis for energy, utilizing exogenous glucose and glycogen stores, we hypothesize that beta-hydroxybutyrate (B-OHB)-the major ketone body present in the blood of ketotic cows-may perturb neutrophil metabolism and, secondarily, their antibacterial response to the mammary pathogen Staphylococcus aureus (S. aureus). We studied 12 clinically healthy Holstein Friesian cows, between 14 and 42 days postpartum, with B-OHB blood levels below 0.8 mM. Neutrophils were isolated from jugular blood and preincubated with 2.5- and 5.0-mM B-OHB before being stimulated with S. aureus (MOI = 10) for 2 h. Preincubation with B-OHB, as well as with the glycolysis inhibitor 2-DG and the glycogenolysis inhibitor CP91,149, decreased the in vitro respiratory burst triggered by S. aureus. During stimulation, S. aureus increased the expression of HK2 and PKM2 but not LDHA. Likewise, S. aureus increased the expression of GLUT1 but not GLUT3. B-OHB exposure decreased the S. aureus-induced overexpression of HK2 and PKM2 but not GLUT1. The S. aureus challenge induced an increase in intracellular glucose but did not affect glycogen stores. B-OHB did not affect intracellular levels of glucose and glycogen. Along with the above, B-OHB did not affect the phosphorylation of GYS1 and PYGL during S. aureus-induced activation but affected the phosphorylation of Akt and

ERK1/2. These results suggest that B-OHB may impair the glycolytic response of neutrophils during the S. aureus challenge, which could contribute to, but not be the main cause of, their lower oxidative response to S. aureus.

**Autores:** Vidal, C.; Durán, D.; Henríquez, C.; Burgos, R. A.; González, C.; Morán, G.; Quiroga, J.  
**Afiliación:** Laboratorio de Inmunometabolismo, Instituto de Farmacología y Morfofisiología, Facultad de Ciencias Veterinarias, Universidad Austral de Chile  
**Area de la Farmacología:** Veterinary pharmacology  
**Dirección de Correo:** [john.quiroga@uach.cl](mailto:john.quiroga@uach.cl)  
**Agradecimientos:** Postdoctoral FONDECYT 3230482; FONDECYT 1250695  
**Socio Patrocinante:** Rafael Agustín Burgos Aguilera

**54. IN SILICO OPTIMIZATION OF THE TRASTUZUMAB ANTIBODY IN THE DETECTION OF HER2 BREAST CANCER USING ARTIFICIAL INTELLIGENCE**

optimización in silico del anticuerpo trastuzumab en la detección de cáncer de mama her2 mediante inteligencia artificial

**Resumen:** Breast cancer arises from the uncontrolled growth of mammary cells. In certain subtypes, a protein called HER2 is overexpressed, promoting excessive cell proliferation; this subtype is known as HER2-positive breast cancer. This form of cancer is highly aggressive and typically associated with a poor prognosis. However, a monoclonal antibody named Trastuzumab has been developed and widely used as the main diagnostic antibody. To enhance diagnostic efficiency in HER2-positive breast cancer, improving the affinity and structural stability of Trastuzumab is essential. Therefore, a rational design approach was developed to strengthen the interaction between the extracellular domain of HER2 and the variable fragment of Trastuzumab, through targeted point mutations. The crystallographic structure of the Trastuzumab-HER2 complex available in the Protein Data Bank was used, repaired, and energetically refined through FoldX, followed by interface mapping and hotspot analysis using alanine scanning. Based on this information, critical residues were subjected to in silico saturation mutagenesis employing protein language models (ESM-1v) and machine learning-based binding energy predictors such as mCSM-PPI2 and MutaBind2. Subsequently, favorable mutations were evaluated using FoldX to estimate changes in free interaction energy (delta delta G). As a selection criterion, a consensus between stability and affinity relative to the original protein was employed. The results highlight residues within the variable domain of the antibody, particularly in the A88-A98 region, where substitutions such as A91Y showed a significant decrease in interaction energy, indicating a more stable energetic and structural profile compared to the native sequence. This demonstrates the usefulness of integrating artificial intelligence with classical structural models to accelerate the optimization of monoclonal antibodies with potential diagnostic applications in HER2-positive breast cancer.

