SIMPOSIO / SYMPOSIUM

YOUNG RESEARCHERS UNIVERSIDAD DE ANTOFAGASTA.
CHAIR: DR. RODRIGO ITURRIAGA

LOS QUIMIORRECEPTORES PERIFÉRICOS COMO SENSORES METABÓLICOS EN REPOSO Y DURANTE EJERCICIO FÍSICA: HALLAZGOS DESDE UN MODELO EXPERIMENTAL Peripheral chemoreceptors as metabolic sensors at rest and during physical exercise: findings from an experimental model.

Traditionally, during maximum incremental exercise, both cardiorespiratory and metabolic responses are associated with meeting the body's metabolic demands. Notably, there has been a long-standing observation that the ventilatory response to exercise increases in parallel with the metabolic response, such as the release of lactate from skeletal muscles. While this phenomenon is widely accepted, there has been a lack of direct evidence to establish whether ventilatory and metabolic responses during exercise are synchronized, or if the metabolic signal initiates the breathing response. The carotid bodies (CB), located at the carotid bifurcation, serve as the principal peripheral chemoreceptors, and respond to various stimuli, including lactate, leading to autonomic and ventilatory responses. However, the role of CB chemoreceptors as metabolic sensors during exercise in physiological conditions has yet to be established. We investigated the lactate-dependent breathing response on the CB. Specifically, we observed that the ventilatory response to lactate was reduced following CB resection. We also examined the role of a metabotropic receptor and found a critical association between the lactate-dependent ventilatory response and this receptor. Intriguingly, 8 weeks of exercise training increase the ventilatory response to an agonist of this receptor. Our findings shed light on the pivotal role of the CB in the lactate-dependent breathing response during exercise. The results revealed that the CB's presence is crucial for this physiological response. Additionally, our study highlighted the significance of a metabotropic receptor in mediating the ventilatory response to lactate. These findings open up new avenues for experimental and human research, contributing to the exploration of previously unconsidered mechanisms associated with exercise physiology.

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USO DE INHIBIDORES FARMACOLÓGICOS EN LA INTERACCIÓN ENTRE LA PROTEÍNA QUINASA A Y EL SISTEMA UBIQUITINA PROTEASOMA EN ESPERMATOZOIDES HUMANOS: UN PAPEL CLAVE EN LA FERTILIDAD MASCULINA. Use of pharmacological inhibitors in the interaction between protein kinase a and the ubiquitin proteasome system in human spermatozoa: a key player in male fertility.

Matured spermatozoa are transcriptionally inactive cells with their genome densely packaged in sperm-specific protamine toroids instead of nucleosomes. Due to the unique nature of the mature spermatozoa, most molecular techniques used in other cell models cannot be applied to them, such as transfection, RNAi, and protein overexpression. Therefore, alternative strategies such as the use of pharmacological inhibitors and activators are used to study the cellular and molecular processes that sperm undergo during their passage through the female reproductive system. Freshly ejaculated mammalian spermatozoa are not able to fertilize an egg until they undergo a series of biochemical and physiological changes known as capacitation. During this process, the soluble adenyl cyclase/cAMP/protein kinase A (SACY/cAMP/PKA) pathway is activated. In human spermatozoa, the presence of the ubiquitin-proteasome system (UPS) has been described. In this study, we aim to present evidence of the involvement of the UPS in human sperm capacitation and its interaction with the SACY/cAMP/PKA pathway. Our results indicate that during in vitro capacitation, several proteasome subunits are phosphorylated by PKA. PKA pharmacological inhibitors block the enzymatic activity of the sperm proteasome, while PKA activators increase its activity. Additionally, pharmacological inhibitors that block the enzymatic activity of the proteasome significantly reduce sperm capacitation. Furthermore, proteasome pharmacological inhibitors block the phosphorylation of PKA substrate proteins are (RRXpS/pT motif) that take place during capacitation. Lastly, once the proteasome is activated by PKA, the proteasome modulates PKA activity. In conclusion, our data reveal a feedback regulation between PKA and the proteasome during human sperm capacitation.

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EXPLORANDO EL IMPACTO DE LAS MANIPULACIONES TEMPRANAS DEL SISTEMA SEROTONINÉRGICO EN LA ENFERMEDAD DE PARKINSON: PERSPECTIVAS DESDE DROSOPHILA MELANOGASTER. Exploring the Impact of Early Serotonergic System Manipulations in Parkinson's Disease: Insights from Drosophila melanogaster.

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by motor symptoms (MS) and the loss of dopaminergic neuron (DNs). A pre-symptomatic phase, characterized by non-motor symptoms (NMS), precedes the onset of MS. Recent PET studies in patients with familial PD reveal alterations in serotonin transporter (SERT) binding before any dopaminergic or motor dysfunction, suggesting that the serotonergic system could play a role in PD progression. This idea has not been tested. One of the best characterized models for PD is the Drosophila Pink1B9 mutant, which exhibits a pre-symptomatic phase with NMS followed by a symptomatic stage with MS. Here, we show lower brain serotonin content and reduced SerT activity during the pre-symptomatic phase in Pink1B9 flies. We explored what are the consequences of an early pharmacological manipulation on the serotonergic system in Pink1B9 animals. Feeding young Pink1B9 flies with fluoxetine, a SERT blocker, prevents the loss of DNs and ameliorates motor deficits in aged flies. Surprisingly, similar interventions in young control flies result in aged animals exhibiting a PD-like phenotype. Furthermore, we employed the GRASP technique to reveal that, like in vertebrates, the serotonergic system in the Drosophila adult brain innervates dopaminergic neurons. These findings suggest that the effects induced by the pharmacological manipulations could be explained by a direct modulation of the activity of DNs by serotonergic neurons. Altogether, these results suggest that an early dysfunction in the serotonergic system precedes and contributes to the onset of the phenotypes associated with the PD fly model. These findings strongly suggest the serotonergic system, particularly SERT, as a potential target for PD early diagnosis and as alternative treatment to slow-down PD progression.

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Agradecimientos: 1) Beca Doctorado Nacional 2016-2019 No. 21160214; RVZ, ANID, Chile. 2) FONDECYT de Postdoctorado No. 3230347; RVZ, ANID, Chile. 3) FONDECYT Regular No. 1231556; JMC, ANID, Chile.

SIMPOSIO / SYMPOSIUM

NORTHERN CHILE AS SOURCE OF NOVEL BIOACTIVE MOLECULES.
CHAIR: DR. WAI-HOUNG CHOU

MICROBIOMA AMBIENTAL DE ATACAMA: UN INMENSO POTENCIAL BIOTECNOLÓGICO PARA LA INDUSTRIA FARMACÉUTICA. Environmental microbiome of Atacama: a huge biotechnological potential for the pharmaceutical industry.

