XLIV ANNUAL MEETING Chilean Society for Biochemistry and Molecular Biology

SBBMCh Week

Kick Off

Mid Year Touchpoint

Annual Wrap Up

XLIV ANNUAL MEETING

OF THE CHILEAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

June – December, 2021

XLIV ANNUAL MEETING OF THE CHILEAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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XLIV ANNUAL MEETING
Chilean Society for Biochemistry and Molecular Biology 2021

Kick Off

- **Opening ceremony**
- **Symposium**

"Latin America single molecule biophysics. A symposium in honor of Carlos Bustamante"

Chair: Christian A.M. Wilson

- "*Fluorescence Fluctuations: From protein oligomerization to excited state dynamics*". Marcia Levitus, Arizona State University, USA
- "*Mechanism of Allosteric Regulation in Protein Kinases: A Single Molecule Approach*". Rodrigo Maillard, Georgetown University, USA
- "*Protein Folding at the single-molecule level: The case of knotted proteins*". Andrés Bustamante, U. de Chile, Chile
- "*Co-transcriptional folding of human Telomerase RNA*". Francesca Burgos-Bravo, University of California, Berkeley, USA
- Words from Dr Carlos Bustamante, University of California, Berkeley, USA
- **Good news from SBBMCh**

June 30th from 15:00 (Chile)

SYMPOSIUM

Latin America single molecule biophysics. A symposium in honor of Carlos Bustamante

1. "Fluorescence Fluctuations: From protein oligomerization to excited state dynamics"
Marcia Levitus, Arizona State University, USA
About 50% of all proteins are oligomeric in nature, and among these, most are homomultimers. For some proteins, the oligomerization state can be modulated by environmental factors such as pH, phosphorylation, ligand binding, etc. Different oligomeric forms of the protein may have different metabolic functions, and the modulation of the oligomerization state by environmental factors can serve as cellular metabolic control mechanism. The oligomerization state of a protein is often difficult to determine. Methods such as size exclusion chromatography, analytical ultracentrifugation, and chemical cross-linking are rarely adequate to identify transient intermediates. Moreover, these techniques are not always amenable to the buffer conditions required to investigate how environmental variables affect the oligomeric state of a protein.
Here, we present a methodology based on fluorescence correlation spectroscopy (FCS) that allows the characterization of the effects of environmental factors on the oligomeric state of a protein. We have derived models to describe the measured autocorrelation function in terms of the relative concentrations of the different oligomeric forms that exist under equilibrium conditions at a given protein concentration. In contrast to most traditional biochemical techniques, FCS allows the determination of the concentrations of different oligomers under true equilibrium conditions. Here, we will illustrate the capability of this powerful approach by discussing our recent research that unraveled previously-unknown mechanisms of modulation of the oligomeric state of the replication processivity clamp of E. coli. We will show that this ring-shaped protein self-assembles to form stacks of rings in the presence of glutamate, glycine betaine, and other osmoprotectants.

2. "Mechanism of Allosteric Regulation in Protein Kinases: A Single Molecule Approach"
Rodrigo Maillard, Georgetown University, USA
Cyclic nucleotide-binding (CNB) domains allosterically regulate the activity of proteins with diverse functions, but the mechanisms that enable the cyclic nucleotide-binding signal to regulate distant domains are not well understood. Here we use optical tweezers and molecular dynamics to dissect changes in the folding energy landscape associated with cAMP-binding signals transduced between the two CNB domains of protein kinase A (PKA). We find that the response of the energy landscape upon cAMP binding is domain specific, resulting in unique but mutually coordinated tasks: one CNB domain initiates cAMP binding and cooperativity, whereas the other triggers inter-domain interactions that promote the active conformation. Inter-domain interactions occur in a stepwise manner, beginning in intermediate-liganded states between apo and cAMP-bound

domains. Moreover, we identify a cAMP-responsive switch, the N3A motif, whose conformation and stability depend on cAMP occupancy. This switch serves as a signaling hub, amplifying cAMP-binding signals during PKA activation.

3. "Protein Folding at the single-molecule level: The case of knotted proteins"
Andrés Bustamante, Universidad de Chile, Chile
Knots are natural topologies of chains. Yet, little is known about spontaneous knot formation in a polypeptide chain—an event that can potentially impair its folding—and about the effect of a knot on the stability and folding kinetics of a protein. Here we used optical tweezers to show that the free energy cost to form a trefoil knot in the denatured state of a polypeptide chain of 120 residues is 5.8 ± 1 kcal mol−1. Monte Carlo dynamics of random chains predict this value, indicating that the free energy cost of knot formation is of entropic origin. This cost is predicted to remain above 3 kcal mol−1 for denatured proteins as large as 900 residues. Therefore, we conclude that naturally knotted proteins cannot attain their knot randomly in the unfolded state but must pay the cost of knotting through contacts along their folding landscape.

4. "Co-transcriptional folding of human Telomerase RNA"
Francesca Burgos-Bravo, University of California, Berkeley, USA
Human telomerase is an essential ribonucleoprotein that maintains genomic stability and whose upregulation has been involved in cancer. The correct folding of its RNA component (human Telomerase RNA, hTR) plays a critical role in the catalytic activity of telomerase. In cells, the folding of RNA molecules is coupled to transcription. Yet, despite its importance, the kinetic control of the hTR folding during transcription and its conformational transitions as it is synthesized are unknown. Since RNA folding begins as it is transcribed, we performed high-resolution optical tweezers experiments to follow in real-time the folding of the wild type hTR as it emerges from human RNA polymerase II. We characterized the full molecular co-transcriptional RNA folding trajectory of this molecule. To assign the folding features in the trajectory to specific portions of the nascent RNA we also collected unfolding force-extension curves to examine intermediate folds adopted by nascent transcripts of incremental length stalled on polymerase at equilibrium. We identified the formation of a G-quadruplex at the 5' end, which may represent an obligatory intermediate structure for the hTR folding, that eventually rearranges into the native fold. Using this single-molecule approach, I will also study how the rate of transcription directs the structural rearrangements that favor the attainment of the native folding of hTR. This research should provide, for the first time, a thorough mapping of the dynamic, out of equilibrium folding pathway that hTR undergoes during transcription, and new relevant information toward understanding how co-transcriptional folding governs RNA function in cells.

XLIV ANNUAL MEETING
Chilean Society for Biochemistry and Molecular Biology 2021

Mid year Touchpoint

(15:00 h) • **Welcome**

• **Cono Sur Simposium**

"When plant stress and development collides underground"

Chair: José M. Estevez

(15:15 h) • *"Improving Drought Resistance in Arabidopsis and Crops"*. Ana Cano-Delgado Centre for Research in Agricultural Genomic (CRAG), España

(15:45 h) • *"Mechanism involved in the adaptation of root meristem under water stress"*. Mariana Sotelo. Universidad de la República, Uruguay

(16:15 h) • *"Heat stress bodies, a uncharacterized Intracellular response to high temperature in Arabidopsis roots"* Ricardo Tejos. Universidad Arturo Prat , Chile

(16:45 h) • *"Root growth mechanisms under low-temperature and low-nutrient stresses"*. José Estevez. Instituto Leloir, Argentina; Universidad Andrés Bello, Chile

(17:20 h) • **Closing words**

CONO-SUR SYMPOSIUM

When plant stress and development collides underground

1. "Improving Drought Resistance in Arabidopsis and Crops"
Ana I. Caño-Delgado, Centre for Research in Agricultural Genomics (CRAG) CSIC-IRTA-UAB-UB. Barcelona E-08193, Spain.
Drought is the primary cause of agricultural loss globally, and represents a major threat to food security. Currently, plant biotechnology stands as one of the most promising strategies to obtain crops capable of producing high yields in water-limited conditions. From the study of Arabidopsis thaliana whole plants, the main response mechanisms to drought stress have been uncovered, and multiple drought resistance genes have been engineered into crops. So far, most of the plants with enhanced drought resistance display reduced yield, encouraging the search for novel approaches to uncouple drought resistance from plant growth. Our laboratory has recently shown that the receptors of brassinosteroid (BR) hormones use tissue-specific pathways to allocate different developmental responses during root growth. In Arabidopsis, we have found that increasing BRL3 receptors of BRs in the vascular tissues confers resistance to drought without penalizing growth, opening up an exceptional opportunity to investigate the mechanisms that confer drought resistance with cellular specificity in Arabidopsis. In the seminar, I will provide an overview of our current finding on phenotypical analysis of drought traits that could be improved biotechnologically to obtain drought-tolerant cereals. In addition, the current advances in translating our results into cereal Sorghum will be presented. In the coming years, great contributions are expected in terms of the identification of sustainable solutions for enhancing crop production in water limited environments.

2. "Root growth sensing under water deficit: a mechanobiology paradigm from root cell to system"
Mariana Sotelo, Universidad de la República, Montevideo, Uruguay
The balance between cell division, regulated cellular expansion, and differentiation in the root apical meristem directs primary root growth in Arabidopsis. Cellular expansion requires cell wall controlled relaxation, which ensures cell integrity during the expansion process. In field conditions, the soil changes its physicochemical properties in the microscale exposing the root to different kinds of stress, among them osmotic stress. Our work aims to dissect root growth and cellular adaptation to osmotic stress by studying root growth parameters, cell wall physical properties and hormonal signaling in osmotic stress hypersensitive mutants.

3. "Formation of heat stress-induced endosomal bodies in response to elevated temperatures and consequences for endocytic trafficking and plant stress tolerance"

Ricardo Tejos Ulloa, Universidad Arturo Prat, Chile

Temperature is a key environmental factor, and all living organisms have developed ways to sense and respond to potentially harmful temperature changes. Elevated temperature or heat stress is one of the major abiotic stresses that limits plant productivity. The heat stress response is an evolutionarily conserved response widely present in eukaryotes and involves the participation of chaperones to overcome the proteotoxic stress that protein unfolding and aggregation produce at elevated temperatures. Our work currently aims to characterize the formation of previously unknown endosomal agglomerations that we have called heat stress-induced bodies (HSIB). Current efforts are in the direction of determining the functional importance of these endosomal agglomerates to Arabidopsis heat shock response.

4. "Root growth mechanisms under low-temperature stress"

José M. Estevez, Foundation Institute Leloir-Argentina and UNAB/ iBIO-Chile

Root hairs (RH) growth are highly influenced by endogenous as well as by external environmental signals that coordinately regulates its final cell size. RHs are part of the active surface root area crucial for nutrient uptake and water absorption. Previously, we have determined that the low-temperature treatment at 10°C is able to trigger, unexpectedly, an exacerbated RH growth compared to the room-temperature control condition (22°C). This plasticity in RH growth at low-temperature was linked to a reduced nutrient availability in the media. In this talk, I will explore the molecular basis of this strong RH growth response by using the Genome Wide Association Studies (GWAS) approach on Arabidopsis thaliana natural accessions. In the second part of the talk, I will show that the long non-coding RNA APOLO recognizes the locus encoding the root hair (RH) master regulator ROOT HAIR DEFECTIVE 6 (RHD6) and controls RHD6 transcriptional activity, leading to cold-enhanced RH elongation through the consequent activation of the transcription factor gene RHD6-like RSL4. Furthermore, we demonstrate that APOLO interacts with the transcription factor WRKY42 and modulates its binding to the RHD6 promoter. WRKY42 is required for the activation of RHD6 by low temperatures and WRKY42 deregulation impairs cold-induced RH expansion. Collectively, our results indicate that a novel ribonucleoprotein complex with APOLO and WRKY42 forms a regulatory hub to activate RHD6 by shaping its epigenetic environment and integrate signals governing RH growth and development.

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SBBMCh Week
October 26th – 28th

- **IUBMB Virtual Jubilee Lecture**
  Dr. Hailing Jin, University of California Riverside , US
- **Cori Conference**
  Dr. Sergio Lavandero, Universidad de Chile, Chile
- **Severo Ochoa Conference**
  Dra. Nuria Casals, Universitat Internacional de Catalunya
- **Oral and Posters Research Sessions**

- **Symposia:**
  - *"Emerging roles of the cytoskeleton in cellular functions"*
    Chair: Christian Gonzalez-Billault, Universidad de Chile
  - *"Emerging Viral Infections: Insight on mechanism, vaccines, and therapeutic approaches"*
    Chair: Alejandro Rojas-Fernandez, Universidad Austral
  - *"Non-Coding Gets Louder: Essential role of ncRNAs in diverse cellular processes"*
    Chair: Verónica A. Burzio, Fundación Ciencia & Vida; U. Andrés Bello
  - *"Young scientists in molecular cancer research"*
    Chairs: Ariel Castro , Universidad de Concepción and
    Julio Tapia, Universidad de Chile

IUBMB VIRTUAL JUBILEE LECTURE

Cross-Kingdom RNAi and extracellular vesicle-mediated small RNA trafficking between plants and fungal pathogens

Hailing Jin
Department of Microbiology and Plant Pathology and Center for Plant Cell Biology, Institute for Integrative Genome Biology, University of California, Riverside, California 92507, USA.

Communication between plants and interacting microorganisms requires the secretion and uptake of molecules to and from the interacting organisms. We discovered that some small RNAs from eukaryotic pathogens, such as *Botrytis cinerea*, are delivered into plant cells and hijack host RNAi machinery to suppress host immunity genes (Weiberg et al., Science 2013). We further demonstrated that such cross-kingdom RNAi is bi-directional (Wang et al., Nature Plants 2016). Plants utilize extracellular vesicles, mainly exosomes, to send small RNAs into fungal cells and silence fungal virulence-related genes (Cai et al., Science 2018). Recently, we identified a set of RNA-binding proteins, which enter extracellular vesicles and contribute to the selective loading and stabilization of small RNAs in the extracellular vesicles (He et al., Nature Plants, 2021). Furthermore, we also discovered that many fungal pathogens can take up RNAs from the environment efficiently (Wang et al., Nature Plants, 2016; Qiao et al., Plant Biotech J. 2021). Applying small RNAs or double-stranded RNAs that target fungal virulence-related genes on plants can effectively inhibit fungal diseases. Such pathogen gene-targeting RNAs represent a new generation of fungicides that are durable and eco-friendly.

Funding: This work in Dr. Jin's lab was supported by the National Institutes of Health (R35 GM136379); the National Science Foundation (IOS2017314), the United States Department of Agriculture National Institute of Food and Agriculture (2021-67013-34258 and. 2019-70016-29067), the Australian Research Council Industrial Transformation Research Hub (IH190100022), as well as the CIFAR Fungal Kingdom fellowship.

OSVALDO CORI LECTURE

Cell signaling mechanisms in the development of cardiovascular diseases

Sergio Lavandero
Advanced Center for Chronic Diseases (ACCDiS), Facultad de Ciencias Químicas y Farmacéuticas y Facultad de Medicina, Universidad de Chile, Cardiology Division, University of Texas Southwestern Medical Center, Dallas, Texas, USA

The heart is an organ that performs tireless mechanical work throughout our entire existence. Its ability to contract and relax depends on complex biochemical processes that occur in cardiomyocytes. Although these cells only represent a third of the total population of cardiac cells, they exhibit unique biological characteristics: i) no proliferative capacity, ii) a large number of mitochondria (providing ~ 6 kg ATP/day), and iii) a specialized excitation-contraction coupling system composed of the sarcolemma, which forms tubules inside the cell able to exchange ions, and the endoplasmic reticulum, which dynamically regulates intracellular calcium levels to control the functioning of the sarcomeres and the generation of energy. These biochemical processes depend on a complex intracellular communication network, which becomes altered under demands for greater work. These higher requirements are initially met by an increase in the number of sarcomeres that expand cell size, causing hypertrophy of the heart. If the stress is intense and permanent, cardiomyocytes experience death by apoptosis, necrosis, and autophagy. These processes are crucial and shared in the development of various cardiac pathologies, which represent the first cause of morbidity and mortality at a global level. During my last 35 years of research, I have described new ideas, concepts, mechanisms, and cellular processes associated with cellular communication involved in cardiovascular diseases. I will present our findings on the communication between plasma membrane-nucleus, mitochondria-endoplasmic reticulum, plasma reticulum-nucleus, mitochondrial dynamics and function, primary cilium, and the molecular bases of heart failure with preserved systolic function (HFpEF). This new knowledge will allow us to understand the molecular bases of these diseases and the development of new drugs for their prevention and/or treatment.

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SEVERO OCHOA LECTURE

Nutrient sensing by neurons and its impact on body weight control, cognition and motor function

Nuria Casals
Basic Sciences Department, Facultat de Medicina i Ciències de la Salut, Universitat Internacional de Catalunya (Barcelona, Spain), and Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III (Madrid, Spain)

Nutrients, hormones and the energy sensor AMP-activated protein kinase (AMPK) tightly regulate the intracellular levels of the metabolic intermediary malonyl-CoA, which is a precursor of fatty acid synthesis and a negative regulator of fatty acid oxidation. In brain neurons, the sensing of malonyl-CoA by carnitine palmitoyltransferase 1C (CPT1C), a pseudoenzyme without catalytic activity, regulates a variety of functions such as the motility of lysosomes in developing axons, the trafficking of glutamate receptors to the neuron surface (necessary for proper synaptic function), and the activity of the endocannabinoid system. I will explain how the sensing of malonyl-CoA by CPT1C regulates those cellular functions and how the impairment of this system can result in the development of obesity, motor disabilities and learning deficits.

SYMPOSIUM 1

Young scientists in molecular cancer research

1. "Zooming into myc biology to battle pancreatic cancer"
Tania Campos, University of Cambridge, UK.
Pancreatic ductal adenocarcinoma (PDAC) is the fourth most frequent cause of cancer-related deaths worldwide, with a 5-year overall survival of less than 7%. This poor prognosis is due to late presentation and limited therapeutic efficacy, partly due to the fibroinflammatory and desmoplastic PDAC microenvironment. We have recently shown that the KRasG12D/Rosa26MycER mouse model faithfully recapitulates the human disease. Acute activation of the transcription factor Myc in pancreatic epithelial cells in vivo is sufficient to coordinate the stromal and immune changes associated with PDAC. We also have shown that Myc-dependent progression to PDAC is reversible: Myc deactivation triggers disassembly of advanced PDAC tumour and stroma. This tumour regression is not simply a reversal of events that originally generated PDAC but exhibits features of a choreographed active programme. However, the mechanism of tumour regression that is elicited by acute Myc denial is unknown. Using the rapid switchability afforded by our MycER mouse model and single-cell transcriptomics we have identified Myc-dependent signalling molecules that are essential in the PDAC regression process. Since there is no therapeutic Myc inhibitor, determining the nature of downstream Myc effectors and their role in instructing tumour-stromal interactions is crucial in identifying novel therapeutic targets.

2. "Targeting MYC through its interaction with NSD3S"
Valentina González, Universidad Católica de la Santísima Concepción, Chile
MYC is an oncogene, a transcriptional regulator and a well validated cancer drug target. However, targeting MYC has been challenging. Because MYC function is controlled by signaling proteins, one approach is to discover critical regulators of MYC and inhibit MYC using protein-protein interactions (PPI) disruptors. Towards this goal we utilized a high-throughput PPI technology and identified a novel MYC partner, an epigenetic regulator, NSD3S which is amplified in multiple cancers and functions as an oncogenic driver. We demonstrated that NSD3S interacts with MYC under physiological conditions in cancer cells. We defined the interaction interface between a 26-amino acid region on NSD3S and MYC internal region. Overexpression of NSD3S increases MYC protein stability and transcriptional activity. Mechanistically, NSD3S binds to MYC and reduces the association of F-box and WD repeat domain containing 7 (FBXW7) with MYC, which results in suppression of FBXW7-mediated proteasomal degradation of MYC and an in increase MYC protein half-life. We designed and developed a time-resolved-fluorescence energy transfer (TR-FRET) assay in a 1536-well ultra-high-throughput-screening (uHTS) format to identify PPI inhibitors. We have screened a library of 130 thousand compounds for NSD3S-MYC PPI disruption with a positive rate of 0.3%. These results support a critical role for NSD3S in the regulation of MYC function and provide a novel mechanism for NSD3S oncogenic function through inhibition of FBXW7- mediated degradation of MYC.

The study suggests a novel regulatory axis between NSD3S and MYC and a novel therapeutic approach for treating patients with MYC-driven tumors.

3. "Polyamines metabolism as target for lung cancer therapy"
Rodrigo López, Universidad Austral de Chile, Chile

Polyamines (putrescine, spermine and spermidine) are small cations essential for tumor proliferation. In non-small cell lung cancer (NSCLC), they have been proposed as early markers of tumorigenesis. Enzymes involved in polyamine synthesis, such as ODC and AMD1, are among the first proteins increased in tumorigenesis. So, polyamine metabolism has become an attractive chemotherapy target. On the other hand, the increase of SSAT, the enzyme that catabolizes polyamines, induces antitumor effects. We have explored inhibitors of the main enzymes of polyamine metabolism: DFMO (an ODC inhibitor), SAM486A and everolimus (which inhibit and decrease protein levels of AMD1, respectively). Also, we have assayed methoctramine, an inhibitor of the recovery polyamine process from their acetylated state. Non-steroidal anti-inflammatory drugs (NSAIDs) increase SSAT levels, affecting the arginine metabolism (including polyamine-related pathways) and show synergistic effects with methoctramine, suggesting that the acetylation and further exporting of polyamines can be exploited as a therapeutic target. Interestingly, these effects seem to be associated with the mutation profile of NSCLC cell lines. The driver mutation of KRAS controls the ODC expression via the MAPK cascade. Among these proteins, MEK has been considered a potential target for KRAS-mutated cancer treatment. Interestingly, MEK activation induces the ODC expression and tumorigenesis. MEK can be inhibited by selumetinib and trametinib. Selumetinib shows a synergistic effect in an NSCLC cell line mutant for KRAS. The new inhibitors of mutant KRAS also decrease the levels of ODC in NSCLC cell lines. Accordingly, KRAS and MEK inhibition could effectively decrease polyamine synthesis in KRAS-mutated NSCLC cells and synergize with polyamine inhibitors.

4. "A novel panoramic glance of the endothelin axis in cancer"
Ignacio Niechi, Universidad Austral de Chile, Chile

Endothelin-1 (ET1) is a mitogenic peptide involved in cancer progression and aggressiveness. Although its role has been widely described in vasoconstriction-related diseases, new advances have proposed ET1 as a therapeutic target in different types of cancer, such as ovary, colon, glioma, among others. ET1 is produced by ECE1 at the cell surface activating its receptors ETAR and/or ETBR. Our research aims to modulate ET1 metabolism and signaling in order to evaluate its effects on cancer cells hallmarks. In this work we studied whether a super-stable variant of ECE1 promotes a stem-like phenotype in glioblastoma cells. Results indicate that ECE1 stabilization promotes self-renewal and enhanced spheroid formation, as well as increased expression of CD133 and CD44 stemness markers. These cells show higher resistance to temozolomide and gemcitabine, potentially through increased expression of the ABCG2 efflux pump. Furthermore, these cells showed augmented adhesion, migration, invasion, and expression of EMT markers. Finally, the blockage of ET1 receptors decreases in vitro cell invasion in gallbladder cancer cells through downregulation of ZEB1 and CD44. All together, these results show that ET1 regulates cancer hallmarks in several cancer types, proposing its signaling and metabolism as plausible therapeutic targets.

SYMPOSIUM 2

Emerging viral infections: Insights on mechanism, vaccines, and therapeutic approaches

1. "B cell and antibodies in antiviral immunity: from basic immunology to universal vaccine"
Davide Angeletti, University of Gothenburg, Sweden.
Every year, infections with influenza lead to 5 million hospitalizations and are lethal for up to 650,000 patients. Additionally, the constant threat of emerging pandemic influenza strains poses a major risk for global health, emphasizing the need for an effective vaccine. Present influenza vaccines provide only short-term protection via the induction of strain-specific antibodies and require annual reformulation. Indeed, a major obstacle to vaccination against antigenically variable viruses is skewing of antibody responses to variable immunodominant epitopes. For influenza virus hemagglutinin (HA), the immunodominance of the variable head impairs responses to the highly conserved stem. In my presentation, I will discuss our recent results elucidating immunological reasons behind stem subdominance. Further, I will describe a range of strategies we have employed to generate broadly neutralizing antibodies that can cross-neutralize different strains, elicit effector functions and protect against a range of viruses of different subtypes. Our findings delineate strategies for overcoming immunodominance, with important implications for human vaccination.

2. "Radiolabeled Nanomedicines – A short overview about existing labeling methods and their applications"
Matthias Herth, University of Copenhagen, Denmark
Nanomedicines e.g. liposomes or monoclonal antibodies (mAbs) play a pivotal role in the treatment of cancers. Their use has been rapidly increasing over the past decades. Recently, the FDA has even approved the application of two mAbs to treat Alzheimer´s disease. Liposomal drug formulations of mRNA-based vaccines have also been shown to be incredibly effective in the fight against COVID-19 and future applications within cancer are on its way. The possibility to use nuclear imaging techniques to quantify the pharmacokinetics of nanomedicines even on an individual basis and thereby select patient groups likely to respond to nanomedicines leads to the possibility to carry out precision medicine. This is for example crucial for nanomedicines based on the EPR-effect. However, and more commonly applied, nuclear imaging techniques can also be used to quantify drug release, to find the optimal dose within clinical trials and to assess the therapeutic efficacy in real-time. In order to use nanomedicines as molecular imaging probes a wide array of labeling methods have been developed. Recently, a new technology – pretargeted imaging - was added to this array. In this talk, I want to touch upon the possibilities that molecular imaging offers with respect to the development and translation of nanomedicines in to the clinic and their respective labeling strategies. Advantages and disadvantages of each strategy will be discussed.

3. "Generation of potent Nanobodies for the neutralization of emergent virus"
Alejandro Rojas-Fernández, Universidad Austral de Chile, Chile
Despite unprecedented global efforts to rapidly develop SARS-CoV-2 treatments, in order to reduce the burden placed on health systems, the situation remains critical around the world. Effective treatment, and prophylactic measures are urgently required to meet global demand: recombinant antibodies fulfill these requirements and have marked clinical potential. Since 2017, our laboratory has been working on the implementation of a Nanobodies platform for direct immunization and isolation of nanobodies in the south of Chile, taking advantage of the geographic locations. We describe a fasttracked development of an alpaca Nanobody specific for the receptor-binding-domain (RBD) of the SARS-CoV-2 Spike protein with potential therapeutic applicability. We present a rapid method for nanobody isolation that includes an optimized immunization regimen coupled with VHH library E. coli surface display, which allows single-step selection of Nanobodies using a simple density gradient centrifugation of the bacterial library. Here, we summarized the most recent results of our neutralizing nanobodies against SARS-CoV-2 and an insight into future challenges of our platform.

4. "Regulating immune responses in emerging viral infections"
Kellie Ann Jurado, University of Pennsylvania, USA
Emerging viruses provide ample opportunity to understand host immune control, including SARS-CoV-2. SARS-CoV-2 bypasses multiple innate immune activation pathways through distinct mechanisms. Here, we show that SARS-CoV-2 can block IRF3 and NF-κB activation early during virus infection and describe the mechanism of immune evasion of two viral proteins.

SYMPOSIUM 3

Non-coding gets louder: Essential role of ncRNAs in diverse cellular processes

1. "Role of mitochondrial translation and dynamics and their dysregulation by lncRNAs in melanoma therapy resistance"
Eleonora Leucci, LKI Leuven Cancer Institute, KU Leuven, Belgium
The activation of the integrated stress response (ISR) in melanoma has been shown to induce the emergence of DTPs (Drug Tolerant Precursors) and linked to drug resistance. We recently demonstrated that besides its role in the induction of quiescence via the downregulation of translation, the activation of the ISR is also essential to confer plasticity to drug-tolerant cells by upregulating mitochondrial translation. Being at the crossroads of most energetic/metabolic pathways in the cell, mitochondria are essential to switch between different DTPs and thus constitute an exploitable vulnerability for melanoma. We have previously shown that the melanoma-specific lncRNA SAMMSON is essential to keep cytosolic and mitochondrial translation balanced and that its downregulation is a threat for proteostasis. We have now identified LENOX induced in drug-tolerant cells upon treatment with MAPK inhibitors. LENOX promotes the association of the RAP2C GTPase with DRP1 and results in increased DRP1 S637 phosphorylation, mitochondrial fusion and oxidative phosphorylation, thus conferring resistance to MAPK inhibition. Accordingly, LENOX and RAP2C silencing cooperate with MAP kinase inhibitors at eradicating melanoma cells. Our work indicates that LENOX, together with MITF and SAMMSON, is part of a SOX10-regulated gene regulatory network acting cooperatively to optimize mitochondrial function during melanoma development and progression.

2. "Pathogenic transfer of microRNA-15a from pancreas to heart during obesity"
Fernanda Carrizo Velasquez, Johns Hopkins School of Medicine, USA
Recent work shows that hyperglycemic conditions stimulate exosomal-microRNA-15a secretion from pancreatic β-cells. These circulating small extracellular vesicles (sEVs) deliver their cargo into the retina and initiate vasculopathy. We hypothesized that obesity increases exo-miR-15a uptake into cardiomyocytes. This cell-cell communication may initiate the molecular process of obesity-induced cardiac dysfunction. Using qPCR, we have identified a progressive increase of miR-15a expression in the heart under a high-fat diet (HFD) regimen. *In vitro* assays, either by culturing myocytes in high glucose or increased lipid inside myocytes, showed no upregulation of miR-15a. Incubating sEVs derived from HFD mice into myocytes isolated from miR-$15^{-/-}$ mice, showed a significant increase in miR-15a expression in myocytes compared to incubation with sEVs from NC animals. The transfer of exo-miR-15a also downregulates Bcl-2 protein, direct target of miR-15a and regulates its cellular function. Using β-cell-specific and cardiac-specific miR-$15a^{-/-}$ mice, we have validated this novel β-cell-to-cardiomyocyte communication by exo-miR-15a in the pathogenesis of obesity induced cardiac dysfunction.

3. "Role of mitochondrial microRNAs in the DNA damage response"

Christopher Fitzpatrick, Fundación Ciencia & Vida/Andes Biotechnologies; Université Paris-Saclay, INRAE, AgroParisTech, France; Universidad Andrés Bello, Santiago, Chile

MicroRNAs are small non-coding RNAs that regulate gene expression of many targets involved in a wide array of cellular processes including apoptosis, proliferation and differentiation among others and their expression differs in a high number of pathological states such as cancer. Published evidence shows that mitochondrial-derived microRNA (Mito-miRs), increase in response to ionizing radiation, thermal injury and SARS-CoV-2 infection in seropositive patients and cell lines. Knockdown of antisense non-coding mitochondrial RNAs (ASncmtRNAs) with antisense oligonucleotides induces an increase in miR-4485-3p and miR-1973 in cancer cells, which are contained in ASncmtRNA-2. Knockdown of miR-1973 by antagomir transfection in the breast cancer cell line MDA-MB-231 inhibits ubiquitination of the double-strand DNA damage marker γH2AX induced by either doxorubicin or by knockdown of the ASncmtRNAs. The presence of multiple repeats of nuclear mitochondrial insertions (NUMTs) and the hypothetical function of these molecules in mitochondrial-nuclear communication will be addressed.

4. "Differential mitochondrial RNA expression in equine melanoma versus skin cells analyzed by a new direct RNA long-read sequencing method"

David Bars-Cortina, Université Paris-Saclay, INRAE, AgroParisTech, France; Ecole Nationale Vétérinaire d'Alfort, Université Paris-Est, Maisons-Alfort, France

Since the discovery of the Warburg effect (1920s), the implications of mitochondrial networks in oncogenesis has been suspected and increasingly investigated, in particular at the genomic level. In the present study, we asked whether mitochondrial transcription in tumor cells is normal or altered. The aim of this study was to analyze whole mitochondrial RNA expression in equine melanoma primary cells versus normal skin cells collected by biopsies for diagnostics. The originality of the method was to use direct native RNA long-read sequencing to measure differential expression. By Deseq2 analysis we detected three significantly differentially expressed genes, 12S rRNA, 16S rRNA and ND5 (corrected p-value <0.05). Despite the model of one transcript spliced in different mitochondrial transcripts, this direct RNA-seq analysis of the mitochondrial transcriptome in equine melanoma cells versus normal skin cells revealed a partial differential expression of the 12S rRNA, 16S rRNA (noncoding transcripts) and ND5 mRNA.

SYMPOSIUM 4

Emerging roles of the cytoskeleton in cellular functions

1. "Microtubule Cartography: How Microtubule-Associated Proteins Define the Cellular Landscape"
Kassandra Ori-McKenney, University California Davis, USA
Cellular function is intimately linked to cellular architecture, which is largely governed by cytoskeletal networks. It is therefore essential to understand the regulatory mechanisms of cytoskeleton organization as a cell develops, changes, or maintains its internal structure, because altering these processes can disrupt cell function and ultimately lead to cellular pathology. Our lab studies the microtubule cytoskeleton and the microtubule-associated proteins (MAPs) that regulate a myriad of network activities. Using in vitro reconstitution of purified proteins, we have found that these MAPs exhibit diverse binding behaviors on the microtubule lattice and differentially affect microtubule motors, highlighting an essential role for MAPs in gating access to the lattice. We are now studying the biochemical and genetic relationships between kinases, MAPs, and motors both in vitro and in vivo using *Drosophila melanogaster* as a model system. We aspire to construct a comprehensive network to elucidate the multiple ways in which disease-relevant proteins modulate the microtubule cytoskeleton during different cellular processes.

