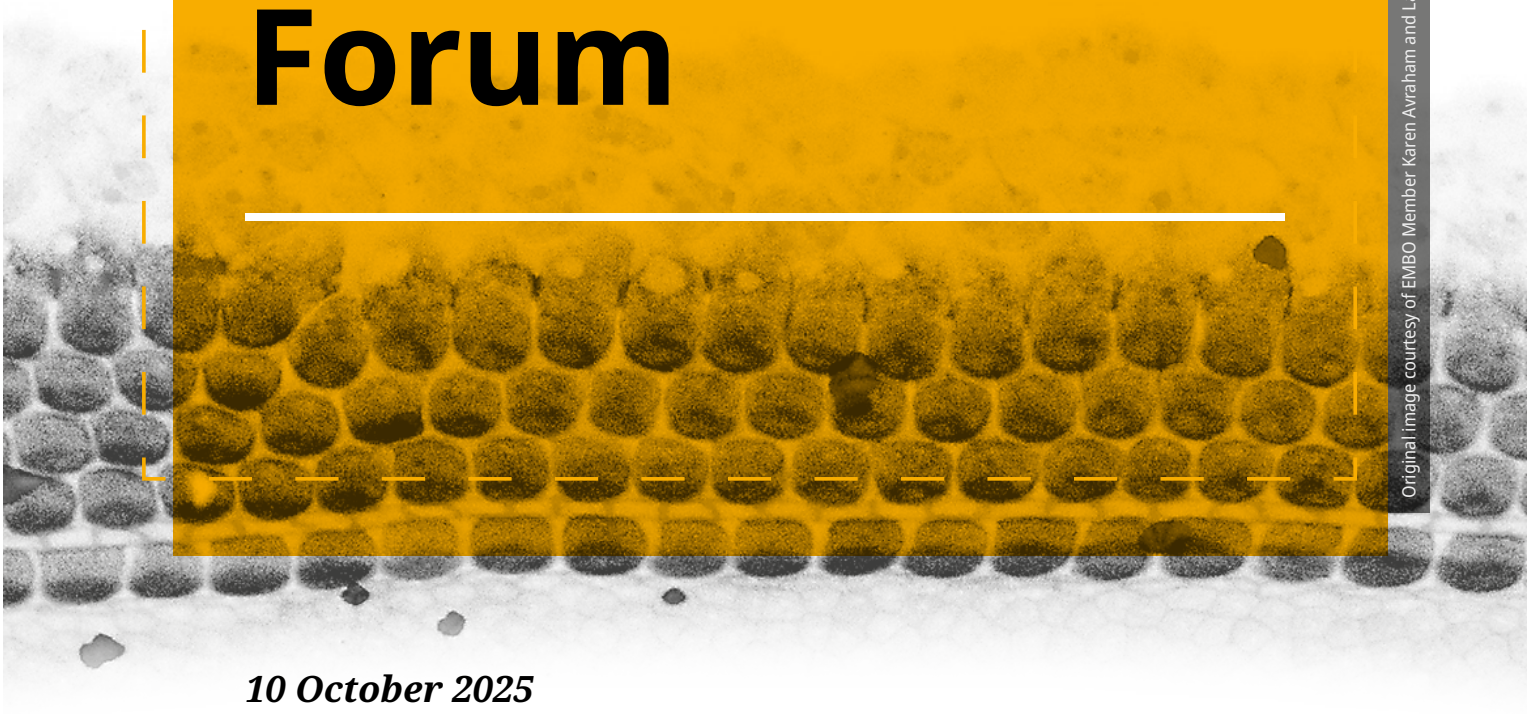
Chile-EMBO Life Science Forum



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Abstract book

Keynote lecture

Plant life at the extremes in the Atacama Desert

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Throughout evolution, plants adapted to flourish in a variety of ecosystems, including extreme deserts. In the current changing climate scenario, it is essential to identify the underlying molecular mechanisms that enable plant resilience extreme conditions. The Atacama Desert, the driest non-polar desert in the world, offers a unique opportunity to explore plant adaptations to extreme environmental conditions. We characterized the three pristine and extreme ecosystems along a natural altitudinal gradient of environmental parameters on the western Andes slopes in the Atacama Desert. We recorded low and unpredictable precipitation patterns, large daily temperature oscillations, low humidity, extremely high radiation levels, as well as soils with consistently low nitrogen levels. Despite these harsh conditions, a diversity of plant species coexist. We sequenced the transcriptome of the most important plant species, representing 14 plant families with diverse phylogenetic origins. Using phylogenomics, we compared the protein-coding sequences of Atacama species to their closest available sequenced species, and identified genes under positive selection in Atacama plants. These genes are involved in various developmental, regulatory and metabolic processes associated with environmental adaptation. Untargeted metabolomics analysis showed metabolic processes play a key role in the adaptation of plants to the extreme Atacama Desert conditions. Our study provides new insights into plant abiotic stress tolerance, and improves our understanding of the highly unique Atacama Desert ecosystem.

Invited speakers' talks

Dissecting sulfate deficiency responses in tomato through gene regulatory networks

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Sulfate deficiency is an emerging constraint on crop productivity, yet the regulatory logic that orchestrates its uptake, assimilation, and the metabolic reprogramming that occurs under this stress remains poorly defined, particularly in non-model plants. To address this challenge, we asked how gene regulatory networks (GRNs) encode sulfate-deficiency responses and whether they can reveal central transcription factors (TFs) as intervention points to improve nutrient use efficiency. We focused on tomato (Solanum lycopersicum), a globally important crop and a major agricultural product in our country that is particularly vulnerable to sulfate limitation.
As a foundation, we developed a comprehensive GRN resource for tomato, inferring regulatory interactions between TFs and target genes from more than 10,000 RNA-seq libraries, and refining regulatory edges with co-expression and TF-binding motif predictions. We next focused on sulfate-deficiency subnetworks, integrating time and organ resolved data. Network topology and node influence analyses converged on the ETHYLENE-INSENSITIVE3-LIKE3 (SlEIL3) TF as a central regulator of the sulfate deficiency response in tomato. Experimental validation of targets using DAP-seq and TARGET assays, confirmed direct regulation of SlEIL3 over genes controlling sulfate uptake and assimilation. Moreover, heterologous overexpression of SlEIL3 in Arabidopsis thaliana enhanced sulfate acquisition and plant growth, while extensively reprogramming the sulfate deficiency transcriptional response. This reprogramming included genes involved not only in sulfur homeostasis, but also in energy metabolism, growth, and abiotic and biotic stress pathways. Our work demonstrates how network-driven discovery can accelerate mechanistic dissection of nutrient-stress responses, establishing GRN-guided approaches as powerful tools for identifying targets to improve nutrient use efficiency and resilience in crops.
Acknowledgements: This work was funded by Agencia Nacional de Investigación y Desarrollo (ANID)-Millennium Institute for Integrative Biology (iBio) ICN17_022, ANID-Millennium Nucleus in Data Science for Plant Resilience (Phytolearning) NCN2024_047, ANID-FONDECYT 1211130 and 1250631, ANID-Vinculación Internacional FOVI230159.

Where genomics and taxonomy meet: Identification of novel yeast species in Patagonia

Francisco Cubillos et al.

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Species delineation in microorganisms is challenging due to the limited markers available for accurate classification. Here, we applied an integrative taxonomy framework that combines extensive ecological sampling, whole-genome sequencing, phenotypic profiling, and reproductive isolation tests. Our study uncovers a distinct lineage of Saccharomyces associated with Nothofagus forests in coastal Patagonia, which we designate Saccharomyces chiloensis sp. nov. Whole-genome comparisons reveal ~7% sequence divergence from S. uvarum, its closest known relative. This new species clusters within the South America-C (SA-C) clade and is phylogenetically close to a divergent S. uvarum lineage found in Oceania (Australia and New Zealand). Ortho Average Nucleotide Identity (OANI) values between S. chiloensis (SA-C and AUS) and S. uvarum fall below the 95% species delineation threshold, supporting their classification as independent evolutionary lineages. Crucially, reproductive isolation was confirmed through reduced hybrid spore viability. Notably, we identified species- and lineage-specific structural variants, including large chromosomal inversions and translocations, that likely contribute to reproductive barriers and highlight intra-species genomic diversity. These SVs, together with distinct phenotypic profiles, reinforce the species status of S. chiloensis and suggest ongoing divergence among its populations. We propose that S. chiloensis diverged allopatrically from S. uvarum during Pleistocene glaciations, followed by post-glacial dispersal across the Pacific. This work exemplifies how integrative genomics, including SV analyses, can uncover cryptic microbial diversity and elucidate mechanisms of speciation in fungi.