Poly-extreme conditions cause microorganism to effectively evolve and adapt to survive, developing several strategies, including metabolic and functional. Among these, are the production of secondary metabolism that aid in their ability to thrive under harsh conditions. In this context the Atacama Desert comprises several ecosystems that are categorized as “poly-extreme” given that it included extreme solar radiation, negative water balance, high concentrations of metal(oids), among many others. We have found a great diversity and novelty in terms of taxonomic distributions and bioactive compounds in microorganism from the Atacama Desert Area. By using multidisciplinary approaches including microbiology, molecular biology and biochemistry we have been able to characterize patterns of production of several compounds with functions associated to antimicrobial, antifungal, antiviral, antioxidant, anti-parasitic, chelating, surfactants, among many others. For instance, Bacillus and Streptomyces isolated from the Altiplano produce Bacitracin, Lichenysin, Fengycin, Bacillibactin, Butirosin, Stenothricin, Chaxapeptin, Mayamycin, Cyphomycin as well as several unidentified molecules. Furthermore, metagenomic survey indicate that thermophile communities are able to produce many RiPPs, betalactones, thiopeptides, NRPS, ranthipeptides, lassopeptides. The use of (meta)genomics enables us to get a big picture of the potential of a microbial community or strain and target cultivation and purification approaches to obtain the necessary biomass to produce a particular metabolite in mass-scale. Additionally, it enables us to determine by sequence similary to function of a previously unknown bioactive compounds, such was the case for the Bacillus NP42 strain that is able to produce Lichenicine VK21, but some of the genes of the pathways were unclassified. Therefore, by combining these approaches we can contribute with novel compounds produced by microorganism that could in the pharmacological field in the current scenario of multiresistant bacteria and the lack of treatments for particular diseases.

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FLORA ALTOANDINA, FUENTE DE NUEVAS MOLÉCULAS CON POTENCIAL ACTIVIDAD BIOLÓGICA. High andean flora, a source of new molecules with potential biological activity.

The north of Chile is geographically located in the driest desert in the world, the Atacama Desert. Despite its great aridity, this desert presents a series of climatic characteristics that allow it to support one of the most important vegetation Áreas in northern Chile, known as the "Puna Atacameña." This Área not only harbors a significant amount of flora but also constitutes the habitat of "Andean Communities" that preserve their ancestral roots. This has allowed them to accumulate a rich knowledge of local flora for use in countering various diseases. One of the most significant issues concerning the usefulness of these medicinal plants is the limited scientific information that supports the use of these species. In this regard, we have initiated a systematic study on the chemical composition and biological activity of these species with recognized medicinal properties. In our studies, extracts from species of the genera Senecio, Xenophyllum, and Parastrephia have shown important cardiovascular and vasodilator activity (in vivo and in vitro). Some of the secondary metabolites isolated from these plants, such as flavonoids, derivatives of p-hydroxyacetophenones, coumarins, and terpenoids, have also displayed significant biological activity. Furthermore, in our search for bioactive molecules present in the flora of the Atacama Desert, we have started to explore different extracts and metabolites with beneficial effects on neurodegenerative diseases. This includes extracts and metabolites from the species Werneria glaberrima, which have been preliminarily evaluated in cellular models of Parkinson's disease. The metabolites from these species have shown moderate neuroprotective and ROS (reactive oxygen species) trapping activity.

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Dr. Gabino Garrido. Departamento de Ciencias Farmacéuticas, Universidad Católica del Norte, Antofagasta, Chile. ***Fruit waste from the Atacama Desert as a source of obtaining antioxidant and hypoglycemic extracts***.

SIMPOSIO / SYMPOSIUM

THE ABC OF SOUTH AMERICAN PHARMACOLOGY: ARGENTINA / BRASIL / CHILE.
CHAIR: DR. GUILLERMO DÍAZ ARAYA.

FARMACOLOGÍA EN CHILE. Pharmacology in Chile.

Pharmacology in Chile traces its roots back to the colonial era, where it leaned heavily on traditional indigenous remedies. Although European pharmacological practices were introduced by Spanish conquistadors and settlers, the field remained in its infancy. In the 19th century, post-independence from Spain, Chile established its educational and scientific institutions. Notably, the Universidad de Chile, established in 1842, played a pivotal role in the development of pharmacology and pharmacy education, formalizing pharmacist training with the establishment of the School of Pharmacy in 1849. Through the late 19th and early 20th centuries, Chilean pharmacology continued to evolve as the nation adopted more modern pharmaceutical practices and regulations. In recent times, numerous universities and research institutions in Chile actively contribute to pharmacological research and education. They explore various facets of pharmacology, encompassing pharmacodynamics, pharmacokinetics, drug discovery, clinical trials, and pharmaceutical formulation. Today, Chile offers a doctoral program in pharmacology through the University of Chile. The representation of pharmacology in Chile is overseen by the Sociedad de Farmacologia de Chile (SOFARCHI), established in 1979 through the dedicated efforts of Dr. Jorge Mardones Restat and other researchers in the field. SOFARCHI's annual congress unites over 200 academics, scientists, and young researchers from all regions of Chile, fostering the advancement of pharmacological sciences. Although the number of fellowships has grown, continued efforts are required to fortify SOFARCHI as a robust and influential society committed to promoting pharmacology in Chile.

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FARMACOLOGÍA EN BRASIL: PASADO, PRESENTE Y FUTURO.
Pharmacology in Brazil: past, present and future.

Our Society has a long history of important contributions to scientific training and the development of research and teaching in Pharmacology in Brazil. Since its foundation 57 years ago, these inputs have been built with the effort, dedication and creativity of many presidents, directors, and council members. The seed for the Society was planted during the II International Congress in Pharmacology held in Prague two years ago when Brazil was selected as the site for the III International Congress in Pharmacology held in 1966 under the auspicious of the International Union of Pharmacology (IUPHAR). Mauricio Rocha e Silva, well known for the discovery of bradykinin in 1949, was in charge of setting up the scientific committee and presiding over the congress. The event was a great success, with more than 1000 attendees from 15 countries, 17 conferences, 11 symposia, 4 round tables, and 715 short communications. The third IUPHAR meeting, which took place in São Paulo, paved the way for the creation of the Brazilian Society of Pharmacology and Experimental Therapeutics (acronym “SBFTE” for the initials in Portuguese) three months later, on October 14th, 1966. As initially established by the founders, the society's mission is to develop research and teaching in pharmacology and experimental therapeutics in Brazil. The focus of my talk will be the SBFTE’s early history, role in Brazil's scientific and social development, and current achievements.

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FARMACOLOGÍA EN ARGENTINA. Pharmacology in Argentina.