2. "Epigenetic regulation of neuronal polarization and axon growth by the histone methyltransferase G9a and the H3K9me2 label"
Carlos Wilson, Instituto de Ciencias Biomédicas, Córdoba, Argentina
Neurons are polarized cells, exhibiting the somato-dendritic and axonal compartments; domains specialized in receiving and transmitting signals, respectively. This compartmentalization is the result of decoding extrinsic/intrinsic stimuli, impacting on signaling pathways able to shape the neuronal morphology. In this regard, cytoskeleton remodeling is crucial, since both microtubules (MT) and F-actin (FA) represent the driving force of polarization and axonal development. Although polarity mechanisms have been reported, the genetic fundamentals remain underexplored. Recently, we reported that the histone methyltransferase G9a promotes polarization and axonal growth in cultured hippocampal neurons, by repressing the RhoA-ROCK pathway, a negative regulator of neuronal polarization. In addition, the loss of function of G9a in situ impaired cortical migration of embryonic neurons, suggesting failures on polarization and migration in vivo. Moreover, bi-methylation of H3K9 (H3K9me2), highly dependent on G9a in developing neurons, parallels axon formation in early and mature stages. Accordingly, genetic deletion of nuclear H3K9me2 impairs axonal maturation, visualized by abnormal assembly of the axon initial segment (AIS); the intra-axonal domain in which voltage-dependent ion channels are recruited. Overall, our results suggest a link between epigenetic regulation and axonal development in central neurons through a G9a-H3K9me2 – dependent mechanism.

3. "Dynamics of neurofilaments in axon"
Anthony Brown, Ohio State University, USA
Neurofilaments are abundant space-filling cytoskeletal polymers that are transported into and along axons where they are aligned longitudinally and in parallel to the long axis of the axon like a bundle of sticks, forming a highly anisotropic array. During postnatal development, these polymers accumulate in myelinated axons causing an expansion of axon caliber which is necessary for rapid electrical transmission. Live imaging in cultured nerve cells has shown that the neurofilaments move rapidly and intermittently along microtubule tracks in both anterograde and retrograde directions. However, it is unclear if neurofilament transport is also bidirectional in vivo. Here, we describe a novel pulse-spread fluorescence photoactivation method to address this in myelinated axons of peripheral nerve segments dissected from juvenile and adult hThy1-paGFP-NFM transgenic mice, which express a photoactivatable fluorescent neurofilament protein. Neurofilaments were photoactivated in a short segment of axon and the proximal and distal spread of the fluorescence due to the movement of the fluorescent neurofilaments was measured over time. We show that the directional bias and velocity of neurofilament transport can be calculated from these measurements. Our data demonstrate bidirectional transport of neurofilaments in myelinated axons, with approximately 60% moving anterogradely. The neurofilament transport rate decreased with age and distance along the nerve, which is consistent with previous reports obtained using radioisotopic pulse labeling. The fact that axons invest metabolic energy to move neurofilaments backwards in such high proportion is puzzling, and it suggests that neurofilament transport is not simply a mechanism to deliver neurofilaments to axons. We propose that the bidirectional movement of neurofilaments also functions to distribute and organize these polymers in axons, establishing and maintaining their longitudinal alignment.

4. "Neuronal soma morphology and neurite initiation are controlled by a novel wreath-like network of septin filaments"
Elias Spiliotis, Drexel College of Medicine, USA
The pyramidal neurons of the cerebral cortex and hippocampus have triangular pyramid-shaped cell bodies, which position and orient their axonal and dendritic arbors along the apicobasal axis. Neuronal cell body shape is coupled to neurite formation and differentiation into axons and dendrites. Neurites develop from the protrusive activity of cell bodies, which extend and retract lamellipodia and filopodia, but how these are spatially regulated to establish cell bodies with proper size, shape and neurite number is unknown. Here, we show that a novel cytoskeletal wreath-like network of septin GTPases regulates actin polymerization and contractility at the base of the lamellar protrusions of the neuronal cell body. This septin network, which is enriched with septin 7 (Sept7), colocalizes with myosin IIB at the base of filopodia and inter-filopodia veils, and demarcates a zone of anterogradely decreasing levels of Arp2/3. Sept7 knock-down results in enlarged cell bodies, which lack pyramidal morphology and are characterized by extensive lamellipodia-like protrusions. Sept7-depleted neurons have an abnormally increased number of neurites, which are highly branched and extend from lamellipodial protrusions rather than directly from the cell body. Rescue of cell body phenotypes with the Arp2/3 inhibitor CK666 and a dominant-negative cortactin suggests that the septin wreath network suppresses Arp2/3-driven protrusions. Conversely, loss of myosin IIB from the base of filopodia in Sept7-depleted cells, which correlates with shorter-lived neurites, and rescue of neurite phenotypes with a constitutively active myosin II

regulatory light chain suggests that the septin wreath network promotes filopodia maturation into neurites. We posit that morphogenesis of pyramidal cell shapes is coupled to neurite formation via a filamentous septin wreath network, which biases protrusive activity toward filopodial than lamellipodia protrusions by favoring actomyosin contractility over Arp2/3 polymerization in the cell bodies of developing neurons.

TECHNICAL TALK

ThermoFisher

"Cellular screening, immunotherapies and cell culture characterization: new frontiers"

Úrsula León, Cellular and protein analysis specialist, ThermoFisher Chile.

The world has changed and it is becoming increasingly important to have new and diverse technologies that allow us to efficiently understand and discover the path to next-generation research. Tools will be presented to carry out the analysis, characterization, detection and validation of your research in routine cell culture applied through classical technologies such as fluorescent antibodies on next-generation platforms.

Oral Session 1

CaMKIV/CREB/BDNF signaling pathway in the Central Nervous System of diabetic mice

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The prevalence of diabetes mellitus (DM) has increased in the last decades, being estimated that 642 million people will suffer this disease in 2040. An association between DM and anxiety and depression has been reported, which may be related to changes in the expression of the CaMKIV/CREB/BDNF signaling pathway in different central nervous system regions. The objective of this study was to determine if diabetic mice with anxiety-like behaviors show alterations in the expression of these proteins, in comparison to non-diabetic mice (NDB). Diabetes was induced in CD1 mice by intraperitoneal injection of steptozotocin. After three months of untreated DM, diabetic mice presented anxiety-type behaviors, and were sacrificed in order to analyze the expression of the proteins by Western blot. We found that, opposite to NDB, diabetic mice had a decreased hippocampal CaMKIV expression, an increased expression of CREB in the amygdala and hypothalamus, as well as a decreased hypothalamic pCREB/CREB expression ($p<0,05$). This is the first time that CaMKIV expression is evaluated in the CNS and related to stress or anxiety-like behavioral changes in diabetic animals. The hippocampus is thought to be one of the most sensitive to DM among the CNS regions. CaMKIV could have a relevant role in the contribution of the possible hippocampal dysfunction to the anxiety-like behavior observed in diabetic mice. However, more evidence is needed to elucidate the mechanisms underlying these alterations, and future work is necessary to determine the existence of a link between CaMKIV and the behavioral anxious profile in diabetic animals.

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Role of soluble Interleukin-6 receptor in vascular smooth muscle cell phenotype

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Vascular smooth muscle cells (VSMC) are components of the vasculature responsible for regulating the artery contraction. Under pathological conditions, they change their phenotype from contractile to migratory/synthetic, generating pathological vascular remodeling. On the other hand, regular physical activity can produce physiological remodeling. It is thought that myokines released during physical exercise may be responsible for this remodeling. Here we evaluated whether IL-6 and its soluble receptor (sIL-6R), which are released in large quantities during exercise, could be involved in the regulation of the phenotypic change of VSMC. A7r5 VSMC were treated with IL-6, sIL-6R and IL-6+sIL-6R. VSMC phenotypic change was evaluated measuring contractile proteins, proliferation, collagen content, and cell migration. We determined that IL-6 did not modify VSMC contractile proteins, cell proliferation and collagen content. However, IL-6 increased VSMC migration in a dose-dependent fashion. sIL-6R inhibits il-6-induced cell migration. Thus, this signaling could be an important mechanism of protection of the vascular health of the artery during exercise.

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Identifying cytokine signaling regulators of tumor dormancy and recurrence in breast cancer using CRISPR/Cas9 screen

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Breast cancer is the leading cause of cancer mortality in women, mainly due to incurable metastatic recurrence arising after initial treatment. Recurrent tumors arise from a presumptive pool of residual tumor cells (RTCs) that persist in a dormant state after targeted therapy treatment. Identifying the pathways underlying tumor dormancy and recurrence is critical to reduce breast cancer mortality. To study tumor dormancy and recurrence, we used transgenic mice conditionally expressing the HER2/neu oncogene (MTB/TAN mice). MTB/TAN mice develop mammary tumors upon oncogene induction, and conversely, tumors regress following oncogene inhibition. However, a small number of RTCs survive oncogene inhibition and persist in a dormant state, and ultimately seed spontaneous recurrent tumors. RTCs have shown an increased interleukin-6 expression (IL-6), and we hypothesized that IL6 signaling– via the JAK-STAT pathway- promotes dormant tumor cells survival in conditions of HER2/neu oncogene inhibition. We performed an *in vivo* CRISPR/Cas9 screen to simultaneously interrogate the function in tumor dormancy and recurrence of genes broadly implicated in JAK-STAT signaling. MTB/TAN-derived tumor cells that express Cas9 were lentivirally transduced with the pooled JAK-STAT library and orthotopically injected into mice. To identify hits, we run massively parallel sequencing and used available CRISPR screen analysis tools and custom designed pipelines. Our screen results showed that inhibition of IL6 function caused enrichment of tumor cells exclusively during dormancy and recurrence. Thus, IL-6 may be acting as suppressor of tumor recurrence. Future *in vivo* studies will help to validate the tumor suppressor function of IL6 in breast cancer dormancy and recurrence.

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DNA damage genes dysregulated by RBBP5 protein is associated with por survival in breast invasive carcinoma

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Breast cancer is one of leading cancer-related cause of disease. Even when advance in detection and therapy have been development, still remains as most lethal cancer worldwide, therefore, it's urgent to identify new molecular targets to increase patients survival.
With the aim to studying gene expression throughout disease progress, we analyzed transcriptional levels associated at each cancer stages (T1 – T4), using cbioportal database. RBBP5 (Retinoblastoma-binding protein 5) levels signficantly increased as well the disease progresses. About 9% of patients (89 patients) shown amplification in RBBP5 gene and 24% (238 patients) have high levels of it transcript. Interesly, high RBBP5 levels correlationed with a poor survival (Logrank P =0.0142). Functional protein association assay, using String database, reveled that RBBP5 interact with different member of Histone-lysine N-methyltransferase family (KMT2A, KMT2C, KMT2D) and MLL1/MLL complex (WDR5) to bound at differents DNA sites. Predict protein-DNA interaction assay (Chip-atlas database) showed 7633 RBBP5'targets genes, which are mostly enriched in DNA repair category (by ontology assay).
Our data suggest that RBBP5 interact with several methyltransferase to modulate DNA repair-associated genes expression, which drive an decrease in survival in patients with breast invasive carcinoma.

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Basal MTOR activation by CK2 phosphorylation in colorectal cancer cells

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In colorectal cancer, CK2 regulates the PI3K/AKT/MTOR pathway, an important nutrient regulated cascade. Here, MTOR forms two different complexes, MTORC1 and MTORC2, with MTORC2 being the first to be activated and followed by MTORC1 downstream in this pathway. Unpublished data from our laboratory indicate that inhibition of CK2 induces the shut-down of both MTOR complexes, suggesting a common mechanism. In this study, three putative phosphorylation sites of CK2 (S1847, S1849 and S1851) were identified on MTOR catalytic subunit by an *in silico* analysis. More importantly, these sites are located on the FAT domain, a known binding site for the negative regulator DEPTOR, which is released and proteasome-degraded upon basal MTOR activation. In this study, we detected *in vitro* CK2 phosphorylation on the three residues. Also, DLD-1 colon cancer and HEK-293T non-tumor cells were serum-deprived together with CK2 inhibition, and then DEPTOR stability, CK2-related MTOR phosphorylation, and specific MTOR interactors were analyzed by mean of whole-cell proteomic techniques (i.e. WB & IP). In serum-deprived DLD-1 cells, CK2 inhibition diminished MTOR phosphorylation, increased DEPTOR stability and promoted MTOR-DEPTOR complex formation. This was not observed on control HEK-293T non-tumor cells. These findings suggest a role of CK2 in the basal activation of MTOR by a direct phosphorylation mechanism, which occurs at expenses of extracellular nutrient stimulus specifically in colorectal cancer cells.

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Cardiovascular effects of extracts and bioactive molecules isolated from medicinal plants from Northern Chile

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Senecio nutans (Sch.) Bip. and *Xenophyllum poposum* (Phil.) V.A. Funk are endemic species of the Andes Cordillera. All of them are widely used by mountain communities to treat altitude sickness and hypertension.
This research aims to study the hypotensive and antihypertensive mechanisms of plant extract and bioactive molecules from *S. nutans* and *X. poposum*.
To improve the biological activity of the plant bioactive molecules, we performed simple structural modifications to synthetize oximes derivatives of natural bioactive molecules.
To evaluate the cardiovascular effect extract and bioactive molecules from *S. nutans*, and *X. poposum*, we used normotensive and hypertensive animal models.
The composition of the endemic Chilean species was investigated using Ultrahigh-Performance Liquid Chromatography, Heated Electrospray Ionization and Mass Spectrometry (UHPLC-Orbitrap-HESI-MS). The extract decreased the blood pressure in hypertensive and normotensive animals by decreasing the heart rate and contractility. The extracts and the isolated compounds caused vasodilation in rat aorta in absence of endothelium and apparently blocked calcium channels. The preincubation with extract decreased the cytosolic calcium on vascular smooth muscle cells in response to phenylephrine. The relaxing effect of oxime-1 and metabolite-2 was dependent on the vascular endothelium and attenuated the contractile response to KCl membrane depolarization or adrenergic response.
The results suggest an important clinical function in hypertension therapy, as *S. nutans* and *X. poposum* and their compounds could decrease the blood pressure in normotensive and hypertensive mice by decreasing the heart rate, contractility, and vasodilatation leading to a reduction in myocardial oxygen demand.

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Oral Session 2

Discovery of novel potential PET hydrolases from polar marine environments

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Polyethylene terephthalate (PET), which represents 10% of the annual production of plastics worldwide, accumulates as waste in oceans at rates paralleling its production level and make up to 90% of marine waste. Despite recent advances in the identification and characterization of PET-degrading hydrolases (PETases), the search for natural enzymes that can depolymerize PET at moderate temperatures is a challenging task. In this regard, enzymes from psychrophilic and psychrotolerant organisms are of special interest since they display optimal catalytic activity at temperatures ranging 0-30ºC, making them promising biocatalysts for industrial and biotechnological applications.
Since plastics have reached remote regions that are rich in psychrophilic and psychrotolerant bacteria such as Antarctica through the ocean currents, we performed a bioinformatic search for novel PETases in three marine metagenomic reference catalogues that include samples from Arctic and Antarctic regions using hidden Markov models (HMM) built from amino acid sequences of experimentally characterized PETases as references. Our analysis led to the identification of 683 novel PETases distributed in seven clades that cluster separately from the evolutionarily related dienelactone hydrolase family. Moreover, we determined through read mapping against metagenome-assembled-genomes that these enzymes are distributed from surface samples up to 3500m depth, and that a single clade groups together with all the reference PETases known to efficiently degrade PET at high and moderate temperatures. We selected 10 novel PETases from this group for experimental evaluation in polycaprolactone nanoparticle degradation assays, determining that 5 of these enzymes have polyesterase activity spanning different optimal temperatures between 14ºC and 50ºC.

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Analysis of transcriptional expression changes during Atlantic Salmon (*Salmo salar*) smoltification through bioinformatics tools

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Salmon farming industry has a great impact in southern Chile economy. Smoltification corresponds to Atlantic salmon adaptation mechanisms that enable them to live in seawater. This process is an important target for scientific study. Bioinformatics analyzes have become an essential tool capable of shortening and directing the path towards understanding this process. The objective of this work was to analyze the Atlantic salmon transcriptome changes that occur during the smoltification process by using bioinformatic tools. We hypothesize that the tissues of Atlantic salmon differentially express different transcripts between Parr and Smolt stages, as part of the multiple physiological changes that occur in the smoltification stage of Atlantic salmon. We aim to build an easy to access and complete transcriptome library. To this end, transcriptomic sequencing was carried out using Massive Illumina RNAseq at AustralOMICS. A complete library of the Atlantic salmon transcriptome with easy-to-adjust parameters was created in 5 different tissues (Gills, liver, hypophysis, anterior and posterior kidney) using Hisat2, Htseq-count, and Excel. Additionally, we observed a downregulation in many transcripts associated with posterior kidney inflammation pathway all of them were listed and portrayed in cytoscape.

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Structural changes correlate with unusual transition state ΔC_p values in archaeal kinases from the ADP-dependent family

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According to the Arrhenius theory, temperature increases enzymatic rates up to an optimum temperature (T_{op}) while decreasing rates above T_{op} are usually attributed to denaturation/aggregation. However, for many enzymes its T_{op} is not correlated with the melting temperature (T_m). The macromolecular rate theory (MMRT) explains why denaturation is insufficient to account for declining enzymatic rates above T_{op}, indicating that is due to a change in the heat capacity ($\Delta C_p^{\ddagger}$) of the transition state. Hence, we characterize two members of the ADP-dependent kinases family (glucokinase, ADP-GK), coming from psychrophilic and mesophilic archaea. Through saturation curves for glucose at different temperatures, we determined the dependence of the k_{cat} with temperature and determine the $\Delta C_p^{\ddagger}$ for both enzymes. Surprisingly, for both enzymes, the temperature-dependent catalysis presents a behavior of two states, one associated with the Arrhenius behavior where $\Delta C_p^{\ddagger}$ is zero, and other where $\Delta C_p^{\ddagger}$ turns up to an extremely negative value, showing besides, that the T_{op} is disengaged to the T_m. Circular dichroism experiments showed that the transition temperature for both states correlate with changes in the secondary structure not associated with aggregation or denaturation processes. Our results show two states with structural changes driven by temperature suggesting an increase in the C_p of the enzyme−substrate complex and/or a decrease in the C_p of the enzyme transition state species. Further studies are required to unravel the molecular mechanism and local structural changes associated with thermoadaptation of enzyme catalysis in these enzymes.

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The effect of NusG and RfaH binding on local and non-local structural dynamics of the bacterial transcription elongation complex

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RNA polymerases (RNAP) are multi-domain enzymes that transcribe all genes in every domain of life. Their activities are modulated by various accessory proteins, among which NusG family is the only universally conserved group of transcription factors. NusG factors increase RNAP processivity for most bacterial genes and couple transcription to translation. An outstanding contrast is found in RfaH, a specialized paralog that promotes the expression of xenogeneic operons encoding virulence factors, whose activity is tightly regulated by base-specific contacts with the DNA and a fold-switch between two native states. Despite these functional and structural differences, both factors establish similar interactions with RNAP, binding above the central cleft surrounding DNA. Although structures of both free- and RNAP-bound NusG and RfaH are available, these structural snapshots are not informative about the dynamic changes occurring upon complex formation.
We employed hydrogen deuterium exchange mass spectrometry (HDXMS) to determine changes in local and non-local structural dynamics of *Escherichia coli* RNAP upon NusG and RfaH binding to transcription elongation complexes (TEC). RNAP showed opposite deuteron incorporation changes in regions that establish similar interactions with NusG and RfaH. On the other, RNAP exhibits deuteron incorporation changes far from the factor-binding site only upon binding of RfaH. Our results provide insights of the differences in structural dynamics exerted by NusG and RfaH binding to TEC that may explain their different functional outcomes and the potential role of allosteric regulation in RfaH action.

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Biophysical characterization of the FtsZ-ZipA complex of *E. coli*, using *in multiplo* and *in singulo* approaches

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FtsZ and ZipA are the first proteins to assemble in the divisome, a multiprotein complex in charge of the division of Gammaproteobacteria. FtsZ is a GTPase that polymerizes in the cytosol of the cell. ZipA is a protein with a transmembrane N-terminal alpha helix that anchors FtsZ filaments to the inner side of the cytosolic membrane, at the middle of the cell. This structure, called Z-ring, sequentially binds the rest of the divisome proteins. Therefore, to study these two proteins and the interaction between them is fundamental to understand the cell division which is one of the most conserved processes in life. In this work we used Isothermal Titration Calorimetry, Steered Molecular Dynamics, and Force Spectroscopy using Optical Tweezers to characterize the dynamics, thermodynamic and kinetic parameters of the heterodimer formation. We found a very dynamic process for the interaction between FtsZ and ZipA. Thermodynamically it is an entropy driven process that lasts around 12 seconds and that it takes 8.3 pN to get a 50% chance of breaking the interaction between these two proteins. We also determined other parameters such as k_{off}, $\Delta G^{\ddagger}$, $x^{\ddagger}$. The dynamics, the apparent entropy and enthalpy change of the interaction between FtsZ and ZipA and the single molecule force measurements allow us to conclude that this complex has the requirements that permit the formation of the divisome and to exert the necessary anchor strength to develope the treadmilling force of the Z-ring for the septation of the membranes at the division site.

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Localization and functional characterization of GLUT8 from mammary gland

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Differentiated mammary epithelial cells responsible for milk synthesis within the mammary gland. These cells are found in the alveolus of the mature gland and are surrounded by myoepithelial cells and a fat-rich stroma. We explored the function and cell-specific expression of the glucose transporter GLUT8 in mammary cells to correlate them with lactose synthesis.
GLUT8 transporter was expressed in adipocytes, epithelial and myoepithelial cells of murine mammary gland during lactation, with a predominant intracellular granular pattern. Colocalization studies in the immortalized human mammary-derived cell lines 1-7HB2, revealed a predominant expression in lysosome, meanwhile that GLUT8 cloned form mammary gland fusioned with GFP showed colocalization with Golgi (Pearson's coefficient correlations of 0.82±0.05 and 0.68±0.16, respectively). Functional studies of GFP-GLUT8 showed a 7 fold increase in 2-deoxy glucose uptake (83.3 v/s 13.1 pmoles/(min*10^6 cells), and a 60±4 /72±6% of decline in 2-deoxy glucose uptake when transport was performed in the presence of 20 and 50 mM fructose, respectively.
We concluded that in lactating gland, functional GLUT8 is expressed predominantly in endomembrane system of mammary epithelial cells. It will be necessary to explore in detail the physiological/pathological function of GLUT8 in mammary gland, including its role in lactation.

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Oral Session 3

In silico and *in vivo* evaluation of transcriptionally rewiring the *Neurospora crassa* circadian clock core-elements

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Circadian clocks are timing devices that enable rhythmic adaptation to the daily changes associated with the earth rotation. In eukaryotes this clock is organized as a transcriptional- translational negative feedback loop (TTFL). In the *Neurospora crassa* clock, White Collar Complex (WCC), consisting of the transcription factors White Collar 1 (WC-1) and 2 (WC-2), activates the expression of the gene encoding for FREQUENCY (FRQ), which represses its own expression by inhibiting the WCC. In addition to the TTFL there are additional loops that connect the elements of the central clock, and the roles and the properties they modulate are not fully understood. The aim of this research is to study how the transcriptional rewiring of the *wc-1* and *wc-2* genes affect the circadian properties of the *N. crassa* clock. A mathematical model was utilized to simulate the behavior of these new systems and then predictions were validated using reporter strains where the promoters of *wc-1* or *wc-2* had been rewired in order to contain explicit additional feedback information. The rewiring of *wc-2* generates a 1 hour increase in period, which according to the model is mainly due to the decrease in WC-2 levels. In the case of *wc-1* rewiring, the period increases 4 hours and, based on the model, could be explain by the changes in the phase of WC-1 oscillations. This indicates a greater importance than expected, in the phase or timing of the oscillations to achieve proper period. Finally, the use of a mathematical model provides a valuable tool that can be used in the future to further dissect properties and robustness of other regulatory circadian architectures.

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Engineering a tunable semi-synthetic circadian oscillator through the integration of transcriptional *cis*-modules and environmental inputs

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Circadian clocks are present across the tree of life, and although the exact molecular components differ among species, they all share a common circuit design: a positive element that controls the expression of a negative element which is then able to inactivate the first one. In the fungus *Neurospora crassa,* these components correspond to the transcription factor White Collar complex (WCC) and the protein FREQUENCY (FRQ), respectively. We have adopted a synthetic biology approach to systematically add *cis*-modules to increase the transcriptional complexity of the negative element. Thus, we have first tested and shown the minimal *frq* promoter ability, containing only the *clock-box* (recognized by WCC), to yield robust and rhythmic oscillations. Then, we have analyzed the effect of adding defined *cis*-modules derived from non-circadian genes combined with the *clock-box*. Hence, we have generated strains where *frq* transcription can also respond to other defined signals (metabolic and environmental). Several resulting strains containing a synthetic combination of transcriptional circadian and non-circadian inputs display circadian behavior and are entrained through different regimes. Remarkably, several exhibit a period longer than 24 hours under free-running conditions transmitted to the conidiation pattern. Thus, for example, we have generated a strain where the clock is now responsive to cellulose presence and where the levels of this complex substrate can modulate the period. These and other approaches provide new insights regarding the clockworks while revealing an unexpected genetic level and transcriptional plasticity of circadian circuits and their ability to integrate, even when forced to, complex transcriptional programs.

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Generating an accurate map of temperature responses mediated by *hsp* promoter elements

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The Heat Shock Response (HSR) is a highly conserved mechanism that provides protection under stressing high temperatures through the action of Heat Shock Proteins (HSP). In the filamentous fungus *Neurospora crassa*, three *hsp* genes responsible for this response have been characterized: *hsp30*, *hsp70* and *hsp80*. However, the degree to which the putative transcriptional regulatory elements present in their promoters are sufficient to modulate expression upon subtle changes in temperature has not been systematically determined. Herein, we analyzed different sections of each *hsp* promoter, by assessing the expression of a destabilized luciferase reporter. We analyzed and mapped their response in a temperature gradient and different treatment times. The results reveal an accurate response depending on the temperature and time exposure with a wide range of response levels, anywhere from 10 to 5000 fold induction. Of the tested promoters only *hsp30* displayed a highly inducible and tunable response, highly sensitive to discrete temperature changes. We are currently defining the minimal cis-elements required to assemble cognate synthetic promoters maintaining the properties of *hsp30* transcripcional dynamics. These studies provide an unprecedented view into the regulation of the *N. crassa hsp* genes while also enabling the use of *hsp30* derived cis-elements as tools for biotechnological or basic research endeavors.

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A synthetic biology approach for studying tomato lipoyl synthase genes and their potential applications

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Lipoic acid (LA) is an eight-carbon molecule with thiol groups at carbons 6 and 8, known for its characteristics as a strong antioxidant. *In vivo*, lipoic acid is synthesised from an 8-carbon octanoate precursor by a lipoyl synthase (LIP1). While lipoic acid acts as an essential cofactor in numerous enzymatic complexes involved in primary metabolism, such as pyruvate dehydrogenase (PDH), and α-ketoglutarate dehydrogenase (kGDH), it has also been shown that application of lipoic acid results in higher resistance to different forms of abiotic stress in plants.
Previous attempts to overexpress *LIP1* genes from *Arabidopsis thaliana* (*AtLIP1*) and *Solanum lycopersicum (*tomato, *SlLIP1)*, under a strong constitutive promoter in *S. lycopersicum* cv. Micro Tom, have yielded mixed results as these plants exhibited defects in growth and seed production. Current strategies involving the use of inducible promoters as well as CRISPR-mediated transcriptional activation are currently underway, as well as the implementation of a recursive synthetic biology assembly system named Loop Assembly. For this system, DNA sequences of interest, such as plant *LIP1* genes, several abiotic stress-inducible promoters, and a dCas9-based transcriptional activation system have been obtained and turned into modular level 0 pieces for further assembly. The construction of these interchangeable modules as part of this assembly system will allow the swift construction of complex vectors in the near future, that will in turn provide a novel tool for the studies of *LIP1* genes and other oligos of interest.

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Unveiling RCOR1 as a transcriptional rheostat at active regions on chromatin

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The RCOR1 co-repressor, also known as CoREST, forms a stable complex with LSD1 and HDAC1/2 enzymes, which erase the transcriptionally-permissive histone modifications H3K4me1/2 and acetylation. RCOR1 is considered a crucial factor for the recruitment and positioning of LSD1 and HDAC1/2 on their chromatin substrates. Here, we examined the genome-wide role of RCOR1 in transcriptional regulation by using high-resolution microscopic, biochemical, and bioinformatics approaches. Unexpectedly, we found RCOR1 preferentially at accessible and transcriptionally-permissive chromatin. Metagenomic analyses of RCOR1 chromatin occupancy revealed RCOR1 peaks at transcriptionally-active chromatin and highly expressed genes. Finally, we demonstrated that RCOR1 controls RNA Polymerase II between transcription initiation and productive elongation, modulating the acetylation of its carboxy- terminal domain and de novo transcription speed on a short time scale. We conclude that RCOR1 is a transcriptional dampener in actively expressed genes.

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Contribution of Sirtuins in transcriptional control of CDKN1A gene in lung tumor cells

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CDKN1A gene encodes the p21 protein, widely studied for its control over the cell cycle and its influence on tumorigenesis, where has been reported a dual and different role depending of the type of cancer. In the tumor cell context, numerous genes are regulated to inhibit their oncosuppressive functions or exacerbate their oncogenic character, one of the gene regulation pathways corresponds to histone acetylation, an epigenetic modification capable of increasing gene transcription. The histone deacetylases remove these epigenetic marks and, as a result, inhibit gene expression. In this study the histone deacetylases Sirtuins (SIRT) 1, 2, 6 and 7 where analyzed, characterizing their expression levels in a non-tumor and tumor lung cells and their binding to the CDKN1A gene. To analyze the CDKN1A gene SIRTs 1, 2 and 6 were detected on the promoter, but only SIRT1 was linked to the promoter only in the tumor model together the disminshed levels of acH3K14 y acH3K56 compared with non-tumoral cells. When SIRT1 was decreased by silencing, we observed what the expression decreased acetylation levels in histone residues substrates in common for SIRT1, SIRT2, and SIRT6, leading us to suggest the possibility of a compensatory mechanism. In summary, these results suggest that SIRT1 participates in the transcriptional regulation of *CDKN1A* in lung tumor cells propose to SIRT1 as a possible epigenetic target in the treatment of lung cancer.

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Oral Session 4

Sucrose promotes Clathrin-Mediated Endocytosis in *Arabidopsis thaliana*

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Sugars command critical signaling and regulatory processes during the development of all organisms. The root system architecture, a determining factor for nutrient uptake in plants, is modulated by the disaccharide sucrose. Particularly in Arabidopsis, accelerated primary root growth sustained by cell elongation is induced under sucrose supplementation. At the cellular level, vesicular trafficking is required to sustain both the plasma membrane (PM) expansion and cell wall deposition during cell elongation. In this work, we aimed to analyze the impact of sucrose in subcellular trafficking of the endocytic pathway. In roots epidermal cells, we have observed that sucrose promotes the PM internalization of the endocytic tracer FM4-64, dependent on a pivotal and conserved endocytic pathway: the Clathrin-Mediated Endocytosis (CME). The PM-resident lipid required for CME the fosfoinositide PI(4,5)P_2 is less abundant in cells of sucrose-grown plants. Consistently, we observed lower levels of two molecular players of CME: the Clathrin Light Chain 2 (CLC2) and μ subunit of AP2 complex. In this condition, the CLC2 dynamics resolved by Total Internal Reflection Fluorescence (TIRF) microscopy revealed a shorter residence time in the PM, suggesting that sucrose induces changes in EMC kinetics. PM-internalization is also induced by monosaccharide fructose, suggesting a CME-sucrose modulation after sucrose breakdown into fructose and glucose. Interestingly, the non-metabolizable sugar alcohol mannitol has no effect, revealing a specific level of trafficking regulation. Our results suggest that key plant-signaling sugars (sucrose/fructose) modulate cell growth through changes in the kinetics of EMC-core components, most likely for coordinating nutritional balance and growth.