Structural evolution of genomes

Gilles Fischer

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Population genomics has traditionally relied on a single reference genome to capture the genetic diversity of a species. However, this approach has reached its limitations and is now being superseded by a new paradigm: the reference pangenome. This model comprises multiple, contiguous telomere-to-telomere genome assemblies that more accurately reflect the full spectrum of genetic variation within a species.
With the advent of long-read sequencing technologies, it is now possible to generate truly complete and phased genome sequences, including repetitive and structurally complex regions that are typically unresolved in traditional resequencing projects. These advances enable the construction of comprehensive reference pangenomes and offer new insights into genome evolution.

Adaptation to the environment through symbiosis - a model systems approach

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Adaptation to the Environment through Symbiosis – a Model Systems' Approach Symbiotic interactions between organisms occur in all domains of life. A prime example is the symbiosis between corals and eukaryotic, photosynthetic dinoflagellates. Each generation, initially symbiont-free coral larvae take up dinoflagellates from the environment and a new, stable symbiotic interaction is established. Symbionts provide essential nutrients such as sugars, amino acids and lipids to their host powering the productivity of reefs ecosystems. Despite of its importance, key aspects about coral symbiosis establishment, maintenance, its evolution and ecosystem functions are still largely unknown. Here, I will present our advances in developing Aiptasia, a marine sea anemone, as a tractable model to dissect fundamental aspects of symbiosis establishment at the mechanistic level. I will give an overview over our current understanding of the mechanisms underlying symbiont uptake via phagocytosis, how the symbionts escape the hosts' defensive strategies to persist intracellularly, and how symbionts integrate into host cell metabolism. Our symbiosis research provides fundamental insight into how two very distinct cells coordinate their cellular functions to adapt to nutrient-poor environments and drive the productivity and biodiversity of the ecosystem.

From penguins to crustaceans: Microbiomes across Antarctic and sub-Antarctic animals

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Animal-associated microbiomes are critical for host health, adaptation, and ecosystem functioning, yet remain poorly characterized in high-latitude environments. In the Antarctic and Sub-Antarctic regions, animals ranging from penguins and marine invertebrates to freshwater crustaceans experience extreme conditions that shape their microbial partners in unique ways.
Our interdisciplinary team at the Millennium Institute BASE investigates these host–microbe associations across diverse taxa. We analyze internal and external microbiomes of sea urchins (Abatus spp.), limpets (Nacella spp.), and notothenioid fishes (Harpagifer spp.), as well as freshwater fairy shrimps (Branchinecta spp.). We also examine soils from colonies of Pygoscelis penguins that act as reservoirs and transmission hubs for microbial diversity. Using metabarcoding, shotgun metagenomics, functional predictions, and oligotyping, we resolve microbial community composition and intraspecific diversity. These approaches reveal selective pressures, functional traits, and phylogeographic patterns that link microbial assemblages to host identity, trophic ecology, and environmental gradients. We further explore co-evolutionary signals, highlighting how microbiomes may facilitate host adaptation to rapidly changing climates.
By integrating ecological, genomic, and biogeographic perspectives, our findings bridge the gap between macro- and micro-biodiversity. They demonstrate that conserving animal populations in these regions also safeguards a hidden microbial diversity essential to ecosystem resilience. Recognizing and protecting these intertwined dimensions of life is critical for anticipating the ecological consequences of global change.

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Population and adaptive genomics: from the Atacama Desert and high Andes to Antarctica

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Chile spans a wide range of extreme environments, from the arid Atacama Desert in the north, through Mediterranean ecosystems and temperate rainforests in the south, to the polar habitats of Antarctica. These diverse habitats drive local adaptations in species, limiting gene flow across ecological boundaries and promoting speciation. Southern Chile was also shaped by ice sheet coverage during the Last Glacial Maximum (LGM). In the Laboratory of Molecular Biodiversity, we investigate genomic diversity, phylogeography, and local adaptation, complemented by species distribution models of vertebrates such as guanacos, foxes, snakes, thorn-tailed rayaditos, hummingbirds, skuas, and penguins. For example, guanacos show strong population structure, with colonization patterns extending from the desert to Tierra del Fuego, and genetic signatures of adaptation to both the high Andes and cold southern environments. In the Southern Ocean, penguins and skuas exhibit isolation or limited gene flow from South America across the Antarctic Polar Front (APF). However, skuas present a notable zone of introgression from the Antarctic Peninsula to Bouvet Island. These studies have advanced our understanding of the region's biogeography, species delimitation, and conservation needs. Currently, Chile is sequencing reference genomes of its eukaryotic biodiversity through the 1000 Genomes Project, which will further illuminate the evolutionary history and adaptive potential of its unique endemic species.
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Neuropathic pain from the skin: investigating mechanisms

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The skin is richly innervated by peripheral sensory neurons, which mediate the detection of mechanical and thermal stimuli via dermal mechanoreceptors and intraepidermal nociceptors. In Recessive Dystrophic Epidermolysis Bullosa (RDEB), a chronic skin fragility disorder, repeated injury leads to disrupted intraepidermal nerve fibres, resulting in neuropathic pain and impaired thermal sensation. Under normal conditions, epidermal reinnervation occurs after injury through collateral sprouting and guided dermal axon regeneration, processes dependent on neurotrophic cues from keratinocytes. In RDEB, this regenerative response appears defective, potentially due to impaired keratinocyte secretion of neurotrophic factors. We investigated the contribution of keratinocyte-derived neurotrophic factors to epidermal reinnervation and tested whether pharmacological activation of their receptors could promote regeneration. We first assessed neurotrophic factor expression in a human in vivo skin wound model. We then analysed the secretome of primary keratinocytes from healthy donors and RDEB patients, and evaluated its effects on neurite outgrowth in sensory neurons derived from embryonic rats, mice, and human induced pluripotent stem cells (iPSCs). Finally, we tested the regenerative potential of TrkA and GDNF receptor agonists (Gambogic amide and XIB4035) both in vitro and in a mouse model of RDEB.

In healthy skin, injury triggered robust secretion of neurotrophic factors, whereas RDEB skin failed to do so. Secretomes from healthy keratinocytes promoted neurite outgrowth in sensory neurons, while those from RDEB keratinocytes did not. Treatment with receptor agonists restored neurite growth in vitro, enhanced intraepidermal innervation, and reversed thermal hyposensitivity in RDEB mice.

Fine-tuning of neuronal polarity: from microtubule codes to novel glutamate signals

Christian Gonzalez-Billault

Universidad de Chile

The establishment and maintenance of neuronal polarity are critical for proper nervous system development and function. This process is orchestrated through intricate regulation of the cytoskeleton and intracellular signaling pathways. Here, we elucidate two complementary mechanisms that converge on the regulation of neuronal morphology, polarity, and organelle trafficking.

First, we demonstrate that tubulin polyglutamylation, a prevalent post-translational modification in neurons, modulates microtubule dynamics essential for neurite outgrowth. Loss of function of the polyglutamylases TTLL1 and TTLL7 results in elongated axons and dendrites, while overexpression—particularly of catalytically inactive mutants—induces microtubule stabilization and impairs polarization, unveiling non-enzymatic roles for TTLLs. We identify MAP1B as a novel negative regulator of polyglutamylation through its interaction with TTLL1 via the LC1 domain. Loss of MAP1B leads to increased α-tubulin glutamylation and disrupted mitochondrial trafficking, underscoring a reciprocal regulation between MAPs and tubulin modifications in controlling neuronal architecture.

Second, we uncover a developmental role for NMDA receptors (NMDARs) and glutamate signaling in neuronal polarization. Functional NMDARs are expressed early in hippocampal neurons and regulate Rac1 activity, actin cytoskeleton dynamics, and H_2O_2 production via NOX2. Pharmacological and genetic manipulations of NMDARs reveal that their activation promotes axon specification and elongation through Ca^{2+} influx and endoplasmic reticulum Ca^{2+} release. Optogenetic Rac1 activation further confirms its dual role in lamellipodia formation and redox signaling.

Together, these findings propose a unifying model wherein cytoskeletal modifications (via MAP1B–TTLL1 interactions) and receptor-mediated signaling (via NMDAR–Rac1 pathways) independently and synergistically support neuronal polarization. This integrated framework offers new insights into the regulation of early neuronal development with implications for neurodevelopmental disorders.