In Argentina, the field of pharmacology is currently experiencing a notably favorable period of growth. This positive trend can be attributed to various policies implemented over the past decade, which have been particularly supportive of advancing beyond fundamental research. These policies have facilitated the establishment of research groups that not only produce world-class scientific breakthroughs but also focus on creating treatments and diagnostic methods applicable not only locally but on a global scale.
Consequently, this transformation has necessitated adjustments in regulations, quality standards, and the establishment of state-of-the-art facilities to conduct preclinical and manufacturing trials adhering to international benchmarks. Notable achievements in this regard include the development of a COVID vaccine, a serum for COVID treatment, and interventions for conditions like hemolytic uremic syndrome, among others. Looking ahead, the future is filled with promise, with investment funds and public-private collaborations actively supporting the emergence of pharmaceutical start-ups. The generation of value through globally recognized scientific endeavors and the translation of these advancements to meet international standards offer the potential for an innovative development model. However, this transformative potential will only be fully realized when considering extensive collaboration with diverse groups. As the pandemic has demonstrated, the future will be defined by cooperation, allowing us to address global challenges with regional solutions.

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SIMPOSIO / SYMPOSIUM

Cardiovascular Pharmacology

NOVEL THERAPEUTICS TARGET IN CARDIOVASCULAR DISEASES.
CHAIR: DR. SERGIO LAVANDERO

CARDIOMETABOLIC DISEASES AND VASCULAR DYSFUNCTION: IN SEARCH OF PHARMACOLOGICAL TARGETS. Enfermedades cardiometabólicas y disfunción vascular: en busca de dianas farmacológicas.

The adipose tissue is not simply a storage site of fat mass, but also an organ that secretes a heterogeneous group of substances, the so-called adipocytokines, which may exhibit paracrine or endocrine actions. Adipocytokines range from classic cytokines, such as interleukin (IL)-1B or tumor necrosis factor-α, to vasoactive peptides or metabolic regulators, such as leptin. They can be released not only by the visceral or subcutaneous adipose tissue, but also by epicardial or perivascular fat depots. In cardiometabolic diseases, such as type 2 diabetes mellitus and obesity, an imbalanced production and release of adipocytokines has been proposed to negatively impact on vascular homeostasis, thus contributing to the development of vascular disease. In this context, adipocytokines have gained interest as potential pharmacological targets to retard or attenuate vascular complications associated to metabolic disorders. In recent years, we have explored the capacity of selected adipocytokines, such as IL-1, visfatin/Nampt or soluble dipeptidyl peptidase-4 (sDPP4), to directly promote features of vascular damage, including vascular cell inflammation, endothelial dysfunction, impaired vascular reactivity or premature cell senescence, as well as the respective mechanisms of action involved. Moreover, we have observed that the pro-inflammatory signalling triggered by IL-1 in human vascular cells is exaggerated by the presence of extracellular glucose levels. This effect seems to rely on a higher uptake of glucose favoured by the adipocytokines. Once inside the cell, part of the excess glucose is diverted via the pentose phosphate pathway, which derives in the over-production of oxygen reactive species resulting in an over-activation of pro-inflammatory signalling. The deleterious vascular effects exerted by different adipokines can be pharmacologically blocked *in vitro* or *in vivo* by drugs that are either under development or already available in clinical practice for non-vascular indications. This opens new therapeutic horizons for the treatment of cardiometabolic complications.

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EXPLORANDO LOS miRNAS COMO OBJETIVOS EN EL INFARTO DE MIOCARDIO: COMPRENDIENDO LA INTERACCIÓN ENTRE SEXO Y ENVEJECIMIENTO. Exploring miRNAS as targets in myocardial infarction: unraveling the interplay of sex and aging.

miRNAs, small single-stranded molecules with pivotal roles in posttranscriptional gene regulation, have emerged as potential molecular tools for diagnosing, and even therapeutically targeting acute myocardial infarction (AMI). Our study delves into the intricate world of miRNAs, analyzing their expression profiles in AMI patients at the acute stage and following a one-year recovery period. Notably, we identified miRNAs, such as miR-99b/let-7e/miR-125a cluster, that displayed dysregulated expression during AMI but reverted to control levels after one year follow-up. To understand their functional implications, experiments on human umbilical endothelial cells (HUVECs) transfected with miRNA inhibitors and mimics revealed that let-7e and miR-125a modulated endothelial function, influencing adhesion, vasculogenesis, and proliferation in distinct ways. Moreover, our work extends to a murine model of ischemic acute myocardial infarction (IAM) developed in senescence-accelerated mice prone (SAMP8) and resistant (SAMR1) as controls. We explored sex differences in miRNA expression profiles, revealing distinct patterns and their associations with key biological pathways. Differentially expressed miRNAs were selected, their conservation in mice and humans was evaluated, and their relevance in AMI patients was validated. In conclusion, our research provides a comprehensive view of the circulating miRNA profile in AMI patients, and establishes the SAMP8/SAMR1 mouse model as a valuable tool for IAM and aging research. It underscores the significance of aging and sex as variables in miRNA studies, offering potential new biomarkers for AMI diagnosis and treatment.

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AFECTACIÓN CARDIACA EN DIABETES Y OBESIDAD; TENEMOS LA DIANA FARMACOLÓGICA EN LA MITOCONDRIA?. Cardiac failure under diabetes and obesity; Do we have pharmacological targets in the mitochondria?.

Type-2 diabetes (T2DM) and arterial hypertension (HTN) are major risk factors for heart failure. Importantly, these pathologies could induce synergetic alterations in the heart, and the discovery of key common molecular signaling may suggest new targets for therapy. Intraoperative cardiac biopsies were obtained from patients with coronary heart disease and preserved systolic function, with or without HTN and/or T2DM, who underwent coronary artery bypass grafting (CABG). Control (n = 5), HTN (n = 7), and HTN + T2DM (n = 7) samples were analyzed by proteomics and bioinformatics. Additionally, cultured rat cardiomyocytes were used for the analysis (protein level and activation, mRNA expression, and bioenergetic performance) of key molecular mediators under stimulation of main components of HTN and T2DM (high glucose and/or fatty acids and angiotensin-II). As results, in cardiac biopsies, we found significant alterations of 677 proteins and after filtering for non-cardiac factors, 529 and 41 were changed in HTN-T2DM and in HTN subjects, respectively, against the control. Interestingly, 81% of proteins in HTN-T2DM were distinct from HTN, while 95% from HTN were common with HTN-T2DM. In addition, 78 factors were differentially expressed in HTN-T2DM against HTN, predominantly downregulated proteins of mitochondrial respiration and lipid oxidation. Bioinformatic analyses suggested the implication of mTOR signaling and reduction of AMPK and PPARα activation, and regulation of PGC1α, fatty acid oxidation, and oxidative phosphorylation. In cultured cardiomyocytes, an excess of the palmitate activated mTORC1 complex and subsequent attenuation of PGC1α-PPARα transcription of β-oxidation and mitochondrial electron chain factors affect mitochondrial/glycolytic ATP synthesis. Silencing of PGC1α further reduced total ATP and both mitochondrial and glycolytic ATP. Thus, the coexistence of HTN and T2DM induced higher alterations in cardiac proteins than HTN. HTN-T2DM subjects exhibited a marked downregulation of mitochondrial respiration and lipid metabolism and the mTORC1-PGC1α-PPARα axis might account as a target for therapeutical strategies.