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The endoplasmic reticulum master regulator protein BiP acts as a ratchet molecular motor in translocation

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Post-translational protein translocation through the endoplasmic reticulum is mediated by a channel called Sec61 complex and an auxiliary motor protein called BiP (Immunoglobulin Binding Protein). The force exerted by BiP has not been completely elucidated and studies suggest that BiP could be involved in a passive rectification mechanism of the movement by Brownian motion (ratchet model) and/or possibly in an active mechanism of direct pulling (power stroke model). To answer this question, we have developed a novel methodology to study forces in bulk. This aims to determine if folded proteins with known unfolding forces, as measured by optical tweezers, could cross microsomal membranes by BiP-mediated unfolding of the protein. We prepared different constructs that included signal peptide, unfolded titin (to allow entry into the microsomes), and the folded protein, and then used these in our translocation assays. First, a 2-titin chimera protein construct was used as a positive control in the protection test, and could be translocated into microsomes with an efficiency of 0.4%/min. Subsequently, the negative control of the Top 7 chimera protein construct is very low efficient translocated (0.01%/min) due to the high unfolding force of this protein (around 35 pN), which is above the level of force that a molecular power-stroke engine could generate. Finally, the CaM chimera protein (unfolding force of around 7 pN) also show to be low efficient translocated (0.04%/min), thus suggesting that the BiP protein would act as a ratchet-type molecular motor in post-translational protein translocation (Exerting around 1 to 3 pN).

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Crosstalk between adipose and liver cells: role of the calcium sensing receptor in cell senescence

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Liver disease biopsies reveal the accumulation of senescent cells which is linked to the presence of pro-inflammatory cytokines. Based on our observations that the activation of the G protein-coupled calcium sensing receptor (CaSR) promotes the TNF-α and IL-1β mRNA expression in liver cells (Villaroel 2016) and their secretion in pre-adipocytes (Mattar 2018; D'Espessailles 2020), we investigated whether the activation of the CaSR in preadipose cells stimulates cellular senescence in liver cells.
We generated conditioned medium (CM) from the pre-adipocyte cell line SW872 treated with vehicle (CM vehicle), the CaSR agonist cinacalcet 2 μM (CM cina) and a pre-treatment with the CaSR inhibitor calhex 231 10 μM plus cinacalcet 2 μM (CM calhex+cina). We used these CM to culture the hepatocyte cell line HepG2 for 120 h and assessed cellular senescence biomarkers SA-β-GAL, mitochondrial proteins, and pro-inflammatory cytokines TNF-α, IL-1β and CCL2.
CM cina-treated cells showed increased senescence-related morphological abnormalities and SA-β-GAL stain, which was absent in TNF-α- and IL-1β-depleted CM. Additionally, we detected that CCL2 mRNA decreased in CM calhex+cina-treated HepG2. CM calhex+cina promoted the expression of mitochondrial proteins PGC-1α and MFN2 and prevented the increase in the mitochondrial fission protein DRP1.
We conclude that TNF-α and IL-1β secreted by SW872 cells after CaSR activation promote HepG2 cell senescence. This investigation provides new evidence about the deleterious CaSR-induced crosstalk communication between pre-adipocytes and liver cells, incorporating cellular senescence mechanisms. Future studies should confirm whether liver cells can be protected from CM cina effect by recovering mitochondrial function.

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Inhibition of PDEδ reduce Rheb-dependent mTORC1 activation and survival of TSC2-null cells

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Rheb is a small GTPase member of the Ras superfamily and is mainly involved in stimulating cell growth through activation of *mechanistic Target* of Rapamycin Complex 1 (mTORC1). Rheb activates mTORC1 on the cytosolic surface of lysosomes. Rheb farnesylation anchorages it to the lysosomal membranes, and the prenyl-binding chaperone PDEδ facilitates its proper membrane localization. The Rheb/mTORC1 pathway is hyperactivated in proliferative diseases, such as Tuberous Sclerosis Complex (TSC) and cancer. Therefore, targeting Rheb-dependent signaling is a rational strategy for developing new drug therapies. Here, we evaluated the impact of a new PDEδ inhibitor, called LDC201114, in Rheb-dependent mTORC1 activation. Because TSC2 is a GTPase-activating protein that inhibits Rheb activity, inactivation of the *TSC2* gene is responsible for the hyperactivation of the Rheb/mTORC1 signaling that supports abnormal cell growth and proliferation in TSC and cancer. Therefore, to evaluate LDC201114, we used *Tsc2*-/- Mouse Embryo Fibroblasts (MEFs), where the Rheb/mTORC1 pathway is hyperactivated. By using a yeast two-hybrid interaction assay, we first validated that LDC20114 disrupts Rheb-PDEδ interaction. Accordingly, we found that LDC201114 reduced mTORC1 targets activation in *Tsc2*-/- MEFs. Also, our results showed that LDC201114 had antiproliferative and cytotoxic effects on *Tsc2*-/- MEFs but did not affect *Tsc2*+/+ MEFs viability. This work proposes pharmacological PDEδ inhibition as a new approach to target abnormal Rheb/mTORC1 pathway activation.

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The use of lipoic acid and total carotenoids as biostimulants to improve tolerance to salinity and drought in tomato plants

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In much of the world, climate change is altering regional growing conditions and making them more unpredictable, and consequently salinity and drought, known as abiotic stress factors, are having dramatic consequences on agriculture. Lipoic acid is a powerful antioxidant that has been used to benefit crop production. Carotenoids are antioxidant pigments that play essential and multiple roles in photoprotection against photooxidative damage and stress via energy dissipation and free radical detoxification, protecting membranes and proteins from ROS and lipid peroxidation. The objective is to study and develop biocompounds that protect tomato plants against abiotic stress. The evaluation conditions were standardised in *Solanum lycopersicum* (tomato) cv. Micro Tom, considering 1 week germination, 2 weeks post germination, 2 weeks of abiotic stress (salinity or drought) and 2 weeks of recovery. These compounds were applied to leaves 3 days before abiotic stress and then as a booster dose, a week into stress treatments. The results indicate an increase in height, chlorophyll content and the number of leaves in Micro Tom tomatoes in both abiotic stress conditions with addition of these antioxidants. From the evaluations carried out, it is concluded that 200 nM lipoic acid and 3 µg/mL total carotenoids exert a biostimulant effect on Micro Tom tomatoes exposed to abiotic stress. In the next stage, the effects on gene expression, and the application of these compounds in the field on "Larga vida" and "Poncho Negro" tomatoes, a salt-tolerant variety from the northern Chile, will be evaluated.

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Changes in Nuclear Morphology Coordinate B Lymphocyte Activation

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B cells are crucial players of adaptive immunity, responsible for antibody production. To become fully activated, B cells must extract and process antigens into peptides and present them to specific CD4+ T cells. A critical step is the recognition and uptake of antigens that are in an immobilized form, where B cells establish an immune synapse with antigen presenting cells, which relies on orchestrated intracellular-trafficking and cytoskeleton remodeling. However, B cells have restricted cytoplasmic space, mainly occupied by a large nucleus, yet the role of nuclear morphology in the formation of the immune synapse has not been addressed. Nuclear morphology is controlled by transmembrane proteins anchored to the nuclear envelope, such as Linc complexes, described as connectors of cytoskeleton and nucleoskeleton. We asked whether B cells undergo changes in nuclear morphology and positioning to adapt their intracellular reorganization and promote polarized membrane trafficking to the immune synapse. Using high resolution-confocal microscopy and analysis of cell imaging, we observed changes in nuclear shape during B cell activation which depended of cytoskeleton and nucleus connections. Moreover, our studies revealed that the Linc complex is crucial to form an organized immune synapse and to promote efficient antigen extraction.
We conclude that B cells adapt nuclear morphology as a critical regulatory step for their activation.

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Poster session

BM1.1 Inhibition of MCT2 expression in hypothalamic neurons alters feeding behavior

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In the arcuate nucleus (ARC) of the hypothalamus, glia-neuron interactions regulate glucose homeostasis and feeding behavior. Previously, we demonstrated that inhibition of monocarboxylate transporters (MCT) 1 and 4 localized in glia affects feeding behavior. MCT2 is localized in the ARC orexigenic (NPY/AgRP) and anorexigenic (POMC/CART) neurons. Here, we produce MCT2 knockdown rats for evaluation of feeding behavior.
Material and methods: Female Sprague-Dawley rats were injected in the ARC with an adeno-associated virus (AAV-sh-MCT2-syn-tdTomato) for generating MCT2-neuron knockdown rats. The reduction of MCT2 mRNA level was confirmed using real-time PCR. Glycemia, feeding behavior, and body weight were measured in MCT2-inhibited rats and compared with rats injected with a control AAV.
Results: The expression of MCT2 mRNA was effectively inhibited, and a significant increase in food intake and body weight were detected.
Our results support lactate transfer as a mechanism underlying tanycyte-neuron communication through monocarboxylates.

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BM1.2 Standardization of a female murine model of heart failure with preserved ejection fraction

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Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent disease in older women and people with metabolic syndrome and, unfortunately, its pharmacological management has shown to be ineffective, so there is a need to understand the multifactorial physiopathology to improve the efficacy of treatments. The standardization of an animal model has become an imperative to study the molecular processes
As described by Dr. Hill's group (Schiattarella et al., 2019) 12-week-old C57BL/6N female mice (n=12) were fed a high-fat diet (60% kilocal fat) and L-NAME (a NOS inhibitor, 0.5 g/L in water) or a control group (n=12) for 15 weeks, where weekly body weight, glycemia, blood pressure, walking test measurements were performed.
We found that HFpEF mice presented metabolic syndrome, with a significant weight gain ($p<0.0001$) and increase in di blood pressure ($p<0.0001$), abnormalities in glucose handling with an increase in the area under the curve of the glycemia test with respect to the control ($p<0.0001$). An increase in heart/tibia weight was also observed ($p=0.0264$), but no changes in lung/tibia weight ($p=0.7486$). The Shapiro-Wilk test was used as a normality test. Statistical difference was determined by t-test or Mann-Whitney test, as appropriate. A $p<0.05$ was considered statistically significant.
We partially reproduce the HFpEF model in female mice, however pulmonary congestion was still not demonstrated. Echocardiographic data are also necessary to demonstrate preserved ejection fraction and diastolic dysfunction. When these data it can be determined we will study in detail the molecular pathways and possible treatments of the disease.

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BM1.3 Angiotensin-(1-9) retroenantiomer prevents lipotoxic stress-induced cardiomyocyte hypertrophy

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Introduction. Angiotensin-(1-9) (Ang-(1-9)), a contra-regulatory peptide of the renin-angiotensin pathway, exerts cardioprotective effects. Still, its half-life of around a few seconds limits its biological activity and future as a cardiovascular drug. We developed the peptidomimetic angiotensin-(1-9) retroenantiomer (RE-Ang- (1-9)) to increase half-life. Evidence has shown that during cardiomyocyte hypertrophy (CH), a compensatory process characterized by an increased cardiomyocyte size, there is a decrease in the mitochondrial oxidative metabolism and mitochondrial fission. Ang-(1-9) blocked this mitochondrial fission in a model of norepinephrine-induced CH. Interestingly, excessive accumulation of lipids (lipotoxicity) in the heart also promotes morphological and metabolic changes in cardiomyocytes related to CH. Aim. To evaluate whether RE-Ang-(1-9) prevents CH induced by lipotoxicity. Methodology. Primary cultures of neonatal rat ventricular myocytes (NRVM) were treated with or without 100 µM RE-Ang-(1-9) or Ang-(1-9) for 6 h before treatment with palmitate (328 µM for 24 h) and then, hypertrophic changes were evaluated. Protein levels of the hypertrophy markers (β-MHC and ANP) were assessed by Western blot. Cell area, perimeter, and mitochondrial volume, and number were analyzed by confocal microscopy. Results. Palmitate significantly increased the levels of β-MHC and ANP, the area and perimeter of the NVRM, and triggered mitochondrial fragmentation. Preliminarily, RE-Ang-(1-9) and Ang-(1-9) prevented the increase in the area and perimeter of the NVRM, together with mitochondrial fission. Conclusions. RE-Ang-(1-9) and Ang-(1-9) prevent the lipotoxic stress-induced CH. Relevance and projections. RE-Ang-1-9) could have higher potency and efficacy than Ang-(1-9) as a cardiovascular drug advising its future as a new pharmacological tool.

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BM1.4 Hemichannel blockade as a new approach to prevent acute pentylenetetrazol-induced epilepsy

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Neuroinflammation in chronic diseases, such as epilepsy, may be the cause of the tissue dysfunction that characterizes the disease. The hemichannels formed by connexin43 or pannexin1 (Cx43 HCs and Panx1 HCs, respectively) expressed by glial (Cx43 HCs) and neuronal (Panx1 HCs) cells contribute to neuroinflammation characterized by increase in cytoplasmic Ca^{2+}. This favors the synthesis and release of pro-inflammatory molecules that promote release of glutamate and ATP, causing seizures. Current antiepileptic drugs (AEDs) have a pleiotropic action on neuronal molecular targets and their action on glial HCs remains elusive. Our results indicate that carbamazepine and valproate, two widely used AEDs, increase the activity of Cx43 and Panx1 HCs in an exogenous expression system, suggesting that they promote neuroinflammation, which may contribute to explain why ~30% of epileptic patients are drug-refractory. Through molecular docking studies, we predicted the preferred binding orientation of each AED on HCs, suggesting that they could directly increase the activity of HCs. Furthermore, D4, a selective Cx HC blocker, prevented the increase in cell membrane permeability by pentylenetetrazol, an epileptogenic drug, in cells of *ex-vivo* hippocampal slices, and in hippocampal cells of pentylenetetrazol-treated animals. Then, new molecules with antiepileptic and HCs blockade activity were searched using a structure-based virtual screening strategy. Several molecules with good binding affinities to HCs, and to other receptors and channels involved in epilepsy were found. Studies are underway to prove their selectivity and potency. Inhibitors of antiepileptic compounds that also block Cx43 and/or Panx1 HC could be useful for improving epilepsy treatment.

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BM1.5 H_2O_2 production during wound healing in bovine corneal endothelial cells in culture does not affect migration

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The production of oxidant species during wound healing has been studied extensively. Several authors has shown that during this process, fast calcium increase induce activation of NADPH oxidases that catalyse extracellular superoxide production, which is subsequentely dismutated to H2O2. In this regard, Lisse et al. has shown that, in scratch assays of human keratinocytes in culture, DPI treatment inhibit H2O2 production and wound clousure, suggesting a role for this molecule in the migration modulation. To further understand the role of oxidants, we have studied the production of reactive oxygen species (ROS) and H2O2 during wound healing in bovine corneal endothelial cells (BCEC) in culture. Our results using inespecific probes like CellROX Green and DCFH2 has shown ROS increase at least during the first 2h of wound healing. Moreover, we has confirmed H2O2 production during the same period in a way inhibited by ML171 incubation (a NADPH oxidases inhibitor). To study the role of H2O2, we quantified migration in a scratching assay in the presence of ML171. Our preliminary studies did not show significant changes in the healing rate during the first 6 h of closure. Taken together, our results suggest that, as for others cells in culture, H2O2 is produced as consequence of wounding, but unlike Lisse results, does not have a role in migration. Further research is needed to determine the role of H2O2 in other process, like proliferation or cell death, during the wound healing of BCEC in culture.

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BM2.1 Targeting of gold nanoparticles to the heart for the delivery of cardioprotective molecules

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This work evaluates a new nanosystem for a targeting therapy able to transport cardioprotective molecules preferentially to the heart to increase its biodisponibility. In cardiovascular diseases a pathological heart remodeling occurs in part by fibrosis. A nanosystem based in gold nanospheres (AuNs) with Rhodamine B (RhodB) as model molecule in transport was modified with Tannic acid (TA), a cardiac tropism molecule with antifibrotic properties. Methodology: The nanosystem (AuNs-RhodB+TA) was characterized by spectrophotometer UV-dis, DLS and HR-STEM. Biocompatibility was evaluated in newborn rats cardiac fibroblasts (CF) and cardiomyocytes (CM) by MTT assays, with 1 – 40 nM AuNs-RhodB+TA. The antifibrotic properties was evaluated in CF by smad pathway inhibition by western blot, induced by TGF-b1 for 30 min. Finally, the targeting was determined *ex vivo* in adult rats at 24 h treated intravenously, with in-vivo FX PRO microscope. Results: In the physicochemical characterization, the AuNs-RhodB+TA hydrodynamic diameter was 38 nm and 16 nm confirmed by STEM. Its zeta potential (pZ) was -20 mV after the functionalization with AT; the plasmonic band for naked AuNs was 522 nm, for AuNs-RhodB was 531 nm and AuNs-RhodB+TA was 535 nm. CF did no decreased its viability with any concentration, but in CM its decreased since 10 nM AuNs-RhodB+TA. With 20 nM AuNs-RhodB+TA it was observed a prevention in the activation of p-smad3. Finally, AuNs-RhodB+TA was observed in the hearts rats compared with AuNs-RhodB rats. Conclusions: The nanosystem (AuNs-RhodB-AT) regulates canonical pathway smad in cardiac fibrosis and TA improves de cardiac targeting of AuNs.

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BM2.2 Analysis of protein-based adjuvants agonist of TLR4, Hemocyanin and SIP, in the MyD88 and TRIF signaling pathways leading to immunostimulation and proinflammatory responses

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The development of vaccine adjuvants is of interest for persistent diseases, cancer, and future pandemics. Toll-like receptors (TLR) have been researched on vaccine adjuvants because they modulate the innate immune system to activate adaptive immunity. TLR4 signaling recruits the adaptor proteins myeloid differentiation marker 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF). MyD88–mediated signaling leads to proinflammatory responses. Besides, TRIF–mediated signaling leads to adaptive immune response. Given the role of TLR4 agonists, most studies have used ligands based on lipopolysaccharides. Although TLR-4 protein agonists (PT4A) have advantages as adjuvants, including their ability to modify their structure for optimal immunogenicity, they have not been thoroughly studied. This work characterizes the effect of two types of PT4As –with proven adjuvant/immunostimulant properties- on downstream TLR4 signaling via MyD88 and TRIF. The PT4As are mollusks' hemocyanins obtained from *Fissurella latimarginata* (FLH) and *Concholepas concholepas* (CCH) and the recombinant Surface Immunogenic Protein from *Streptococcus agalactiae (rSIP)*. First, the effective concentration (EC_{50}) of these PT4As was determined using HEK-blue TLR4-reporter cells. Results exhibited a dose-dependent response to both PT4As, being more potent rSIP than hemocyanins. Next, in bone marrow-derived dendritic cells, the expression of genes associated with MyD-88 (IL-6; Cox-2; CD80) and TRIF (IFIT-1; IP-10; CD86) were evaluated by RT-qPCR. Finally, difference in the immunological potency induced by both proteins in *THP-1 human monocyte cell line knockout* for MyD88 and TRIF are currently in evaluation. Collectively, these data may explain how these PT4As can act as vaccine adjuvants by activating TRIF-dependent immunostimulation and MyD88-dependent inflammatory responses.

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BM2.3 Estrogens and 4-Methoxyestradiol effects on human pulmonary artery smooth muscle cells proliferation and mitochondrial activity

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Introduction: Pulmonary arterial hypertension (PAH) is a chronic, incurable disease whose current treatments are insufficient to improve life quality of those who suffer from it. In its idiopathic form, iPAH affects mainly women, being its biggest risk factor elevated estrogen (E2) plasma levels. Despite this knowledge, it is unknown how E2 directly affects pulmonary artery smooth muscle cells (hPASMC), the main cell type related with this pathology. Parallel, 4-Methoxyestradiol (4-ME), a poorly studied E2 metabolite, increases proliferation and viability in lung epithelial cells but its effect in hPASMC has not been described. Moreover, in iPAH, hPASMC present a higher proliferation and a decreased mitochondrial oxidative metabolism. Therefore, the effects of E2 and 4-ME in hPASMC proliferation and mitochondrial function will be evaluated. Methods: To analyze whether E2 or 4-ME modulates proliferation of hPASMC, the expression of the proliferation marker Ki67 will be evaluated by immunofluorescence and cell cycle will be studied by flow cytometry. Mitochondrial potential and changes in oxygen consumption will be measured using OROBOROS Oxygraph-2k. Results: E2 10 and 100 nM, or 4-ME 5 nM increases hPASMC proliferation. Oxygen consumption was upregulated by E2, and mitochondrial potential were downregulated by E2 and 4-ME treatments, suggesting mitochondrial uncoupling or overexpression of ETC elements. Conclusions: E2 and 4-ME treatment increases hPASMC proliferation, decreases mitochondrial membrane potential and increases mitochondrial respiration, thus suggesting mitochondrial dysfunction by uncoupling. To our knowledge, this is the first report that describe a mitochondrial effect of 4-ME in hPASMC in the context of iPAH.

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BM2.4 Ubiquitin ligase MUL1 as a pharmacological target in Heart Failure with Preserved Ejection Fraction?

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Heart Failure with Preserved Ejection Fraction (HFpEF) is an increasing concern for health care systems, due to the high budget required for patient's hospitalization. This pathology is clinically featured by diastolic disfunction, cardiac hypertrophy, exercise intolerance and pulmonary congestion. Currently, despite the known clinical phenotype, there is a lack of successful pharmacological interventions aiming to decrease heart failure-related hospitalization and HFpEF associated mortality. Recently, it was reported a mechanism responsible for the HFpEF pathophysiology implicating a decreased in IRE1a signaling due to its nitrosilation. We recreated *in vitro* the decreased IRE1a activity by using its inhibitor MKC866 in conditions of palmitate-induced cardiomyocyte hypertrophy, finding that during these conditions there is an increase in the levels of the mitochondrial protein ubiquitin E3 ligase 1 (MUL1). Thus, we decided to assess the levels of this protein and its targets in an animal model of HFpEF featured by decreased IRE1a activation. After 15 weeks of a high fat diet supplemented with the hypertensive toxin L-NAME, C57BL6/N mice displayed increased body weight and blood pressure, impaired glucose tolerance, cardiac hypertrophy, and exercise intolerance, accompanied of preserved systolic function. The ventricular cardiac tissues derived from these HFpEF mice model had increased MUL1 protein levels and decreased levels of its ubiquitination target MFN2. Despite of that, whether increased MUL1 is a protective mechanism limiting the progression or a mediator of HFpEF pathogenesis is still unclear, therefore more research is needed to evaluate its role in HFpEF as a novel pharmacological target.

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BM2.5 FoxO1 and contractile protein expression in arteries of mice with heart failure with preserved ejection fraction

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Cardiovascular diseases (CVD) are the leading cause of death in Chile and worldwide, causing 30% of annual deaths. Heart failure (HF), defined as the inability of the heart to supply the energetic demands of the body, represents the final stage of most CVD. HF with preserved ejection fraction (HFpEF), mainly characterized by diastolic dysfunction, accounts for approximately 50% of HF patients. So far, there are no pharmacological treatments that significantly reduce HFpEF morbidity and mortality. We measured the expression of FoxO1, a transcription factor involved in vascular remodeling and recently described as an essential player in HFpEF pathogenesis. We also evaluated contractile protein expression in the aorta and femoral arteries as a readout of vascular remodeling. To develop a HFpEF mice model, 11–12-week-old mice were treated with HFD and L-NAME for 15 weeks. Blood pressure, exercise tolerance, glucose levels, and systolic and diastolic function were determined to confirm the HFpEF phenotype. Thoracic aorta and femoral arteries were isolated, and FoxO1, alpha-smooth muscle actin (aSMA), and smooth muscle 22 alpha (SM22) mRNA levels were determined by RT-qPCR. We found a significant increase in FoxO1 expression in both aorta and femoral artery. aSMA and SM22 expression were significantly increased only in femoral arteries. Mice with HFpEF displayed increased FoxO1 expression in arteries but with a different profile of contractile protein expression. These results provide a better understanding of the mechanisms behind HFpEF and will contribute to the future development of new therapies to treat this disease.

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BM3.1 Effect of HDAC6 inhibition on the expression of genes involved in the immune response in colorectal cancer cells

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Colorectal cancer (CRC) is one of the most common malignant neoplasm in Chile and according to the WHO, represents the second cause of death from tumors in the world. Current therapies include surgery, chemotherapy, radiation therapy and, recently, immunotherapy aimed at inhibiting the immune checkpoints, as Programmed Dead 1 (PD-1) receptor, that interact with his ligand (PD-L1) in the tumor. However, there is a percentage of patients who don't respond to this therapy, making it necessary to search for alternative or adjuvant treatments. Histone deacetylases (HDAC) have been positioned as candidates in the treatment of cancer, since they modulate the immune response, and being involve in tumor progression. Here, we investigated the effect of HDAC6 inhibitors on the expression of genes involved in the immune response. For that, Nexturastat A (NextA) an HDAC6i, was used to treat CRC cells. A time lapse with high concentration of NextA showed decrease in the expression of PD-L1. Also, to emulate an inflammatory environment, we treat the cells with Interleukin-6 (IL-6) and with or without NextA, observed a very marked increase in the expression of PD-L1 where induce with IL-6 and a clear decrease in the expression of PD-L1 with dual treatment in both CRC cells. Finally, preliminary RNAseq data showed that NextA reduced the expression of other genes involved in immunomodulatory pathways. Therefore, HDAC6 can by suggested as an interesting target as an adjuvant in immunotherapy in CRC.

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BM3.2 Long non-coding RNAs involved in cardiac differentiation are differentially expressed in iPSCs from Down Syndrome patients

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Down syndrome (DS) is a condition characterized by the presence of an extra chromosome 21, which leads to an increased risk of pathologies including congenital heart diseases that affect ~50% of infants with DS. It causes a genetic imbalance that disturbs the transcriptome and various cellular processes, including cardiogenesis. Long non-coding RNAs (lncRNAs) are usually tissue specific, acting as important regulators of cardiac development. Also, cardiac differentiation in cells derived from DS patients (3S) is altered compared to non-trisomic individuals (2S). Here, we hypothesize that "lncRNAs associated with cardiogenesis are differentially expressed (DE) in induced pluripotent stem cells (iPSC) from DS patients". To evaluate it, we performed a meta-analysis of transcriptome datasets focusing specifically on lncRNAs. First, a database search was performed in GEO, using the keywords "iPSCs", "trisomy" and "*Homo sapiens*". Then, four 2S/3S microarray studies that compared the expression profile of iPSCs from 2S/3S patients with individuals under normal conditions were selected. The microarray platforms were reannotated using BioMart, allowing the identification of probed lncRNAs. Next, the sets of 2S/3S DE lncRNAs were determined for each study using GEO2R (p-value <0.05, FC >1.5). Finally, we found a total of eight lncRNAs as systematically DE in all studies (shared DE lncRNAs), suggesting that they could affect 3S iPSC cardiac differentiation. Our next goal is to functionally characterize those lncRNAs involved in cardiac development and carry out experimental validations using cellular and molecular biology approaches.

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BM3.3 Role of HERPUD1 protein as modulator of vascular calcification

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Calcifications correspond to accumulation of calcium-phosphate crystals in different tissues. Normally occurs during bone mineralization, or abnormally in soft tissue as vessels, where vascular smooth muscle cells (VSMC), among other mechanisms, acquire an osteoblast-like phenotype promoting the extracellular matrix secretion and pathological accumulation of calcium crystals on tunica media.
The function of every specialized secretory cell involves a high demand of endoplasmic reticulum (ER) function and therefore requires strict control of proteostasis. The ER membrane protein HERPUD1 is a key component of the ER-associated degradation and proteostasis control. We have demonstrated its importance in mineralization processes of bone cells *in vitro*. The aim of this study was to establish whether HERPUD1, as part of secretory pathway, play a role in VSMC calcification *in vitro*.
Primary rat VSMC and cell line A7R5 were undergo mineralization conditions in presence and absence of HERPUD1 for 7 days, calcium deposits levels were evaluated through alizarin-red staining. Collagen and non-collagenous proteins (NCP) secretion were determined through Sirius Red/Fast Green Collagen Staining Kit (Chondrex) and HERPUD1 and osteo-conversion gene levels was determined by qPCR and Western blot analysis.
We found that HERPUD1 expression increased in calcification of VSMC progressed. The absence of HERPUD1 reduced mineralization *in vitro* and collagen and NCP secretion. On the other hand, HERPUD1 overexpression activated the mineralization *in vitro* without changes in collagen and NCP secretion.
Our results show that HERPUD1 is important for mineralization processes and may be useful new target to understand, diagnostic or treatment of mineralization disorders.

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BM3.4 Simultaneous and spatially-resolved analysis of T-lymphocytes, macrophages and PD-L1 immune checkpoint in rare cancers

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Cancer that occurs in fewer than 15 out of 100,000 people each year is designated as rare. Rare cancers such as penile, vulvar and anal neoplasms show an incidence lower than 0.5% per year in Chile, however its impact in life quality and survival remains high. These three types of cancer are related to human papilloma virus (HPV) infection and are characterized by a multistep progression from intraepithelial lesions to carcinoma, and immune infiltration. In this work, we established a platform based on multiplexed immunofluorescence for the simultaneous detection of tissue biomarkers in FFPE applying tissue segmentation and cell phenotyping of CD8, CD68, PD-L1, Cytokeratin (CK) and Ki-67 to interrogate the tumor microenvironment in retrospective cases of penile, vulvar and anal cancer of Chilean patients. Overall, the three tumors showed distinctive levels of immune cells infiltrating the tumor and the stroma. CD8+ lymphocytes were more abundant in penile and vulvar cancer than in anal tissue. CD68+ macrophages were increased in penile and anal tumors but decreased in vulvar cancer. PD-L1 was only detected in penile cancer, and it showed a membranous-cytoplasmic staining pattern in tumor and non-tumor cells. The proliferation rate (Ki-67+ cells) was high in tumor and lower in non-tumor adjacent tissue as we confirmed in CK+ cells. As conclusions, we developed a suitable approach to measure up to 5 biomarkers simultaneously and optimized the use of limited samples for the comprehensive study of tumor microenvironment, and it may be apply for the study of many other solid tumors.

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BM4.1 Fenofibrate (a PPAR-α Agonist) administered during ethanol withdrawal reverts ethanol-induced astrogliosis and restores the levels of glutamate transporter in ethanol-administered rats

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High-ethanol intake induces a neuroinflammatory response, which has been proposed as responsible for the maintenance of chronic ethanol consumption. Neuroinflammation decreases glutamate transporter (GLT-1) expression, increasing levels of glutamate that trigger dopamine release at the corticolimbic reward areas, driving long-term drinking behavior. The activation of peroxisome proliferator-activated receptor alpha (PPARα) by fibrates inhibits neuroinflammation, in models other than ethanol consumption. However, the effect of fibrates on ethanol-induced neuroinflammation has not yet been studied. We previously reported that the administration of fenofibrate to ethanol-drinking rats decreased ethanol consumption. Here, we studied whether fenofibrate effects are related to a decrease in ethanol-induced neuroinflammation and to the normalization of the levels of GLT-1. Rats were administered ethanol on alternate days for 4 weeks (2 g/kg/day). After ethanol withdrawal, fenofibrate was administered for14 days (50 mg/kg/day) and the levels of glial fibrillary acidic protein (GFAP), phosphorylated NF-κB-inhibitory protein (pIκBα) and GLT-1, were quantified in the prefrontal cortex, hippocampus, and hypothalamus. Ethanol treatment increased the levels of GFAP in the hippocampus and hypothalamus, indicating a clear astrocytic activation. Similarly, ethanol increased the levels of pIκBα in the three areas. The administration of fenofibrate decreased the expression of GFAP and pIκBα in the three areas. These results indicate that fenofibrate reverts both astrogliosis and NF-κB activation. Finally, ethanol decreased GLT-1 expression in the prefrontal cortex and hippocampus. Fenofibrate normalized the levels of GLT-1 in both areas, suggesting that its effect in reducing ethanol consumption could be due to the normalization of glutamatergic tone.

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BM4.2 Mechanisms underlying hemocyanin antigen processing and presentation through MHC-I and MHC-II dependent pathways

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Mollusk hemocyanins are oligomeric glycoproteins with complex quaternary structures and heterogeneous glycosylations. They are widely used in biomedicine as adjuvants/immunomodulators because they bias towards Th1 immunity when inoculated in mammals. Structural features of hemocyanins support these effects; nevertheless, the underlying mechanisms are not entirely understood. Antigen-presenting cells (APCs) bind hemocyanins through mannose-binding C-type lectin receptors and Toll-like receptors. After clathrin-mediated internalization, hemocyanins are processed and presented to T lymphocytes. Antigen presentation of exogenous proteins commonly occurs through MHC-II to CD4+ T lymphocytes, although mannose-recognizing immune receptors may promote cross-presentation, where exogenous antigens bind MHC-I to stimulate CD8+ T lymphocytes. Cross-presentation is essential for antitumor responses, and it would partially explain hemocyanin-induced effects. Hence, we hypothesize that hemocyanins undergo both MHC-I and MHC-II dependent antigen presentation by APCs. Using J774.2 murine macrophages as APCs, and *Fissurella latimarginata* hemocyanin (FLH), our results show that these glycoproteins are presented through MHC-II pathways. Indeed, pharmacological inhibitors of MHC-II pathway decreased FLH-induced cytokine secretion by macrophages, assessed by ELISA. Interestingly, inhibitors of the vacuolar MHC-I pathway had comparable effects, suggesting cross-presentation. Immunoblot confirmed different FLH proteolysis patterns in macrophages treated with different inhibitors of both MHC-I and MHC-II pathways. Flow cytometry experiments showed an FLH-dependent upregulation of CD80 and CD86, which are essential for immunological synapse. The effect of pharmacological inhibitors is currently being determined, and the FLH-dependent upregulation of MHC-I and MHC-II. Overall, these results will provide novel information on the mechanisms underlying antigen presentation of FLH, a model mannose-rich protein.