Harnessing dendritic cell function through the unfolded protein response

Fabiola Osorio

Universidad de Chile

Dendritic cells (DCs) are central orchestrators of immune responses, with specialized subtypes driving distinct functional programs.
Recent findings reveal pivotal and subtype-specific
roles for the unfolded protein response (UPR), particularly the sensor IRE1 (inositol-requiring enzyme 1), in regulating key aspects of DC biology.
This talk will explore how environmental stressors and metabolic cues engage IRE1-mediated signaling to fine-tune DC function, highlighting the integration of endoplasmic reticulum (ER) stress with immune
cell programming.
Emerging evidence also links IRE1 activity to tissue-specific immunosurveillance, particularly in the intestine, where IRE1-dependent signaling in DCs supports homeostasis
and barrier integrity. I will present complementary approaches, uncovering mechanisms by which IRE1 governs intestinal DC function and contributes to the immune equilibrium in the gastrointestinal tract.
By dissecting the context and lineage-specific roles of IRE1 activity across DC subsets, this work positions the UPR as an emerging regulator of myeloid cell specialization and identifies IRE1 as a promising target for therapeutic modulation in inflammatory and barrier-associated
diseases.

Shaping early epigenomes: Endogenous retroviruses and their repressors

Daniel Messerschmidt

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A hallmark of mammalian preimplantation development is the extensive erasure and reprogramming of epigenetic marks inherited from sperm and oocytes. This resetting is fundamental for establishing totipotency, yet certain epigenetic information, most prominently genomic imprints (but also other loci) must resist this wave of reprogramming to ensure correct embryonic development. The balance between erasure and inheritance is therefore both highly specific and indispensable for viability.
We and others have identified the transcriptional co-repressor TRIM28/KAP1 as a key factor in safeguarding these resistant epigenetic marks. TRIM28 is recruited to defined genomic sites by KRAB-domain zinc finger proteins (KRAB-ZFPs), the largest family of transcription factors in mammals, where it nucleates complexes of histone and DNA-modifying enzymes. This targeting in oocytes and early embryos establishes protective chromatin states that ensure faithful transmission of essential epigenetic information across generations.
The remarkable expansion of KRAB-ZFPs is thought to reflect an evolutionary arms race with endogenous retroviruses (ERVs) and other transposable elements. These repetitive sequences, which comprise nearly half of the mammalian genome, represent both a threat to genome integrity and a source of regulatory innovation. By binding ERVs, maternal KRAB-ZFPs and TRIM28 not only silence parasitic sequences but also shape the embryonic epigenome, influencing chromatin accessibility, transcriptional networks, and developmental trajectories.
In this presentation, I will discuss our recent efforts to unravel the molecular interplay between maternal KRAB-ZFPs, TRIM28, and their ERV targets. I will highlight how these interactions mediate selective resistance to epigenetic reprogramming, stabilize regulatory circuits during the critical preimplantation period, and ultimately contribute to the establishment of developmental potential in the early embryo.

Tuning B cell immune responses through mechanotransduction

Maria-Isabel Yuseff

Pontificia Universidad Católica de Chile

B lymphocytes possess a unique ability to generate antibody responses against invading pathogens. A key step in their activation involves the extraction and processing of antigens at the immune synapse, a process modulated by the physical properties of the antigen-presenting surface. However, the mechanistic links between mechanotransduction and antigen processing remain incompletely understood. Our studies show that B cells activated on stiff substrates engage mechanotransduction pathways that trigger the translocation of the acetylase ATAT1 from the nucleus to the cytoplasm, resulting in increased α-tubulin acetylation. This post-translational modification facilitates the release of GEF-H1 at the immune synapse, where it drives the formation of actin foci required for antigen extraction. Additionally, acetylated microtubules also enable B cells to stabilize and position lysosomes at the synapse center, thereby coupling actin-dependent extraction to antigen processing and presentation. Notably, B cells lacking ATAT1 fail to organize actin foci and lysosomes at the synaptic interface, leading to impaired antigen extraction and reduced presentation to T cells. Collectively, these findings reveal how BCR-dependent mechanotransduction induces microtubule modifications to orchestrate lysosome positioning and actin remodeling at the immune synapse.

A synthetic biology approach to illuminate the transcriptional landscape underlying circadian clock regulation and photoentrainment

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Circadian clocks are based on transcriptional-translational negative feedback loops (TTFLs), where a positive element activates the expression of a negative one, which in turn feeds back to repress its own transcription. In Neurospora crassa, the White Collar Complex (WCC) and the phosphoprotein FRQ function as the positive and negative elements, respectively. The frq promoter stands out among fungal promoters: despite spanning nearly 3 kb, it appears to contain only two discrete cis-elements essential for frq clock function. These elements, the clock-box (c-box) and the proximal light-responsive element (pLRE), are both recognized by the WCC. In constant darkness, the WCC rhythmically binds the c-box, driving daily oscillations in frq expression, whereas light-activated WCC targets the pLRE, boosting frq transcription and enabling photoentrainment.
To learn about the genetic plasticity of circadian circuits, we adopted a synthetic biology approach and engineered Minimal Synthetic Oscillators (MiSOs) composed of various configurations of the c-box and pLRE. Using luciferase and frqluc fusion reporters, we systematically assessed how synthetic promoter architecture impacts rhythmicity, phase, light responsiveness, and temperature compensation. Most MiSOs preserved core circadian features, including the ability to propagate rhythms to output pathways. Light-pulse experiments revealed that promoter architecture not only dictates the direction (advance vs. delay) of phase shifts, but also modulates the oscillator's sensitivity to light duration and timing. Interestingly, comparative genomic analyses reveal natural variation in the pLRE across Neurospora species, which may reflect adaptations to distinct ecological niches. Together, our results show that variations of these cis-element configurations are sufficient to reconstruct key properties of circadian regulation even in the absence of a large fraction of frq native promoter, and that their arrangement finely tunes phase, amplitude, and environmental responsiveness. MiSOs offer a versatile platform for dissecting transcriptional control in biological oscillators and for reprogramming clock function.
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Metamorphic proteins and how to study them: RfaH as a quintessential example

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A recently described class of metamorphic proteins is able to fold-switch between two native states to encode or regulate different biological functions. RfaH, a member of the universally conserved family of transcription factors NusG, is a quintessential example due to its all-α to all-β fold-switch of a whole protein domain to regulate its function.
RfaH and other metamorphic proteins constitute a challenge when it comes to elucidate their molecular mechanisms using experimental methods, and AI-guided protein structure prediction methods such as AlphaFold2 (AF2) only predict one of their two states.
Using RfaH as a case study, we will show how the use of simplified structure-based models and molecular dynamics unveils the refolding pathways of RfaH both in isolation and when bound to RNA polymerase. We will also demonstrate how the use of local energetic frustration across protein sequences in a multiple sequence alignment (MSA) and AF2 predictions of alanine scanning mutants aid in identifying key residues involved in its fold-switch behavior, some of which we have experimentally validated.
Finally, reasoning that all the information controlling the fold-switch of RfaH is coevolution-encoded, we implemented an iterative single position MSA masking method in AF2 to perturb specific coevolutionary signals, termed AlphaMask, that enables exploration of the conformational landscape of RfaH and the effect of mutations in changing this landscape.
These results have applications beyond metamorphic proteins, such as the study of key residues that enable conformational changes in transmembrane proteins and domain motions required for catalytic activity in several enzymes.

Tension-driven transitions in embryo development

Miguel Concha

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The earliest stages of animal development are critical, as they establish the fundamental body plan of the embryo. Among vertebrates, annual killifish display a striking departure from canonical early developmental programmes, having evolved a distinctive strategy to withstand extreme, drought-prone environments. In contrast to zebrafish, whose embryonic cells follow a deterministic programme largely governed by maternal cues, annual killifish embryos depend extensively on self-organisation. Their development begins with a dispersed population of cells exhibiting random migratory behaviour, which subsequently transitions into coordinated, directional movements culminating in cellular aggregation—the point at which embryogenesis is initiated. The mechanisms underlying this crucial developmental transition remain poorly understood. Here, using light-sheet fluorescence microscopy, quantitative image-based analyses, and assessments of actomyosin cytoskeletal dynamics, we show that the dispersion–aggregation shift in the annual killifish Argolebias nigripinnis is tightly coupled to tension-mediated mechanical changes in the extra-embryonic environment, particularly those associated with epiboly—a morphogenetic movement that enables extra-embryonic tissues to engulf the yolk. These findings underscore the pivotal role of physical forces and interactions with the extra-embryonic milieu in orchestrating self-organising events that drive the onset of vertebrate embryogenesis.
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Kissing X chromosomes specifies sex-specific gene expression patterns in flies

Benjamin Prud'homme

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My lab studies the mechanisms underlying the formation and evolution of morphological and behavioral traits between Drosophila species. Our focus is on two experimental systems: the development and evolution of wing pigmentation patterns, and the egg-laying behavior.
Regarding wing pigmentation pattern evolution, we are investigating the regulation of the yellow gene in Drosophila biarmipes, a species that has evolved male-specific wing pigmentation spots. Specifically, we are interested in the mechanism responsible for the sexually dimorphic yellow expression in the wing. We have recently discovered that the difference in yellow expression between the sexes is controlled by transvection, a regulatory interaction between two alleles. Since the yellow gene is linked to the X chromosome, this interaction can only occur in XX females, and not in XY males. This interallelic interaction results in the sexually dimorphic regulation of yellow. Using this experimental system, we are studying how transvection works, focusing particularly on how the alleles find each other in the nuclear space and how their physical proximity affects their regulation.
We hypothetize that other X-linked genes are also sexually regulated by transvection, rather than by the canonical sex determination pathway. We are searching for these genes, particularly in the adult brain.