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Agradecimientos: FUNDING: SPACE2-CV-COVID-CM grant supported by REACT-EU, Comunidad de Madrid, and the European Regional Development Fund. Fondo de Investigación Sanitaria-IS. Carlos III (ref.: PI20/00923). ACKNOWLEDGMENTS: CIBERDEM, Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas.

PHARMACOLOGICAL TARGETS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF). Dianas farmacológicas en insuficiencia cardíaca con fracción de eyección conservada (HFpEF).

Heart failure with preserved ejection fraction (HFpEF) is a common and complex syndrome with high morbidity and mortality for which there are no evidence-based therapies. We have recently described the first experimental model of HFpEF by combining a high-fat diet and L-NAME that recapitulates the cardiovascular features of HFpEF in humans. We have identified two novel pharmacological targets to prevent the development of HFpEF: the transcription factors spliced form of X-box-binding protein 1 (XBP1s) and FoxO1. In this talk, we will present and discuss the current evidence that supports pharmacological intervention at the levels of both transcription factors and future development in this Área.

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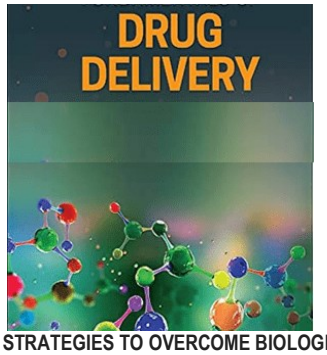
SIMPOSIO / SYMPOSIUM



DRUG DELIVERY STRATEGIES TO OVERCOME BIOLOGICAL BARRIERS.
CHAIR: DR. JAVIER O. MORALES.

METODOLOGÍAS DE ENCAPSULACIÓN PARA MOLÉCULAS ACTIVAS PARA MEJORAR SU POTENCIAL BIOLÓGICO. Encapsulation methodologies for active molecules to improve their biological potential.

This talk is related with the application of non-pollutant and cheap methodologies to improve the biological potential of several natural and synthetic active molecules whose activity is limited by their physicochemical characteristics (hydrophilic/hydrophobia, molecular weight, instability, oxidation, etc.). In general, we will discuss about the kind of soft interactions stablished between the active molecules and excipients, and the results obtained after in vitro and in vivo evaluations. Among the proposals to be presented in this talk, we underline: 1) the development of interferon-beta-loaded nanoparticles for intranasal delivery to control the neuroinflammation, and evaluated in vitro and in a preclinical model of multiple sclerosis; 2) a strategy to create nanocarriers containing hydrophilic low molecular-weight drugs containing aromatic groups and subjected to Pi-Pi stacking after interacting with aromatic polymers, to providing very efficiently drug loading and prolonged drug release; 3) nanoemulsions loaded with curcumin or avocado peel extract to prevent tumor reincidence/metastasis, and evaluated in vitro, in preclinical models and in animal patients; and 4) a proposal to entrap stem cell secretion products in dry formulations to treat psoriasis, and evaluated in vitro and in preclinical models.

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INCORPORACIÓN / INCORPORATIONS

ESTRATEGIAS DE ENTREGA DE FÁRMACOS EN INFECCIONES POR BIOPELÍCULAS BACTERIANAS. Drug delivery strategies in bacterial biofilm infections.

Biofilms are microbial aggregates growing within an extracellular polymeric substance (EPS) that protects the community against harmful environmental agents. Biofilms are the predominant growth form of bacteria in nature, compared to the free-floating (planktonic) form. However, clinical microbiology knowledge was built on studies that favor planktonic growth. Since the identification of Pseudomonas aeruginosa aggregates in the airways of cystic fibrosis patients in the 80s, biofilms have been increasingly studied using novel microbiological techniques, and P. aeruginosa has become the model pathogen of biofilm research. Biofilms mainly affect patients with underlying diseases (such as cystic fibrosis) that compromise their immune response, and once established, they are extremely difficult to eradicate. EPS was the first mechanism of resistance described in biofilms, which limits the diffusion of antibiotics and immune factors. The continuous and inefficient immune response damages the surrounding tissue and results in chronic inflammation. Therefore, biofilms were studied in conditions characterized by chronic inflammation, including urinary tract infections, otitis media, gastric ulcers, chronic wounds, and endometriosis. A second mechanism is given by a subpopulation of bacteria within the biofilm. These bacteria, known as persisters, are cells with a low metabolic state induced by the lack of nutrients and oxygen in deeper regions of the biofilm. Since most antibiotics aim to disrupt bacterial processes such as DNA replication, or protein synthesis, persisters survive the treatments. Different strategies have been explored to treat and prevent biofilm infections, including the use of EPS-degrading enzymes, probiotics, bacteriophages, compounds that synergize with antibiotics, modified antibiotics with enhanced diffusion, and excipients that enhance antibiotic retention on the site of action. These strategies have shown promising results in facing these challenging infections.

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Agradecimientos: FONDECYT 11190348 (2019) and PAI 77190010 (2019)

MICELAS DE NÚCLEO LIPÍDICO FUNCIONALIZADAS CON PÉPTIDO PARA AUMENTAR LA PERMEACIÓN BUCAL. Enhanced buccal permeation through novel peptide-functionalized lipid-core micelles.

The main objective of this research was to develop lipid-core micelles functionalized with a trifunctional peptide sequence, capable of enhancing the absorption of poorly water-soluble drugs through the buccal route, followed by bioresponsive activation by matrix metalloproteinase and targeting to cardiomyocytes. For this, the peptides of interest were efficiently obtained using solid phase synthesis, with a purity greater than 90%. Then, the different synthesized peptides were conjugated with a customized lipid, through the maleimide-thiol chemistry, obtaining derivatives with an almost total percentage of functionalization. Subsequently, lipid-core micelles were obtained from the lipid matrix and the functionalized lipid, yielding diameters at the nanometric scale, with high entrapment efficiency of rhodamine 123, as a model molecule. Furthermore, these micelles proved to be stable for at least 6 h at a storage temperature of 4 and 25 ºC, eliciting rapid instability at 37 ºC. In addition, the release of rhodamine 123 showed an initial burst release profile, allowing the entrapped molecule to be released in high amount during the first hours, following a Peppas-Sahlin diffusional kinetic model. In terms of permeation, functionalized lipid-core micelles showed higher permeation through buccal epithelium compared to the non-functionalized micelles and rhodamine 123 in solution as controls. Regarding to the sensitivity to matrix metalloproteinase, the conjugated peptide sequence on the surface of the micelles maintains the bioresponsive cleavage. Finally, the lipid-core micelles conjugated with the residual peptide after bioresponsive cleavage showed less binding to cardiomyocytes compared to the micelles conjugated with the peptide targeting cardiomyocytes as control; however, it was significantly higher compared to non-functionalized micelles, and might be related to the presence of integrin receptors located on the surface of cardiomyocytes.