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BM4.3 Meta-analysis of mitochondrial ubiquitin ligase-1 (MUL1) and its relationship with cardiac ischemia/reperfusion injury

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Myocardial infarction develops when *major* coronary arteries supplying the heart with blood become damaged or blocked due to atheroma limiting blood flow. These ischemic and reperfusion events cause functional and structural alterations of mitochondria. The mitochondrial protein E3 ubiquitin ligase 1 (MUL1) has been involved in heart disease in preclinical models, regulating apoptosis, mitophagy, and mitochondrial dynamics. However, there is little information on how MUL1 exerts its biological role in response to ischemia/reperfusion in patients. Through bioinformatics, we performed a meta-analysis of transcriptomic studies in 5 clinical studies in patients with myocardial infarction to elucidate the expression profile of MUL1 under this condition. We observed that the expression of MUL1 was not altered in patients with coronary artery disease and myocardial infarction. However, we identified MUL1 expression networks where the expression of *TLR4, DYSF,* and *CTSD* genes was inhibited in the study condition. These molecules have been associated with cardiac ischemia/reperfusion injury. Under this observation, MUL1 putatively has a regulatory effect on the expression of these genes. Thus, ischemia/reperfusion-induced cardiac damage could be mediated by MUL1 by unknown intracellular pathways in the context of myocardial infarction. However, their roles will be addressed in future studies.

Funding: FONDECYT Nº 1200490 and FONDAP Nº 15130011.

BM4.4 Recombinant ND1 domain of flagellin from *Vibrio anguillarum* promotes *in vitro* overexpression of proinflammatory cytokines in human immune cells

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Flagellin is the principal component of flagellum in Gram negative and positive bacteria, and is the ligand for the Toll-like receptor 5 (TLR5). The activation of TLR5 induces pro-inflammatory cytokines and chemokines, and promotes the subsequent activation of T cells. In this work, we evaluated a recombinant peptide from the amino-terminus D1 domain (rND1) of flagellin from *V. anguillarum,* a fish pathogen, as immune modulator in mammal cells. This rND1 contains key amino acids needed to bind teleost TLR5, and it has shown IL-8 and TNF-α overexpression in salmon and trout, therefore rND1 may bind human TLR5 inducing inflammation. The biological effects of rND1 were assessed *in vitro* using isolated human peripheral blood mononuclear cells (PBMCs) and monocyte-derived dendritic cells (MDCs). The cytokines production was measured by RT-qPCR and Luminex, and the functional phenotyping was carried out using flow cytometry. The results showed, at transcriptional level, that rND1 induced a time- and concentration-dependent pro-inflammatory response in PBMCs, generating a pick for IL-1β (220-fold), IL-8 (20-fold) and TNF-α (65-fold) at 3h post-stimulation with 1μg/ml respect to the vehicle, and the profile of secreted proteins was concordant with a chemotactic signature compared to LPS or flagellin. The MDCs treated with rND1 showed low levels of co-stimulatory and MHC-II molecules and kept an immature phenotype with a decreased phagocytosis of dextran. We probed that rND1 from a non-human pathogen promotes immune modulation in human cells and it may be considered for further studies in adjuvant therapies based on pathogen-associated molecular patterns.

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BM4.5 Increased cell proliferation in neurogenic niches involved in the regulation of food intake

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Introduction: Adult neurogenic niches share markers of radial glia such as vimentin, Sox2 and GLAST. In the adult brain, glia-radial like cells are located and in the dorsal vagal complex (DVC) and in the hypothalamus. Both brain areas have an important role in feeding behavior. However, only in the hypothalamus, the effects of high-fat diet over the neurogenesis have been reported. Here we evaluated and compared the neurogenic impact of a glucose-rich diet in both areas.
Material and methods: Using qRT-PCR, neurogenic genes were identified and quantified in hypothalamus and DVC. Adult rats were feeding with a control (ND) or high-sucrose diet (HSD) and injected with BrdU for 7 days. We evaluated food intake, body weight and the number of proliferating cells in hypothalamus and DVC. In addition, neurogenic markers such as vimentin and nestin was identified by immunohistochemistry.
Results: Both glia radial like cells express the progenitor markers. After 8 days with HSD, no significant differences in daily food intake, body weight or glycemia were detected compared to control groups. Interestingly, the number of proliferative cells increased with a HSD in both areas showing a main proliferation in the DVC.
Discussion. We showed that radial-glia like cells from the DVC share a phenotypical marker expression with hypothalamic tanycytes. For the first time, we demonstrated that DVC cells proliferate in response to HSD and, the proliferative rate in the DVC was more than in the hypothalamus. Our results could represent a long-term adaptive mechanism in response to dietary changes.

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CS.1 VCAM-1 mediates the protective effect of TNF-α preconditioning against isquemia/reperfusion injury in cultured cardiomyocytes

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VCAM-1 is a transmembrane protein expressed in mammals whose expression is induced by TNF-α and a wide variety of pro-inflammatory stimuli in several tissues. Although the role of cardiac VCAM-1 is not fully understood, several studies have shown that its expression is increased in different cardiovascular diseases. Our previous results showed that VCAM-1 is associated with cardiomyocyte survival in a simulated ischemia model. This work evaluates the protective role of VCAM-1 on TNF-α preconditioning against simulated ischemia/reperfusion (sI/R) injury in cardiomyocytes. Cultured neonatal rat ventricular cardiomyocytes were treated with 10 ng/mL TNF-α. Protein and mRNA levels of VCAM-1 were measured by Western blot and RT-qPCR. VCAM-1 knockdown cardiomyocytes were pre-treated with 10 ng/mL TNF-α for 24 h and incubated under ischemic conditions for 6 h. Then, the ischemic medium was replaced by DMEM/M199 containing 10% FBS and cardiomyocytes were exposed to normoxia for 18 h. Cell death was assessed by LDH release at the end of reperfusion. Additionally, prosurvival gene expression was evaluated in VCAM-1 knockdown cardiomyocytes. Data show that TNF-α preconditioning induced VCAM-1 expression through a transcriptional mechanism and protects cardiomyocytes from sI/R injury. This effect seems to be mediated by VCAM-1. Interestingly, VCAM-1 knockdown exacerbates sI/R-induced cardiomyocytes death and attenuates prosurvival gene expression such as TNF-α, IL-6, and SOD2. In summary, VCAM-1 knockdown exacerbates I/R injury in cardiomyocytes and could be mediating the protective effect of TNF-α preconditioning against sI/R damage. Nevertheless, further research is needed to establish the protective mechanism of VCAM-1 in cardiac I/R injury.

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CS.2 IRE1 endoribonuclease activity inhibits melanoma invasion and metastasis through the selected degradation of targets mRNAs

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Malignant melanoma is one of the most metastatic tumors. Despite the efforts dedicated to early detection, most patients develop metastasis at the time of clinical intervention. Melanoma cells are exposed to several perturbations that alter the protein homeostasis engaging an adaptive response termed as unfolded protein response (UPR). This pathway is regulated by the protein IRE1 that controls the expression of the transcription factor XBP1s and the stability of multiple mRNAs by regulated IRE1-dependent decay (RIDD). IRE1 also signals through Filamin A inducing actin cytoskeleton dynamics and migration; however, no evidence regarding the role of IRE1 in melanoma invasion has been described. We aim to define functional consequences of IRE1 signaling (XBP1s, RIDD, and Filamin A) in melanoma invasion and metastasis. We performed actin cytoskeleton, transmigration, and invasion assays in IRE1-deficient human melanoma cells and using an IRE1 endoribonuclease inhibitor. We validated our findings using melanoma resection-metastasis assays and the analysis of human patient databases. Unexpectedly, our results indicated that IRE1 expression suppresses melanoma invasion independently of Filamin A and XBP1s but relying on the endoribonuclease activity suggesting RIDD as a major regulator of invasion. Analysis of TCGA databases identified several mRNAs coding for proteins that promote metastasis that can be degraded by RIDD. Using melanoma metastasis assays, we observed that IRE1 deficiency generated smaller primary tumors but increased incidence of lung metastasis. Our data demonstrated that targeting IRE1 inhibition might not be an option for melanoma intervention due to the enhancement of metastasis.

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CS.3 Studying the implication of the presence of the master waiver of the genome in extracellular vesicles secreted by the ovarian tumor cell line A2780 when received by normal epithelial ovarian cells

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The master waiver of the genome CTCF modulates the differentiation and heterogeneity of eukaryotic cells through its interaction with the genome. Its functions include the structuring of the genome in loops to regulate the physical interaction between enhancer and promoter sequences, direct promotion, and inhibition of gene expression, and even modulates nucleosome positioning. For this reason, the study of its role in cancer becomes crucial for understanding the progression of this disease. One of the fundamental mechanisms for cancer development is the control of the tumor microenvironment, and in this category extracellular vesicles (EVs) are crucial. To date, its presence and role in EVs have not been described. In this study we characterize the presence of this protein and its transcript in EVs secreted by A2780 ovarian cancer cells. EVs were characterized through western blot, NTA and electron microscopy CTCF protein was detected by WB and CTCF mRNA through RT-qPCR . It has recently been discovered that CTCF has a region capable of binding RNAs, which makes us suspect that this protein may be capable of sequestering RNAs and incorporating them into micro vesicles. Our bioinformatics studies showed that the RNAs with the highest probability of being sequestered in patients with ovarian cancer are MALAT1, NEAT1, PLEC, CPNE1, PNN, HGS and ADRM1. The next steps are to study the capacity of these CTCF+ EVs in modulating crucial tumor-promoting o cancer-related properties/characteristics such as invasion (Wound and transwell assays, clone, and spheroids) in the normal ovarian epithelium cells.

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CS.4 Cooperative effects of IRE1 signaling promotes glioblastoma multiforme invasion

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Glioblastoma multiforme (GBM) is the most frequent malignant brain tumor. Despite the best treatments available, a patient's overall survival is only 15 months due to the highly invasive behavior of GBM cells. Alterations to proteostasis that affects endoplasmic reticulum (ER) function engage the unfolded protein response (UPR). This pathway is governed by IRE1 controlling the expression of the transcription factor XBP1s or the stability of multiple mRNAs by regulated IRE1-dependent decay (RIDD), supporting GBM progression. IRE1 regulates cell migration capacity in multiple types of cancer; nevertheless, a systemic analysis of IRE1 signaling in GBM has not been described. Additionally, we have shown that IRE1α regulates Filamin A function inducing actin cytoskeleton dynamics and cell migration; therefore, we hypothesized that IRE1 governs GBM invasion through the engagement of distinct signaling outputs involving XBP1s, RIDD, and Filamin A. We performed actin cytoskeleton, transmigration, and invasion assays followed by monitoring the expression of MMPs and TIMPs in IRE1- and XBP1-deficient mouse GBM cells. We validated our findings by implanting mouse brain tumors and the analysis of human patient databases. Our results indicate that IRE1 induce GBM invasion by multiple mechanisms involving (*i*) cytoskeleton regulation and migration through Filamin A, (*ii*) epithelial-to-mesenchymal transition through XBP1s, and (*iii*) MMP enzymatic activity and extracellular matrix remodeling by regulating TIMPs expression through RIDD in vitro, mouse models and TCGA databases. Our data demonstrate the synergistic effects of IRE1 signaling defining its relevance in GBM progression and the value of IRE1 as a possible therapeutic target.

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CB1.1 Bioinformatic study of MUL1 in human heart failure

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Mitochondria play a crucial role in regulating cardiac energy metabolism by contributing high levels of ATP to myocardium contraction. Alteration of mitochondrial structure and function has been associated with the development of cardiac diseases. MUL1, an E3 ubiquitin ligase, is anchored to the outer mitochondrial membrane. This protein regulates the mitochondrial function and dynamics through the ubiquitin and SUMO ligase activity of its RING zinc finger domain exposed to the cytoplasm. Ischemia/reperfusion-induced myocardial damage in rat hearts increases total and mitochondrial protein levels of MUL1 that leads to mitochondrial dysfunction, increases mitochondrial membrane potential and ROS production, and decreases ATP production. However, the role of MUL1 on the development of heart failure (HF) is poorly explored. Therefore, we performed a meta-analysis of independent studies on HF in humans. This study was conducted to determine the expression patterns of different genes in samples obtained from humans under HF conditions. The results showed that the gene expression of MUL1 was not altered in patients with HF. Furthermore, the expression of TBC1D15 and NLRP3 genes associated with the regulation of mitophagy and inflammasome formation, respectively, were differentially decreased. Thus, mitophagy could be induced independently of MUL1 gene expression in humans under HF conditions, and further studies are required to test this hypothesis.

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CB1.2 Bioinformatic analysis of the binding of the long non-coding RNA MALAT1 and the PRC2 complex to genomic sites in cancer cells

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The long non-coding RNA MALAT1 and the histone modifier Polycomb Repressive Complex 2 (PRC2) participate in the regulation of genes associated with cancer development and progression. Despite being characterized independently as chromatin binders and some evidence of MALAT1-PRC2 interaction, it is unknown whether these molecules collaborate at the genomic level. We hypothesize that MALAT1 recruits PRC2 to a set of genes. As a first *in silico* approach, to identify the binding sites of MALAT1 and PRC2 throughout the genome, we downloaded public files of CHART-seq and ChIP-seq, respectively, obtained from MCF-7 breast cancer cells. We processed the sequencing files using the "Histone ChIP-sep processing pipeline", recommended by the ENCODE project, and identified ~25,000 peaks within the human genome where each molecule is found significantly enriched. Importantly, we identified ~3,500 genomic sites where MALAT1 and PRC2 concur. Such sites are located in genic and intergenic regions and include several gene promoters. In sum, we identified genomic sites where MALAT1 and PRC2 are found together, allowing us to perform biochemical and molecular biology studies in key target genes.

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CB1.3 Exploring the Protein-Ligand Dissociation Paths in Aurora A/B kinases with Enhanced Molecular Dynamics Simulations

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Residence time (τ) is a kinetic parameter that measures the time that a compound remains inhibiting a protein. The estimation of this parameter is one of prominence importance because it is related to the affinity and effectiveness of a drug *in vivo*. Several computational techniques such as molecular dynamics (MD) and enhanced MD have been developed to calculate τ in drugs and to gain insight about the molecular determinants affecting τ. Here, we attempted to describe the dissociation process, through Well-Tempered Metadynamics (WT-MetaD) simulations, of Danusertib against Aurora A and B kinases. Danusertib is a potent type I inhibitor with K_d(M) values of $1{,}69 \times 10^{-9}$ and $1{,}44 \times 10^{-9}$ for Aurora A and B, respectively. However, τ value for Danusertib is higher for Aurora B (15976 s) than for Aurora A (1153 s), without a clear molecular and energetic explanation. To study these biological systems, we performed 4 classical 100-ns molecular dynamics (cMD) simulating the two protein-drug complexes. Then, 20 replicates using WT-MetaD from each cMD were employed to describe the dissociation process of Danusertib from the active sites. Several metastable states of Danusertib along different dissociation pathways were found. Based on those results, differences in the relative τ (ns) were found in accordance with experimental data and key amino acids that can contribute to the differential values of τ for Aurora A and B were identified. Future work will consist in the characterization of the free energy profiles along dissociation paths using the metastable states of the ligand with umbrella Sampling.

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CB1.4 A receptophore model for binding sites of local anesthetics in relevant atrial ion channels

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An alteration of ion channels behavior generates abnormal cardiac phenomena such as atrial fibrillation (AF), the most common arrhythmic condition worldwide. In this context, potassium channels hKv1.5 and hTASK-1 as well as sodium channel hNav1.5 seem to be promising drug targets for AF treatment because of their relevance in this illness. It is well known that ropivacaine, bupivacaine, and lidocaine (local anesthetics-LAs-) exhibit a multi-target behavior, because each LA can inhibit these three channels simultaneously. Interestingly, these types of drugs have been shown better efficacy and safety parameters than those highly selective ones. For that reason, the presence of a common nature among their binding sites (BSs), defined as receptophore[1], is a plausible hypothesis for the discovery or rational design of novel drugs with polypharmacological profiles. Methods: Molecular Dynamics (MD) were performed for each ion channel. Reported residues that have a significant role on channel-LAs interaction were used to perform a MD clustering and retrieve the centroid of the most populated cluster. Then, a comparison of geometric patterns of these centroid-BSs was performed by pairs, using Geomfinder. Finally, an atom coordinates K-means clustering where performed in R-studio to generate residue groups for each BS and its geometric center calculation as well as distance measurements were performed in VMD, to propose the receptophore model. Discussion and conclusion: A preliminary receptophore model for LAs BS is presented, enlightening the common nature of hKv1.5, hTASK-1, and hNav1.5 binding sites. This has a tetrahedral shape where the vertices are the geometric center of residue groups which share similar physicochemical properties, i.e. (1 and 2) aliphatic, (3) aromatic and (4) sulfur residue groups.

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CB1.5 *In silico* analysis of thermal stability in hydroxymethyl pyrimidine kinases from bacteria

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Microorganisms have colonized different Earth environments , including some with very high temperatures. One of the requirements for life to adapt to these extreme conditions is the existence of enzymes that can remain folded and active at high temperatures. In this work, using Ancestral Sequence Reconstruction, we studied the evolutionary divergence of thermal stability between enzymes of a thermophilic and a mesophilic lineage from the microorganisms *Thermus thermophilus* and *Salmonella typhimurium,* respectively. For this purpose, the enzyme hydroxymethyl-pyrimidine-phosphate kinase(HMPPK) that participates in the biosynthetic pathway of thiamine was used as a model system. In order to study the structural basis of the divergence in thermal stability between the enzymes of both lineages, we prepared and performed molecular dynamics simulations with time analysis over one μs. This scale time allows us to analyze their conformational flexibility and the amount of non-covalent interactions. The results indicate that the enzymes from both lineages show similar conformational flexibility considering the time scale analyzed, with differences only in localized regions. We also examined possible insertions and deletions in the protein scaffold, which would generate relevant changes in the protein dynamics. The analysis of non-covalent interactions showed that the enzyme of the thermophilic lineage have a higher amount of hydrophobic contacts than the mesophilic lineage although a similar amount of hydrogen bonds and salt bridges. These results confirm the relevance of the hydrophobic core for enzyme's stability and adaptability to high temperatures.

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CB2.1 Bioinformatic study and selection of negative regulator genes to drought and salinity stress tolerance and their expression analysis in tomato (*Solanum lycopersicum*) var. Poncho Negro

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Climate change is a dramatic global phenomenon that involves a rise of drought and salinity of soils, abiotic stresses that impair crop developing and yield. At the molecular level, plants respond to this stress through abscisic acid-induced mechanisms. Nevertheless, negative regulator genes expression produce susceptibility to abiotic stress in plants. Tomato (*Solanum lycopersicum*) is the most cultivated and important vegetable in the world and in Chile; however, drought and salinity of soils impairs the yield and quality of the fruits. Tomato var. Poncho Negro (PN) it's an endemic, whose better salt stress-tolerance makes it as a great alternative as rootstock for commercial varieties. Upon bibliographic research we identified five negative regulator genes to drought and salinity stress in different plants (*OsDIS1, SlACO2, AtACS6, OsSRFP1* and *OsiSAP7*), which were selected as candidates to gene editing trough CRISPR-Cas9 to obtain rootstocks of PN more tolerant to drought and salinity. *OsDIS1, OsSRFP1* and *OsiSAP7* encodes for E3 ubiquitin-ligases which signal factors conferring stress tolerance to proteosome-dependent degradation; while SlACO2 and AtACS6 are ethylene biosynthesis enzymes, a hormone that confers susceptibility to salt and drought stress. Then, we identified between 3-4 orthologues on tomato genome and made a phylogenetic and multiple sequence alignment analysis to select the most conserved paralogues. Through eFP Browser we test its root-expression. Furthermore, we evaluated the gene expression on PN roots in an acute salinity and drought stress treatment. Taken together, these results allow us to select the best candidates for PN gene editing.

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CB2.2 Genome-wide identification of genes encoding for JAZ proteins in octoploid strawberry *Fragaria* × *ananassa* (Duch.)

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Commercial strawberry (*Fragaria ×ananassa*) is a complex allopolyploid (2n = 8x = 56), composed of four subgenomes, and obtained by hybridization of two wild octoploid species. Until now, all the genomic approaches on this species have been performed through its dominant subgenome, *Fragaria vesca.* Nevertheless, the other three extant relatives subgenomes (*Fragaria nipponica*, *Fragaria iinumae*, and *Fragaria viridis*) have not been widely studied. Lastly, a near-complete chromosome-scale assembly for *F. ×ananassa* 'Camarosa' reference genome was reported, and it´s present as a powerful platform for new molecular studies. On the other hand, jasmonates (JAs) are signaling molecules that regulate many aspects of plant growth, development, secondary metabolism biosynthesis, and defense. In strawberry, it proposed that JAs could regulate early fruit development. The JAZ (JAsmonate ZIM-domain) proteins are one of the main components of JA signaling however, they have not been fully characterized at the genomic level yet in strawberry. In the present research, we identified 42 JAZ genes and 47 putative proteins on the four subgenomes of *F. ×ananassa.* Also, we analyzed their gene structure, characteristic domains, genomic position, and phylogenetic relationships. JAZ proteins showed high conservation to their orthologs in *Arabidopsis thaliana*, *F. vesca*, and *F. ×ananassa* previously reported proteins along with other fleshy-fruit species such as *Vitis vinifera*. These newly reported putative JAZ proteins can be helpful for molecular studies hereinafter but the role of these genes in the JA signaling pathway in strawberry fruit development remains to be understood.

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CB2.3 Identifying modified amino acids with potential inhibitory activity against human bitter taste receptors activated by steviol glycosides through structure-based virtual screening

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Two bitter taste receptors, hT2R4 and hT2R14, specifically mediate the bitter off-taste of steviol glycosides (SG), triggering this mouth feel and affecting stevia-sweetened foods and beverages acceptance by the consumer. The objective of this work was to identify modified amino acids that inhibit the human bitter taste receptors activated by SG through structure-based virtual screening. To this end, we built comparative models for hT2R4 and hT2R14 using as template the crystal structure of human delta opioid receptor (PDB 4N6H) and nociceptin/orphanin FQ peptide receptor (PDB 5DHG), respectively. 209 modified amino acid commercially available in the Sigma-Aldrich catalogue were taken for this study. Ligands structures were obtained from PubChem NCBI database. Then, we resorted to virtual screening using Autodock Vina software. Finally, graphical analyses of the molecular docking studies were performed using VMD software. Complementarily, *in silico* absorption, distribution, metabolism and excretion (ADME) properties of the preferred best lead molecules were analyzed using QikProp of the Schrödinger Suite. Docking results showed that two derivatives, Fmoc-D-Homoser(Trt)-OH and Fmoc-Ser(tBu)-ODhbt, have lower binding energy (ΔG_{bin}) values than stevioside and rebaudoside A into both hT2R4 and hT2R14. Both derivatives share the same binding site than SG into hT2R14. However, *in silico* ADME results showed that only Fmoc-Ser(tBu)-ODhbt accomplish the Lipinski's rule of five and the Jorgensen's rule of three. It will be necessary to validate and confirm experimentally the theoretical results found for these compounds and particularly, for those with better ΔG_{bin} values.

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CB2.4 A receptophore model for negatively charged activators in K+ channels

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A Master key mechanism related to the pharmacophore of negatively charged activators (NCAs) to activate TREK-2, BKca and hERG K+ channels was discovered[1]. Moreover, a polypharmacological behavior of NCAs was proved, because every NCA could activate more than one potassium (K^+) channel. However, the role of the nature of the binding site (BS) of the NCA remains unknown. For that reason, an important role of the BSs is proposed for the correct recognition of NCAs in different K^+ channels. In this context, the presence of a common nature among BSs (defined such as receptophore, Nuñez-Vivanco et al, 2018), appears to be a valid hypothesis. Methods: Experimental residues that have a significant role on channel-NCAs interaction were retrieved (Schewe et al, 2019). Subsequently, a comparison of geometric patterns of these BSs was performed by pairs, using Geomfinder. Finally, an atom coordinates K-means clustering where performed in R to generate residue groups for each BS and its geometric center calculation and distance measurements were performed in VMD, to propose the receptophore model. Discussion and conclusion: A receptophore preliminary model for NCAs BS is proposed, suggesting that residue distribution might have a non-negligible impact on the polypharmacological behavior of the NCAs. This has a tetrahedral shape where the vertices are the geometric center of residue groups which share similar physicochemical properties. Finally, a Molecular Dynamics approach could be used in further research for enlightening the relation between the pharmacophore and receptophore of NCAs.

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CB2.5 Elucidating populations of marine phages carrying amgs involved in the antarctica biogeochemical cycles

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The Western Antarctic Peninsula (WAP) has experienced temperature rising throughout the past years, affecting directly or indirectly the marine primary production. The effect of abiotic factors on the Antarctic microbial communities has been deeply studied, however, biotic factors such as the effect of viruses remains poorly explored. Chile Bay is a representative ecosystem of the coastal environment of the WAP, influenced by freshening due to glacier ice melting, where summer microbial communities change yearly under different productive scenarios. The aim of this study was to elucidate the bacteriophage community, as relevant bacterial killing agents that impacts in the structure and composition of the bacterial community, under different summer productive conditions in Chile Bay. We analyzed the phage taxonomic composition and diversity of seven metagenomes obtained from 2014 - 2019 summers. Furthermore, we searched and evaluate the relevance of this phage community as carriers of auxiliar metabolic genes (AMGs) that can drive changes in their bacterial hosts metabolisms involved in Chile Bay biogeochemical cycles. The results demonstrate a marked presence of DNA viral communities (778 vOTUs) belonging to the families Siphoviridae, Myoviridae, Podoviridae and Phycodnaviridae for which the protein profile suggests the presence of known but also potentially new AMGs involved in biogeochemical cycles and bacterial metabolisms. This study will lead to a better understanding of the viral role in the Antarctic coastal environment, a hardly affected region of the planet by climate change.

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EM1.1 Overexpression of endogenous *lipoyl synthase* (*SlLIP1*) in *Solanum lycopersicum* fruits to increase their lipoic acid content

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Oxidative stress is generated by an increase in reactive oxygen species (ROS) which can cause cell damage. As a response, antioxidants are produced due to their capacity to neutralise ROS. Of these, lipoic acid is extremely powerful, as well as being amphipathic, regenerating other antioxidants and functioning in both oxidised and reduced forms. Also, lipoic acid is a cofactor that is associated with several enzymes, including the pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (kGDH) complexes. The lipoylation process occurs through two routes, de novo synthesis and the salvage of free lipoate. Lipoyl synthase (LIP1) is common in both pathways. In order to obtain a tomato fruit with a higher content of lipoic acid, lipoyl synthase gene (SlLIP1) from Solanum lycopersicum was expressed under the control of a fruit-specific promoter (Polygalacturonase, PG). The tomato cv "Micro-Tom" was successfully transformed and 3 lines overexpress SlLIP1 transcripts in fruits. These lines do not show altered vegetative growth and their fruits are similar in size to those of wild type plants, but a parthenocarpic phenotype was detected. The degree of lipoylation is being determined and we hope to obtain a correlation between the levels of lipoic acid and the antioxidant capacity in transgenic tomato fruits. In addition, the PG promoter is induced under high salt conditions, so the progeny of transgenic lines are being molecularly verified to study their response to saline stress conditions and the effect on their development.

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EM1.2 Application of a new recombinant laccase in the biodegradation of antibiotics

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Laccases are multicopper oxidases that use a broad range of phenolic and non-phenolic substrates. They are widely distributed in nature and have been also found in extremophilic microorganisms. Laccases have interesting characteristics for biotechnology, specifically in bioremediation, because they only used oxygen as co-substrate, producing water as the only product.
In the world currently 200.000 tons of antibiotics are yearly used. The indiscriminate use of them has increased the antibiotic presence in the ecosystem, rising the probability to generate (multi)resistant bacteria. Several types of antibiotics have been detected in rivers around the world, and quinolones and macrolides have been even identified in the Antarctic Sea. Consequently, research for new tools to treat these contaminated waters in an ecofriendly way is an urgent need. The use of laccases appears as an interesting method to decontaminate water.
In Fundacion Biociencia a novel laccase from a thermoalkaliphilic microorganism has been isolated and heterologously produced. This enzyme has a great activity using syringaldazine as substrate (>450.000 U/mg) at 70°C and pH 6,0. In this work, we evaluate the capacities of this recombinant laccase in the biodegradation of three family of antibiotics: β-lactams, tetracyclines and quinolones at 40°C, assessing the decrease of antibiotics ecotoxicity after treatment with this laccase using different mediators. First results indicate that this enzyme is able to degrade these three kinds of antibiotics at 0,5 mg/mL after 1h, in the presence of the mediators acetosyringone and ABTS, demonstrating the degradative efficiency of this laccase and its great biotechnology potential for biorremediation.

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EM1.3 Computational study of first- and second-generation statins interacting with the human HMG-CoA reductase enzyme: Understanding the structural and energetic elements of their rational drug design

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Cholesterol is an essential lipid for cell membranes and is a biosynthetic precursor of steroid hormones, but the excess of cholesterol in the body can cause severe cardiovascular disease. In order to counteract cholesterol levels, statins were designed as a group of drugs that reduce cholesterol by acting as enzyme inhibitors.
The study of the protein-ligand complexes was carried out using the enzyme 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMG-CoA reductase) and a group of type I (Mevastatin, Lovastatin, Pravastatin, and Simvastatin) and type II statins (Atorvastatin, Cerivastatin, Rosuvastatin, Fluvastatin, and Pitavastatin). These two groups of molecules are responsible for inhibiting the rate of cholesterol biosynthesis; because they possess a "head" group that can mimic the natural substrate and bind to the active site using the same interactions.
Molecular docking was used to assess the orientation taken by the ligands within the active site of the protein. The crystallographic orientation of Rosuvastatin and other statins within HMG-CoA reductase was reproduced, predicting their positions and a favorable energy score in all cases.
Regarding the interactions obtained by docking, the ligands interact with the protein residues through hydrogen bonds; supporting the results of the reference ligand (Rosuvastatin) since the orientation of its polar site (head group) seems to overlap in the same or similar way as the substrate, obtaining an RMSD of 0.73 Å.
The analysis of ligands within the HMG-CoA binding site allowed us to understand and highlight the main intermolecular interactions established by each ligand. The latter starting protein-ligand complexes opened the way to perform structural and energetic analyses with molecular dynamics (DM) and binding free energy calculations (MM-GBSA).

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EM1.4 Rewiring NADPH metabolism in *Escherichia coli*: Integrating protein and metabolic engineering to obtain an NADPH-dependent lactic fermentation

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Lactic acid (LA) production in bacteria has become an attractive process in the last few years. Recent interest in modulating the cofactor specificity of D-lactate dehydrogenase has been motivated by the production of LA in different bacterial hosts using the reducing power of NADPH. First, we addressed the structural and kinetic aspects of changing the cofactor specificity of the D-lactate dehydrogenase from *Escherichia coli* (*Ec*LDH) from NADH to NADPH. The characterization of the kinetic mechanism and cofactor preference of the *Ec*LDH showed a 160-fold preference for NADH over NADPH. A crystallographic structure was obtained in complex with NADH showing that residues in the β7-α7 loop provide interactions that favor the NADH affinity. To reverse the cofactor specificity, we focused on residues of this loop. Using structural evolutionary approaches and analysis by statistical potentials we predicted changes that could invert cofactor preference and characterized the mutants by enzyme kinetics and X-ray crystallography. The best mutant obtained showed almost 9200-fold of reversal cofactor specificity over the wild-type enzyme. Moreover, two NADPH-dependent *Ec*LDH mutants were expressed in a Δ*pgi E. coli* strain, a mutant that shows slow growth rate due to NADPH overproduction when glucose is the sole carbon source. Notably, the overexpression of an NADPH-dependent LDH lead to an increment of the growth rate, concomitantly with D-lactate production. Thus, our results provide the basis to understand and control cofactor specificity in D-lactate dehydrogenases to rewire NADPH metabolism, allowing LA production in *E. coli* under aerobic conditions.