Flash talks

I wanna dance with some(anti)body: A role for TANGO1 in antibody secretion

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Plasma cells secrete thousands of antibodies per second during the humoral immune response, placing extraordinary demands on the secretory pathway. This is made possible by the tailored expansion of the endoplasmic reticulum (ER) and Golgi, alongside elevated levels of proteins involved in secretion. The predominant antibody isotypes released are IgG and IgM, with IgM typically forming pentamers approximately 45 nm in diameter. The large size and abundance of IgM pentamers strain the secretory pathway, as each COPII vesicle can carry only a limited number, making sustained high-level secretion challenging. TANGO1 has been identified as a key COPII adaptor that supports the generation of oversized vesicles necessary for collagen trafficking. By preventing the coupling of the inner and outer COPII coats, it delays Sar1 activation and membrane scission, allowing the carrier to expand further before detaching from the ER.
Given the capacity of TANGO1 to enable the formation of large transport carriers, we evaluated whether it might play a role in promoting enhanced secretory demands of plasma cells. To investigate the role of TANGO1, we isolated primary B cells from mouse splenocytes and differentiated them in vitro into antibody-secreting plasma cells. We observed a significant upregulation of TANGO1 during plasma cell differentiation by immunofluorescence microscopy, which accumulated closely to sites where IgM was located within the early secretory pathway. Accordingly, plasma cells with diminished expression of TANGO1 displayed an accumulation of IgM within the ER, measured by increased colocalization with the ER marker calnexin.
Our results suggest that plasma cells increase TANGO1 to enable the export of antibodies from the ER via large carriers, thereby supporting the high secretion rate.

Exercise suppresses necroptosis and preserves axonal integrity and cognitive function in the aging brain

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Physical exercise ameliorates age-related cognitive decline and neuroinflammation, but the underlying mechanisms remain unclear. One candidate is necroptosis, a pro-inflammatory cell death pathway that becomes increasingly active in the aging brain and has been linked to age-associated neuroinflammation and neurodegeneration. Here we show that long-term voluntary exercise in aged mice suppresses hippocampal necroptotic signaling, accompanied by reduced neuroinflammation and preserved axonal integrity. Exercised aged mice exhibited lower activation of necroptosis mediators (RIPK3, MLKL) in hippocampal neurons, decreased microglial activation and pro-inflammatory cytokine expression, and improved hippocampus-dependent memory relative to sedentary controls. Proteomic analyses revealed that exercise restored synaptic plasticity and cytoskeletal-related protein expression in the aged hippocampus to a more youthful profile, similar to that of necroptosis-deficient (MLKL knockout) aged mice. Mechanistically, serum from sedentary aged mice, but not from exercised peers, induce RIPK3-dependent necroptosis and axonal degeneration in cultured neurons. Conversely, aged mice lacking RIPK3 or in mice with neuronal RIPK3 knockdown showed preserved axonal architecture and memory performance comparable to exercised mice. Together, our findings demonstrate that exercise mitigates a necroptosis-driven degenerative cascade in the aging brain, preserving structural connectivity and cognitive function, and highlight necroptotic signaling as a modifiable target to promote healthy brain aging.

A key INO2 allele boosts ethanol resistance in industrial *Saccharomyces cerevisiae*

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Ethanol toxicity is a major bottleneck for industrial Saccharomyces cerevisiae, reducing cell growth, fermentation efficiency, and overall yields. This study investigated the molecular mechanisms underlying ethanol tolerance in three previously characterized industrial strains with distinct ethanol resistance levels and membrane lipid compositions. The bioethanol production strain AJ4 exhibits high ethanol tolerance and a highly adaptable membrane; the wine strain MY3 shows moderate tolerance with intermediate membrane plasticity; and the agave fermentation strain MY26 displays low ethanol tolerance and more rigid, less adaptable membranes.

To explore the molecular basis of these phenotypes, we combined transcriptomic profiling and phenotypic characterization to capture dynamic gene expression responses under ethanol stress. Our analyses revealed that the tolerant AJ4 strain strongly upregulated genes involved in lipid remodeling, particularly ergosterol and phospholipid biosynthesis, enabling more effective membrane adaptation to ethanol. Crucially, AJ4 carried a unique INO2 allele with two amino acid substitutions (V263I and H86R) in the Ino2p transcription factor. Functional validation using CRISPR-Cas9 demonstrated that reverting these substitutions to the wild type significantly reduced ethanol tolerance and disrupted expression of lipid biosynthesis genes, confirming the pivotal role of Ino2p in regulating membrane homeostasis under ethanol stress.

These findings demonstrate that ethanol tolerance is a complex, multifactorial trait shaped by transcriptional regulation of lipid metabolism and interactions with strain-specific genomic backgrounds. In tolerant strains, ergosterol enrichment, balanced phospholipid composition, and fatty acid desaturation collectively modulate membrane integrity and fluidity, helping cells mitigate ethanol-induced damage. Our results also support a nuanced model in which localized membrane microdomains integrate rigidity and fluidity, maintaining cellular homeostasis in high-ethanol environments.

By identifying INO2 as a key genetic determinant of ethanol tolerance, this study not only provides fundamental insight into yeast stress biology but also offers actionable targets for the rational engineering of more robust industrial strains.

Meta-transcriptomic dissection of drought-responsive networks reveals directional transcription factor control in grapevine and hybrid rootstocks

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Drought events pose a significant challenge to Vitis vinifera, a cornerstone of global viticulture and one of the world's most economically important crops, with nearly all wine-producing regions located in temperate zones. To combat the adverse effects of drought, understanding and enhancing grapevine drought tolerance is imperative. Over the past 15 years, vast amounts of publicly available transcriptomic data have accumulated, providing an opportunity to explore the genetic basis of stress resistance. In this study, we performed a meta-transcriptomic analysis to identify consistently differentially expressed genes (DEGs) by drought in V. vinifera and two hybrid rootstocks (M4 and 101-14).
From 23 drought-control comparisons, we identified a core set of 4,617 drought-responsive genes that were consistently upregulated across multiple experimental conditions. Of these, 2,563 were up-regulated, while 2,054 were down-regulated genes. This core gene set was used to construct gene regulatory networks (GRNs), which incorporated genome-wide transcription factor (TF) binding motif analysis and machine learning techniques. We identified key TFs, including Abscicid-Acid-Responsive Element Binding Factor (ABF2) and a HMGbox domain protein, as central regulators within the network. Importantly, we found that upregulated TFs predominantly activate upregulated targets, while downregulated TFs are mainly associated with repression of downregulated genes. Moreover, the network exhibits hierarchical structure among abscisic acid (ABA)-related TFs, with families such as AP2/ERF, bZIP, MYB, and bHLH operating at distinct regulatory levels. Some TFs act as central hubs coordinating broad regulatory programs, while others likely contribute to more specific branches of the drought response. These findings offer novel insights into the transcriptional control of drought tolerance in grapevine and provide valuable targets for future breeding and biotechnological strategies aimed at improving stress resilience.

Structure-based polypharmacology of ion channels and its application to atrial fibrillation

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The regulation of cardiac function relies on ion channels. Disruptions in ion channel activity can result in irregular cardiac events, such as atrial fibrillation (AF). Potassium channels hKv1.5 and hTASK-1, along with the sodium channel hNav1.5, serve as therapeutic targets for AF due to their involvement in the disease. A contemporary drug development strategy, polypharmacology, presents an approach to tackling AF by addressing multiple targets simultaneously. This involves designing multi-target-directed ligands (MTDLs). Local anesthetic (LA) agents such as ropivacaine, bupivacaine, and lidocaine are known for their ability to interact with and inhibit these ion channels. To examine how LAs bind to their specific sites, alanine scanning mutagenesis was performed to identify the binding sites of ropivacaine and bupivacaine in hKv1.5. Additionally, molecular docking analyses were conducted for ropivacaine and bupivacaine in Kv1.5, lidocaine in Nav1.5, and bupivacaine in hTASK-1 using previously established binding site data. To integrate this structural knowledge into MTDL design, two distinct strategies were employed. The first utilized the pharmacophore model of LAs to guide the synthesis of new compounds that retain key pharmacophore characteristics. These compounds were then ranked based on molecular docking and MM-GBSA energy calculations. The second strategy applied the LA pharmacophore as a filtering criterion for the FDA database, generating a library of potential drug candidates. Then, LA-ion channel systems were subjected to Molecular Dynamics Simulations to characterize and compare these LA binding sites based on their chemical and structural attributes. Using these insights, a novel computational framework was developed to establish a common LA-binding pattern, termed a receptophore, across these ion channels. A virtual screening process guided by the receptophore was then executed using the previously generated drug library. The most promising

candidates identified through both approaches underwent electrophysiological testing, ultimately leading to the discovery of new MTDLs.