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RUTAS ALTERNATIVAS DE ADMINISTRACIÓN PARA SISTEMAS NOVEDOSOS DE LIBERACIÓN DE FÁRMACOS. Alternative routes of administration for novel drug delivery systems.

The investigations undertaken in the Lab of Drug Delivery are centered on advancing drug delivery technologies to enhance therapeutic outcomes and patient convenience, leading to patient adherence. One major focus of research is directed towards the buccal route of administration for drugs, biologics, and nanocarriers. We have successfully developed and implemented a novel inkjet printing technology for drug-loaded film manufacturing, allowing for precise control over drug release profiles and tailored dosing regimens. In recent years, the potential of buccal delivery systems as a non-invasive and patient-friendly route for therapeutic interventions has sparked tremendous interest. More recently, gastroretentive formulations have emerged as a valuable strategy to prolong drug residence time in the stomach, facilitating controlled drug release and enhancing drug absorption. Advancements in this field made by us will be discussed, emphasizing their significance in improving the oral delivery of various drugs. Furthermore, our lab has made significant strides in developing nanocarriers for treating urinary tract infections (UTIs). Through our research, we aim to harness the potential of nanocarriers to precisely target infected sites, reduce systemic side effects, and improve patient outcomes. Lastly, this talk will highlight our work in computer simulations for nanocarrier development. By employing computational models and simulations, we can model nanocarrier properties, such as size, surface charge, and drug loading, to achieve enhanced drug delivery efficacy.

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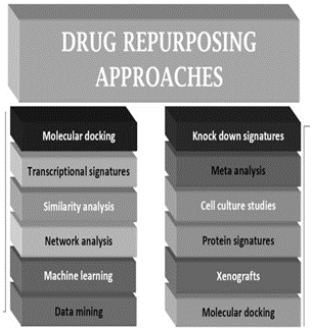

REPOSITIONING DRUGS: NOVEL PHARMACOLOGICAL APPROACHES FOR CHALLENGING DISEASES.
CHAIR: DR. ALFREDO MOLINA BERRÍOS

ANTIINFLAMATORIOS NO ESTEROIDALES (AINES) COMO AGENTES ANTIBIOPELÍCULA SOBRE CANDIDA ALBICANS. Non-steroidal anti-inflammatory drugs (NSAID) as antibiofilm agents against Candida albicans.

The biofilms produced by Candida albicans lead to recurrent and widespread infections, including oral candidiasis and denture stomatitis. Currently available antifungal agents are ineffective against biofilms, which results in the development of chronic infections and drug resistance. Consequently, there is a compelling need for the development of new antibiofilm drugs. Prostaglandin E2 (PGE2) is essential for C. albicans adhesion, filamentation, and biofilm formation, which are key events in virulence and drug resistance. Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, inhibit the synthesis of PGE2 and could exert antibiofilm effects against C. albicans. In addition, adding a nitric oxide (NO) releasing group to aspirin (NO-aspirin), increases significantly its inhibitory effects on biofilm features such as filamentation, and morphogenesis. To evaluate if other NSAIDs could present similar effects, we tested naproxen and indomethacin as antibiofilm agents. Their effects were similar to aspirin, but contrary to observed with NO-aspirin, the addition of a NO releasin group did not improve their antibiofilm effects. The antibiofilm mechanism of action of NSAIDs is not fully understood. Some authors suggest that the diffusion of these drugs through the biofilm may influence these results. While our team had previously reported a potent antibiofilm effect of NO-Aspirin, our results suggest that this property may be specific to the drug.

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REPOSICIONAMIENTO DE ITRACONAZOL E HIDROXICLOROQUINA IN EL TRATAMIENTO DEL CÁNCER. Repositioning of itraconazole and hydroxychloroquine in the treatment of cancer.

This project aimed to determine the cytotoxic effects of itraconazole, an antifungal drug, and hydroxychloroquine, an antimalarial and immunomodulator, on oral cancer cells. We also investigated whether combining these drugs could synergistically enhance the efficacy of conventional chemotherapeutic agents like cisplatin. Oral cancer, while affecting a relatively small proportion of the global population, exhibits high resistance to chemotherapy, leading to a mortality rate exceeding 50% among diagnosed patients. Therefore, identifying novel therapeutic approaches to augment existing therapies is crucial for improving treatment outcomes. This project explored the potential of repurposing two approved drugs to expedite the process from laboratory design to clinical trials and eventual human use. To bridge the gap between in vitro and in vivo results, we employed models that mimic the high chemotherapy resistance observed in oral cancer, such as hypoxic and spheroid cultures of head and neck cancer cells. Our findings demonstrate that the combination of hydroxychloroquine and itraconazole exerts a synergistic cytotoxic effect by inducing mitochondrial dysfunction and energetic stress in tumor cells with some degree of selectivity. Both drugs also exhibited cytotoxic effects in both chemotherapy resistance models. However, neither drug significantly potentiated the effect of cisplatin, but they did enhance the efficacy of 5-FU. In vivo results show that the drug combination induces a decrease in tumor volume. These preliminary results could represent a significant advancement in oral cancer treatment efficacy and expand treatment opportunities and accessibility, particularly for lower-income populations, given the widespread availability and affordability of both drugs.

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MODULACIÓN DE FACTORES DEL HOSPEDERO USANDO ESTRATEGIAS FARMACOLÓGICAS PARA EL TRATAMIENTO DE LA ENFERMEDAD DE CHAGAS. Modulation of host factors using pharmacological strategies for the treatment of Chagas diseases.

En 30% de los sujetos con enfermedad de Chagas crónica se desarrolla una cardiomiopatía que puede llevar a la muerte, y la cual es resultado de un proceso inflamatorio permanente, secundario a la persistencia del protozoo flagelado Trypanosoma cruzi, agente etiológico de esta dolencia. Este daño, inmunológicamente mediado, involucra activación endotelial con generación de microfocos isquémicos, infiltración de linfocitos T, macrófagos y la generación de citoquinas predominantemente proinflamatorias, incluyendo TNF-alpha, INF-gamma, IL4 IL-1beta, entre otras, que perpetúan la inflamación. Además, la persistencia del parásito también impide la activación apropiada de los mecanismos que conducen a la resolución de la inflamación, particularmente aquellos mediados por los lípidos resolutorios derivados del ácido araquidónico, EPA y DHA. Fármacos como aspirina y el grupo de las estatinas tiene la capacidad de gatillar la generación de estos lípidos, mediante la inducción de un cambio metabólico en la enzima ciclooxigenasa 2, cambiando la producción de prostaglandinas a la de 15-epi-lipoxina A4 y Resolvina D1. Los resultados de nuestra línea de investigación sugieren que estas moléculas, en modelos in vitro e in vivo, pueden favorecer la disminución de la carga parasitaria en el tejido cardiaco. Al descartarse in vitro la actividad tripanocida de estas moléculas, se propone que, al eliminar el proceso de inflamación, el sistema inmune es capaz de eliminar de manera más eficiente al parasito en el tejido miocárdico, eliminando así la fuente de daño miocárdico promovida por el patógeno.