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EM1.5 Computational study of CDK4/CyclinD/Rb complex: homology modeling, molecular docking and molecular dynamics for understanding its enzymatic activity

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Protein kinases play a fundamental role in the cell cycle. The CDK4/cyclinD1/Rb complex is relevant because the Retinoblastoma (Rb) protein, in a state of hypo phosphorylation, represses the transcription of genes necessary for the progress of the cell cycle. Therefore, deregulation of Rb phosphorylation could lead to cancer cell proliferation. A notable example is Retinoblastoma type cancer, a non-treatable tumor that appears in the eye of children in their first years of life and leads to the removal of the eyeball.
This work aimed to obtain models of the CDK4/ cyclinD1/Rb complex in its reactive state and perform its structural analysis using several computational tools. In this way, the structural models were built by combining the homology modeling algorithms as implemented in the Modeller suite with Glide's Molecular Docking methodology. The CDK4/cofactor's (ATP+Mg) binding site was modeled using the CDK2's analog complex reported with the PDB ID: 1QMZ. The structure of CDK4 was modeled from the CDK4's structures reported with the PDB IDs: 3G33 and 2W96, taking the second structure to model the CDK4/CyclinD1 interactions. This procedure was performed in stages, modeling first the CDK4/cofactors complex and then the CDK4/CyclinD1 complex. The Rb peptide was docked into the CDK4 active site by molecular docking experiments using the Glide module. The CDK4/CyclinD1/Rb complex models obtained by this methodology were refined and studied through a classical molecular dynamics (cMD) methodology using the tools available in the AMBER20 suite. The selected models showed to be structurally adequate and stable during the MD simulations.

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EP.1 Ancestral Sequence Reconstruction reveals a phytase activity as an evolutionary novelty in the histidine acid phosphatases from *Enterobacteriales*

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In the phylogeny of the histidine acid phosphatases, phytases and glucose-1-phosphatases (G1Pases) from *Enterobacteriales* are closely related and share a highly similar structure. Nonetheless, phytases hydrolyze myo-inositol hexakisphosphate molecules (InsP6) as substrate whereas G1Pase acts mainly on glucose-1P. However, G1Pase displays a promiscuous activity for InsP6 but with low efficiency and acting only over one phosphate of the substrate, although both enzymes hydrolyze InsP6 at the same optimal pH and with similar affinity. Sequence alignment shows slight differences in the conserved N-terminal catalytic motive "RHGXRXP" found in phytases, where Asn replaces the Gly residue in G1Pases.
In this work, we have traced the evolutionary history of the phytase and G1Pase lineages from enterobacterial to address substrate binding residues responsible for specificity.
We perform Ancestral Sequence Reconstruction (ASR) to reconstruct the last common ancestor for G1Pases (ancEnG1P), the ancestor of phytases (ancEnPhy) and the common ancestor between G1Pases and phytases from *Enterobacteriales* (ancPhyG1P) and by homology modeling the active site residues of the three enzymes were evaluated.
The results show that, despite ancPhyG1P have the same N-terminal motif of phytases, substrate binding residues are G1Pases-like, which suggests that the phytase activity would be the evolutionary novelty in the history of this enzyme family being the G1Pase activity the conserved trait.

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EP.2 The evolutionary trajectory of the activation by AMP in the family of ADP-dependent kinases from the archaeal phyla *Euryarchaeota*

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In the *phyla Euryarchaeota* of archaea, the glycolytic flux proceeds through a modified version of the Embden–Meyerhof pathway, where the phosphofructokinase (PFK) and glucokinase (GK) enzymes use ADP as the phosphoryl donor instead of ATP, as in the canonical pathway described in *Eukarya* and *Bacteria.* Moreover, ADP-dependent GK/PFK enzymes have been described in the orders *Methanococcales and Methanosarcinales* from archaea*,* where both reactions take place at the same active site.
Although initial kinetic characterization of the GK and PFK enzymes from Archaea indicate that these enzymes were not regulated by the classical effectors, we recently report that PFK/GK enzymes from the order *Methanococcales* are activated by the product reaction AMP.
We explore the evolutionary trajectory of the AMP activation in the ADP-dependent kinases family from *Euryarchaeota*. Here we used a comparative kinetic study among ancestral bifunctional enzymes from *Methanococcales* and *Methanosarcinales*, and ancestral specific PFK enzymes from *Thermococcales.* We established that the activation by AMP is an ancestral trait in the ADP-dependent kinases, which is conserved in the bifunctional lineage but lost in the evolutionary branch leading to specific PFK, which are inhibited by the product reaction, AMP. Furthermore, employing *in silico* protocols of docking and molecular dynamics, we identified putative allosteric sites able to bind and stabilize the AMP-protein interactions, which allow estimating the binding free energy of the complex and the recognition of key residues for this interaction. Altogether, these results led us to propose an allosteric site for AMP regulatión in ADP-dependent kinases.

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EP.3 First body of evidence suggesting a role of a tankyrase-binding motif (TBM) of vinculin (VCL) in epithelial cells

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Poly(ADP-ribose) polymerases (PARPs) catalyze the synthesis of poly(ADP-ribose) (PAR) as a posttranslational modification. Four PARPs synthesize PAR, namely PARP-1/2 and Tankyrase-1/2 (TNKS). In the epithelial belt, adherens junctions (AJ), whose composition has not been completely disclosed, are accompanied by a PAR belt and a subcortical F-actin ring. Vinculin (VCL) participates in the anchorage of F-actin to the AJ, regulating its functions. We hypothesized that TNKS poly(ADP-ribosylates) (PARylates) epithelial belt VCL, affecting its functions in AJ, including cell shape maintenance. Tankyrase-binding motif (TBM) sequences in hVCL gene were identified and VCL sequences from various vertebrates, *Drosophila melanogaster* and *Caenorhabditis elegans* were aligned and compared. As predicted by the hypothesis, (1) VCL TBMs were conserved in vertebrate evolution while absent in *C. elegans*; (2) TNKS inhibitors disrupted the PAR belt synthesis, while PAR and an endogenous TNKS pool were associated to the plasma membrane; (3) a VCL pool was covalently PARylated; (4) transfection of MCF-7 cells leading to overexpression of Gg-VCL/_TBM induced mesenchymal-like cell shape changes. This last point deserves further investigation, bypassing the limits of our transient transfection and overexpression system. In fact, a 5th testable prediction would be that a single point mutation in VCL TBM-II under endogenous expression control would induce an epithelial to mesenchymal transition (EMT). To check this, a CRISPR/Cas9 substitution approach followed by migration, invasion, gene expression and chemo-resistance assays should be performed.

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EP.4 Structural and functional analysis of AMP regulation in glycogen phosphorylase from the *Methanococcales* order of archaea

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The archaeal metabolism is characterized by unusual enzymes and novel metabolic pathways. However, based on the inability to find regulated enzymes it has been proposed that archaeal enzymes are not subject to allosteric control. Nonetheless, recent studies of glycogen metabolism, polysaccharide present in the main archaeal groups, indicates that in *Methanococcales,* a methanogenic order of archaea, enzymes associated to glycogen metabolism, are regulated by AMP.
To identify novel control points in *Methanococcales* glycogen metabolism, we selected the glycogen phosphorylase enzyme from the model organism *M. maripaludis* (Mm-GP), which catalyzes the first step in glycogen degradation. Multiple sequence alignment and fluorescence studies indicates that *Methanococcales* GP enzymes, holds the PLP cofactor within the active site through a covalent bond established by a threonine residue instead of lysine, as found in others family members. Kinetic characterization of MmGP indicates that the enzyme prefers long and branched glucose polymers. Nevertheless, preliminary studies indicate that AMP does not regulate enzyme activity. Prediction of the 3D structure of Mm-GP with the artificial intelligence program AlphaFold2[1] shows that this enzyme presents an identical fold to other structures determined in eukarya and bacteria, even when these enzymes share only an 11% of sequence identity. Taken together, our analysis reveals that GP enzymes from *Methanococcales* share a similar fold with previously characterized enzymes and prefer substrates like glycogen. However, further studies are needed to address if *Methanococcales* GP enzymes are regulated by other metabolites than AMP.

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PS.1 Identification and characterization of the regulatory iron binding site from the *Acidithiobacillus ferrooxidans* transcription factor FUR

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Acidithiobacillus ferrooxidans is a bacterium of biotechnological interest due to its particular physiological properties. It has the ability to gain energy from the oxidation of iron (Fe^{+2}), and lives in an acidic environment (pH 2) that can have very high concentrations of iron. *A. ferrooxidans* has developed a highly efficient system to regulate iron homeostasis, maintaining intracellular concentrations of iron to prevent oxidative stress damage and balancing the availability of iron as an essential micronutrient versus its use as an energy source.
One of the key components for this is the transcription factor Fur (Ferric Uptake Regulator) in charge of sense and respond to fluctuations in iron availability, mainly through the iron-sensing. In *E. coli*, FUR regulates the expression of more than 100 genes that are implicated in iron transport and storage, ROS resistance, and pathogenicity. The capability to be a global regular, make it an attractive putative therapeutic target for antibacterial drugs.
Using Biophysical analysis and bioinformatic predictions, it was possible to characterize the metal-binding sites and determine the critical amino acids for functioning. Bioinformatic approaches predicter three possible metal binding sites where the residue Cys96, Cys145, His91 and His93 are key to protein functioning, as demonstrated by EMSA and ICP-MS analyzes.

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PS.2 Bioinformatic analysis and characterization of the Superfamily Fur and Fur protein from *Acidithiobacillus ferrooxidans*

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The Fur protein from *Acidithiobacillus ferrooxidans* (Fur_{AFE}) is a protein of biotechnological interest due to its ability to control various physiological processes. In *E. coli*, it has been shown to regulate more than 100 genes.
The FUR Superfamily is composed of several regulatory proteins (Fur, Zur, Nur, Mur, Irr, PerR) that respond to different metals and control a wide variety of processes.
The purpose of the research was to study the amino acid sequence and structural characteristics of the Fur_{AFE} protein and compare them with known Fur-type proteins. For this, a series of bioinformatic analyzes were implemented, such as sequence alignment; search for conserved motifs and domains; sequence/structure conservation analysis; studies of the evolutionary relationships of the Superfamily regarding Fur_{AFE}; search and analysis of the amino acids that participate in the union to DNA and metal described in the literature for the different crystallized proteins.
The comparison between Fur_{AFE} and the members of the subfamily shows the existence of structural homology. Most of the conservation of amino acid corresponds to metal-binding sites and the residues of the DNA recognition helices, which present at least one helix towards the N-terminal end. All were determined to possess the DNA-binding HTH motif. Through comparative modeling, for Fur_{AFE}, it is identified that it possesses a structure similar to Fur orthologs, even so, for the most divergent subfamilies of the Superfamily, MntR, PerR, Nur.

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PS.3 Structural and evolutionary analysis of HMP-P phosphorylation in *ThiD* hidroxymethil-pyrimidine-phosphate kinases

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The ATP-dependent vitamin kinases family from bacteria are related to enzymes involved in thiamine and pyridoxal phosphate pathways. The thiamine biosynthesis requires the phosphorylation of hydroxymethyl-pyrimidine (HMP) to hydroxymethyl-pyrimidine-diphosphate (HMP-PP), forming hydroxymethyl-pyrimidine-phosphate (HMP-P) as intermediate. Two homologous enzymes can carry out the HMP phosphorylation: a specific hydroxymethyl-pyrimidine phosphate kinase encoded by the *ThiD* gene (*ThiD*-HMPPK) that can phosphorylate HMP twice to produce HMP-PP; and a bifunctional pyridoxal kinase encoded by the *pdxK* gene (PLK/HMPK) that only phosphorylate HMP to produce HMP-P, beside the phosphorylation of pyridoxal.
The PLK/HMPK reaction is analogous to the one described for other family members, being its mechanism and key residues involved in catalysis identified. On the other hand, few kinetic characterizations of *ThiD*-HMPPK have been reported, and the catalytic mechanism or structural determinants for HMP-P phosphorylation are unknown.
To identify structural determinants of HMP-P phosphorylation, we performed X-ray crystallography of the last common ancestor of HMPPK from *Enterobacteriales* (ancEnHMPPK). Furthermore, we analyzed active site residues through the evolutive trajectory of these enzymes to identify key mutations that could have led to the emergence or loss of HMP-P phosphorylation in *ThiD*-HMPPK enzymes.
The crystallographic structures obtained from ancEnHMPPK show that His179 and Thr211 should be important for HMP-P phosphate group stabilization. Moreover, sequence alignments and phylogenetic analysis indicate that these residues are highly conserved in *ThiD*-HMPPK but not in the PLK/HMPK group. These results provide valuable information for the understanding of the mechanism of the second phosphorylation of HMP in *ThiD*-HMPPK enzymes.

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PS.4. The new emerging role of nuclear NUAK1 in RNA processing

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NUAK1 is a serine/threonine kinase overexpressed in several cancer types. We previously showed that NUAK1 locates in nuclear and cytoplasmic compartments, suggesting molecular targets and functions depending on its subcellular location. Interestingly, nuclear NUAK1 has a punctate distribution, resembling nuclear speckles, regions enriched in pre-mRNA splicing factors, including snRNPs and SR proteins. We performed a Multidimensional Protein Identification Technology analysis (MudPIT) of nuclear NUAK1-associating proteins. Consistent with the nuclear NUAK1 distribution, an ontological analysis of the MudPIT data identified several proteins related to RNA processing. More remarkable, we validated by co-immunoprecipitation studies that nuclear NUAK1 associates with heterogeneous nuclear ribonucleoprotein K (hnRNPK), a protein involved in processes related to gene expression. The hnRNPK binds to RNA of genes involved in tumor progression, regulating processes such as transcription, splicing, and mRNA stability. Using the GPS (Group based Prediction System) bioinformatics web server, we identified two putative NUAK1 phosphorylation sites on hnRNPK, Ser-89 located at the KH1 domain and Ser-417 at the KH3 domain. Finally, we performed a protein docking modeling between NUAK1 and hnRNPK using the 3D structures from AlphaFold Protein Structure Database server (NUAK1:O60285, hnRPNK: P61978). Our studies identified that the NUAK1 kinase domain directly interacts with the KH1/KH3 RNA-binding domains of hnRNPK. Moreover, the phosphorylation sites predicted (S89, S417) locate at the docking region. Since phosphorylation of KH domains of hnRNPK inhibits its binding to nucleic acids, we propose that nuclear NUAK1 may affect RNA processing of genes involved in tumor progression through phosphorylation and inhibition of the hnRNPK.

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PS.5 Structural studies of *Concholepas concholepas* hemocyanin: A combined approach using X-ray crystallography and Cryo-EM

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Hemocyanins are giant extracellular glycoproteins present in the hemolymph of mollusks and arthropods. Nowadays, hemocyanins are used as natural, non-toxic, and non-specific immunostimulants in biomedical and clinical applications. Mollusk hemocyanins present a complex structural organization, being the quaternary structure a didecamer formed by one or two subunits containing eight globular domains called functional units (FU). *Concholepas concholepas* hemocyanin (CCH) presents unique structural properties and is highly effective in inducing beneficial immunomodulatory responses.
Despite the biomedical potential of CCH, its structure and even its amino acid sequence remain unknown. Preliminary biochemical characterization reveals that CCH corresponds to a heterodidecamer conformed by two distinct subunits (CCHA and CCHB). Employing RACE sequencing, we obtain the partial sequence of two genes from both CCH subunits. We used the two following approaches to get structural information regarding the functional units: 1) Since we identified the sequence from two FUs, we synthesized *de novo* these genes for their recombinant expression in *E. coli*. 2) We intend to get the FUs from native CCH. For this, we induced the dissociation of subunits from native CCH and digested the CCHB subunit with elastase. After FU purification by anion exchange chromatography, we perform crystallization assays, obtaining several crystals.
The preliminary Cryo-EM dataset of CCH allows us to obtain a quaternary structure reconstructed at 4.5 Å resolution. These results are promising to determine the CCH structure through an approach that combined fitting high-resolution crystal structure of an FU into a lower resolution Cryo-EM density map of the whole didecamer.

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GE1.1 SALL2 expression in colon cancer progression and its association with AXIN2

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SALL2 is a developmental transcription factor involved in the regulation of cell proliferation and survival. Massive data analyses of cancer versus normal tissues indicate that *SALL2* mRNA is significantly decreased in colorectal cancer (CRC), a cancer type characterized by hyperactivation of the WNT pathway. Interestingly, our unpublished ChIP-seq analyses suggest that SALL2 regulates genes associated with the WNT pathway, including the negative regulator AXIN2. However, the role of SALL2 in CRC and its relationship with the WNT pathway are yet unknown. To evaluate a role for SALL2 in CRC, we constructed a tissue microarray of 129 samples from Guillermo Grant Benavente's Hospital comprising normal colon, adenoma, and CRC. We evaluated changes in SALL2 protein levels and/or location during CRC progression by Immunohistochemistry (IHC). SALL2 expresses in the nucleus and cytoplasm of the normal colon epithelium and the stroma. However, SALL2 expression decreases in adenoma and is absent in CRC. Results were further validated by analyzing massive public data using Limma library in R and through qPCR, immunoblot, and IHC of CRC cell lines. We confirmed that SALL2 expresses in normal colon epithelial cells (CCD-841-CoN) but not in CRC cell lines. Finally, we evaluated AXIN2 expression in wild-type and SALL2-null CCD-841-CoN cells. We found a positive correlation between AXIN2 and SALL2 expression upon treatment of cells with WNT pathway activators LiCl and CHIR99021. Our study suggests that SALL2 positively regulates the transcription of AXIN2, acting as a negative regulator of the WNT pathway. Loss of SALL2 could contribute to CRC progression.

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GE1.2 Science and society: The role of professional Biochemistry in the Chilean science institutionalization between the years 1957 and 1980

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Is important to study the history of experimental sciences research in Chile to understand the social impact of science in the country. In 1957, the University of Chile creates the first experimental science career in the country: Biochemistry. This career sparked new possibilities for scientific labor and public space for professional scientists. Later, in 1967, President Frei created the National Commission of Science and Technology, which was highly influenced by this new generations of professionals.
Among these scientists, foundational for biochemistry, can be distinguishes for its scientific contributions and its participation in the public policy discussion: Osvaldo Cori, cofounder of the Biochemistry career and investigator of biomolecules; Hermann Niemeyer, founder of the first Ph.D. program in science and researcher in carbohydrate metabolism; Jorge Allende, coordinator of the first Molecular Biology classes and one of the principal researchers of the biosynthesis of proteins. From these personalities and their research, the relationship between biochemistry and the national science institutionalization can be traced.
This scientific sociohistorical work aims to analyze and interpret the scientific contributions of these pioneers in biochemistry to the institutionalization and strengthening of the experimental sciences between 1957 and 1980. We have discovered connections between these investigators and how the lack of resources and poor conditions of making science pushed them to seek for representativity and lead them to important position in the principal institutions that administrates scientific research. The relevance of this project is to contribute to the disciplinary understandings of the public science institutions in Chile.

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GE1.3 Identification of xyloglucan transglycosylase/hydrolase (*XTH*) genes in raspberry and characterization of *RiXTH9* at protein and transcriptional levels

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Raspberry (*Rubus idaeus* L.) is a species with fruit of high nutritional value, but with a short shelf life because it softens quickly. In different fruits, softening has been associated with modifications in the cell wall structure and composition due to the action of different enzymes. The xyloglucan transglycosylase/hydrolases (XTHs) are a family of enzymes related to plant growth and development. XTHs are associated with modifications in the cell wall catalyzing the breakdown and connection of xyloglucan molecules and modifying the fiber-xyloglucan composite structure. In fruits, a relationship of some XTHs with a dual-action, i.e., the maintenance and loss of firmness, has been reported. During raspberry ripening, analysis of differential gene expression suggests the participation of an *XTH* gene in this process. However, the XTH family has not been identified at the genomic level in raspberry, and the expression of this *XTH* gene in other fruit ripening stages and tissues is unknown. In this work, 19 *XTH* genes were identified in a raspberry genome draft. The gene structure of the *RiXTHs* was determined, and the protein sequences were analyzed, identifying the characteristic XTHs motif. A three-dimensional model of the protein deduced from the differentially expressed *RiXTH9* gene was built, which indicated that it has a β-jellyroll-type structure typical of the XTHs family, and relative gene expression analyses indicate that it is expressed in fruit tissues -drupelets and receptacle- during ripening and also in leaves, being its expression higher in drupelets and receptacle during the first stages of fruit ripening. This study provides valuable information for future investigations of the role of XTHs enzymes in changes of raspberry firmness during fruit ripening.

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GE1.4 The SALL2 transcription factor: A new regulator of cell migration through integrin β1 expression

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Cell migration is a multistep process orchestrated by several proteins and signaling pathways. Deregulated cell migration has been associated with several diseases, including tumor formation, and spreading to other tissues. SALL2, a member of the *Spalt* gene family, is a poorly characterized transcription factor, which has been indirectly related with cell migration, due to its crucial function in optic fissure closure and neurite outgrowth. However, the role of Sall2 in cell migration remains unclear. Here, we evaluated the different steps of the migration process separately, by using immortalized *Sall2*-deficient and wild-type Mouse Embryo Fibroblasts (MEFs) and an inducible gain of function MEF model. We found that Sall2 is required for cell migration, assessed by wound healing and transwell assays. In fact, Sall2 regulated focal adhesion turnover and consequently cell adhesion, as observed by confocal microscopy and cell detachment assays. Intriguingly, *Sall2*-deficient MEFs depicted a significant decrease in Focal Adhesion Kinase (*FAK*) autophosphorylation at Y397 and integrin β1 expression level, when compared with wild-type cells. The transcriptional regulation of integrin β1 by SALL2 was confirmed by real-time PCR, a luciferase reporter assay, and Chromatin Immunoprecipitation (ChIP), which proved a direct binding of SALL2 to the *ITGB1* promoter. Thus, we propose a molecular mechanism by which SALL2 promotes cell migration, involving the expression of integrin β1 as a key component of focal adhesion dynamics. The role of SALL2 in cell migration might have implications in disease.

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GE1.5 Transcriptional regulation of the TCF7L2/TCF4 gene in response to Wnt/β-catenin signaling activation

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The Wnt/β-catenin signaling pathway plays essential roles in cell differentiation and proliferation, tissue regeneration and cell death, among many other biological processes. Alterations in the levels of the signaling pathway could contribute to the development of a wide range of diseases, such as neurodevelopmental disorders and neurodegenerative diseases. The T-cell transcription factor 4 (TCF7L2/TCF4) is considered a key component of the Wnt/β-catenin signaling pathway and acts as the main transcriptional mediator. The expression of TCF7L2 generates multiple isoforms, including a full length TCF7L2 isoform, which have the β-catenin binding domain that allows the activation of Wnt/β-catenin targets and the dominant-negative isoforms, which acts as repressors of the signaling cascade. Although it has been postulated the TCF7L2 could have an important role during neurodevelopment, to date there are no indication of mechanisms for regulating its expression in this context. Therefore, we studied the effect of the activation of Wnt/β-catenin with CHIR99021 and a constitutive β-catenin in the levels of different isoforms of TCF7L2 in H9 neuronal progenitor cells and human kidney embryonic cells (HEK293). We observed that activation of the signaling cascade induces quickly the transcription of TCF7L2 at 4h in H9 neuronal progenitor cells but decreased 24-48h post treatment. Instead, in HEK29 TCF7L2 mRNA and protein levels increased significantly at 4h, 24 and 48h post activation of Wnt/β-catenin signaling pathway. Our results indicate that TCF7L2 could be an interesting biomarker for several pathologies were there are found high levels of Wnt/β-catenin signaling activity.

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GE2.1 Identification of novel transcription factors involved in cardiac hypertrophy trough human transcription regulatory networks

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Heart failure (HF) is a complex condition where the heart cannot pump enough blood to the body. HF onset is preceded by cardiac hypertrophy (CH), an adaptative response to the increased workload that is characterized by an increase in cardiomyocyte size. Cardiac stressors such as Norepinephrine (NE) activate a global transcriptional response, controlled by different signaling cascades of master transcription factors (TFs, e.g., NFAT, GATA4, MEF2). Using a systems biology approach, in this work we build a human genome-scale transcriptional regulatory network (TRN) to identify novel TF involved in CH/HF. To this end, we first selected different public articles and databases to consolidate a human TRN template that comprises TF-TF and TF-gene interactions. Second, we analyze public human HF transcriptomic datasets (RNAseq) to obtain differentially expressed genes. By integrating HF global gene expression in the human TRN, we were able to generate a model of TRN activated by CF/HF. Interestingly, the network contains several TF involved in CH along with novel uncharacterized factors, selecting BCL6 as a putative new regulator. To study BCL6 transcriptional response under a CH condition, we performed RT-qPCR in neonatal rat cardiomyocytes treated with NE (20 μM, 48 h). We observed an increase in BCL6 mRNA levels (2.4 times increase), correlated with the overexpression of classical hypertrophy marker genes (ANP and BNP). This is the first report showing a human TRN for HF, a model which contains interesting new TF activated during CH, such as BCL6.

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GE2.2 Potential involvement of abscisic acid (ABA) pathway-related genes during raspberry fruit ripening

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The raspberry (*Rubus idaeus* L.) fruit is characterized by its functional molecules and high nutritional value, but the softening of raspberry limits its quality during postharvest. The raspberry drupelets have a particular ripening regulation, depending partially on the effect of ethylene produced from the receptacle. However, the role of other hormones in raspberry ripening is not clear. In grapes, abscisic acid (ABA) plays a major role during ripening, accelerating fruit softening and increasing grape color and ethylene production. Also, genetic and biochemistry analyses have shown the role of ABA pathway-related genes during the ripening of strawberries and grapes. While the genes encoding for enzymes related to ABA biosynthesis (9-cis-epoxycarotenoid dioxygenaselike/*NCED*) and perception genes (*PYRs*-like receptors) have been well characterized in these fruits; the profile of ABA pathway-related genes have not been described during raspberry ripening. In this study, the quality parameters show typical changes during ripening: a drastic loss of firmness, increase in soluble solids content, loss of acidity, and turning to red color from large green stage to full-ripe fruit. Along with the slight ethylene increase observed in drupelets attached to the receptacle, an increase of the *RiNCED1*, *RiPYRs* genes was observed from the large green stage to the full-ripe stage in drupelets and receptacle tissues. This study is the first approach to the profile of ABA pathway-related genes and the potential role of ABA during the ripening of raspberry fruit, together with other plant hormones such as ethylene.

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GE2.3 Comparation of phenotypic and genotypic assays associated with the evaluation of the antibiotic resistance using *Helicobacter pylori* strains isolated from patients of the Biobio region-Chile

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Helicobacter pylori is a pathogen that it's present in the 50% of world population. This data is relevant because *Helicobacter pylori* is the principal risk factor of gastric cancer, and that's also the reason of the importance of the treatment in infected patients. The necessity to evaluate the antibiotic resistance of *Helicobacter pylori* has grown significantly, not only because the increased percentage of the strains with clarithromycin resistance, but also because that the pattern of susceptibility depends of the geographic region where are evaluated. There are several phenotypic and genotypic assays to evaluate the susceptibility of the strains that are faster and simple to do than the Gold Standard stablished by the CLSI, agar dilution. The objective of the study was to compare the susceptibility results obtained by different methodologies and the Gold Standard. We used 15 strains isolated from patients of the Biobio region-Chile, donated by the Laboratory of Bacterial Pathogenicity of the University of Concepcion. The strains were subjected to E-test, disk diffusion, PCR-RFLP and agar dilution. The statistical correlation between the assays and the Gold Standard was obtained by the analysis Kappa (k), using the software Stata V.14. The concordance values obtained were k= 0.7, 0.85 and 0.58 by disk diffusion, E-Test and PCR-RFLP, respectively. We can conclude that the best alternative to agar dilution is the E-test. As a projection of the work, tests with more strains will be carried out, which will generate a more robust statistical analysis.

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GE2.4 Genome-wide transcription induced by Wnt/β-catenin signaling in Human Neural Stem Cells H9-derived (hNSC H9-d)

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The Wnt/β-catenin signaling pathway has an essential activity during neural development, in different fetal and early postnatal stages. Here we examined the whole transcriptional program in Neural Stem Cell H9-derived (NSC) directed by the canonical Wnt/β-catenin signaling using CHIR99021, a pharmacological activator of the cascade signaling with concentrations of 4 and 8 μM. For both concentrations, we extracted total RNA at the 6 and 48 h of treatment. We sequenced the samples in a *Novaseq* 6000 platform with an extension of 100 pb pair-end (2x100bp PE) and 20M reads of data output. We aligned the raw reads to human genome GRCh37 after verifying the quality controls of all samples, and used *DESeq2* to analyze differential expression. We found 89 and 158 differentially expressed genes (pAdj <0.05; 4 and 8 μM, respectively), and the number of genes expressed at the 48 h increased to 202 and 1102 genes. Notably, ontological analyses revealed that the cascade is important in axon development/guidance, neuron projection, synapsis assembly, regulation of nervous system development, neuron migration, neurogenesis, among others biological processes. Since many of these processes are altered in neurodevelopmental disorders, including autism spectrum disorder (ASD), our results advance our knowledge regarding the identification of markers for diagnostic and/or therapeutic intervention.

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GE2.5 Mitophagy as molecular crosstalk between Down Syndrome and Alzheimer's Disease

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Down syndrome (SD) is the most common chromosomal disorder. Adult individuals affected with this condition present higher rates of Alzheimer's disease (AD), the most prevalent neurodegenerative disease globally. DS brains present early neuropathological hallmarks characteristic of AD, including accumulation of amyloid-β and tau hyperphosphorylation. Common intracellular mechanisms associated with these hallmarks include the trisomy of the *APP* gene, present in chromosome 21, and the dysfunction of autophagic and lysosomal pathways. However, limited information is available regarding other genes, apart from *APP*, related to premature AD development in DS. Using a systems biology approach and meta-analysis of public databases, we determined genes with the same expression profile shared in both conditions (DS and AD) that participate in autophagy and mitophagy. We found a list of genes overexpressed in both conditions, selecting the neighbor of the *BRCA1* gene (*NBR1*) that codifies for a selective autophagy receptor as an interest target. We validated the *NBR1* overexpression gene in DS and AD iPSCs and brain tissues of the AD transgenic mouse model, 5xFAD. Additionally, in postmortem brain tissues from AD patients, we observed an increase in the staining of the protein NBR1 together with the mitochondrial marker HSP70. To our knowledge, this is the first study showing a direct relationship between NBR1 and the etiology of both AD and DS. Moreover, our data pinpoint NBR1 as a new potential biomarker and/or therapeutic target for AD and propose that our systems biology approach can be experimentally replicated to improve future AD diagnosis.

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MC1.1 Odegus4: an endogenous parvoviral element that reduces a parvovirus replication

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Endogenous viral elements (EVEs) are viral-derived DNA sequences present in the genome of extant species. Some of them possess open reading frames (ORF) that can express proteins with physiological roles in their host. Furthermore, it has been described that some EVEs exhibit a protective role against exogenous viral infection in their host. Previously our laboratory demonstrated that an EVE derived from *Parvoviridae*family is transcribed in the liver of *Octodon degus*. This EVE, named Odegus4, contains an intact ORF that possess the Rep protein domain of adeno-associated virus, where Rep is an essential protein for viral DNA replication. We also demonstrated that in cells transfected with a plasmid encoding Odegus4, a protein with nuclear localization is expressed. These characteristics lead us to speculate that ORF Odesgu4 may function as a cellular coopted protein in degu. The aim of this work is to demonstrate Odegus4 as protein with an antiviral role against exogenous parvovirus. We extracted RNA from different degu's tissues and performed a qRT-PCR, finding Odegus4 transcript at different expression levels in every tissue. In addition, we extracted proteins from tissues and ran western blots using the serum against Odegus4 finding it, indeed, as protein in degu. Besides, we generated Minute Virus of Mice (MVM), a model of autonomous parvovirus, in cells expressing or not Odegus4, resulting in a less effective viral generation when Odegus4 was present. Our results demonstrate the presence of Odegus4 as a protein in degu and suggests a protective role against existing parvovirus in degu.

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MC1.2 Effect of cardiomyocyte-specific overexpression of MUL1 on myocardial function

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Introduction: MUL1, a mitochondrial E3 ubiquitin ligase that participates in biological pathways associated mitochondrial dynamics. Increase in Mul1 affects the balance between fission/fusion, affecting the mitochondrial function, which plays a crucial role in myocardial function. Therefore, it is interesting to evaluate the effect of cardiomyocyte-specific overexpression of MUL1 on myocardial function.
Aim: To study whether the cardiomyocyte-specific overexpression of MUL1 in mice plays a crucial role in the function and metabolism of the heart.
Methods and results: C57BL/Tg transgenic male mice with cardiomyocyte-specific overexpression of Mul1 (n= 10) and control (n=4) were evaluated at 12- and 17-weeks. The determination of the glucose tolerance curve was carried out to assess metabolic capacity. No significant changes were observed between the groups. Treadmill test and systolic and diastolic myocardial function and systolic pressure were evaluated by echocardiography and CODA equipment, respectively. No changes were observed in any of these parameters.
Conclusions: Cardio-specific overexpression of MUL1 in mice without any treatment does not affect cardiac function. Further research should evaluate the effect of cardiomyocyte-specific overexpression of MUL1 under pathological conditions.