Molecular memory in response to fluctuations in nitrate availability in *Arabidopsis thaliana*

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Plants integrate environmental cues and can respond in an optimized manner to future environmental challenges based on prior experiences, a phenomenon known as “memory”. While well-studied in various (a)biotic-stress contexts, its role in response to fluctuating nutrient-availability remains unexplored. Here, we investigated whether Arabidopsis thaliana plants have a “nutritional-memory” that modulates their responses to fluctuating nitrate-availability, the primary N-source in aerobic soils.
First, we tested whether prior exposure to N-deficiency modulates plant responses to nitrate-treatments. Primed-plants displayed longer primary-and-lateral roots than unprimed-plants, adopting a “foraging”-strategy to optimize nitrate-interception, whereas unprimed-plants suppressed root elongation, consistent with a “survival”-strategy. This altered response to a triggering-stimulus constitutes a memory phenotype. Despite potential resource allocation costs incurred by memory, primed-plants accumulated greater total, shoot-and-root biomass than unprimed plants after triggering. A reduced shoot-to-root ratio in primed-plants indicated preferential investment in root growth, while still maintaining higher shoot biomass than unprimed plants. Interestingly, nitrate-signaling, rather than internal N-status, may drive this memory-phenotype, as total-N content remained unchanged between primed-and-unprimed plants.
Notably, memory influences Nitrogen Use Efficiency (NUE), as primed-plants exhibited higher NUE post-triggering. In addition, primed-plants showed enhanced nitrate-uptake during the recovery-phase, suggesting that priming improves nitrate-absorption upon re-exposure to the nutrient.
RNA-seq analysis demonstrates that, during recovery, primed-plants exhibit higher transcript levels of prototypical nitrate responsive-and-signaling genes, including high-affinity nitrate-transporters and their transcriptional regulators, which correlated with their enhanced uptake-capacity. Interestingly, transcript levels of nitrate-assimilation related genes were also

upregulated in primed-plants, suggesting priming may enhanced nitrate-assimilation efficiency.
Finally, our systems biology regulatory network analysis uncovered several key regulatory hubs potentially orchestrating memory, and ongoing mutant analyses aim to validate their role. Overall, our results suggest that plants can retain a form of nutritional-memory, which enhances their ability to adapt to fluctuating nutrient conditions.

Transcriptional reprogramming drives cold adaptation during long-term starvation in *Saccharomyces eubayanus*

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Understanding how microorganisms endure prolonged periods of low temperature is a fundamental question in biology. Saccharomyces eubayanus, the most cryotolerant species of its genus and the wild parent of lager yeast, represents an outstanding model to address this question. Its natural Patagonian habitat is characterized by long, cold winters, imposing strong selective pressures for survival under sustained cold and nutrient scarcity. To mirror these conditions, we investigated whether the adaptive strategy of S. eubayanus relies on the selection of stable genetic mutations or on a more plastic physiological reprogramming.
To test this, an S. eubayanus strain (H216.1) was aged at 4°C for 60 days. Aged isolates exhibited significantly enhanced growth and freeze-thaw viability compared to the parental strain. Whole-genome sequencing of these adapted isolates revealed a low number of single nucleotide polymorphisms, suggesting that the accumulation of point mutations is not the primary driver of the phenotype. However, transcriptomic analysis uncovered a profound and coherent reprogramming of gene expression. This rewiring was characterized by a robust upregulation of genes involved in mitochondrial energy production—including oxidative phosphorylation and ATP synthesis—and a concurrent downregulation of costly anabolic pathways, such as amino acid biosynthesis. This adapted state was also supported by the overexpression of canonical stress-response genes, including molecular chaperones (HSP26, HSP104) and the master regulator MSN4.
In conclusion, our results demonstrate that the superior fitness acquired by S. eubayanus during long-term cold exposure is not primarily explained by the selection of new genetic variants. Instead, the dominant molecular mechanism is an extensive transcriptional reprogramming that shifts the cellular economy towards a highly efficient, resilient state of enhanced mitochondrial respiration and stress defence, providing a clear physiological basis for survival in its challenging native environment.

Regulated IRE1-dependent decay maintains cDC1 differentiation, survival, and function

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Effective antitumor and antiviral immunity relies on the optimal function of conventional type 1 dendritic cells (cDC1), whose biology is tightly regulated by the Unfolded Protein Response (UPR). Among its sensors, inositol-requiring enzyme 1 (IRE1) is the most conserved, linking endoplasmic reticulum (ER) homeostasis to immune function through two outputs: splicing of XBP1 mRNA and regulated IRE1-dependent decay (RIDD) of RNA substrates. While IRE1–XBP1 signaling has been implicated in cDC1 development, survival, and function, the physiological role of RIDD in tissues remains poorly defined.
We investigated the contribution of physiological RIDD to cDC1 survival and pro-inflammatory responses using conditional knockout and knock-in mouse models: CD11c-Cre XBP1fl/fl (lacking XBP1 in cDCs, with hyperactive RIDD), CD11c-Cre IRE1fl/fl (lacking the IRE1 RNase domain, abolishing both RIDD and XBP1 splicing), and a novel IRE1A/A line carrying the S729A mutation, which selectively disables RIDD while preserving XBP1 activity. Immune cell populations were also analyzed in the lungs and intestines of IRE1A/A mice.
Our results show impaired in vitro differentiation and reduced survival of IRE1A/A cDC1 derived from bone marrow precursors compared with wild-type (WT) cells. Conversely, cDC1 with hyperactive RIDD displayed enhanced resistance to staurosporine-induced apoptosis. In tissues, IRE1A/A mice exhibited decreased frequencies of lung cDC1, and reduced cDC1 and macrophages in the small intestine. These findings are consistent with the survival defects observed in vitro and suggest a survival dependence on RIDD for maintaining cDC1 populations in tissues. Functional assays further revealed altered microRNA profiles in IRE1A/A cDC1, including elevated expression of the pro-inflammatory miR-155 and reduced levels of its targets, such as C-fos and Ship1. Unexpectedly, Poly I:C–stimulated IRE1A/A cDC1 produced lower IL-12 and TNF-α, suggesting additional compensatory mechanisms.
These findings identify physiological RIDD as a basal, XBP1-independent mechanism sustaining cDC1 homeostasis, promoting survival while restraining inflammatory responses, potentially via microRNA modulation.

It's all about effective communication: IP3, GPCRs and microtubules as key players in long-range endothelial cell communication

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Every blood vessel in your body, from the smallest capillary up to the largest artery, is lined with endothelial cells. These cells perform many essential functions, such as regulating blood pressure, vascular permeability and vascular tone. Intercellular communication and vessel function are inextricably linked; the endothelium regulates nearly all aspects of vascular function through rapid intercellular communication that coordinates cellular activity across spatial scales. Central to this communication is Ca^{2+} signalling, which governs both intra- and intercellular processes via production of Ca2+ events and waves. Despite it's importance, the mechanisms governing intercellular Ca2+ signalling in the vascular endothelium are poorly understood.
In intact resistance arteries, precision photolysis of IP3 combined with high--resolution mesoscale Ca2+ imaging, targeted drug application, and advanced analytical techniques, was used to determine the mechanisms underlying regenerative propagation of IP3-evoked Ca2+ signals in the endothelium. Here, we show that intercellular Ca2+ waves arises from regenerative IP3-mediated IP3 release, and that their propagation is counterintuitively Ca2+ independent. For the first time, we show that elevated IP3 in the initiating cell triggers a noncanonical inside-out signaling mechanism that leads to transcellular activation of a Gαq/11-coupled receptor in a neighboring (receiving) cell. This, in turn, initiates canonical outside-in signaling via PLC, leading to the hydrolysis of PIP2 and production of IP3. We also show for the first time that these intercellular Ca2+ waves are dependent on an intact microtubule network; microtubule dissassembly constrained Ca2+ wave to the photolysis region, and inhibition of molecular motors reduced propagation extent.
Our findings uncover previously unrecognized mechanisms of endothelial communication, highlighting a novel framework for intercellular coordination in the vascular endothelium.