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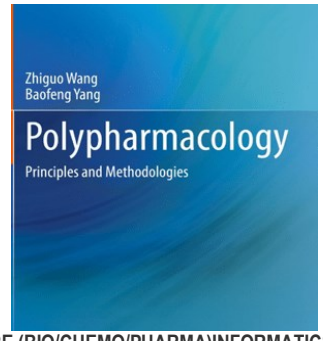

BRIDGING THE GAP: WHERE (BIO/CHEMO/PHARMA)INFORMATICS MEETS PHARMACOLOGY.
CHAIR: DR. DAVID RAMÍREZ

POLIFARMACOLOGÍA DE LOS CANALES IÓNICOS. Unlocking Atrial Fibrillation using Polypharmacology and Drug Repurposing.

Atrial fibrillation (AF), the world's most prevalent arrhythmia, is caused by the alteration of atrial ion channels, leading to cardiac rhythm deterioration. To address the complexity of AF, a polypharmacology (PP) approach could be a promising strategy. PP focuses on discovering a molecule capable of modulating multiple targets associated with the same condition, known as a multi-target directed ligand (MTDL). To restore cardiac rhythm in AF, it is essential to target atrial-selective potassium channels Kv1.5 and TASK-1, along with the cardiac sodium channel Nav1.5. Local anesthetics (LAs) like lidocaine, bupivacaine, and ropivacaine are examples of MTDLs as they block these channels. This study aimed to identify new MTDLs that specifically targets these cardiac ion channels. A bioinformatic protocol was developed, employing Molecular Dynamics Simulation frames of the three channels to compare LAs' binding sites (BSs). Representative frames and equivalent residue groups were extracted to guide a virtual screening of FDA-approved drugs with the LAs' pharmacophore. This led to the identification of one hit, WE2, displaying binding affinity to all three channels while interacting with equivalent residues in their respective BSs, indicating a potential polypharmacological behavior. At a concentration of 10µM, WE2 exhibited similar blockage percentages across the three channels. Importantly, no activity was observed in other cardiac channels like hERG, Kir2.1, and Kv4.3, confirming WE2's role as an MTDL. Additionally, as WE2 is an FDA-approved drug, it offers a promising avenue for drug repurposing in the treatment of AF.

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SIMILITUDES DE SITIOS DE UNION, UNA BASE PARA LA BÚSQUEDA DE NUEVAS DROGAS POLIFARMACOLÓGICAS. Binding sites similarities, as the basis for the search of novel polypharmacological drugs.

For years, pharmacologists have considered selectivity as a property of paramount importance when designing/searching compounds with potential therapeutic usefulness. This is based on the idea that drugs acting on a single target involved in disease progression will have minimum side effects and maximal efficacy. However, mounting evidence indicates that "promiscuous" drugs, i.e. simultaneously targeting multiple receptors, might show better profiles regarding both efficacy and side effects. This has led polypharmacology to emerge as an alternative to reduce the high levels of attrition that have characterized drug discovery in the last two decades. Thus, the drug discovery process is markedly shifting from a "one-drug-one-target" paradigm to a conceptual framework in which the multitarget profile of small organic molecules is proactively pursued. The rational design/search of multitarget drugs faces at least two major challenges, including a) the need to identify a combination of nodes in a biological network whose perturbation results in a desired therapeutic outcome, and b) to develop drugs whose polypharmacological profile allows those nodes to be perturbed specifically. Even though several promising strategies have been followed to address these challenges, it is clear that it is not an easy task either to determine how many and which targets are most adequate to affect the multifactorial nature of complex diseases or to develop multitarget compounds. Noteworthy, all of these strategies are continuously fueled by the development of computational tools enabling advances in different Areas related to polypharmacology, as well as by a remarkable progress in structural biology which has provided the high-resolution crystal structures of several important biological receptors. In this context, it seems reasonable to think that a given compound will be able to interact simultaneously with two or more relevant targets if they have similar binding sites. Therefore, the search of similar binding sites in protein targets involved in different conditions is a promising strategy for the design/repurposing of novel polypharmacological drugs. General concepts and a handful of examples of computational and experimental approaches to this aim will be discussed.

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COMBINANDO FORMA, ELECTROSTÁTICA Y CRIBADO VIRTUAL RÁPIDO PARA DESCUBRIR MODULADORES ALOSTÉRICOS DEL RECEPTOR MINERALOCORTICOIDE. Combining shape, electrostatics and fast virtual screening to discover allosteric modulators of the Mineralocorticoid Receptor.

The Mineralocorticoid Receptor (MR) is a key member of the nuclear receptor superfamily involved in regulating fluid and electrolyte homeostasis in both epithelial and non-epithelial cells. Conventional MR antagonists like Spironolactone and Eplerenone are plagued by off-target interactions with Glucocorticoid (GR), Androgen (AR), and Progesterone (PR) receptors. This underscores the urgent need for more specific MR modulators. Here, we emphasize the largely untapped potential of allosteric sites in developing highly selective, non-steroidal MR antagonists. We employed a novel integrated ligand and structure-based virtual screening strategy focused on these allosteric sites. Crystal structures for ligand-binding domains of AR, GR, PR, and MR were sourced from the PDB databank and aligned. Using vROCS and LigandScout, shape-based queries and pharmacophore models were established. Our extensive in-house database of approximately 30 million compounds was stringently filtered using the FILTER software based on ADME/Tox attributes. Allosteric-focused virtual screening was conducted using ROCS and EON, further refined via FRED. From an initial pool of over 35 million compounds, a library of 30 million filtered compounds and 5.0 billion conformers was generated. Among the top 500 hits, 8.9% demonstrated significant binding affinity specifically at MR's allosteric sites. An AUC score of 0.86 validated the efficacy of our query models. A selection of 25 compounds, predicted to target MR allosteric sites with high specificity, were further subjected to biological assays in SW872 cells, displaying impactful modulation of SGK-1 and Na+/K+ ATPase expression levels. In conclusion, our study provides a strategy for the identification of allosteric-directed, non-steroidal MR modulators, setting the stage for ongoing validation and future clinical applications.

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FARMACOLOGÍA DE SISTEMAS: NUEVAS HERRAMIENTAS PARA ENTENDER CÓMO FUNCIONAN LOS FÁRMACOS. Network Pharmacology: New tools to understand how drugs work.