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MC1.3 Effects of HDAC6 inhibition on the functionality of the transcription factor STAT3 on colorectal cancer cells

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Cancer is one of the most frequent disease worldwide and currently, treatment failures are caused by pharmacological resistance or low success rate of conventional approaches. In particular, colorectal cancer (CRC) has a high incidence and mortality rates, which is why there is a need to study new strategies for future therapies. Histone deacetylase 6 (HDAC6), a mainly cytoplasmic protein, is involved in several cellular processes including tumor immunogenicity. Specifically, it has been observed that HDAC6 stimulates STAT3 activity, a transcription factor involved in immunogenicity. STAT3 plays a role as a transcriptional inducer of different genes, as PD-L1 (programmed death ligand 1), while over-expression of PD-L1 on some cancer cells promotes inhibition of T lymphocyte activation in immune response. Therefore, we will focus on pharmacological inhibition of HDAC6 in CRC cell due to its potential as adjuvants to avoid immunotolerance in cancer therapy. Here, we investigate whether HDAC6 affects STAT3 activation in CRC cells. Treatments with Nexturastat A (NextA), a specific HDAC6 inhibitor, decreases the levels of activating post-translational modifications on STAT3 analyzed by Western blot and immunocytochemistry. These results suggest that treatments with specific HDAC6 inhibitors would reduce the functionality of STAT3 in CRC cells. Therefore, the use of specific HDAC6 inhibitors may be a reasonable and an interesting adjuvant strategy for immunotherapy, since HDAC6 inhibitors would indirectly decrease PD-L1 expression, one of the checkpoint inhibitors of immune system.

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MC1.4 Role of adenosine receptor A_{2B} in maintaining GSC stemness in hypoxic conditions

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Glioblastoma (GB) has the worst prognosis of all brain tumors. GB tumors contain glioblastoma stem-like cells (GSCs), which can be further classified into two subtypes: proneural (GSC-PN) and mesenchymal (GSC-MES). GSCs secrete large amounts of adenosine, especially under hypoxia conditions. We aimed to determine the role of the A_{2B}AR adenosine receptor in maintaining GSC stemness under hypoxic conditions. We incubated GSCs under normoxic (21% O_2) and hypoxic (0.5% O_2) conditions treated with the A_{2B} receptor antagonist MRS1754. We measured the transcript and protein expression of genes related to stemness and differentiation. We evaluated stemness characteristics via self-renewal and colony formation assays. Our results suggest that A_{2B}AR blockade alters the expression of stemness and differentiation-related genes such as YKL-40, S0X2, GFAP, self-renewal capacity and colony formation under hypoxic conditions. Additionally, A_{2B}AR blockade under hypoxic conditions regulates the GSC stemness maintaining Wnt/β-catenin and NF-κB signaling pathways involved. In conclusion, the A_{2B}AR receptor regulates the stemness of hypoxic GSCs subtypes.

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MC1.5 Exploring a functional relationship between Tet enzymes and the metabolic sensor Ogt in T cells

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Tet enzymes participate in the DNA demethylation process via the iterative oxidation of 5mC. The first catalytic product of this oxidation, 5hmC, accumulates in the genome, and is linked with transcriptional activity. Tet proteins are reported to directly interact with Ogt, a metabolic sensor and only enzyme that post-translationally adds GlcNAc to serines and threonines. Transcription factors (TF) O-GlcNAcylation modulates their function leading to transcriptional changes. Ogt recruitment to promoters is mediated by Tet, in turn Tet-O-GlcNAcylation stimulates its catalytic activity. Since Tet enzymes are key for immune cell development we explored the functional Tet-Ogt-TF axis in T cells.
We performed immunoprecipitation followed by mass spectrometry analysis in T-CD4$^+$ cells showing that Ogt interacts with Tet1. This result supports the notion that both proteins share a functional role in immune gene regulation. To identify TFs cooperating with Tet1 and Ogt in the modulation of chromatin configuration in T-CD4$^+$ cells, we curated a list of TFs targets of O-GlcNAcylation, expressed in this cell type using our RNAseq datasets. Employing genome wide chromatin accessibility data generated by the Immgen project and the TOBIAS footprinting analysis pipeline, we predicted chromatin occupancy for the previous list of TFs in T-CD4$^+$ cells, identifying regulatory regions potentially under TF-Ogt control. By intersecting these regions with our DNA hydroxymethylated enriched regions (HER) identified in T-CD4$^+$ cells, we generated a list of candidate genes, predicted to be regulated by a Tet-Ogt-TF axis currently under validation. In conclusion, regulation of these candidate genes can be influenced by glucose metabolic changes, impacting on immune differentiation and function through the Tet-Ogt-TF axis, findings of potential relevance for immune disorders.

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MC2.1 The adenosine A3 receptor modulates autophagic flow in glioblastoma

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The therapeutic failure of glioblastoma (GB) has largely been attributed to a subpopulation of glioblastoma stem cells (GSCs). GSCs often live in hypoxic niches. Their chemoresistance stems from increased adenosine production, A3 adenosine receptor activation and PI3K/Akt and MAPK/Erk pathway activity. Autophagy promotes chemoresistance in GSCs and can be activated by hypoxia, radiation therapy, and chemotherapy. Autophagic flow is also regulated by the PI3K/Akt and MAPK/Erk pathways. However, it is not known whether adenosine signaling contributes to GSC chemoresistance. We proposed that A3AR modulates autophagy and promotes chemoresistance in GSCs under hypoxic conditions via the PI3K/Akt and MAPK/Erk pathways. We evaluated autophagic flow and autophagosome formation in hypoxic GSCs treated with an A_3AR antagonist (MRS1220) via western blot and LC3-GFP distribution. We also evaluated whether A_3AR modulates autophagy through the PI3K/Akt and MAPK/Erk pathways by phosphorylating Akt and Erk. Finally, we conducted cell viability assays on hypoxic GSCs treated with MRS1220 and chemotherapeutic drugs. A3AR antagonization in GSCs increases the expression of autophagy markers and decreases autophagic flow. In conclusion, A_3AR signaling modulates autophagic flow and affecting GSC sensitivity to chemotherapy.

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MC2.2 Modification of transcriptional expression of Colorectal Cancer biomarkers after expose to Histone DeACetylase inhibitors (HDACi)

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Colorectal cancer (CRC) is the most frequent malignant neoplasm of the digestive tract, being one of the main causes of incidence and mortality worldwide. CRC is a highly heterogeneous disease that includes both genetic and epigenetic modifications, where microsatellite instability (MSI), DNA methylation, and DNA repair defects are mechanisms involved in the alteration of colorectal cells. Most of the genes involved in these mechanisms undergo epigenetic modifications, where DNA methylation and histone modifications play a transcendental role during tumor progression. Both mechanisms work together, through the repression of the expression of certain genes. Histone DeACetylases (HDACs) regulate gene expression by removing the acetyl group from histone, resulting in chromatin condensation and inactivating transcription. Therefore, in this study we seek to know how four specific HDAC inhibitors (HDACi) can modify the mRNA of CRC biomarkers, such as MSH2, MLH1, SEPT9 and p16, and how these treatments can affect the cell viability of CRC cells. Obtained those biomarkers increase or decrease their mRNA expression (qPCR), depending on which inhibitor was used for treatment. By other side, cell viability assay (XTT) showed that normal colon cells are more resistant to HDACi than CRC cells, however, in CRC depends on the origin of the cells if they are more affected by the treatment. Together, these results suggest, that these biomarkers can be used as prognostic markers for treatment with HDACi in CRC, and these inhibitors could be more effective with one cell type than another, by affecting viability depending on the tumor cell type.

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MC2.3 Potential influence of calcium dynamics in the reduced cell death of Down Syndrome iPSC-derived cardiomyocytes after ischemia/reperfusion injury

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A myocardial infarction (MI) results in irreversible heart muscle damage due to a lack of oxygen. This damage triggers cardiomyocytes necrosis induced by ischemia/reperfusion (I/R) injury, which is mainly due to Ca^{2+} overload. Down Syndrome (DS) incidence is 1 in 700 live births worldwide, and in Chile, this incidence increases to 2,47 in 1000. People with DS present elevated cardiovascular risk markers mainly due to obesity high prevalence, but only ~7% died from MI, compared to 32% in the general population. Currently, if Ca^{2+} signaling is altered in DS cardiomyocytes and whether this could be a protective factor in I/R induced cell death, is unknown. Therefore, we hypothesized that: "DS cardiomyocytes show reduced cell death induced by I/R due to alterations in sarcoplasmic Ca^{2+} homeostasis". Methodology: We performed a differential expression and enrichment analysis of induced pluripotent stem cells (iPSC) DS RNAseq public data. Additionally, DS iPSC were differentiated to cardiomyocytes (iPSC-CM) for 17 days, and then underwent I/R (6 and 16 h, respectively). Finally, cardiac markers and cell death were evaluated by qPCR and LDH release, respectively. Results: Differential expression and enrichment analysis suggested that DS iPSC presents differences in Ca^{2+} release from the sarcoplasmic reticulum and cardiac muscle relaxation. DS iPSC-CMs also showed decreased expression of cardiac markers and reduced cell death after I/R, compared to control iPSC-CMs. Conclusions: Bioinformatic analyses indicate that calcium signaling is probably altered in DS iPSC, but whether this is the cause of their reduced cell death after I/R is currently under analysis.

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MC2.4 Differential expression of chemoresistance-related genes under the effect of Adenosine A3 Receptor antagonist in glioblastoma stem-like cells

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Drug-resistant is a major barrier to achieving long-term benefit to treatment Glioblastoma (GBM). This is fundamentally given by the existence of GSC, which generate high levels of extracellular adenosine, causing the A3AR activation, with the subsequent increase in the expression and activity of the MRP1 transporter. Therefore, studies focused on the regulation of the activation of this efflux pump (MRP1) by A3AR, currently represent a fundamental therapeutic target. The objective of this work was to perform a transcriptomic analysis using an RNA-seq in GSCs treated with the A3AR antagonist MRS-1220. In this analysis, the genes that were up-regulated and down-regulated because of the blockade of A3AR were determined, both in normoxia and hypoxia, and it was analyzed which of them are related to chemoresistance. Blockade of A3AR by MRS1220 had much less effect on gene dysregulation under hypoxic conditions than under normoxic conditions. Hypoxic conditions generated greater gene dysregulation than MRS1220 blockade of A3AR. Among the post-treatment downregulated genes, those that have been described as genes related to drug resistance in different types of cancer are LIMD1, SH3BP1, TRIP2. On the other hand, the genes related to chemoresistance and that were upregulated in cells treated with MRS1220 were SPRY2, NFE2L2, HAS2 and NOTCH2. The discovery of these genes is very important because in addition to being related to chemotherapy-resistance, they are also involved in processes such as proliferation, and regulation of Twist1, an important chemoresistance transcription factor that could be regulating the expression of the gene that codes for MRP1.

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MC2.5 Role of Phytocrome A (*DcPHYA*) in carotenoid synthesis in the carrot taproot of the orange Nantes variety

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Carotenoids provide yellow, orange and red colors to flowers and fruits, participate in photosynthesis, protect molecules against photo-oxidative damage, and are precursor of plant hormones. In vegetative tissue and fruits, light promotes carotenoid synthesis through light signaling molecules, such as photoreceptors (PHYs). Contrary, the orange carrot taproot (Nantes var.) synthetizes and accumulates high level of carotenoids growing underground, and light impairs both, carotenoid synthesis and root development. To understand the genetic regulation, we performed a RNA-seq between root grown in White light (R/WL) and underground (R/D). Genes related to light signaling, such as *DcPHYA* are overexpressed in R/D (Arias, *et al*., 2020). PHYA is activated and stable under Far-red (Fr) light. In Arabidopsis, Fr is transmitted through the xylem reaching the roots but *AtPHYA* expression is not regulated by WL. Here we present that *DcPHYA* is expressed preferably in R/D than in R/L during carrot taproot development. *In silico* analysis showed that DcPHYA has a 73% of amino acid identity with AtPHYA in their functional domains. Moreover, carrot transgenic lines with a decreased relative expression of *DcPHYA* present up to 80% reduction in carotenoid content in the taproot compared to wild-type plant. The relative expression of carotenogenic genes will be also shown. These results suggest that *DcPHYA* could be involved in carotenoids synthesis in the carrot taproot of the orange Nantes variety.

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MC3.1 Saturated fatty acids inhibit Chaperon Mediated Autophagy (CMA) in hypothalamic POMC like neurons

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Autophagy, a lysosomal dependent pathway that degrades proteins or organelles, can be divided in macroautophagy, microautophagy and chaperone mediated autophagy (CMA). In CMA, soluble proteins containing at least one KFERQ-like pentapeptide interact with the HSC70 chaperon to be degraded by the lysosome in a LAMP2A dependent manner. CMA dysregulation has been associated with several human diseases, including obesity. Proopiomelanocortin neurons (POMC) are one of the hypothalamic cells regulating the appetite. Here, we studied if fatty acids (SatFAs) affect CMA in a POMC cell line. After incubation of POMC with SatFAs (palmitic acid (PA), stearic acid (PA)) or BSA (control), total LAMP2A protein and mRNA levels were determined by western blot and qPCR. Also, the CMA activity was assayed by using a specific CMA-florescent reporter and by evaluating the GAPDH (CMA substrate) protein levels. Followed SatFAs treatment, lysosomes were isolated to determine the LAMP2A protein levels and performed a proteomic analysis. Total and lysosomal LAMP2A protein levels decreased after SatFAs exposure. CMA activity was inhibited, and changes in putative CMA substrates were observed after SatFAs exposure. Our results show that a SatFAs exposure in POMC can inhibit CMA and probably affect the fate of different CMA protein substrate. Other studies showed that both, SatFAs accumulate in hypothalamus of obese mice and that macroatophagy and insulin response are inhibited in POMC cells after SatFAs challenge. Thus, a generalized autophagy dysregulation could occur in obese individuals, affecting the function of neurons regulating the appetite.

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MC3.2 The HIV-1 Rev protein: a new key element in the field of mitochondria and HIV-1

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It has been described that CD4 + T cells infection with the human immunodeficiency virus type 1 (HIV-1), together with antiretroviral therapy, causes mitochondrial dysfunction. Although there are several described HIV-1 proteins that affect mitochondria, it is still unknown if there are other viral proteins causing this effect and which of them is the main inducer of mitochondrial dysfunction. Previous immunoprecipitation and massive sequentation data from our laboratory suggested that the HIV-1 Rev protein could interact with several mitochondrial mRNA. In order to establish a direct relationship between Rev and mitochondria, we investigated the effect of Rev on mitochondrial function and the expression of mitochondrial-encoded genes. We overexpressed Rev in HEK293T cells and determined mRNA mitochondrial levels using RT-qPCR and, both mitochondrial mass and mitochondrial membrane potential using flow cytometry. Our results show that Rev overexpression decrease mitochondrial overall mRNA levels and mass, accompanied by an increase in the mitochondrial membrane potential of the remaining mitochondria. This last response, probably as an energy compensatory mechanism. To our knowledge this is the first report characterizing a relationship between Rev and mitochondria, thus positioning Rev as a new participant in the control of the cellular metabolism that occurs during HIV-1infection.

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MC3.3 Estrogen regulates mitochondrial E3 ubiquitin ligase MUL1 in hypertrophied cardiomyocytes

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Cardiovascular disease risk is higher in men than in premenopausal women of the same age, but this female advantage is lost after menopause. Whether decreased estrogen (E2) synthesis could be associated with the development of cardiac hypertrophy remains unclear. Mitochondrial protein ubiquitin E3 ligase 1 (MUL1) catalyzes the ubiquitination of several target proteins, including the mitochondrial fusion protein mitofusin 2. Interestingly, and MUL1 is highly expressed in the heart. MUL1 also affects the dynamic balance between mitochondrial fission and fusion by promoting mitochondrial fragmentation, which is linked to the development of heart hypertrophy.
Aims: To study *in vitro* the effects of E2 on cardiomyocyte hypertrophy and MUL1 protein levels.
Methods and results. Cultured neonatal rat ventricular myocytes (NRVM) were preincubated with or without E2 before the treatment with norepinephrine (NE) for 48 h. NE increases the protein levels of the hypertrophy marker ANP and MUL1 assessed by RT-qPCR and Western blot, respectively, as well as cardiomyocyte area, mitochondrial fragmentation, and decreased ATP levels. All these parameters were prevented with the pre-treatment with E2 (100 nM).
Conclusions: E2 decreases cardiomyocyte hypertrophy markers and prevents the increase in MUL1 and the mitochondrial fragmentation triggered by NE. MUL1 knockdown prevents the increases of hypertrophic markers. However, it remains to investigate the molecular link between these findings.

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MC3.4 *In vitro* study of the cardiac anti-fibrogenic effect of angiotensin (1-9) and its synthetic analog

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The development of cardiac fibrosis, orchestrated by cardiac fibroblasts (CF), is the excess deposition of extracellular matrix (i.e., collagen I (COL I) or fibronectin (FN)) in the cardiac muscle and is mediated by TGF-β1. We have previously shown that angiotensin-(1-9), a peptide of the renin-angiotensin contra-regulatory pathway, exerts anti-fibrotic in the heart. To increase its half-life, we generated an Ang-(1-9) synthetic analog. Whether this new peptide exerts anti-cardiac fibrogenic effects remains unexplored.
Objective. To study the anti-fibrogenic effects of Ang-(1-9) and its synthetic analog.
Methodology. In primary cultures of CF from neonatal rats, the activation of TGF-β1 and the optimal response time were tested by measuring the phosphorylation of Smad3 and the levels of FN and COLI by Western blot. Cytotoxicity was then studied at different concentrations of the peptides by trypan blue assay and LDH assay. The effect of these peptides with TGF-β1 was studied, measuring the protein levels of FN and COL I by Western blot and collagen gel contraction assays. Data are mean ± SEM, n=4-8. Statistical analysis was performed by ANOVA.
Results. The optimal response time for TGF-β1 was 72h in cultured CF. None of the peptide concentrations generate cytotoxic effects. Both peptides were ineffective in preventing the increase in COL I and FN and the contraction of the gels induced by TGF-β1 in any of the concentrations.
Conclusions. Ang-(1-9) and its synthetic analog do not prevent TGF-β1-dependent fibrogenesis in cultured FC.

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MC3.5 Small extracellular vesicles from hypoxic glioblastoma stem-like cells promote a highly chemoresistant phenotype in glioblastoma

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Glioblastoma (GB) has the worst prognosis of all brain tumors. GB tumors contain highly chemoresistant glioblastoma stem-like cells (GSCs) that produce large amounts of extracellular adenosine (Ado) levels, especially under hypoxic conditions. Ado activates signaling pathways that promote a chemoresistant phenotype. Extracellular Ado is produced by CD73 and PAP and causes chemoresistance through an MRP1 and MRP3 dependent mechanism via A_3AR and A_2BAR receptors. Small extracellular vesicles (sEVs) mediate intercellular tumor communication, regulate chemoresistance and promote malignancy in GB cells. We investigated whether sEVs express Ado axis markers, as well as MRPs, and promote greater chemoresistance under hypoxic conditions. We hypothesized that this increased chemoresistance is caused by the delivery of these proteins to receptor cells via sEVs. We incubated GSCs (from the U87 human GB cell line) under hypoxic and normoxic conditions, isolated sEVs from conditioned media by differential ultracentrifugation and measured mRNA and protein levels by RT-PCR and western blot. The size distribution and concentration of sEVs were analyzed using NanoSight NS300. We observed transcripts for CD73, A_3AR, MRP1 and MRP3 in GSCs-sEVs and detected increased CD73 expression in hypoxic GSCs-sEVs. We also observed a morphological change towards a more chemoresistant phenotype in U87 cells treated with GSC-sEVs. In conclusion, we observed MRPs and Ado axis markers expression in GSCs-sEVs and found they promote a highly chemoresistant phenotype in GB cells.

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IC.1 German Research Foundation Opportunities for International Collaboration

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The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) is a central and independent funding organization for basic research in Germany and the largest in Europe. With a budget of 3.3 billion Euro in 2020, provided by the federal government and the federal states, it promotes the advance of science and humanities by funding research projects, research centers and collaboration networks, facilitating cooperation between researchers. The DFG promotes the advancement of young researchers and gender equality in the German Scientific and academic communities, provides advice on science policy, promotes relations with the private sector and between scientists and academics in Germany and abroad and it represents Germany on scientific issues at the international level. Organizationally, the DFG is a private-law association with 97 member organizations. Its members are universities, extra-university research centers such as the Max Planck Society, Fraunhofer Society, Helmholtz Association, Leibnitz Association, scientific associations, and academies of science..

New member Session 1

Emergent interdomain interactions control the refolding mechanism of the metamorphic protein RfaH

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Most proteins fold into a single three-dimensional structure suited for its biological function. However, about 2% of known proteins display an oddity termed fold-switching, where their amino acid sequences encode two or more folds whose structural interconversion is responsible for their functional regulation. The bacterial elongation factor RfaH is one of such proteins, which increases the transcriptional processivity of RNA polymerase for a specific subset of genes and strongly activates their translation by completely refolding its C-terminal domain (CTD) from an α-helical hairpin associated to the polymerase-binding N-terminal domain (NTD) into a β-barrel fold that physically recruits the ribosome.
To understand the thermodynamics of RfaH during its fold-switch and the local sequence and structure determinants of this process, we combined molecular dynamics of varying granularity and spanning different timescales with high-resolution biophysical experiments such as hydrogen-deuterium exchange mass spectrometry. These combined approaches led to identify a localized region in the NTD-CTD interdomain interface of RfaH, particularly near the tip of the α-helical hairpin, that concentrates most of the stability associated with the helical formation. Moreover, folding simulations strongly suggest that RfaH traverses both the unfolded state and a stable □-intermediate during its structural interconversion. This intermediate is part of the small □-barrel formation process, but it is deeply stabilized by the accompanying NTD, suggesting its role in impeding the activation of RfaH in the absence of a trigger. Our research suggests that emerging NTD-CTD interactions encoded throughout protein evolution suffice to drive the fold-switching behavior of RfaH.

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Mitochondrial Ca^{2+} overload in the neurodegeneration associated with early-onset familial Alzheimer's disease

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Familial Alzheimer's disease (FAD) is characterized by mutations in the presenilin-1 (PS1) gene. PS1 mutations affect intracellular Ca2+ homeostasis, and any imbalance between mitochondrial Ca2+ uptake and removal leads to opening of the permeability transition pore (mPTP), causing the loss of mitochondrial membrane potential (Δym), uncoupling of the respiratory chain, and consequent drop of ATP. Accumulation of mitochondrial free Ca2+ causes mitochondrial Ca2+ overload, which is toxic and induces an apoptotic process irreversibly contributing to the disease pathogenesis.
Objective: We investigated the role of InsP3R-mediated exaggerated Ca2+ signals on mitochondrial function in FAD using two in vitro cell models.
Methods: We used SH-SY5Y cells transfected with wild-type PS1, EGFP, or mutant PS1-M146L and fibroblast from FAD, sporadic AD (SAD), and control patients. We performed simultaneous measurements of [Ca2+]m uptake and Δym in permeabilized cells using Fura-2FF and TMRE, respectively, to measure MCU-mediated Ca2+ uptake activity. Live-cell imaging experiments were performed to estimate qualitatively and quantitatively [Ca2+]m, using Ca2+ indicators.
Results: Mutant PS1 cells were subjected to elevated mitochondrial Ca2+ levels, but no significant differences in mitochondrial Ca2+ uptake through MCU or Δym were found. Basal levels of [Ca2+]c and [Ca2+]m were significantly higher in mutant PS1 SH-SY5Y cells and fibroblasts from FAD and SAD patients. Excess of Ca2+ levels in PS1-M146L cells triggered a sensitivity to successive Ca2+ challenges, causing a loss of Δym. This vulnerability was reverted by depleting ER Ca2+ stores. We found a decreased expression of NCLX in mutant PS1 cells, suggesting an impaired mitochondrial Ca2+ efflux. The OCR was significantly diminished in PS1-mutant cells suggesting an altered ATP consumption or synthesis.
Conclusions: These features may explain these cells' increased vulnerability and eventual death due to progressive mitochondrial dysfunction, promoting a pathological cycle essential to disease progression.

Host-Pathogen interaction: The Herpes simplex virus type 2 glycoprotein D and host IRE-1alpha pathway modulate the functions of Dendritic cells after infection with this virus

Angello Retamal, Departamento de Biotecnología, Facultad de Ciencias del Mar y de Recursos Biológicos, Universidad de Antofagasta.

Herpes simplex virus type 2 (HSV-2) is highly prevalent in the human population and is the leading etiological agent of genital ulcers and neonatal encephalitis. Dendritic cells (DCs) are key immune cells that initiate and regulate antiviral responses, and HSV-2 interferes with their function. We studied the interaction between DCs and an HSV-2 mutant that lack for the glycoprotein D gene (ΔgD-2), this mutant virus was attenuated in DCs, unlike other HSV-2 glycoprotein mutants or wild-type HSV-2 (WT). ΔgD-2-inoculated DCs activated virus-specific CD8+-T cells (gBT-I) and antigen-specific CD4+-T-cells (OT-II) in vitro. Moreover, mice inoculated with ΔgD-2 displayed increased CD103+-DC migration to lymph nodes and displayed both activated CD8+ and CD4+ T cells. Mice primed with ΔgD-2-inoculated DCs in vitro, displayed significantly reduced infection and pathology after genital challenge with virulent HSV-2, indicating that these cells can elicit a protective immune response. These results showed that ΔgD-2 activates DCs to promote antigen presentation, and this characteristic likely contributes to the immunogenicity, protective capacity and suggests that ΔgD-2 can be an attenuated vaccine. Noteworthy, the interaction of ΔgD-2 with DCs elicited a different unfolded protein response (UPR) than the WT virus. We also found that the pharmacological inhibition of the RNase activity of the UPR signaling molecule IRE-1α in DCs hampered HSV-2 replication in cultures. Overall, this effect increased DC viability and supported the activation of virus-specific CD8+ T cells in vitro. Remarkably, MHC-I expression in DC cultures infected with HSV-2 was restored to basal levels upon treatment with an IRE-1α inhibitor. These results indicate that HSV-2 induces an IRE-1α mediated UPR in DCs that is detrimental to their function. Taken together, we described both viral and host factors that modulate the outcome of the interaction between DCs and HSV-2 and thus could be based to design novel therapies to limit viral replication and dissemination.

New member Session 2

Understanding the structure-function properties of expansin plant proteins during fruit ripening

Felipe Valenzuela-Riffo, Instituto de Ciencias Biológicas, Universidad de Talca, Chile.

Plant cell walls are a dynamic and complex supra-molecular assembly composed of crystalline cellulose microfibrils, surrounded by an amorphous non-crystalline matrix of polysaccharides of hemicellulose and pectin, such as heteroxylans, (1,3; 1,4)-β-D-glucans, xyloglucans, Rhamnogalacturonan I and II and other polysaccharides, as well as inorganic molecules and proteins. Additionally, molecular dynamics (MD) simulations are a theoretical technique that provides the behavior of biological macromolecules in atomic detail to the experimental measurements particularly through careful benchmarking and validation against experiments. MD simulations often correctly predict the outcome of experiments and provide new and interesting avenues of investigation. Comparative modeling and MD simulations of the structure-function properties over the last years it has been utilized in our laboratory to understand the fundamental role of the proteins in the regulation of diverse processes related with the fruit ripening and cell wall remodeling, with special attention to the protein providing a dynamic view of interaction between these proteins and cellulose as putative cell wall ligands at the molecular scale.

Funding: Initiation FONDECYT grant N° 11150543.

Regulation of Pattern-Recognition Receptor activity by modulation of their availability at the plasma membrane in tomato

Lorena Pizarro, Laboratorio de Inmunidad Vegetal, Instituto de Ciencias Agroalimentarias, Universidad de O'Higgins, San Fernando, Chile.

The first layer of plant immunity relies on plasma membrane (PM) receptors that recognize Microbial Associated Molecular Patterns (MAMPs), called Pathogen Recognizing Receptors (PRRs). After MAMPs recognition, PRRs trigger a signal cascade leading to the activation of immune responses. Plants have two well-characterized PRR: LeEIX2, a Receptor-Like Protein; and FLS2, a Receptor-Like Kinase. LeEIX2 recognizes the fungal endoxylanase EIX (ethylene inducing xylanase), whereas FLS2 recognizes a peptide from bacterial flagellin (flg22). PRR availability at the PM; and PRR endocytosis from the PM and the recycling back determine the possibility to recognize and propagate the signal to the cell. Treatment with the plant hormone Cytokinin enhanced tomato response to the MAMPs EIX and flg22, augmenting resistance to pathogens. Under Cytokinin treatment, LeEIX2 localization at the PM and endosomes increases; similarly, FLS2 availability at the PM also increased. Interestingly, Cytokinin treatment modulates endocytosis and cytoskeleton distribution. Therefore, it is essential to explore the function of the molecular machinery involved directly in intracellular trafficking and its effect on PRR function. Over-expression of tomato Dynamin-Related Proteins (DRPs) facilitated LeEIX2 endosomal residence and recycling, enhancing immune response to EIX. While the tomato Prenylated RAB Acceptor, SlPRA1A regulated trafficking of LeEIX2, but not FLS2, directing it to degradation. SlPRA1A over-expression leads to LeEIX2 degradation in a vacuolar dependent process, inhibiting EIX response. This evidence shows that modulating LeEIX2 and FLS2 subcellular localization is crucial to recognize pathogens in the extracellular space, activating plant immunity and consequently plant resistance against pathogens.

By their unique permeation and regulation properties, the Plant Channels from the Glutamate receptor family are a keystone of cell environmental sensing

Erwan Michard, Instituto de Ciencias Biológicas, Universidad de Talca, Chile

Ion channels forming glutamate receptors comprise an evolutionarily conserved family essential for calcium (Ca^{2+}) and electrical signaling in animal nervous system. In plants, we demonstrated the role of those channels (*At*GLRs) as calcium transporters involved in calcium signaling in the pollen tube from Arabidopsis thaliana and later in the chemiotaxis of the sperm cell of the moss *Physcomitrelum patens (Pp*GLR1*)*. Despite the relation of all glutamate receptors to be dependent on homologous amino acid-binding receptors, we report the function of plant GLR, characterized by a weak ligand gating, relies on the quaternary structure of the channel, and specifically on the molecular properties of the ion channel pore. We established that a conserved trait between *Pp*GLR1 and *At*GLRs is a high anion to low Ca^{2+} relative permeability. By swapping out *Pp*GLR1's pore selectivity filter for the human GluA2 (Q-form) selectivity filter improved *Pp*GLR1's cationic and Ca^{2+} permeability as well as granted a gain-of-function for ligand-gating. These results propose a mechanistic framework illustrating the pore confers channel properties specific for plant signaling. Structure function studies of GLR channels including cryoEM structure demonstrate that the regulation of the GLRs activity and dependent calcium entry into the cell is further controlled by the glutathione reduction agent, putting the GLR channel at the crossroad of calcium and redox signaling, two important signal in plant adaptation to biotic and abiotic stresses.

Funding: Fondecyt 1210920

Dynamic Gene Regulatory Networks controlling environmental responses in plants

José Miguel Alvarez, Centro de Genómica y Bioinformática, Universidad Mayor, Santiago, Chile.

Adaptation of organisms to the environment involves genome-wide changes in gene expression. However, capturing gene regulatory networks (GRNs) controlling transcriptional responses offers both a promise and a challenge. The promise is that capturing and modeling GRNs will allow us to understand how organisms adapt to a changing environment. The ability to mount a rapid transcriptional response to environmental changes is especially important in nonmotile organisms such as plants. The challenge is to capture these dynamic, genome-wide events and model them in GRNs. Our research focuses on capturing dynamic interactions of transcription factors (TFs) with their targets at the genome-wide level and how by discovering these GRNs, we better understand specific phenotypes. In particular, we investigate plant adaptations to variation in nitrogen (N), an essential nutrient found in many macromolecules. Plant roots acquire bioavailable N as nitrate or ammonium and assimilate N from these inorganic molecules into amino acids for use in protein synthesis and the synthesis of nucleic acids, chlorophyll, and other secondary metabolites throughout the plant. Besides its role as a nutrient, N is a potent signal that rapidly regulates changes in gene expression. Our recent studies uncover the path by which NLP7 – a master TF - regulates dynamic and early transcriptional N responses and where it fits in the temporal hierarchy of the N transcriptional network. NLP7 interact transiently with their targets – several of them are secondary TFs – to initiate a rapid N-response cascade. Our work on *Arabidopsis thaliana* provides a more nuanced understanding of how plants sense and appropriately adjust their metabolism to different N levels and establishes a predictive framework for identifying critical components of N responses that can be targets for crop improvement.