Ecological filtering and diversity patterns in Sub-Antarctic yeast communities under warming conditions

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Most ecosystems on Earth depend on dynamic microbial communities that play a central role in environmental nutrient cycling. In this context, there is growing concern that climate change may profoundly impact the intricate networks formed by microbial species linked through complex biochemical interactions. Due to their short generation times and high genetic diversity, microbial populations serve as excellent models for studying how abiotic factors, such as temperature, influence community composition.
In this study, we used a metabarcoding approach to investigate the response and dynamics of fungal communities from Patagonian soils subjected to temperature shifts. Rhizosphere samples (n=5) were collected from Karukinka Natural Park and incubated at temperatures ranging from 10°C to 35°C for two months. DNA was extracted from each sample before (T0) and after incubation (T2-month), and the fungal ITS region was amplified for community profiling. Our results indicate that the five most abundant fungal families across samples were Aspergillaceae, Pseudeurotiaceae, Leptodontidiaceae, Mortierellaceae, and Myxotrichaceae, encompassing diverse ecological roles such as saprotrophs, ectomycorrhizal fungi, and ericoid mycorrhizae. While these families appeared consistently across temperature treatments, analysis at the genus level revealed distinct phylogenetic profiles emerging under different thermal regimes.
Importantly, we observed that increasing temperature was associated with a higher likelihood of detecting thermotolerant fungal genera, including members of the genus Candida, which includes species with known pathogenic potential. These findings underscore how rising temperatures may reshape microbial communities in ways that not only alter ecosystem functions but also increase the presence of potential opportunistic pathogens.

Poster presentations

Cell-scale investigation of cytoskeletal and nuclear mechanical responses in B cells during immune synapse formation

Pablo Aceiton , Maria Isabel Yuseff , Isidora Riobo , Teemly Contreras , Nelson Barrera , Jheimmy Diaz , Romina Ulloa

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B lymphocytes are essential components of the adaptive immune system, responsible for antibody production and antigen presentation. Upon recognition of immobilized antigens by the B-cell receptor (BCR), B cells form an immune synapse (IS) where antigen extraction, processing, and presentation occur. Synapse formation is influenced by the physical properties of the antigen-presenting surface, which B cells sense and interpret through mechanotransduction. Our previous work showed that these cues propagate through the cytoskeleton, influencing lysosome dynamics and nuclear positioning. Central to this mechanotransduction is the reorientation and deformation of the nucleus away from the IS, a process facilitated by the LINC complex proteins Nesprin-1 and SUN1/2. As a mechanosensitive organelle, the nucleus adjusts its position and morphology according to the properties of the antigen-bearing surface, aligning the nuclear groove with the synaptic membrane where the microtubule-organizing center (MTOC) and lysosomes dock, thereby promoting efficient antigen extraction. In this study, we investigated how integrin LFA-1 engagement of ICAM-1 drives this mechanotransductive pathway. We found that ICAM-1–dependent adhesion increases spreading and cortical tension and is accompanied by robust nuclear remodeling: reduced sphericity, increased ellipticity, and alignment of the nuclear groove toward the synaptic plane. These architectural changes correlate with centrosome docking and polarized lysosomal trafficking. Functionally, ICAM-1 significantly enhances DQ-OVA activation on rigid substrates, linking integrin-mediated adhesion to measurable antigen degradation. Disruption of the LINC complex (Nesprin-1 or SUN1 perturbation) abrogates nuclear repositioning and impairs antigen processing, establishing the necessity of nucleo-cytoskeletal coupling.
Together, our findings identify LFA-1–ICAM-1 as a primary regulator that couples extracellular adhesion to nuclear mechanosensing via LINC, organizing intracellular polarity and optimizing antigen processing at the B-cell immune synapse.

Changes in LSD1 isoforms as a mechanism for the establishment of compulsive behavior in an OCD model

Pilar Aguilera Maturana, Bastián I. Rivera and María Estela Andrés Coke

Pontificia Universidad Católica de Chile

Compulsive behavior consists in repetitive acts that an individual feels compelled to perform despite being aware that such acts comprise negative consequences. These behaviors are central to several psychiatric disorders, including obsessive-compulsive disorder (OCD) and addiction. A well-characterized animal model used to study this phenomenon is the one described by Szechtman et al. (1998), in which compulsive checking behavior is induced through repeated administration of the selective D2/D3 dopamine receptor agonist, Quinpirole (QNP). A wide range of neurochemical and behavioral aspects of compulsiveness have been described in this model. Nonetheless, the molecular basis by which dopaminergic dysregulation contributes to compulsive behavior development remains unclear. Lysine Specific Demethylase 1 (LSD1) is an enzyme that demethylates H3K4me1/2 epigenetic mark, acting as a transcriptional corepressor. LSD1 has two main isoforms resulting from alternative splicing, a neuron-specific variant (nLSD1) which retains a 12-bp mini-exon (E8a), important for neuronal plasticity, and a ubiquitously expressed isoform (uLSD1). Notably, nLSD1 exhibits diminished transcriptional repressor activity, pointing to a relevant role for uLSD1/nLSD1 variations in the transition between transcriptionally repressed and active states. In line with this, it has been observed that uLSD1/nLSD1 ratio changes in response to QNP treatment within the mesolimbic system, suggesting a mechanism that contributes to the establishment of neuronal response observed in this OCD animal model's dopaminergic neurons, underpinning the development of compulsive behavior.

Control of lysosomal function by the RNase activity of IRE1 in conventional type 1 dendritic cells

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The unfolded protein response (UPR) is a cellular mechanism that maintains endoplasmic reticulum (ER) proteostasis under cellular stress. Among its sensors, IRE1 plays major roles in controlling the function of conventional type 1 dendritic cells (cDC1), a myeloid subset specialized in driving antiviral and antitumor T cell responses.
Beyond its role in splicing XBP1 mRNA, the endoribonuclease activity of IRE1 mediates selective degradation of mRNAs with diverse functions via Regulated IRE1-dependent decay (RIDD). Intriguingly, several RIDD substrates are linked to lysosomal biogenesis.
We previously identified Lamp1 mRNA, a canonical marker of lysosomal maturation, as a putative RIDD target in cDC1s. However, the consequences of RIDD-mediated Lamp1 degradation on lysosomal biology remain unexplored.
We determined the role of RIDD in lysosomal biology by studying cultured cDC1s derived from conditional knockout mouse models: CD11c-Cre x XBP1fl/fl (lacking XBP1, exhibiting active RIDD), CD11c-Cre x IRE1fl/fl (lacking the IRE1 RNase domain, preventing RIDD activation), and a novel IRE1 S729A knock-in model, which selectively disables RIDD while preserving XBP1 splicing. We further analyzed human monocyte-derived DCs (moDCs) treated with the IRE1 RNase inhibitor STF-083010. LAMP1 expression and lysosomal function were analyzed using confocal microscopy, flow cytometry, and qPCR.
Our results show that cDC1s with heightened RIDD activity exhibit reduced LAMP1 expression compared to wild-type cells. These cells exhibited less acidic lysosomes and decreased lysosomal enzymatic activity compared to control cells, underscoring a functional impact of RIDD on lysosomal function. Consistently, inhibition of IRE1 RNase activity in human moDCs led to accumulation of LAMP1 protein, supporting a conserved RIDD-mediated regulation of lysosomal competence across species.
Our study uncovers a novel role for RIDD in regulating lysosomal homeostasis in DCs through modulation of Lamp1 levels and underscores a previously unrecognized axis of lysosomal control with potential implications for manipulating DC functions in immunotherapeutic settings.