The traditional one-drug/one-target/one-disease approach to drug discovery has been facing many challenges, such as the high failure rate of clinical trials, the rising cost of drug development, and the emergence of drug resistance. In recent years, there has been a growing interest in systems biology and polypharmacology approaches as methods for multiomics data integration and multitarget drug design, which offer new ways to understand how drugs work and to design more effective and safer therapies. Network pharmacology is a novel approach that integrates both systems biology and polypharmacology. It uses mathematical and computational methods to analyze the interactions between drugs, targets, and pathways in a biological network, allowing to study the effect of drugs on both the interactome and the diseasome level. This allows researchers to gain a more comprehensive understanding of the systemic mechanisms of drug action, to identify new drug targets and therapeutic strategies, to predict the potential side effects of drugs, to design more effective and safer drug combinations, and to personalize drug therapy for individual patients, among others. The use of new tools based on network pharmacology also has some benefits, it can help to reduce the cost and time of drug development and to improve the success rate of clinical trials. Network pharmacology is a promising new approach to drug discovery that has the potential to revolutionize the way we treat diseases. It is a rapidly evolving field, and there is still much to learn about its potential. However, the early results are very promising, and network pharmacology is likely to play an increasingly important role in the future of pharmacology.

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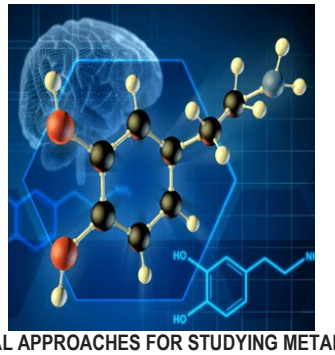

NOVEL PHARMACOLOGICAL APPROACHES FOR STUDYING METABOLISM IN BRAIN TISSUE.
CHAIR: DR. MARIO HERRERA-MARSCHITZ

ESTRATEGIAS FARMACOLOGICAS DIRIGIDAS A REEMPLAZAR NIVELES DE NAD^+ PARA RESCATAR DE LAS DEFICIENCIAS METABOLICAS INDUCIDAS POR ASFIXIA PERINATAL. Pharmacological strategies targeting NAD^+ replacement for rescuing from the long-term deficiencies induced by perinatal asphyxia (PA).

Labour and delivery demand for a complex and sequential metabolic and physiologic cascade, guaranteeing a successful childbirth, vulnerable, however, to any condition interrupting oxygen supply, leading to an energy crisis (PA) inducing cell death, even when re-oxygenation is promptly restored. The consequences of PA depend upon the length of the oxygen-deprivation period, resuscitation/re-oxygenation manoeuvres, and upon the developmental stage of the affected brain regions, being mesencephalon and hippocampus highly vulnerable regions. With a model of PA in rat, we have identified relevant targets responsible for the metabolic cascades linked to neurodevelopmental impairments. Severe PA induces a sustained effect on redox homeostasis, increasing oxidative stress, decreasing metabolic and tissue antioxidant capacity in vulnerable brain regions, even weeks after the insult. Following PA there is a cellular failure for producing NADPH, perpetuating a pro oxidative stress condition, probably involving mitochondrial Complex I. Supplementation with NAD+ would promote mitochondrial function, targeting dinucleotide replacement, modulating relevant sentinel proteins, including PARP-1, reducing oxidative stress and apoptosis, hence rescuing from the long-term deficiencies induced by PA. We report here pharmacological studies treating asphyxia-exposed and control rat neonates with nicotinamide analogues (nicotinamide, nicotinamide riboside) for replenishing NAD+ levels and with biguanides (metformin, phenformin) for decreasing ROS formation, evaluated in vivo and with organotypic cultures.

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Agradecimientos: Grants from FONDECYT- (1231443, 1190562, 1180042, 1200287, 3210771) and ANID-Chile are acknowledged, as well as the excellent technical support by Mr. Robel Vasquez, Ms. Carmen Almeyda, Mr. Juan Santibáñez and Mr. Alejandro Leiva.

TECNOLOGIA SEAHORSE TECNOLOGÍA PARA MONITOREAR LA FUNCIÓN MITOCONDRIAL *IN VIVO*: UNA NUEVA ESTRATEGIA EN EL DESCUBRIMIENTO DE FÁRMACOS. Seahorse technology for monitoring *in vivo* mitochondrial function: A new strategy in drug discovery.

Alterations in mitochondrial function participate in several pathologies such as brain injuries and tumorigenesis. Upon metabolic stress, energy demands are supplied through dynamic changes in the metabolism. This process, known as metabolic plasticity, allows cells to remodel the energy-producing pathways (e.g., metabolic shifts between glycolysis versus oxidative phosphorylation), preference for mitochondrial oxidable substrates (e.g., pyruvate, glutamine versus fatty acid), and synthesis of intermediates of the tricarboxylic acid cycle, which depends on changes in substrate availability, such as oxygen, glucose, and amino acids. In this work, our advances in understanding the adaptive mechanisms dependent on mitochondrial bioenergetics in response to drugs are presented. From the use of Clark electrode for electron transport chain study to real-time analysis of metabolic plasticity by Extracellular Flux Analyzer XF based on a new high-content, automatized imaging platform, we have identified promising new small molecules and peptides that target the mitochondrial function. These compounds produce a reduction of migration, drug response, and secretion of pro-inflammatory factors in different cell lines. Recently, we described a new Complex I inhibitor that acts on D-active conformation reducing mitochondrial respiration, as valeted by sub-mitochondrial particles obtained from breast cancer in vivo models and OXPHOS-deficient cells. The applications of high-thought screening based on cellular metabolism and bioenergetics in the molecular pharmacology and drug discovery Areas are discussed.

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Agradecimientos: This research was funded by Agencia Nacional de Investigación y Desarrollo (ANID)-Chile, Anillo Grant-ACT210097, FONDECYT-11201322, FONDEQUIP EQM220164 and VID-UChile UM-03/22.

HUMAN BRAIN ORGANOIDS AS AN *IN VITRO* MODEL OF NEURODEGENERATIVE DISEASES. Organoides del cerebro humano como modelo in vitro de enfermedades neurodegenerativas.

Neurodegenerative diseases resulting from a progressive loss of neurons and function contribute to different degrees of brain damages and loss of cognition. The incidence of neurodegenerative diseases increases abruptly with age. It is estimated that the aging worldwide population will result in over 150 million patients suffering of dementia by the year 2050. The cause of neurodegenerative diseases is still poorly understood, but their final stage usually means loss of memory, reasoning, difficulties to speech, and other cognitive functions. The lack of successful treatments for these diseases has high economic impact on the society, current treatment options being very limited, turning to *in vitro* models for studying better the disease mechanisms. The development of organoid cultures has produced great expectation among the research community, as a tool for obtaining valuable information for understanding the mechanisms of disease development. The Karolinska Institutet Stem Cell & Organoid Unit is constantly working to develop more accurate and scalable organoid culture methods. We have developed a 3D-organiod culture system, which utilizes hydrogel encapsulation, using spinning bioreactors, as well as a microgravity based rotary wall vessel bioreactor to mimic the natural microenvironment required for brain development. The objective of this lecture is to provide knowledge and information about development of organoids/3D culture research, supporting research groups that look forward to incorporate reliable and advanced organoid models into their ongoing and future research projects/studies, focusing on *in vitro* models of Alzheimer disease**.**

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SUBSTANCE ABUSE DISORDERS: INSIGHTS INTO ITS MECHANISMS AND POTENTIAL TREATMENT STRATEGIES.
CHAIR: DR. MARIO RIVERA-MEZA.