XLIV ANNUAL MEETING
Chilean Society for Biochemistry and Molecular Biology 2021

Annual Wrap up

- **Welcome**
- **Symposia**

➢ "Open source biotechnologies in action: from research to applications"

Chairs: Fernán Federici & César Ramírez-Sarmiento

- *"Expanding access to biomanufacturing through open source technologies"*. J. Molloy, University of Cambridge, UK
- *"Open tools for diagnostic, research & education"*. I. Nuñez, P. Universidad Católica de Chile, Chile
- *"Robotic microscopy for everyone: the OpenFlexure microscope"*. R. Bowman, University of Bath, UK
- *"Bioleft: Open source in seeds and digital technologies"*. A. Cremaschi, Anabel Marin, Bioleft, Argentina

➢ "Immunoepigenetics in Cancer"

Chair: Matias Hepp

- *"Epigenetic Regulation of Foxp3 and Treg Function in Lung Cancer"*. W. Hancock, University of Pennsylvania, USA
- *"Targeting repetitive elements to reverse cancer immune evasion"*. K. Chiappinelli, George Washington University, USA
- *"Reprogramming Macrophages for Cell Therapy"*. A. Villagra, George Washington University, USA
- *"Role of Histone deacetylases in Non-Hodgkins Lymphomas"*. E. Sotomayor, Tampa General Hospital, Tampa, USA

- **Awards**
  - ✧ **Herman Niemayer Medal**
  - ✧ **Tito Ureta Award**
- **SBBMCh members meeting**

SYMPOSIUM 1

Open source biotechnologies in action: From research to applications

The Free/Libre and Open Source (FLOS) ethos has expanded from software to hardware to biological technologies. This FLOS approach reduces costs in scientific research and leads to a more participative, equitative and diverse technological development. Its international scientific community is now thriving in many fronts, from autonomy in the rapid response against infectious diseases to sovereignty in biological resources.
This symposium, which is proposed to be held in December 2021, will provide exemplar cases of the successful development and use of open source biotechnologies in Europe and Latin America through seminars given by 5 speakers.

Chairs: César A. Ramírez-Sarmiento & Fernán Federici, Institute for Biological and Medical Engineering (IIBM) and ANID Millennium Institute for Integrative Biology (iBio), Pontificia Universidad Católica de Chile.
César A. Ramírez-Sarmiento is an Assistant Professor at the Institute for Biological and Medical Engineering (IIBM) from Pontificia Universidad Catolica de Chile and Adjunct Researcher at the Millenium Institute for Integrative Biology (iBio). His research group employs experimental and computational strategies to unveil the folding-function-evolution relationships of metamorphic proteins, prototypical models to understand the emergence of novel protein folds in nature, and of bacterial enzymes that hydrolyze PET, a widely used plastic that accumulates as waste in landfills and natural environments at similar rates to its production. Recently, his research has been focused on the development of open-source protocols for the local production of enzymes and reagents used in the detection of viral infections, including SARS-CoV-2, alongside Dr. Fernán Federici.

1. "Expanding access to biomanufacturing through open source technologies" Jennifer Molloy, University of Cambridge, UK
In this talk we will explore what open approaches to producing and sharing technology mean in the context of biotech and their importance for national and regional bioeconomy strategies that centre bio-based technologies as the future of sustainable manufacturing for everything from medicines to food and materials to biofuels. Through a number of case studies of tools, policies and approaches we will address some common misconceptions, examine the contexts in which openness can be a strategic approach to technology transfer and intellectual property management and understand how several projects and companies are adopting open sharing of their technologies as a means to build a more equitable, sustainable and resilient global bioeconomy.

2. "Open tools for diagnostic, research & education"
Isaac Nuñez – ANID, Millennium Science Initiative Program, Millennium Institute for Integrative Biology (iBio); Institute for Biological and Medical Engineering (IIBM), Pontificia Universidad Católica de Chile
The COVID-19 pandemic has evidenced a limited autonomy in countries of the Global South to respond efficiently to the great demand for molecular diagnostics for SARS-CoV-2. A centralized production model, shaped under strict international intellectual property protection, has given rise to dependencies that are prone to failure during a global crisis such as a pandemic, resulting in supply disruptions with serious implications to countries of our region. However, some of the enzymes and procedures most used for nucleic acid amplification tests (e.g. RT-PCR and RT-LAMP) are in the public domain (i.e. off-patent), which allows freedom to operate. In this presentation, we will show the development of a free-to-use enzyme toolkit for the local production of public domain reagents. In collaboration with FreeGenes, OpenBioeconomy Lab, and Ginkgo Bioworks, among others, we have designed the ReClone collection, whose components are compatible to the common standards for DNA assembly (i.e. uLoop/MoClo/Golden Gate). This collection is distributed under the openMTA, a new legal tool that allows the open and fast distribution (and redistribution) of the materials to any person. We will also show the elaboration and characterization of enzymes required for RT-LAMP and RT-PCR. Moreover, we will show the value of using open hardware in the production process itself and in the implementation of final applications in diagnostics and education.

3. "Robotic microscopy for everyone: the OpenFlexure microscope"
Richard Bowman, University of Bath, UK
The OpenFlexure Microscope has been replicated hundreds of times around the world, from African makerspaces to superresolution microscopy labs. Its main offering to the scientific community is a high performance flexure stage for precise XYZ motion that can be almost entirely 3D printed, but we have since added many optical, mechanical, and software features to make it a versatile instrument in its own right. In this talk we'll cover what is possible using our frugal instrument, and take a tour around the increasingly broad community that has grown up around it. This includes our detailed calibration of the microscope's optics and mechanics, as well as recent developments towards error correcting "smart" microscopy. The microscope is used in applications from malaria research through to education in schools, and we will highlight several projects that make use of it. Some of the most exciting developments have come from integrating the OpenFlexure Microscope with other projects – including UC2 (YouSeeToo) and ImJoy.io. As well as mentioning what is possible by combining projects together, we will discuss how we are using Internet of Things technologies to make it easier to link projects together across programming languages, operating systems, and hardware architectures.

4. "Bioleft: suporting open source seed systems with open digital technologies"
Almendra Cremaschi – Centro de Investigaciones para la Transformación (CENIT), Escuela de Economía y Negocios UNSAM, Argentina
Anabel Marin – Institute of Development Studies, University of Sussex, UK; Centro de Investigaciones para la Transformación (CENIT), Escuela de Economía y Negocios UNSAM, Argentina.

The extension of restrictive intellectual property rights to living organisms, together with the development of genetic engineering has resulted in a deep process of market concentration, which has led to an unprecedented loss of biocultural diversity. Inspired by open source software, Bioleft has been working on an open source seed system in order to ensure that seeds can be freely used and shared in perpetuity. One of the biggest challenges in applying open source to living material is its capacity to self-replicate, and therefore, the difficulties to trace it. We found that a web platform could be a useful tool.

In this talk we will share our experience in co-designing a virtual platform to trace seeds, and particularly how the co-design process has fostered the expansion of its functionalities, becoming a virtual fieldbook to support participatory breeding. With this, Bioleft is not only protecting germplasm but also developing new one collaboratively. We will focus on the learnings and challenges of building open and decentralized seed systems through the combination of open source and new technologies.

SYMPOSIUM 2

Immunoepigenetics in Cancer

1. "HDAC8 Targeting Impairs Foxp3+ T-regulatory (Treg) Cell Function and Promotes Anti-Tumor Immunity"
Wayne Hancock, University of Pennsylvania, Philadelphia, USA
HDAC8 is an evolutionarily distinct, X-linked, zinc-dependent class I histone/protein deacetylase involved in various diseases including intellectual disability, parasitic infections and cancers. We present data on conditional targeting of HDAC8 in T-cells and the effects of selective HDAC8 inhibitors (HDAC8i). First, as a genetic approach, we produced mice with floxed exon 3 suitable for conditional deletion of HDAC8 and demonstrated that conditional deletion of HDAC8 in T-cells: (i) impairs Foxp3+ Treg cell function while preserving conventional T-cell responses; (ii) impacts gene expression (enhances *p21*, *granzyme B*, and decreases *pd-1* gene expression); (iii) enhances proliferation of CD4 and CD8 T cells; (iv) increases expression of *socs3* and *integrin b1* within Tregs while impairing *hsp70* in Tregs; (v) impairs Foxp3 stability *in vitro*; (vi) increases IL-2 production by CD4 T cells; and (vii) promotes anti-tumor immunity in immunocompetent hosts, as shown using lung adenocarcinomas in syngeneic mice. Next, in a pharmacologic approach, we tested newly developed isoform-selective inhibitors of HDAC8 (OJ-1 and others) and found that such HDAC8i compounds: (i) impair murine Treg suppressive function *in vitro* and *in vivo*; (ii) decrease Treg function in homeostatic proliferation assays; and (iii) decrease intra-tumoral Tregs and increase CD8 T cell responses. Efforts are currently underway to delineate the effects of HDAC8 targeting on Tregs vs conventional T cells, and to identify HDAC8 targets. Overall, our combined genetic and pharmacologic studies establish the importance of HDAC8 in Foxp3+ Treg cells and show that therapy with selective HDAC8 inhibitors may be a novel approach in immuno-oncology.
Funding: This work was supported by the National Institutes of Health (5R01CA177852).

2. "Targeting repetitive elements to reverse cancer immune evasion"
Katherine Chiappinelli, George Washington University, Washington, USA
Repetitive elements (REs) comprise the majority (45%) of the human genome. In most somatic tissues, REs are silenced by DNA methylation and other epigenetic modifications to prevent their transcription. We demonstrated that treating OC cells with DNA methylation inhibitors (DNMTis) increases immune signaling from tumors through demethylation of REs and production of RE double-stranded RNA to activate the interferon response. Further, we showed that DNMTis plus the epigenetic modulator histone deacetylase inhibitors (HDACis) cause RE transcription and interferon signaling in OC, which recruits CD8+ T cells and NK cells to sensitize tumors to anti-PD-1 immunotherapy.
Our recent work has shown that adding histone deacetylase inhibitors (HDACis) to DNMTis augments the upregulation of specific ERVs and the resulting downstream interferon response in human ovarian and lung cancer cell lines. Other noncoding RNA species including LINE1 and Alu elements are increased by DNMTi (and augmented by

HDACi) and may contribute to the interferon response. We observe significant differences in RE transcriptional regulation in cancer cell lines with mutations in P53, which has been shown to regulate REs in model organisms.
Lastly, we use an in vitro cancer immortalization and transformation model to determine the timing and cause of RE deregulation in cancer. In samples from 20 ovarian cancer patients (taken at surgery), we have shown significant correlations between ERV RNA, interferon response genes, and infiltrating immune cells (specifically CD3+CD8+ T effector cells).

3. "Reprogramming Macrophages for Cell Therapy"
Alejandro Villagra, George Washington University, Washington, USA
Several research groups, including us, have shown that some HDACis are potent modulators of immune-related pathways in cancer and immune cells. These functional characteristics, mostly unexplored and distant from their canonical cytotoxic-centered role in cancer cells, position HDACis as attractive options to potentiate ongoing immunotherapeutic approaches.
Supporting the above premise, we found that ultra-selective HDAC6is can control the expression and function of immunomodulatory mediators in cancer cells and antigen-presenting cells and regulate the metastatic potential of solid tumors. We identified some relevant cellular processes: regulation of macrophage phenotype, antigen presentation, modulation of epithelial-mesenchymal transition (EMT) and immunosuppressive receptors, and phagocytosis. Another innovative aspect of HDAC6is is that their use in ex vivo treatment improves the antitumoral phenotype of macrophages, as demonstrated by the reduction in tumor growth after the adoptive transfer of these reprogrammed macrophages into tumor-bearing mice. Thus, our data suggest that the transplantation of macrophages pre-treated with HDAC6is decreases immunosuppressive pathways, potentiates antitumor immune responses, and reduces the metastatic potential of solid tumors.

4. "Immunoregulatory properties of Histone deacetylase 11 (HDAC11) represent an enticing target for cancer immunotherapy"
Eduardo Sotomayor, University of South Florida, Tampa, USA
In recent years, a large body of evidence has highlighted the role of epigenetic mechanism(s) in determining the phenotype and function of immune cells under normal physiological as well as in different pathological conditions, including cancer. Chromatin modifications, induced by acetylation/deacetylation of histone tails has, gained particular attention. HDAC11, the novel member of the HDAC family of enzymes has been shown to induce phenotypic or functional outcomes in immune cells that is dependent upon their type and/or maturational stage. For instance, in T-cells genetic disruption of HDAC11 resulted in cells that have a lower threshold for activation, are hyper-proliferative and displayed enhanced production IFN-γ and antitumor activity both *in vitro* and *in vivo*. Similarly, neutrophils lacking HDAC11 are more functional and displayed increased migratory and phagocytic capacity due to increased expression of TNFα, IL6, MIP2 and CXCR2 gene in these cells. In MDSC's the absence of HDAC11 also enhanced the maturation and function of these cells, which in this case is to exert a stronger immunosuppressive effect. Mechanistically, HDAC11 regulates the expression of C/EBPβ in MDSCs and in its absence (as in HDAC11KO or DAC11 KO LyZ-Cre MDSCs) and increased immunosuppressive function was observed. In spite of the functional

differences among these cells of the immune system, a common theme that has emerged is that at the steady state in HDAC11 KO mice, there is a markedly high expression of HDAC11-regulated genes which might "prime" them to unleash their full functional potential (ie, activation for T-cells and neutrophils or immunosuppression for MDSCs) when stimulated with growth factors and or cytokines *in vitro* or in the tumor microenvironment *in vivo*. Of note, the overall pro-inflammatory status of mice devoid of HDAC11 is conducive to strong antitumor immune responses and delayed in tumor growth *in vivo.*

Understanding the mechanism(s) by which HDAC11 orchestrates a fine-tuned balance of pro- or anti-inflammatory cells might provide important clues for the design of targeted epigenetic therapies to amplify antitumor immune responses.

IUBMB Virtual Jubilee Lecture

Hailing Jin, University of California, USA

Hailing Jin received her PhD from the Shanghai Institute of Plant Physiology and Ecology, Chinese Academy of Sciences. She conducted postdoctoral work at the John Innes Center with Dr. Cathie Martin and became a research specialist in University of California, Berkeley with Dr. Barbara Baker before she joined the Department of Microbiology and of Plant Pathology at the University of California, Riverside as an Assistant Professor in 2004. Dr. Jin received tenure in 2009 and was promoted to Full Professor in 2013. She currently holds the position of Cy Mouradick Endowed Chair Professor. Dr. Jin's research program is focused on the regulatory mechanism of small RNAs in plant immunity and pathogen virulence, with an overall goal to develop effective means for disease control. Her lab discovered cross-kingdom RNAi and extracellular vesicle-mediated small RNA trafficking between hosts and fungal pathogens. She was elected a Fellow of the American Association for the Advancement of Science (AAAS) in 2015, a CIFAR Fellow (Canadian Institute for Advanced Research) in 2019, and a Fellow of American Academy of Microbiology (AAM) in 2020. She received Ruth Allen Award from APS in 2017. She was also recognized as a highly cited researcher by Web of Science in 2019. She received the Maximizing Investigators' Research Award (MIRA-R35) from NIH in 2020 and National Science Foundation Career Award in 2007. Dr. Jin was also named as an Honorary Professor of University of Queensland, Australia.

Osvaldo Cori Lecture

Sergio Lavandero, Universidad de Chile, Chile. University of Texas Southwestern Medical Center, Texas, USA

Sergio Lavandero was trained at the Universidad de Chile. His training began with his undergraduate studies in Pharmaceutical Chemistry and later, he obtained the degree of Ph.D. in Biochemistry from Universidad de Chile, with a Ph.D. fellowship from the Fundación Andes. He completed further training at the National Heart & Lung Institute of the Imperial College (London, UK); Erasmus Universitat (The Netherlands); National Institutes of Health (USA), St. Vincent's Hospital, Research Cardiovascular Center (Australia) and the University of Texas Southwestern Medical Center (USA). His current appointments are: Professor, Faculty of Chemical and Pharmaceutical Sciences and Faculty of Medicine, Universidad de Chile; Adjunct Professor, University of Texas Southwestern Medical Center (Dallas, USA) and Director of the FONDAP Advanced Center for Chronic Diseases (ACCDiS). His 35-year scientific research career developed in the area of cell signaling of non-communicable chronic diseases. He is the author of 304 publications in indexed international journals, some published in journals ranked top 10% of their disciplines. His h-index: 68 (Google Scholar) and 56 (ISI Web Science) and citations: 26.565 (Google Scholar); 17.197 (ISI Web Science). Prof. Lavandero has contributed to the training of 212 new researchers/professionals, 70 are currently working at university or research institutions in Chile and abroad, and includes 25 postdoctoral fellows, 87 Ph.D. students, 14 M.Sc students and more than 86 undergraduate students. His administrative activities include his participation as President of the Superior Council of Sciences in FONDECYT (2003-2004); President of the Chilean Society for Biochemistry and Molecular Biology (2013-2014). At Universidad de Chile, he was a member of the Evaluation Council (2008-2013), Vice-President for Research and Development (2012-2014), and currently integrates the University Senate (2018-2022). He is also member of the Chilean Academy of Sciences (2018-), member and President of the Chilean Academy of Pharmaceutical Sciences (2011-) and member of the Latin American Academy of Sciences (2017-).

Severo Ochoa Lecture

Nuria Casals, Universitat Internacional de Catalunya (Barcelona, Spain), and Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III (Madrid, Spain)

My main expertise is the role of lipid metabolism in the mammalian brain. My PhD Thesis (under the supervision of Fausto Garcia Hegardt) was about the regulation of mevalonate synthesis, independent of cholesterol. As a result, I published 6 articles, 4 of them in the first quartile. Then, I worked as a postdoc in the laboratory of Xaveir Estivill, in Institut de Recerca Oncologica-IRO (Barcelona), where I learned genetic tools for the study of hereditary diseases. Later, in 1998 I got a position of Assistant Professor at the Department of Basic Sciences at Universitat Internacional de Catalunya, where I started my own group or research.

In the first period as a group leader (1998-2004) I focused in the study of hereditary metabolic diseases related to fatty acids and ketone bodies. As a result, I published 19 articles, 9 of them in the first quartile.

In 2002, a new carnitine palmitoyl transferase-1 was identified, CPT1C, which was expressed only in brain neurons, and its function was unknown. I started a new line of research focused in elucidating CPT1C function. We have demonstrated that CPT1C is a sensor of malonyl-CoA that regulates the function of other proteins interacting with CPT1C. Since malonyl-CoA is a precursor of fatty acid synthesis, and its levels fluctuate in response to nutrients and hormones, we can say that CPT1C acts as a mediator of nutrients and hormones in the regulation of different pathways in neurons, such as the synthesis of lipid droplets, the trafficking of AMPA receptors necessary for synaptic plasticity, or the anterograde motility of lysosomes necessary for proper axon growth. Moreover, we have demonstrated the involvement of CPt1C in the control of food intake and energy homeostasis, and its role in cognition. I have been funded with 6 competitive projects as a PI in this field, and I published 38 articles, 35 at the first quartile.

Currently, my group of research (Neurolipid Group) is part of the CIBER de Fisiopatología de la Obesidad y la Nutrición (CIBERobn), and part of the Catalan Research consolidated group METALIP (Metabolism of lipids)

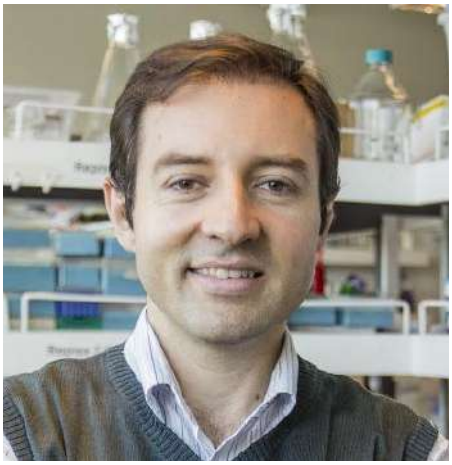
Moreover, I have been the Dean of the Faculty of Medicine and Health Sciences, at UIC, the director of the Dentistry Research Master at UIC, and currently I'm the Director of the PhD School at UIC.

SYMPOSIUM
Latin America single molecule biophysics. A symposium in honor of Carlos Bustamante

Chair : Christian A.M. Wilson

Speakers : Marcia Levitus
Rodrigo Maillard
Andrés Bustamante
Francesca Burgos-Bravo

Christian A.M. Wilson, Universidad de Chile, Chile



Christian A.M. Wilson was trained as a Biochemist and obtained his Ph.D. from the University of Chile, Chile in 2011. CW performed a postdoctoral training at University of California, Berkeley, USA with Dr. Carlos Bustamante and Dr. Susan Marqusee (2011-2013). He then joined the Faculty of Chemistry and Pharmaceutical Sciences at the University of Chile in 2013, where he is currently an Associate Professor at the Biochemistry and Molecular Biology department. His laboratory focuses in single molecule manipulation of biomolecules. This area is a new field of research and allows studying the effect of the forces on the structure of proteins and the concomitant changes in their function. It also permits to determine the forces and torques developed in the course of the mechanochemical conversion in molecular motors. Inside the cell, mechanical forces are produced in molecular processes as diverse as transcription, replication, translation, chromosomal segregation, protein unfolding, translocation of proteins across the membranes and cellular movement. Now, their work is focused in determining the importance of the force associated to the domain movements of BiP (immunoglobulin heavy-chain binding protein) protein during protein translocation in the ER in a collaboration with Randy Schekman's group, also focusing in the kinetic properties of BiP and in the conformational changes that occur during its ATPase cycle, as it is working in the translocation process. Dr. Wilson lab has assembled the first optical tweezers instrument to measure force in individual molecules in the country.

Marcia Levitus, Arizona State University, USA

Marcia Levitus earned her undergraduate degree in Chemistry from the University of Buenos Aires in 1995, and obtained a Ph.D. in Physical Chemistry from the same university under the supervision of Pedro F. Aramendía in 1998. After a postdoctoral stint in the laboratory of Miguel Garcia-Garibay at UCLA, she joined the laboratory of Carlos Bustamante at UC Berkeley, where she spent four years as a postdoctoral associate (2000-2004). She joined Arizona State University as an assistant professor in 2005 and moved through the ranks to become full professor. She is now also serving as Editors-in-Chief of the journal Methods and Applications of Fluorescence. Dr. Levitus started her academic career as a physical chemist working in the fields of photophysics and fluorescence spectroscopy. It was only until she joined the group of Bustamante in Berkeley that she became interested in the field of biological fluorescence, and in particular in single-molecule approaches. Her current research interests include DNA repair, protein-protein interactions, and fluorescent probes for single-molecule research.

Rodrigo Maillard, Georgetown University, USA

Rodrigo Maillard, Assistant Professor, Department of Chemistry, Georgetown University (http://www.maillardlab.org). Dr. Maillard received his Ph.D. in biophysical chemistry from the University of Texas Medical Branch (2007) that was followed by a postdoctoral fellowship in the field of single molecule biophysics with Carlos Bustamante at University of California, Berkeley (2007-2013). In 2014, Dr. Maillard joined the faculty of the Department of Chemistry at Georgetown University to study protein folding and dynamics, and allosteric regulation mechanism of protein kinases.

Andrés Bustamante, Universidad de Chile, Chile

Andrés Bustamante was trained as a Biochemist and obtained his MSc and PhD. from the University of Chile, Chile. He performed his master's thesis under the supervision of Dr. Mauricio Baez at the Biochemistry Laboratory in the Faculty of Chemical and Pharmaceutical Sciences of the University of Chile. He studied the folding of knotted proteins at the single-molecule level, characterizing the entropic energy cost of knot formation in the unfolded state of proteins. Then, he followed his PhD thesis with Dr. Baez and Dr. Jorge Babul, studying the effect on the folding kinetics of non-trivial topologies such as knotted and domain-swapped proteins using optical tweezers. Currently, he is a postdoctoral researcher in the Molecular and Cell Virology Laboratory at the Faculty of Medicine of the University of Chile, with the sponsorship of Dr. Ricardo Soto-Rifo. His research is funded by the FONDECYT 2020 Postdoctoral Grant, and is centered on the study of the Mechano-chemical mechanism of the Reverse Transcriptase (RT) of the HIV-1 virus and how Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) affect its mechanical behavior, using high resolution optical tweezers and single-molecule FRET. Because RT is important in the early stages of viral infection, it is the primary target for pharmaceutical control of HIV infection and AIDS disease.

Francesca Burgos-Bravo, University of California, Berkeley, USA

Francesca Burgos-Bravo is Biochemist, MSc and PhD in Biochemistry from Universidad de Chile. She performed her doctoral thesis under the supervision of Dr. Lisette Leyton and Dr. Andrew Quest at the Advanced Center for Chronic Diseases (ACCDiS), where she characterized the adhesion proteins-dependent neuron-to-astrocyte communication occurring under inflammatory conditions and implicated in the non-permissive environment for axonal regeneration. Currently she is a postdoc fellow in the laboratory of Professor Carlos Bustamante at University of California, Berkeley and a member of the 2018 class of Pew Latin American Fellows in the Biomedical Sciences. Her postdoctoral research examines how RNAs fold as they are being synthesized (co-transcriptional RNA folding) and how RNA polymerase II transcriptional dynamics direct the attainment of their correct folding at the single-molecule level using high- resolution optical tweezers. She is particularly interested on the co-transcriptional folding of the RNA component of human Telomerase. The correct folding of this RNA plays a critical role in the catalytic activity of Telomerase, mutations that disrupt the folding of this RNA cause human diseases associated with blood disorders such as aplastic anemia.

CONO-SUR SYMPOSIUM
When plant stress and development collides underground

Chair : José M. Estevez

Speakers : Ana I. Caño-Delgado
Mariana Sotelo
Ricardo Tejos
José M. Estevez

José M. Estevez, Foundation Institute Leloir-Argentina and UNAB/ iBIO-Chile

José M. Estevez is a Principal Researcher at the National Council for Scientific and Technical Research (CONICET) in Argentina and Invited Professor at UNAB (Chile). He is a graduate of the Bachelor of Biological Sciences with an orientation in Botany from the Faculty of Natural Sciences of the University of La Plata (UNLP). In 2004 he obtained the title of Doctor in Biological Sciences from the Faculty of Exact Sciences at the University of Buenos Aires (UBA). In the period 2005-2008, he developed as a Post-Doctoral Fellow in the Laboratory of Dr. Chris Somerville at the Carnegie Institution at Stanford University, USA and at UC Berkeley, USA. From 2009 to May 2015, he directed the group of Molecular Bases of Plant Development at IFIBYNE (CONICET) and since June 2015 he has transferred his research group to the Leloir Institute Foundation (FIL)-IBBA. He is also currently the head of the laboratory at the UNAB Center for Plant Biotechnology (CBV).

Ana I. Caño-Delgado, Centre for Research in Agricultural Genomics (CRAG) CSIC-IRTA-UAB-UB. Barcelona E-08193, Spain.

Ana I. Caño-Delgado is a CSIC Investigator and coordinator of the Plant Signaling & Development Program at the Centre for Research in Agricultural Genomics (CRAG) in Barcelona. She did a PhD in Biology at John Innes Centre (UK) and was a HFSPO Postdoctoral Fellow at Salk Institute (US). She is internationally recognized for publishing numerous high-impact scientific journals, has received awards in science and entrepreneurship and is an elected EMBO Member since 2016. At CRAG, she leads the Brassinosteroid signaling group supported by an ERC CoG grant to engineering crops able to grow on severe drought. These achievements are the results of two decades of studies in plant steroids hormones, Brassinosteroids, in which she pioneers the study of signaling mechanisms with cell-specificity. Her team discovered that vascular steroid receptors confer resistance to drought without penalizing growth. In the context of a climate emergency, Caño-Delgado is currently translating her scientific results to crops to ensure food security. In addition, Caño-Delgado is an engaged science communicator chasing two specific goals: encouraging women in science leadership and acceptance of gene edition tools in agriculture.

Mariana Sotelo, Universidad de la República, Montevideo, Uruguay

Mariana Sotelo is Associate Professor in Biochemistry at the Facultad de Agronomía, Universidad de la República, Montevideo, Uruguay. She studied Agricultural Engineering at Universidad de la República and received her PhD in Plant Biotechnology from LANGEBIO, Mexico; working in fruit development. Now, she works with the model plant Arabidopsis thaliana to explore how root growth is maintained under water deficit.

Ricardo Tejos Ulloa Universidad Arturo Prat, Chile

Ricardo Tejos is Biotechnology Engineer from Universidad de Chile and holds a PhD in Science, Biotechnology from Gent Universiteit. He is Associate Professor at the Faculty of Natural Renewable Resources, Universidad Arturo Prat, Chile. Currently, he focuses his research to the study of the cellular mechanisms underlying Arabidopsis thaliana response to high temperature and salinity.

SBMMCH WEEK SYMPOSIUM 1
Young scientists in molecular cancer research

Chairs : Ariel F. Castro and Julio C. Tapia

Speakers : Tania Campos
Valentina González
Rodrigo López
Ignacio Niechi

Ariel F. Castro, Universidad de Concepción, Chile

Ariel Castro graduated as a biochemist from the University of Buenos Aires (UBA) and obtained a PhD at the same institution. He did a post-doc at the University of Texas Medical Branch and at Indiana University Purdue University at Indianapolis. From 2005 to 2010, he was Assistant Professor at the University of California San Francisco. Since 2010, he is an Associate Professor at the Department of Biochemistry and Molecular Biology at the University of Concepcion.

Julio C. Tapia, Universidad de Chile, Santiago, Chile

Julio C. Tapia is biochemist from the Universidad de Santiago de Chile and PhD in Biomedical Sciences from the University of Chile, doing his thesis with Prof. Jorge Allende. He did a post-doc at the Center for Molecular Studies of Cell (CEMC), Faculty of Medicine. In 2008, he got an Assistant Professor position and from 2012 is an Associate Professor at the UCH, currently affiliated to the Cellular and Molecular Biology Program, Institute of Biomedical Sciences (ICBM), Faculty of Medicine.

Tania Campos, University of Cambridge, UK

Tania Campos studied Bioengineering, then obtained a Masters in Biochemistry and Bioinformatics, followed by a PhD in Cellular and Molecular Biology at the Univ ersity of Concepcion. During her doctoral thesis, directed by Dr Ariel Castro, she became increasingly aware of the value of in vivo models that more closely mimic complex diseases like cancer. Consequently, in 2016 Tania moved to the Department of Biochemistry, University of Cambridge, to become Research Associate in Professor Gerard Evan's group, resulting in high impact cancer research and publications.

Valentina González, Universidad Católica de la Santísima Concepción, Chile

Valentina González received her Bachelor in Biochemistry and Master degree in Clinical Biochemistry and Immunology from Universidad de Concepción, Chile. She was awarded the Fulbright scholarship for her Ph.D. studies in the Cancer Biology program of Emory University, United States. Dra. González joined the faculty of UCSC this year and was awarded the "Programa de Subvención a la Academia" grant from ANID. Her work focusses on protein-protein interaction and signaling pathways in cancer. Specifically, she works on an epigenetic modulator, NSD3S, that interacts and controls the function of MYC, an oncogene, making contributions to publications in prestigious journals such as, Nature Communications, Oncogene, and Bioinformatics. She also has received awards recognizing her work on cancer, such as the William and Catherine Rice Award in 2018.

Rodrigo López, Universidad Austral de Chile, Valdivia, Chile

Rodrigo Lopez is Pharmacist and Dr. in Pharmacology from the University of Chile. In his undergraduate and postgraduate training, he studied pharmacological strategies against Chagas disease. In this context, he studied the role of cyclooxygenase and its relationship with thiol and nitric oxide metabolism, contributing to the first description of the anti-Chagas role of pro-resolutory lipids derived from cyclooxygenase acetylation. During 2010 and 2014, he was Assistant Professor of the Pharmacology Program at the Faculty of Medicine, Universidad de Chile, working in polyamine transporters of Trypanosoma cruzi. In 2015, he moved to Universidad Austral in Valdivia. Currently, Dr. López dedicates his research to studying the polyamine metabolism in non-small cell lung cancer, and its relationship with KRAS mutation, focusing on systematic approaches to study drug combinations.

Ignacio Niechi, Universidad Austral de Chile, Valdivia, Chile

Ignacio Niechi obtained his degree in Molecular Biotechnology Engineering and his Ph.D in Biochemistry, both from the Universidad de Chile. In his doctoral training with Dr. Julio C. Tapia he studied post-translational modifications and its effects on migration and invasion in colon cancer cells. After his postdoctoral training at the Universidad Austral de Chile with Dr. Claudia Quezada, Dr. Niechi became a Professor of the Instituto de Bioquímica y Microbiología, Universidad Austral de Chile. His research group is focused on the study of invasive processes in malignant tumors and in the search for novel biomarkers and new therapeutic targets.