**Autores:** Valencia A. 1; Arias M. 1; Guerra B. 1; Oneto J. 1; Pritzke K. 1  
**Afiliación:** Facultad de Ciencias Agropecuaria y Medioambiente  
**Area de la Farmacología:** Molecular pharmacology  
**Dirección de Correo:** [a.valencia01@ufromail.cl](mailto:a.valencia01@ufromail.cl)  
**Agradecimientos:** Ciencia 2030: Ciencia para la innovación consorcio sur-súbarntario  
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Schedule						
	Tuesday 2nd		Wednesday 3rd	Thursday 4th		Friday 5th
9:00-11:00	<b>Symposium</b> <i>"Innovating in pharmacology: neuroimmune, aging, natural compounds for neuroprotection, and intestinal microbiota-based therapies"</i>	9:00-11:00	<b>Symposium</b> <i>"Experimental models for studying mitochondria metabolism in long-term diseases"</i>	<b>Symposium</b> <i>"Obesity: Emerging Pathophysiological Mechanisms and Novel Therapeutic Opportunities"</i>	9:00-11:00	<b>Symposium</b> <i>"Immunometabolic Modulation: Emerging Pathways for Therapeutic Development"</i>
11:00-11:30	Coffee Break (SOFARCHI)	11:00-11:30	Coffee Break (SOFARCHI)	Coffee Break (SOFARCHI)	11:00-11:30	Coffee Break (SOFARCHI)
11:30-13:00	<b>Symposium</b> <i>"Novel targets in cancer pharmacology: basic, clinical, and technological approaches"</i>	11:30-12:00 12:00-13:00	<b>Conference</b> <i>"Pentameric ligand-gated ion channels: Bridging molecular insights and clinical promise"</i> <b>Dra. Cecilia Bouzat</b> <i>(Universidad Nacional del Sur, AR)</i>	<b>Conference</b> <i>"The therapeutic potential and molecular signature of cannabidiol in depression"</i> <b>Dra. Samia Joca</b> <i>(Aarhus University, DK)</i>	11:30-13:00	<b>Symposium</b> <i>"Innovative Drug Discovery Strategies for Neurodegenerative Diseases"</i>
13:00-14:30	Free lunch	13:00-14:30	Free lunch	Free lunch	13:00-14:30	Free lunch
14:30-16:00	Oral Communications	14:30-16:00	Posters Presentations	Posters Presentations/ Presentations to Maria Eugenia Letellier Award	14:30-16:00	Posters Presentations
16:00-16:30	Coffee Break (SOFARCHI)	16:00-16:30	Coffee Break (SOFARCHI)	Coffee Break (SOFARCHI)	16:00-16:30	Coffee Break (SOFARCHI)
16:30-17:30	<b>Opening Conference</b> <i>"Dra. Katia Gysling: una vida dedicada a la neurofarmacología y a la formación de personas"</i> <b>Dra. María Estela Andrés</b> (Universidad Católica, CL)	16:30-17:00 17:00-18:00	<b>SOFARCHI Incorporations</b> <b>Conference</b> <i>"Mapping GLP-1R Signaling in Human POMC Neurons: A Central Mechanism of Anti-obesity Drug Action"</i> <b>Dr. Simone Mazzaferro</b> <i>(University of Cambridge, UK)</i>	<b>Symposium</b> <i>"Bridging the Gap: Advanced In Vitro, Ex Vivo, and In Vivo Models for Characterizing and Predicting the Performance of Drug Delivery Systems"</i>	16:30-17:00 16:30-17:30	<b>Conference (Dr. Luis Nuñez)</b> <i>"From Occupation Theory to Biased signaling, 100 years of Pharmacology Thinking and Experimentation"</i> <b>Dr. Juan Pablo García-Huidobro</b> <i>(Universidad de Santiago, CL)</i>
17:30-18:30	Opening Ceremony /Cocktail				17:30-18:30	Closing Ceremony
				Closing reception with a catamaran cruise on the rivers of Valdivia. (paid event: CLP\$29.000)		

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Semenova M. M., Maki-Hokkonen A. M., Cao J., Komarovski V., Forsberg K. M., Koistinaho M., Coffey E. T. and Courtney M. J. (2007) Rho mediates calcium-dependent activation of p38alpha and subsequent excitotoxic cell death. *Nat. Neurosci.* 10, 436-443.

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- Agradecimientos: Se pueden incluir las fuentes de financiamiento que permitieron el desarrollo del trabajo, indicando claramente a que autor corresponde la fuente de financiamiento. También se pueden incluir agradecimientos a personas que prestaron ayuda técnica o de revisión del manuscrito. En esta sección se debe declarar si existió conflicto de interés. En caso de no haber conflicto de interés se debe mencionar esta situación. Se recomienda consultar la siguiente dirección URL <http://zl.elsevier.es/es/revista/neurologia-295/conflicto-intereses-publicaciones-cientificas-90101004-editorial-2012> para aclarar en concepto y situaciones de conflicto de interés.
- Referencias: En el texto se deben citar las referencias con el apellido del primer autor, sus iniciales y el año de la publicación. En la sección de referencias se deben ordenar las mismas por orden alfabético. Se recomienda utilizar algún programa de manejo de referencias como EndNote con el formato de referencias de Journal of Neurochemistry.