LA DOPAMINA REVISITADA 50 AÑOS DESPUÉS. Dopamine revisited 50 years later.

Early views on the function of brain dopamine (DA) regarded it as involved in extrapyramidal motor functions. In early '70s, however, Crow and Wise linked DA to reward by showing that DA rather than noradrenaline neurons, support intracranial self-stimulation (ICSS). In the same period Ungherstedt mapped mesolimbic DA neurons projecting from VTA to n accumbens as distinct from the classic nigrostriatal pathway. In the mid '70s various studies had shown that various depressant drugs of abuse like opiates and ethanol, facilitate ICSS and stimulate locomotion, suggesting that they are homologous to psychostimulants and therefore act as reinforcers via stimulation of mesolimbic DA transmission (Wise and Bozarth, 1987). However, no direct in vivo evidence for such a general role of DA was provided in that review. Indeed, such evidence, had been obtained already in 1985 and in 1986 by our laboratory for ethanol (Imperato & Di Chiara, EJP, 1985; Di Chiara & Imperato, JPET, 1986) and nicotine (Imperato et al, EJP 1986) and in 1988 for opiates (Di Chiara and Imperato, JPET 1988) by the technique of brain microdialysis, originally developed by Ungherstedt and adapted by us to freely moving rats (Imperato and Di Chiara, JN,1985). Further studies with vertical probes, showed that the shell is indeed the Area where drugs of abuse preferentially increase dialysate DA, consistently with a role of DA in nicotine (Pontieri et al, Nature 1996), heroin and THC reward (Tanda et al, Science 1997). This presentation will show to which extent the role of DA in drug reward has resisted the impact of studies investigating causality by means of newer techniques such as optogenetics and fiber photometry.

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UN NUEVO FÁRMACO QUE DISMINUYE TANTO EL CONSUMO DE ALCOHOL COMO LA NEUROINFLAMACIÓN. A new drug that decreases both alcohol consumption and ethanol-induced neuroinflammation.

High-ethanol intake induces a neuroinflammatory response, which has been proposed as one of the mechanisms responsible for the maintenance of chronic ethanol consumption. Neuroinflammation increases glutamate levels, that trigger dopamine release at the corticolimbic reward Areas driving relapse and long-term drinking behavior. The activation of PPAR-α by fibrate drugs inhibits neuroinflammation, in models other than ethanol consumption. However, the effect of fibrates on ethanol-induced neuroinflammation had not been studied. We previously reported that the administration of fenofibrate to ethanol drinking UChB rats increased catalase levels in the liver, which accelerates the rate of ethanol oxidation to acetaldehyde. Accordingly, animals showed a marked accumulation of acetaldehyde in the blood, which would lead to aversive effects that decreased ethanol consumption. Now, we studied whether the administration of fenofibrate in the withdrawal stage after chronic ethanol consumption reduces voluntary intake when alcohol is offered again to the animals (relapse-type drinking). Animals treated with fenofibrate decreased alcohol consumption by 80% during post-abstinence relapse. One possibility is that fenofibrate could be normalizing the glutamatergic tone since a reversal of the alcohol-induced decrease in astrocytic glutamate transporter (GLT-1) expression was observed. Furthermore, fenofibrate decreased the expression of the proinflammatory cytokines TNF-α, IL-1 and IL-6, and of an oxidative stress-induced gene (heme oxygenase-1) in the hippocampus, nucleus accumbens, and prefrontal cortex. Fenofibrate also reduced oxidative stress, as well as increased M2-type microglia (with anti-inflammatory properties) and decreased phagocytic microglia in the hippocampus. These findings highlight the potential of fenofibrate, an FDA-approved dyslipidemia medication, as a supplementary approach to alleviating relapse severity in individuals with alcohol use disorder (AUD) during withdrawal.

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ACTIVADORES DE LA ALDH2 COMO UN NUEVO TIPO DE AGENTES FARMACOLÓGICOS PARA EL TRATAMIENTO DE LOS DESÓRDENES DE USO DE ALCOHOL Y NICOTINA. Activators of ALDH2 as a new type of pharmacologic agents for the treatment of alcohol and nicotine-use disorders.

Some 80% of individuals showing alcohol-use disorders are also chronic smokers. However, no pharmacological alternatives are available for the treatment of its co-consumption. The chronic use of both ethanol and nicotine results in marked oxidative stress and the generation of cytotoxic aldehydes affecting glutamate homeostasis. These factors have been associated with the perpetuation of the addiction and the relapse after a withdrawal period. Alda-1is a pharmacological activator of ALDH2 that has been linked to neuroprotection due to its capacity to detoxify cytotoxic aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). Studies in our laboratory have shown that Alda-1 administration reduces chronic ethanol intake in drinking UChB rats. Also, the administration of Alda-1 markedly reduces relapse-like ethanol consumption in rats exposed to chronic ethanol consumption and deprivation. These protective effects were accompanied by normalizing accumbal glutamate levels and a reduction of whole-brain MDA levels. Regarding nicotine, the administration of Alda-1 leads to a significant reduction of both chronic and relapse-like nicotine intake in UChB rats. We also observed that the administration of Alda-1 elicited a noticeable reduction in the concurrent consumption of nicotine and alcohol that was reversed upon the discontinuation of Alda-1. Flurbiprofen, a non-steroidal anti-inflammatory drug, is also able to increase ALDH2 activity as Alda-1. Animal studies also showed that oral administration of flurbiprofen was effective in reducing the acquisition of alcohol consumption in UChB-drinking rats. Flurbiprofen showed a similar potency to Alda-1 in reducing chronic alcohol consumption in UChB rats. These results suggest that the pharmacological activation of brain ALDH2 could represent a pharmacological target for treating alcohol and nicotine use disorders.

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SON LOS PSICODÉLICOS LA SOLUCIÓN MÁGICA PARA TRATAR LA ADICCIÓN?. Are psychedelics the magic bullet to treat addiction?.

Addictive behavior is characterized by a relapsing course of harmful drug use, excessively biased choices towards the drug over healthy activities, and an apparent resistance to change this dysfunctional behavior, making treatment development very demanding. Existing pharmacotherapies have limited efficacy and new medications are warranted. The current 'psychedelic renaissance' rekindled some optimism, initially inspired by promising anecdotical accounts of lasting improvements after a single or a few therapeutic sessions, and now reinforced by the emergence of governmentally funded clinical trials in some countries. These trials are focusing mostly on treatment efficacy, but rarely address any mechanism of action that are crucial for treatment development. Here we will show data with psilocybin in DSM-based animal models of alcohol and cocaine addiction and will describe mGluR2-based and BDNF-based mechanisms underlying the action of psychedelics.

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