It's all about effective communication: IP3, GPCRs and microtubules as key players in long-range endothelial cell communication

Charlotte Buckley [1, 2], Xun Zhang [2], Matthew Lee [2], Calum Wilson [2], John McCarron [2]

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Every blood vessel in your body, from the smallest capillary up to the largest artery, is lined with endothelial cells. These cells perform many essential functions, such as regulating blood pressure, vascular permeability and vascular tone. Intercellular communication and vessel function are inextricably linked; the endothelium regulates nearly all aspects of vascular function through rapid intercellular communication that coordinates cellular activity across spatial scales. Central to this communication is Ca^{2+} signalling, which governs both intra- and intercellular processes via production of Ca2+ events and waves. Despite it's importance, the mechanisms governing intercellular Ca2+ signalling in the vascular endothelium are poorly understood.
In intact resistance arteries, precision photolysis of IP3 combined with high--resolution mesoscale Ca2+ imaging, targeted drug application, and advanced analytical techniques, was used to determine the mechanisms underlying regenerative propagation of IP3-evoked Ca2+ signals in the endothelium. Here, we show that intercellular Ca2+ waves arises from regenerative IP3-mediated IP3 release, and that their propagation is counterintuitively Ca2+ independent. For the first time, we show that elevated IP3 in the initiating cell triggers a noncanonical inside-out signaling mechanism that leads to transcellular activation of a Gαq/11-coupled receptor in a neighboring (receiving) cell. This, in turn, initiates canonical outside-in signaling via PLC, leading to the hydrolysis of PIP2 and production of IP3. We also show for the first time that these intercellular Ca2+ waves are dependent on an intact microtubule network; microtubule dissassembly constrained Ca2+ wave to the photolysis region, and inhibition of molecular motors reduced propagation extent.
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PTPsigma regulates amacrine cell positioning and synapse localization in the developing and mature retina

Eliseo N. Bustos , Monserrat Irarrázabal Figueroa , Marcela Paz Gonzalez , Evelyn C. Avilés

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Functional neural circuit assembly depends on coordinated cell migration, neuron positioning and synapse formation and localization. Tissue polarity proteins direct these processes by orienting cells in the complex environment of the developing tissue. The Type-IIA Receptor-type Protein Tyrosine Phosphatase (RPTP) family of proteins have been identified as synapse organizers. Additionally, the fly ortholog of PTPsigma, a member of this family, directs cell protrusions during collective cell migration. The implication of PTPsigma in both synapse formation and cell migration makes it an ideal candidate to regulate tissue polarity establishment during central nervous system (CNS) development.
The retina is a highly organized neural circuit that serves as a powerful model for studying CNS development. Different neurons, such as amacrine cells, must migrate and reach the correct final position in the laminated retina, and subsequently develop synapses. Defects in these processes often result in abnormal retinal lamination. The aim of this work is to assess the role of PTPsigma in the organization of the retina and to elucidate whether earlier developmental defects in amacrine cell migration and positioning result in abnormal lamination in the mature system. The methodology consists of immunofluorescence analysis of amacrine cell positioning, and synapse localization in Ptprs-/- (PTPsigma knock-out) mouse retina compared to Wild-type littermates. The results show that PTPsigma is not necessary for amacrine cell migration in early development, but it does impact amacrine cell positioning and synapse localization in the developing and mature retina, possibly in an activity-dependent manner.

Molecular memory in response to fluctuations in nitrate availability in *Arabidopsis thaliana*

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Plants integrate environmental cues and can respond in an optimized manner to future environmental challenges based on prior experiences, a phenomenon known as “memory”. While well-studied in various (a)biotic-stress contexts, its role in response to fluctuating nutrient-availability remains unexplored. Here, we investigated whether Arabidopsis thaliana plants have a “nutritional-memory” that modulates their responses to fluctuating nitrate-availability, the primary N-source in aerobic soils.
First, we tested whether prior exposure to N-deficiency modulates plant responses to nitrate-treatments. Primed-plants displayed longer primary-and-lateral roots than unprimed-plants, adopting a “foraging”-strategy to optimize nitrate-interception, whereas unprimed-plants suppressed root elongation, consistent with a “survival”-strategy. This altered response to a triggering-stimulus constitutes a memory phenotype. Despite potential resource allocation costs incurred by memory, primed-plants accumulated greater total, shoot-and-root biomass than unprimed plants after triggering. A reduced shoot-to-root ratio in primed-plants indicated preferential investment in root growth, while still maintaining higher shoot biomass than unprimed plants. Interestingly, nitrate-signaling, rather than internal N-status, may drive this memory-phenotype, as total-N content remained unchanged between primed-and-unprimed plants.
Notably, memory influences Nitrogen Use Efficiency (NUE), as primed-plants exhibited higher NUE post-triggering. In addition, primed-plants showed enhanced nitrate-uptake during the recovery-phase, suggesting that priming improves nitrate-absorption upon re-exposure to the nutrient.
RNA-seq analysis demonstrates that, during recovery, primed-plants exhibit higher transcript levels of prototypical nitrate responsive-and-signaling genes, including high-affinity nitrate-transporters and their transcriptional regulators, which correlated with their enhanced uptake-capacity. Interestingly, transcript levels of nitrate-assimilation related genes were also upregulated in primed-plants, suggesting priming may enhanced nitrate-assimilation efficiency.
Finally, our systems biology regulatory network analysis uncovered several key regulatory hubs potentially orchestrating memory, and ongoing mutant analyses aim to validate their role. Overall, our results suggest that plants can

retain a form of nutritional-memory, which enhances their ability to adapt to fluctuating nutrient conditions.

Comparison of pupation behavior in socially isolated and group-reared *Drosophila melanogaster* larvae

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Introduction:
Pupation behavior is crucial for the survival of Drosophila melanogaster larvae, as they must select a safe environment to complete metamorphosis and avoid hostile conditions. Social experiences during development may influence this decision-making process, particularly when larvae face toxic environments such as those containing ethanol.
Methods:
Larvae from an isomaternal line of the Canton-S strain of D. melanogaster were raised under two conditions: (i) social isolation (one egg per 4-cm Petri dish with Burdick medium), and (ii) group condition (30 eggs per dish). At 96 hours of development, a single larva was placed at the center of a 4-cm Petri dish divided into two halves: one containing Burdick medium with 10% ethanol and the other with plain medium. The final location of pupation was recorded.
Results:
Group-reared larvae showed a preference for pupating on the 10% ethanol side, while isolated larvae avoided the ethanol zone and preferred to pupate on the non-ethanol side.
Discussion:
These findings suggest that social isolation during larval development modulates pupation decisions in the presence of environmental toxicity. Isolated larvae appear to exhibit stronger avoidance responses to aversive stimuli, potentially reflecting altered environmental perception, risk tolerance, or adaptive decision-making mechanisms.

Effects of social isolation on the response to ethanol exposure in *Drosophila melanogaster* larvae

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Introduction:
Social isolation during early development can alter sensitivity and behavioral responses to environmental stimuli in model organisms. This study aimed to examine how the lack of social interaction affects the response of Drosophila melanogaster larvae to a toxic substance, ethanol at 10% concentration, commonly used as an aversive or reinforcing agent.
Methods:
Third-instar larvae from an isomaternal line of the Canton-S strain of Drosophila melanogaster were raised under two conditions: (i) social isolation (one larva per 4-cm Petri dish with Burdick medium), and (ii) group condition (30 larvae per identical dish). At 72 hours of development, individual larvae were tested in a 4-cm dish divided into two halves: one containing 10% ethanol agar, and the other containing plain agar. Each larva's location was recorded every minute for 10 minutes (N=30 per group).
Results:
Socially isolated larvae showed a clear preference for the ethanol zone, whereas group-reared larvae preferred the non-ethanol zone. Additionally, isolated larvae exhibited higher recurrence in choosing the ethanol area and had difficulty discriminating between the two zones, suggesting alterations in sensory processing or decision-making mechanisms.
Discussion:
These findings indicate that early social isolation modulates larval preference behavior toward a chemically aversive stimulus. This may reflect changes in

sensory perception, motivational systems, or decision-making processes. The larval model of Drosophila offers a valuable tool for investigating the neurobiological effects of early social deprivation

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From polar to temperate: Genomic signatures of warm-range shifts in notothenioids

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Notothenioid fishes (Notothenioidei) are predominantly found in Antarctic and subantarctic regions. Antarctic waters are cold and oxygen-rich with relatively stable temperatures, whereas subantarctic and temperate environments are warmer, more seasonally variable, and less oxygenated. The Antarctic radiation of notothenioids was facilitated by key innovations and adaptations. However, prolonged environmental stability in Antarctica likely relaxed selection on functions that are otherwise conserved in vertebrates living in more variable conditions. Despite this history, multiple notothenioid lineages have independently recolonized subantarctic and temperate regions, and the adaptations enabling these shifts remain unclear. To investigate the genomic basis of colonization into warmer waters, we analyzed genomes from 19 species spanning Antarctic, Antarctic/subantarctic, and subantarctic/temperate distributions. Our results indicate that positive selection associated with the colonization of the subantarctic and temperate areas is concentrated in genes involved in development, morphogenesis, and metabolism, consistent with a shared genomic signature of adaptation to warmer, less-oxygenated, more seasonal environments.