SBMMCH WEEK SYMPOSIUM 2
Emerging viral infections: insights on mechanism, vaccines, and therapeutic approaches

Chair : Alejandro Rojas-Fernández

Speakers : Davide Angeletti
Matthias Herth
Alejandro Rojas-Fernández
Kellie Ann Jurado

Alejandro Rojas-Fernandez, Universidad Austral de Chile, Valdivia, Chile

Alejandro Rojas-Fernandez is Assistant Professor at the Austral University of Chile. Awarded a PhD fellowship from DAAD degree awarded at the university of Konstanz in Germany, with Martin Scheffner who discovered the molecular mechanism by which HPV virus promote cancer by controlling and redirecting the ubiquitin-proteasome system against. Later we work as Postdoctoral researcher of the MRC-PPU in the United Kingdom with Dr. Ron Hay focusing on the posttranslational modification SUMO and the development of advances technologies such as Crisp/Cas9, proteomic, and Protacs using Alpacas Nanobodies. Currently director of the first platform for the generation of Nanobodies in Chile against emergent virus, Dr. Rojas awarded the medal 2nd of October the highest recognition of the region of Los Rios, and the medal of the city of Valdivia for its contribution to scientific innovation.

Davide Angeletti, University of Gothenburg, Sweden

Davide Angeletti is Assistant Professor at the Department of Microbiology and Immunology, University of Gothenburg, Sweden. He received his PhD from Karolinska Institutet, Sweden (2013) and he was a postdoctoral research at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) 2014-2018, before establishing his lab in 2018. His lab focuses on viral immunology, with emphasis on B cell and antibody responses, with the long-term goal of designing or improving current vaccines. His laboratory employs classical immunology and virology techniques, combined with state-of-the-art high throughput sequencing and systems immunology methods. Current work includes characterization and manipulation of B cell immunity to influenza virus glycoproteins, Hemagglutinin and Neuraminidase, discovery of novel cross-reactive antibodies and longitudinal studies of immunity in COVID19 patients and vaccinees.

Matthias Herth, University of Copenhagen, Denmark

Matthias Herth is Assistant Professor at the University of Copenhagen, Denmark. Radiopharmaceutical chemist who has worked for 18 years with the development of radiopharmaceuticals. He received his PhD in 2009 at the Johannes Gutenberg University, Mainz, Germany under the supervision of Prof. Frank Rösch. In 2010, he moved to Copenhagen and started a PostDoc with Prof. Gitte M. Knudsen. Thereafter, he was promoted to an Assoc. Prof. for radiopharmaceutical chemistry at the Department of Drug Design and Pharmacology, University of Copenhagen, Denmark, where he currently carries out his research. His research mainly focusses on pretargeted imaging and therapy as well as on theranostics.

Kellie Ann Jurado, University of Pennsylvania, USA

Kellie Ann Jurado is Presidential Assistant Professor Term Chair (2019) University of Pennsylvania, Named 100 inspiring Hispanic/Latinx scientists in America (2020). Our research group focuses on delineating disease pathogenesis of emerging viruses in order to uncover mechanisms of immune control. We primarily focus on emerging viral pathogens that present with unknown mechanisms of disease in the nervous system or placenta. Both regions of infection have interfaces (maternal-fetal and blood-brain) that provide extra protection to an essential organ or allogenic fetus. Graduate Ph.D. (Medical Sciences) Harvard University with the Harvard University's Albert J. Ryan Fellowship, 2015. International Uta Von Schwedler Prize for "Outstanding Thesis", 2017 L'Oreal USA Women in Science Fellowship, Charles H Revson Senior Fellowship in Biomedical Sciences and 2018 STATnews STAT Wunderkind.

SBMMCH WEEK SYMPOSIUM 3
Non-coding gets louder: Essential role of ncRNAs in diverse cellular processes

Chair : Verónica A. Burzio

Speakers : Eleonora Leucci
Fernanda Carrizo Velásquez
Christopher Fitzpatrick
David Bars-Cortina

Verónica A. Burzio, Fundación Ciencia & Vida; Andes Biotechnologies SpA; Faculty of Life Sciences, Universidad Andrés Bello; Santiago, Chile

Verónica A. Burzio is a Biochemist from the Universidad Austral de Chile (Valdivia, Chile) and PhD in Molecular and Cell Biology and Neuroscience from the Universidad de Chile in Santiago. Her PhD Thesis versed on the protein kinase CK1 from zebrafish, under the direction of Dr. Jorge Allende. Since 2002, she has been working as Associate Researcher at Fundación Ciencia & Vida in Santiago, Chile, on the role of noncoding mitochondrial RNAs in cancer and their application as targets for cancer therapy. She is also Associate Professor of Cell Biology and Molecular Genetics at the Faculty of Life Sciences, Universidad Andrés Bello.

Eleonora Leucci, LKI Leuven Cancer Institute, KU Leuven, Belgium

Eleonora Leucci obtained her PhD in Medical Biotechnology at the University of Siena (Italy) in 2007. She then moved to BRIC, University of Copenhagen (Denmark) where she worked on small and long non-coding RNAs in the lab of Anders Lund as a postdoctoral fellow. Since 2012 she works in Belgium, where she was first a Marie Curie/VIB postdoctoral fellow in Chris Marine's lab and then as FNRS research associate at ULB, studying the role of lncRNAs in skin cancer. Since 2017 Eleonora Leucci leads the laboratory for RNA cancer biology and heads the PDX platform TRACE at KU Leuven, Belgium. Her lab studies RNA metabolism in cancer with particular focus on the characterization of long non-coding RNAs involved in therapy resistance.

Fernanda Carrizo Velasquez, Johns Hopkins School of Medicine, USA

Fernanda Carrizo Velásquez is a PhD student at the National University of La Plata, Argentina. She is currently a research trainee at the John Hopkins University School of Medicine, Baltimore, USA, under the direction of Dr. Sam Das, working on a project that involves the study of cell-specific small extra-cellular vesicle-derived microRNAs in the pathophysiology of diseases, which includes type 2 diabetes and heart failure.

Christopher Fitzpatrick, Fundación Ciencia & Vida/Andes Biotechnologies; Université Paris-Saclay, INRAE, AgroParisTech, France; Universidad Andrés Bello, Santiago, Chile

Christopher Fitzpatrick is a Biotechnology Engineer from the Andrés Bello University in Santiago, Chile, and obtained his Master's Degree in 2014. In 2017 he obtained his PhD in Biotechnology from the Andrés Bello University, under the direction of Dr. Verónica Burzio, working on miRNAs involved in cell cycle effects of ASncmtRNA knockdown in cancer cells. He is presently Adjunct Professor at the Andrés Bello University and is currently working as a post-doctoral fellow at the Institut National de la Recherche Agronomique (INRAE), Jouy-en-Josas, France, under the direction of Dr. Eric Barrey, working in the application of antisense oligonucleotides for therapy against SARS-CoV-2.

David Bars-Cortina, Université Paris-Saclay, INRAE, AgroParisTech, France; Ecole Nationale Vétérinaire d'Alfort, Université Paris-Est, Maisons-Alfort, France

David Bars-Cortina is a Bsc. in Biology at the Universitat Autònoma de Barcelona, Spain. He has a Master's Degree in Human Nutrition and obtained his PhD Degree in Food and Science Technology at the University of Lleida (Catalonia, Spain) in 2019, focusing on the study of potential benefits of anthocyanins from red-fleshed apples towards the initial phases of colorectal cancer in animal models. In 2020, he performed a short post-doc stay in a non-coding RNA project in the research group of Dr. Eric Barrey, at the Institut National de la Recherche Agronomique (INRAE), Jouy-en-Josas, France. He is currently an Assistant Professor in the MSc. Program in Nutrition and Health at the online university «Open University of Catalonia». He also works as lab technician at the Spanish office of Al Dahra Europe, a company dedicated to alfalfa and forage production and commercialization.

SBMMCH WEEK SYMPOSIUM 4
Emerging roles of the cytoskeleton in cellular functions

Chair : Christian González-Billault

Speakers : Kassandra Ori-McKenney
Carlos Wilson
Anthony Brown
Elias Spiliotis

Christian Gonzalez-Billault, Universidad de Chile, Chile

Christian Gonzalez-Billault is a Chilean biochemist and member of the Chilean Society for Biochemistry and Molecular Biology, recognized for his work in neuronal cytoskeleton. He was trained at Centro de Biologia Molecular Severo Ochoa, Madrid, under the supervision of Jesus Avila. He described the importance of the microtubule-associated protein 1B in neuronal morphology, axonal guidance, and neuronal migration. In 2001 he returned to Chile, where he started his own group at the Faculty of Sciences, Universidad de Chile. In 2012 he became a full professor at the Dept of Biology, Faculty of Sciences, and in 2019 full professor at the Department of Neuroscience at the Faculty of Medicine, Universidad de Chile. He has served several committees at national and international scientific organizations, and in 2020 he became the first Chilean EMBO member. In 2001 he initiated the successful biennial series of international workshops entitled Emerging Concepts of the Neuronal Cytoskeleton that brought to Chile the most important and renowned scientist in the cell biology of the neurons field. The series allowed many Chilean and Latin American students to improve their training and access international rotations, postdoctoral and academic positions at universities and research centers worldwide. Currently, he is the Director of the Geroscience Center for Brain Health and Metabolism (GERO), a center devoted to understanding the cellular and molecular aspects that control brain functions during aging.

Kassandra Ori-McKenney, University California Davis, USA

Kassandra Ori-McKenney performed her graduate work on the microtubule motor, cytoplasmic dynein in the lab of Richard Vallee at Columbia University. After receiving her PhD, she moved across the country to pursue her postdoctoral work with Yuh Nung Jan at UCSF, where she focused on the organization and regulation of the microtubule cytoskeleton during neuronal development. In January 2016, she joined the Department of Molecular and Cellular Biology at UC Davis and her lab now studies how microtubule-associated proteins are coordinated on the lattice to direct motor transport and contribute to proper neuronal function. Kassandra has received the March of Dimes Basil O'Connor Award, the Simons Foundation Pilot Grant, the Pew Biomedical Scholar Award, and an NIH MIRA Grant.

Carlos Wilson, Instituto de Ciencias Biomédicas, Córdoba, Argentina

Carlos Wilson is Biochemist and Ph.D. in Neurosciences from Universidad de Chile. After his PhD in the Christian González Billault's laboratory (Department of Biology, Faculty of Sciences at UChile), where he studied the role of redox balance on neuronal polarization, he started a post-doctoral training in the laboratory of Alfredo Cáceres (Instituto Ferreyra, Córdoba, Argentina), studying epigenetics mechanisms controlling neuronal differentiation. Currently, Carlos holds a position in the Scientific and Technological Researcher Career (Assistant Researcher) at the National Council of Sciences (CONICET, Argentina), running his laboratory in the Biomedical Sciences Institute of Córdoba (Argentina). His lab is focused on bridging chromatin regulation by the histone code with mechanisms controlling the differentiation of neurons and axon dynamics.

Anthony Brown, Ohio State University, USA

Anthony Brown obtained his PhD in Biophysics from King's College, University of London, and then moved to the USA to conduct post-doctoral training in the labs of Ray Lasek at Case Western Reserve University in Cleveland, Ohio and Mark Black at Temple University in Philadelphia, Pennsylvania. After his postdoctoral training, he joined the Department of Biological Sciences at Ohio University in 1993 and then the Department of Neuroscience at Ohio State University in 2001, where he is currently Professor and Co-Director of the Interdisciplinary Graduate Program in Molecular, Cellular and Developmental Biology. Tony was introduced to neurofilaments as an undergraduate in the lab of Peter Eagles and has been studying them for almost 40 years. Over the years, his work has revealed surprising and novel dynamic behaviors for these structural cytoskeletal polymers, including rapid transport along axonal microtubules, complex folding and unfolding behaviors, distinct kinetic states, novel severing and end-to-end annealing mechanisms, and regulation of the pausing behavior by myelinating cells. Recently the lab has developed methods to visualize neurofilament transport by live imaging in mature myelinated axons ex vivo, which will be the subject of this talk.

Elias Spiliotis, Drexel College of Medicine, USA

Elias Spiliotis received his Bachelor of Science from Boston College and Doctor Philosophy from The Johns Hopkins University. Subsequently, he moved to Stanford University, where he held a post-doctoral fellowship from The Jane Coffin Childs Memorial Fund for Medical Research. In the lab of cell biologist James Nelson, he focused on the regulation of the cytoskeleton and its functions by a novel family of GTP-binding proteins termed septins. Since 2008, Dr. Spiliotis has been a faculty in the Departments of Biology, and Neurobiology and Anatomy at Drexel University in Philadelphia, USA. He's the founder and director of the Cell Imaging Center, and serves as the Director of the Biology Graduate Program. He is a member of the American Society for Cell Biology, and has been featured by The Scientist magazine's "Scientist to Watch" and the Journal of Cell Biology's "People & Ideas". In his spare time, Dr. Spiliotis has djed radio shows, written music reviews, and performed and recorded with an independent post-punk band.

ANNUAL WRAP-UP SYMPOSIUM 1
Open source biotechnologies in action: From research to applications

Chairs : César A. Ramírez-Sarmiento and Fernán Federici

Speakers : Jennifer Molloy
Isaac Núñez
Richard Bowman
Almendra Cremaschi
Anabel Marín

César A. Ramírez-Sarmiento and Fernán Federici, Institute for Biological and Medical Engineering (IIBM) and ANID Millennium Institute for Integrative Biology (iBio), Pontificia Universidad Católica de Chile, Chile

César A. Ramírez-Sarmiento is an Assistant Professor at the Institute for Biological and Medical Engineering (IIBM) from Pontificia Universidad Catolica de Chile and Adjunct Researcher at the Millenium Institute for Integrative Biology (iBio). His research group employs experimental and computational strategies to unveil the folding-function-evolution relationships of metamorphic proteins, prototypical models to understand the emergence of novel protein folds in nature, and of bacterial enzymes that hydrolyze PET, a widely used plastic that accumulates as waste in landfills and natural environments at similar rates to its production. Recently, his research has been focused on the development of open-source protocols for the local production of enzymes and reagents used in the detection of viral infections, including SARS-CoV-2, alongside Dr. Fernán Federici.

Jennifer Molloy, University of Cambridge, UK

Dr. Jenny Molloy is a Senior Research Associate at the University of Cambridge, researching the potential for local, distributed manufacturing of enzymes to improve access and build capacity for biological research and innovation. This work combines technical development using synthetic biology-based platform technologies with qualitative research on challenges faced by molecular biologists globally through interviews and case studies. Since 2015 she has co-founded four social enterprises and nonprofits making open source tools more accessible to researchers and building communities for open source tool developers. Dr Molloy is also the 2020-21 Fellow of the World Economic Forum Global Futures Council on Synthetic Biology and a member of the Country Support Working Group in the Diagnostics Pillar of the WHO Access to COVID-19 Tools Accelerator (ACT-A).

Isaac Nuñez – ANID, Millennium Science Initiative Program, Millennium Institute for Integrative Biology (iBio); Institute for Biological and Medical Engineering (IIBM), Pontificia Universidad Católica de Chile

Isaac Núñez is an Engineer and PhD candidate in biotechnology at Pontificia Universidad Católica de Chile and iBio Milenio Institute whose research focuses on Synthetic Biology, DNA Assembly and Open Hardware-Software development. He is a passionate advocate for open & free/libre technologies, exploring how they can boost innovation and development in a democratized way, empowering communities to solve their own problems. He actively participates in communities such as GOSH and TecnoX that promote the use of open technologies and is frequently running national and international workshops to share, develop and apply open knowledge and tools. Isaac is interested in increasing the access to cutting edge technologies by researchers, schools and developers to improve local and national capabilities.

Richard Bowman, University of Bath, UK

Dr Richard Bowman is a Royal Society URF and Proleptic Reader at the University of Bath, who works on lab automation, microscopy, and open source hardware. He has led the OpenFlexure project over the last 6 years, from Friday-afternoon prototype to a well-tested design that's been replicated hundreds of times and is under evaluation for malaria diagnostics in Tanzania. He is passionate about the benefits that smarter equipment can bring to scientific research, particularly when it is coupled with researchers who are able to automate it. He hopes that the hardware and software innovations that make the OpenFlexure microscope a useful research tool will "trickle up" to more expensive and conventional projects, as we move towards a more open and interconnected ecosystem of scientific instruments in our labs.

Almendra Cremaschi – Centro de Investigaciones para la Transformación (CENIT), Escuela de Economía y Negocios UNSAM, Argentina

Almendra Cremaschi is a doctoral student at the University of La Plata and a fellow of the National Council for Scientific and Technological Research (CONICET), investigating how to support transitions towards more sustainable seed systems. She is based at the Center for Transformation Studies (CENIT) -UNSAM, Argentina and is an associate professor of Sustainable Development at the same University. Almendra is co-founder of Bioleft, an open and collaborative system for the development of seeds (http://bioleft.org/).

She is also interested in how participatory methods contribute to more decolonized, open, transgressive, and feminist forms of co-creating situated knowledge that supports transformations in socio-ecological systems. She has recently started to collaborate with Umbela (https://en.umbela.org), through the project Cultivating ways of knowing for transformations and with the Institute of Development Studies (IDS) looking at transformations in science and knowledge systems for development.

Anabel Marin – Institute of Development Studies, University of Sussex, UK; Centro de Investigaciones para la Transformación (CENIT), Escuela de Economía y Negocios UNSAM, Argentina

Dr. Anabel Marin is currently a Research Fellow and the Leader of the Business, Markets & State Cluster at the Institute of Development Studies (IDS). She is also chair of the Global Network for Open Source Seed Initiatives (OSSI) and the director of Bioleft (http://bioleft.org/), an open source initiative for seed breeding. She has a degree in Economics (Cordoba University), a Masters in Development (University of General Sarmiento) and a PhD in Science and Technology Policy Studies (SPRU, Sussex University).

Anabel is interested in the use of multidisciplinary approaches to address problems of economic, sustainable and inclusive development. Her work combines research, policy advice, activism and the development of cultural products for sustainable development (see: https://www.youtube.com/watch?v=jnFP4g_0BV4). Her current projects are on the topics of: transformations in science and knowledge systems for development; open and collaborative forms of innovation; sectoral systems of production and innovation of biotechnology drugs in Latin America.

ANNUAL WRAP-UP SYMPOSIUM 2
Immunoepigenetics in Cancer

Chair : Matías Hepp

Speakers : Wayne Hancock
Katherine Chiappinelli
Alejandro Villagra
Eduardo Sotomayor

Matías Hepp, Universidad Católica de la Santísima Concepción, Chile

I'm assistant professor and PI of Epigenetic and Immunotherapy Unit of Biomedical Research Laboratory, Medicine Faculty of Universidad Catolica de la Santisima Concepcion since December 2018, my lab focus on elucidating the processes that involve transcriptional regulation in general, epigenetic mechanisms, and molecular processes in different pathologies associated with aging, specifically, in cancer. We are focused on studying colorectal cancer, since it is one of those with the highest incidence in the Biobío region and in Chile, in addition, its main treatment continues to be invasive (surgery). For this reason, we study the cellular response to different therapeutic compounds in cancer, thus giving future options for co-treatments that may be more effective. We focus on histone deacetylase inhibitors (HDAC) in combination with monoclonal antibodies (immunotherapy), but we also work with natural extracts of different origins. Our purpose is to help find a dual therapy that improves the response to immunotherapy in cancer, by modifying the processes involved in epigenetic regulation, specifically in solid tumors. In the laboratory, to solve these questions, we handle different techniques of cellular and molecular biology, with in vitro and in vivo approaches.

Wayne Hancock, University of Pennsylvania, Philadelphia, USA

After medical and PhD degrees, and board certification as a pathologist (FRCPA), my lab search for therapeutic strategies to enhance outcomes post-transplant led to studies of the anti-inflammatory properties of anticoagulant molecules, ways to improve the outcomes of xenotransplantation via induction of "protective" genes, back to allotransplantation and studies of novel costimulation molecules, and then the roles of chemokine and their receptors in alloresponses. For the past decade, my work has focused on biochemical, molecular and therapeutic studies of Foxp3+ T-regulatory (Treg) cell biology. With regard to translational aspects of our Foxp3 work, my group has shown using genetic and pharmacologic targeting that histone/protein deacetylase inhibition (HDACi) can increase Foxp3 acetylation and thereby enhance suppressive actions of this cell type, in vitro and in vivo, including prolonging allograft survival and protecting against development of inflammatory bowel disease in murine models. This approach is now being tested in clinical trials. Likewise, my lab showed that histone/protein acetyltransferase inhibitors (HATi) could diminish Foxp3 acetylation and thereby impair Treg functions without necessarily curtailing associated effector T cell responses, opening up a new area of research involving HAT targeting to decrease Treg suppression and enhance host anti-tumor immunity. By now, my lab has investigated the roles of members of each of the main HAT families in Treg biology, including GCN5 and PCAF (GNAT family), CBP and p300 (CBP/p300 family), and Tip60 (with a current R01 from NCI on the topic) and Myst1 (Myst family), as well as the functions of all 11 classical zinc-dependent HDACs. However, a recurring theme in all this work has been how best to selectively target Foxp3+ Treg cells? To tackle this issue in the most direct manner feasible, I have developed and am testing various antisense oligonucleotides (ASO) directed against various regions of murine and human Foxp3.

Katherine Chiappinelli, George Washington University, Washington, USA

My laboratory studies the epigenetic changes in cancer and how epigenetic drugs can reverse these, specifically focusing on noncoding regions of the genome and the anti-tumor immune response. A major focus of my research is epigenetic regulation of repetitive elements in cancer and how they contribute to innate immunity. During postdoctoral training with Dr. Stephen Baylin, I performed experiments to determine the mechanism for activation of immune signaling in ovarian cancer cells by DNA methyltransferase inhibitors (DNMTis). My NIH F32-funded postdoctoral work showed that DNMTis upregulate double-stranded RNA, including endogenous retrovirus transcripts (ERVs) that are normally hypermethylated, to activate the interferon response. My independent laboratory, funded by R21 and R37 grants and a DOD OCRP award, continues to focus on epigenetic modifications of the noncoding genome, and in translational work, on combining epigenetic and immune therapy to fight cancer. I am strongly supported by the excellent basic and translational research environment in the Department of Microbiology, Immunology, & Tropical Medicine and the GW Cancer Center, where my colleagues have particular strengths in epigenetics and immunology. My expertise in the area of epigenetic regulation of repetitive elements and immune signaling in cancers has been widely recognized in many ways, including invitations to speak at national and international forums (Gordon Conference on Cancer Genetics and Epigenetics and the FASEB meeting on Mobile DNA in Mammalian Genomes) and invitations to serve as a reviewer for high impact scientific journals and NIH grants.

Alejandro Villagra, George Washington University, Washington, USA

My primary areas of expertise are tumor immunology and epigenetics. During my scientific career, I have explored the role of epigenetic modifiers in the modulation of signaling pathways controlling the phenotype and function of immune and cancer cells. My study models have been diverse and have included multiple solid tumors and hematological malignancies. Overall, my current research areas are focused on the identification and characterization of the immunomodulatory roles of HDACs and other epigenetic modifiers in myeloid and lymphoid cells. A special emphasis in my research is to discover and evaluate new selective small-molecule inhibitors able to selectively control the activity of epigenetic modifiers in immune and cancer cells with the final goal of improving antitumor immune responses. My experimental approaches have essential translational components, including syngeneic animal and patient-derived xenograft models, which give me the possibility to extend my investigations into the clinical area. These particular characteristics allow my research to maintain continuous feedback and keep goals focused on the relevant biomedical aspects of my scientific endeavors. The present application will create new, highly specific HDAC6 inhibitors to evaluate the effect of epigenetically modified macrophages as a new therapeutic anticancer therapy. Such new knowledge would, in turn, aid the design of tailored and more efficacious therapeutic approaches in solid tumors and other malignancies.

Eduardo Sotomayor, University of South Florida, Tampa, USA

On April 2021, I became the inaugural Director of The Tampa General Hospital (TGH) Cancer Institute in Tampa, Florida. Previously, I was the Dr. Cyrus Katzen Family Endowed Director of the George Washington Cancer Center at George Washington University (GW). At the beginning, I was involved in the initial work that led to the demonstration that antigen-specific CD4+ T-cells were rendered tolerant early during tumor growth. Furthermore, we found that induction of this unresponsive state coincided with loss of therapeutic vaccine efficacy, unveiling for the first time the obstacle that immune tolerance imposes to active immunotherapy. In addition, we found that activation of APCs through CD40 ligation could convert T-cell tolerance to tumor antigens into effective T-cell priming and enhanced response to vaccination. After that, my lab identified several signaling pathways that, by regulating the inflammatory status of the APC were shown to be central in the decision leading to T-cell activation vs T-cell

tolerance. One of the intracellular pathways we identified was STAT3 signaling, now recognized as an important negative regulator of inflammation in APCs. In addition, we also demonstrated that ligation of TLR5 in the APC by the TLR5 ligand, flagellin, induces inflammatory cells that by being unable of producing the immunosuppressive cytokine IL-10, elicit productive T-cell responses rather than T-cell anergy. We have also explored how epigenetic changes influenced the inflammatory status of the APC. In particular, we have studied the consequences of chromatin modification by deacetylation of histone tails (mediated by histone deacetylases) upon the expression of genes involved in the inflammatory response. We showed for the first time, that the histone deacetylase 11 (HDAC11) negatively regulates the expression of the anti-inflammatory cytokine IL-10 in APCs. Such an effect not only determine the inflammatory status of these cells but also influence priming versus tolerance of antigen-specific CD4+ T-cells. Finally, our interest in B-cell lymphomas goes back to the opening in 2004 of a Phase II clinical trial using the GM.CSF.CD40Ligand bystander vaccine approach for patients with untreated or relapsed mantle cell lymphoma and our subsequent interest in seeking a better understanding of the genetics, epigenetics and immunology of B-cell NHL with the overarching goal to develop novel immunotherapies for these lymphomas, including viral-associated lymphomas.

NEW MEMBERS

Lorena Pizarro, Universidad de O'Higgins, San Fernando, Chile

I'm a plant biologist with a Ph.D. in Science from the "Molecular Biology, Cell Biology and Neuroscience" program at the Universidad de Chile. Currently, I am an Assistant Professor at the Instituto de Ciencias Agroalimentarias, Animales y ambientales (ICA3) from the Universidad de O'Higgins. My research is focused on Plant Immunity, describing defense responses in fruit trees and identifying the pattern recognition receptors that sense the pathogens. I have a broad background in plant biology, with specific training in cell biology and live-cell microscopy. I participate as Main Investigator in the "Anillo-O'Higgins Grant – ACTO190001" entitled "Deep insight into cherry plant defense responses to bacterial canker disease in a scenario of water restriction" and l lead two grants focused in the study plant immunity on stone fruit trees: "Peach (Prunus persica) pathogen recognition receptors (PRRs) and their role in pathogen resistance" (Fondecyt de Iniciación 2020 N°11200934); and "Activación de la inmunidad en frutales del género prunus para el potenciamiento de su tolerancia a enfermeddes fungosas y bacterianas"(PAI 77190027). With this research, I aim to promote sustainable strategies for plant protection in our agriculture.

Marioly Müller, Universidad de Chile, Santiago, Chile

I recently finished a Ph.D. program in Biomedical Sciences at the University of Chile. It has not been easy to have scientific achievements because I have been an assistant professor with a doctorate for less than a year. However, I have been working in science since my undergraduate thesis on Calcium-dependent transduction pathways in skeletal muscle cells and later during my graduate formation in the Master's program in Cell Biology. I had the opportunity to research at the University of Pennsylvania on calcium dysregulation in Alzheimer's disease (AD). This work focused on exploring the enhanced CREB phosphorylation mediated by familial AD mutant presenilin one associated exaggerated Ca2+ signaling. I have contributed to significant publications in the Alzheimer's field, cellular bioenergetics, and autophagy with relevance for neurodegenerative diseases and cancer. I am currently working on intracellular Ca2+ signaling, mainly linked to mitochondrial functions and bioenergetics in different models, and hopefully, we will produce important scientific achievements.

Valentina González, Universidad Católica de la Santísima Concepción, Chile

Valentina González received her Bachelor in Biochemistry and Master degree in Clinical Biochemistry and Immunology from Universidad de Concepción, Chile. She was awarded the Fulbright scholarship for her Ph.D. studies in the Cancer Biology program of Emory University, United States. Dra. González joined the faculty of UCSC this year and was awarded the "Programa de Subvención a la Academia" grant from ANID. Her work focusses on protein-protein interaction and signaling pathways in cancer. Specifically, she works on an epigenetic modulator, NSD3S, that interacts and controls the function of MYC, an oncogene, making contributions to publications in prestigious journals such as, Nature Communications, Oncogene, and Bioinformatics. She also has received awards recognizing her work on cancer, such as the William and Catherine Rice Award in 2018.

Angello Retamal-Díaz, Universidad de Antofagasta, Chile

Angello Retamal-Díaz is an Assistant Professor of the Biotechnology Department, Facultad de Ciencias del Mar y de Recursos Biológicos, Universidad de Antofagasta, Chile. His science career started as a Biochemist at the Universidad de Concepción, Chile, and he received a Ph.D. in Molecular Genetics and Microbiology at the Pontificia Universidad Católica de Chile. He performed post-doctoral training at the Millennium Institute on Immunology and Immunotherapy and associated researcher at the Chilean Army Health Command. His research focuses on the host-pathogen interaction, the immune response against infectious agents, vaccine and antiviral design with Systems Immunology based approaches. His laboratory works with platelets-virus interaction and Human herpesvirus type 6. Contributed to the collaborative initiative for COVID-19 vaccine clinical trials and SARS-CoV-2 sequencing surveillance platform. He participated in many science outreach activities and is co-author of the first Technology Assessment article, a collaborative work by the Millennium Scientific Initiative and Chilean Congress Library. Dr. Retamal-Díaz is a member of the American Society for Microbiology and contributing as a journal reviewer of Frontiers Immunology and Frontiers in Biotechnology. He also received an honorable award for their Doctoral thesis by the Chilean Society for Microbiology, as well as an Excellence Certificate awarded by the Ministry of Economy, Development, and Tourism.

Erwan Michard, Universidad de Talca, Chile

I am a principal investigator at the Instituto de Ciencias Biológicas at the University of Talca (Chile). I am working on the molecular mechanisms that generate calcium and electrical signals in plants during adaptation to environmental stresses. I was first interested in plant electrical signaling, and potassium channel involvement, a work that I stated during my PhD in Montpellier (Supagro, France) and continued in a first post-doc in Golm (MPI-MP, Germany). I then joined the group of Prof. José Feijó in Oeiras (IGC, Porttugal) and later at the University of Maryland (USA) where we demonstrated a role of ion channels from the glutamate receptor family (GLR) in calcium signaling during plant reproduction and development. My research is now focused on the molecular structure and function of GLRs, in order to understand how they act on both calcium and electrical signals.

Felipe Valenzuela-Riffo, Universidad de Talca, Chile

Felipe Valenzuela-Riffo studied Engineering in Bioinformatic at the University of Talca and received his degree in 2014. He actually is a PhD student in plant Science with mention in genetic engineering from the University of Talca. His research main topic focuses in the study of molecular aspects in the formation and degradation of primary plant cell wall. The strategies used involve: structural bioinformatics, biochemical characterization, and functional genomics. To describe genes, proteins, enzymes and how they modulate the response to different events occurring in the plant cell wall. It has also been approached the study of enzymes involved in the study of quality traits of fruits in strawberry.

José Miguel Alvarez, Universidad Mayor, Santiago, Chile

José M. Alvarez is a plant scientist researching chromatin remodeling and transcriptional programs in response to environmental changes in plants. Dr. Alvarez is particularly interested in applying genomics and systems biology principles to challenges in agricultural sustainability with a specific interest in nitrogen and drought effects on transcriptional programs, plant development, and plant production. He earned his Ph.D. in molecular genetics and microbiology at Pontificia Universidad Católica de Chile in 2013. During his postdoc at New York University, he used time-based systems biology approaches to capture dynamic gene regulatory networks in plants. He contributed to identifying relevant transcription factors that modulate plant growth and adaptation to nitrogen nutrient signals. Dr. Alvarez is currently serving as an assistant professor at Universidad Mayor in Santiago and an adjunct researcher at Millennium Institute for Integrative Biology (iBio). His research is funded by ANID-FONDECYT regular project, National Science Foundation (NSF) grant, and Iniciativa Científica Milenio.

Pablo Galaz-Davison, Institute for Biological and Medical Engineering, ANID – Millennium Science Initiative Program –Universidad Católica de Chile, Santiago, Chile

I graduated from biochemistry and master in biochemistry from Universidad de Chile in 2017. The very next year I started my PhD in chemical engineering in Pontificia Universidad Católica de Chile, where I have been working for the past few years. My research on biophysics and protein sciences has provided me with several opportunities to work abroad, twice in the US and once in Argentina, where I gathered experience in proteomics, x-ray crystallography, coarse-grained molecular dynamics and co-evolutionary analysis. This led me to publish my research three times as first or co-first author, while one of our articles got selected as paper of the year in the biophysical journal. I hope to finish my PhD in 2022 and continue working in the protein sciences as a postdoc.

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