**Ejemplos:**

Semenova M. M., Maki-Hokkonen A. M., Cao J., Komarovski V., Forsberg K. M., Koistinaho M., Coffey E. T. and Courtney M. J. (2007) Rho mediates calcium-dependent activation of p38alpha and subsequent excitotoxic cell death. *Nat. Neurosci.* 10, 436-443.

La abreviación de los títulos de las revistas debe de acuerdo a el listado de revistas indexadas en *Index Medicus* (Superintendent of Documents, US Government Printing Office, Washington, DC 20402, USA, DHEW Publication No. 95-267). Ejemplo: *Acta Neurol. Scand. Acta Physiol. Scand. Anal. Biochem. Arch. Biochem. Biophys. Biochem. J. Biochem. Pharmacol. Biochim. Biophys. Acta Biol. Chem. Hoppe Seyler Br. J. Pharmacol. Eur. J. Pharmacol. Experientia J. Biol. Chem. J. Cell Biol. J. Mol. Biol. J. Pharmacol. Exp. Ther. J. Physiol. (Lond.) Mol. Pharmacol. Nature Proc. Natl Acad. Sci. USA Proc. Soc. Exp. Biol. Med. Science*

**Leyendas para las Figuras:** Los títulos y leyendas de las Figuras deben presentarse en forma clara y corta. Se debe identificar y explicar todo símbolo, como flecha, número o letra que haya empleado para señalar alguna parte de las ilustraciones. En la reproducción de preparaciones microscópicas, explícite la ampliación y los métodos de tinción empleados.

**Unidades de Medida y Nomenclaturas:** Use unidades correspondientes al sistema métrico decimal. Las abreviaturas deben ser definidas la primera vez que aparecen en el texto. El listado de abreviaturas debe ser de acuerdo a la siguiente publicación *Biochem. J.* (1978) 169, 1-27. Al finalizar este instructivo se mencionan las abreviaturas que no deberían ser definidas (el listado esta en idioma inglés). La nomenclatura que se refiere a drogas y sustancias químicas no terapéuticas deben nombrarse de acuerdo a la nomenclatura IUPAC (International Union of Pure and Applied Chemistry). Mientras que para fármacos solo se acepta el nombre genérico INN (DCI). Respecto a los nombres de fantasía solo pueden ser nombrados entre paréntesis con el signo ® siempre que esté registrada la patente y que no exista un conflicto de interés evidente con el laboratorio fabricante del fármaco.

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**Abreviaciones Permitidas sin necesidad de definición en el texto:**

ADP, CDP, GDP, IDP, UDP, 5(pyro)-diphosphates of adenosine, cytidine, guanosine, inosine, and uridine AMP, etc. -5-phosphates of adenosine, etc. ANOVA, analysis of variance ATP, etc.-5' (pyro)-triphosphates of adenosine, etc. ATPase, adenosine triphosphatase bp, base pair Ci, curie CoA and acyl-CoA-coenzyme A and its acyl derivatives (e.g., acetyl-CoA) cpm, counts per minute CNS, central nervous system CSF, cerebrospinal fluid Cyclic AMP, 3,5-cyclic adenosine monophosphate Cyclic GMP-3,5-cyclic guanosine monophosphate DNA, deoxyribonucleic acid DNase, deoxyribonuclease DOPA, 3,4-dihydroxyphenylalanine dpm, dps-disintegrations per minute, disintegrations per second EDTA, ethylene-diaminetetraacetate EEG, electroencephalogram EGTA, ethyleneglycol bis(aminoethylether)tetraacetate ELISA, enzyme-linked immunosorbent assay FAD, FADH<sub>2</sub>, flavin-adenine dinucleotide and its reduced form FMN, flavin mononucleotide g, average gravity GABA, gamma-aminobutyric acid (not Gaba) GLC, gas-liquid chromatography GSSG, GSH, glutathione, oxidized and reduced forms h, hour HEPES, N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid HPLC, high performance liquid chromatography Ig, immunoglobulin IR, infrared kb, kilobase kDa, kilodalton im, micron min, minute MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine NAD<sup>+</sup>, NADH-oxidized and reduced forms of nicotin-amide-adenine dinucleotide NADP<sup>+</sup>, NADPH-oxidized and reduced forms of nicotin-amide-adenine dinucleotide phosphate NAD, NADP may be used when the oxidation state need not be indicated NMDA, N-methyl-D-aspartate NMN, nicotinamide mononucleotide NMR, nuclear magnetic resonance PCR, polymerase chain reaction Pi, orthophosphate (inorganic) PNS, peripheral nervous system PPI, pyrophosphate (inorganic) rpm, revolutions per minute RNA, ribonucleic acid RNase, ribonuclease RT, reverse transcription s, second SEM, standard error of mean SD, standard deviation TLC, thin-layer chromatography Tris, 2-amino-2-hydroxymethylpropane-1,3-diol UV, ultraviolet