Bridging the gender gap in mental health: Correlational insights and a sensitive proposal for addressing social isolation in Chilean older people

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Background: Social isolation is a significant modifiable risk factor for cognitive decline and dementia (Livingston, G. et al., 2024). Our study on post-pandemic social isolation and loneliness in a cohort of Chilean older adults revealed critical sex-specific correlations. Women showed stronger associations between loneliness, social isolation, depression, and pandemic-related concern, while men exhibited notable links between age and social isolation and negative associations with Loneliness and pandemic-related concerns (Gierke, C., et al., 2024). These findings highlight the need for tailored interventions addressing the unique psychosocial dynamics of each gender.
Objective: To propose sensitive therapeutic strategies for managing social isolation in older adults.
Methods: A Sensitive Protocol for Social Isolation (SPSI) is proposed to guide strategies emphasizing emotional, cognitive, and social engagement tailored to the unique needs of older adults.
Results: Three principles constitute the SPSI: Equity & tailoring, Intersectionality, and Proactive Prevention. The SPSI includes single interventions (separated by sex), categorizing Clinical, Psychosocial, and Community-based. And shared interventions (men and women) including Social Prescribing, Digital Literacy, Community Resilience Initiatives, and Evaluation & Monitoring.

Conclusion: Sex-specific therapeutic strategies are essential for effectively managing modifiable risk factors like social isolation and depression in older adults. For women, addressing emotional needs through connection and support is key, while for men, interventions should focus on fostering purpose and rebuilding social roles.
These approaches not only reduce depressive symptoms but also enhance overall well-being, contributing to the prevention of long-term health risks, such as cognitive decline and dementia. Integrating these findings into public health initiatives can pave the way for more impactful mental health interventions.

Genomic and phenotypic characterization of *Saccharomyces paradoxus* isolates from introduced Quercus spp. and Fagus spp. in Chile

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Yeasts of the Saccharomyces genus are unicellular fungi broadly distributed in nature, especially in temperate forests. Saccharomyces paradoxus, a close wild relative of S. cerevisiae, is commonly associated with oak trees (Quercus spp.) primarily in Europe and North America. Its populations strongly defined by geographic boundaries and high genetic diversity, make it an excellent model for studying microbial evolution and adaptation. Although S. paradoxus has a wide distribution in the Northern Hemisphere, it is rarely found in its southern counterpart, likely due to its ecological preference for Quercus and other Fagaceae, native to the Northern Hemisphere but introduced in urban areas of central and southern Chile. This study reports the isolation and identification of S. paradoxus from bark and soil associated with Quercus spp. and Fagus spp. in five Chilean cities: Santiago, Talca, Temuco, Valdivia, and Osorno. From 86 trees sampled, 15 S. paradoxus strains were isolated alongside S. eubayanus and S. uvarum. Whole-genome sequencing and population genomics revealed that the Chilean isolates form a distinct clade closely related to the European lineage, suggesting a European origin. Phylogenetic and population structure analysis, together with estimates of population genetic parameters, support a founder effect for the Chilean

population. Phenotypic characterization further confirmed distinct growth traits compared to other global populations. This is the first report of S. paradoxus in Chile and includes the southernmost isolate of this species, contributing to the understanding of its global biogeography and the mechanisms shaping yeast distribution in novel environments.

Study of the impact of the polypyrimidine tract-binding protein on the translational activity of the IRES elements present in the sense and antisense mRNAs of HTLV-1

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Introduction: The capped sense mRNA of the human T-cell leukemia virus type 1 (HTLV-1) harbors an internal ribosome entry site (IRES) and can initiate translation via a cap-dependent or IRES-dependent mechanism. HTLV-1 also expresses two antisense transcripts, spliced and unspliced versions, which encode for two isoforms of the HBZ protein, associated with the virus's pathogenicity. The spliced HBZ mRNA (shbz) harbors an IRES. IRES activity is modulated (stimulated or decreased) by RNA-binding proteins (RBPs), termed IRES trans-acting factors (ITAFs). The polypyrimidine tract-binding protein (PTB), a well-characterized ITAF for IRESs present in the mRNAs of several viruses, binds to the HTLV-1 RNA in the region that harbors its IRES activity. Three isoforms of PTB exist (1, 2, and 4), which stimulate the activity of various IRESs differentially. This study evaluated the impact of PTB1 and PTB4 on the HTLV-1 IRES and sHBZ IRES activity.
Materials and Methods: PTB overexpression and siRNA-mediated knockdown assays were performed in HEK293T cells expressing a Renilla/Firefly luciferase bicistronic RNA, harboring the HTLV-1 IRES or sHBZ IRES in their intercistronic region.
Results: Neither PTB1 nor PTB4 overexpression significantly impacts the HTLV-1 IRES activity, although high amounts of PTB levels induced changes in sHBZ IRES activity. Endogenous PTB partial knockdown did not show significant changes in the HTLV-1 IRES or sHBZ IRES activity.
Discussion: Together, these findings indicate that PTB is not an ITAF for the HTLV-1 IRES or sHBZ IRES. This finding challenges the prevailing notion that all RBPs associated with the RNA region that harbors an IRES function as an ITAF.

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Extracellular vesicle microRNAs in preeclampsia: potential modulators of blood-brain barrier permeability via CLDN5

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Preeclampsia is a pregnancy-specific disorder characterized by hypertension and systemic complications for both mother and fetus. Although its complete pathophysiology remains unclear, the placenta is considered the main source of disease signals. Placental extracellular vesicles (EVs) are increasingly recognized as key mediators of maternal–fetal communication and are found in higher concentrations during preeclampsia compared to normal pregnancies. Their molecular cargo, including microRNAs (miRNAs), differs between these conditions. miRNAs are small non-coding RNAs that typically inhibit protein translation and thereby modulate diverse cellular processes. Among the maternal complications of preeclampsia, cerebrovascular alterations are particularly relevant, as they involve blood–brain barrier (BBB) disruption mediated by decreased expression of tight junction proteins, especially Claudin-5 (CLDN5). To explore whether EV-derived miRNAs from preeclamptic placentas may contribute to this phenomenon, we performed an integrative bioinformatic analysis. We retrieved miRNAs reported to be overexpressed in preeclamptic placental EVs, predicted miRNAs directly targeting CLDN5, and those affecting transcription factors known to regulate CLDN5 (RUNX1, CBFB, STAT1, STAT3, RELA, GTF3A, TCF3). Overlapping analyses identified five candidate miRNAs of interest: hsa-miR-370-3p, hsa-miR-526b-5p, hsa-miR-584-5p, hsa-miR-744-5p, and hsa-miR-199a-3p. These miRNAs may impair CLDN5 expression either directly or indirectly through modulation of transcriptional regulators such as RUNX1 and CBFB. Our findings support the hypothesis that EV-derived miRNAs contribute to BBB permeability alterations in preeclampsia by targeting tight junction proteins. Future experimental validation in brain endothelial cells and murine models will be required to confirm these candidates and assess their potential as biomarkers or therapeutic targets.

Systems biology of life at the limits: metagenomic, paleogenomic, and agronomic insights from the Atacama Desert

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The Atacama Desert represents a unique natural laboratory to investigate the limits of life, where organisms across multiple biological scales have evolved singular strategies to persist under extreme conditions. Our research aims to understand how biodiversity endures in these environments, from the evolutionary history preserved in sediments to the resilience of native crops. At the Salar de La Isla (Atacama Region, Chile), an ecosystem shaped by high salinity, low water availability, and extreme climatic fluctuations, we applied an integrated metagenomic–paleogenomic–biogeochemical approach. From water, soil, plant, rhizosphere, and sediment samples, we performed metabarcoding (16S, ITS, trnL/rbcL, COI) alongside geochemical and isotopic profiling. These analyses revealed a highly specialized microbial, fungal, and plant biodiversity, and enabled reconstruction of paleoenvironmental transitions and community shifts over time. This baseline contributes to evaluating the impacts of natural and anthropogenic perturbations, including lithium extraction, and opens opportunities for the biotechnological exploration of extremophiles.
In parallel, we characterized Hoffmannseggia doellii (Kulchao), a native legume traditionally consumed by indigenous peoples. This species thrives under drought, high UV radiation, and nutrient-poor soils, partly through associations with nitrogen-fixing rhizobacteria. We established reproducible protocols for its propagation (seeds, tubers, in vitro micropropagation) and carried out pilot cultivation trials in the Andean highlands under low-water and low-nitrogen conditions. Agronomic and physiological traits were monitored, while tuber analyses revealed high levels of fiber, polyphenols, antioxidant activity, and notably vitamin B12, together with favorable sensory attributes.
Together, these projects highlight the value of the Atacama Desert as a model system to explore the biology of extremes. By integrating multi-omic and systems biology approaches across distinct levels of organization, we demonstrate how both microbial communities and native plants provide

fundamental insights into adaptation and resilience in one of the most inhospitable environments on Earth.

Simulation of social presence throughout the life cycle in *Drosophila melanogaster* through chemical signals: a neurochemical-behavioral study

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Introduction:
Social isolation is an environmental stressor with significant effects on behavior and brain neurochemistry, even in model organisms such as Drosophila melanogaster. Previous studies show that perceiving social signals, even indirectly, can modulate emotional regulation, synaptic plasticity, and gene expression. This study explores whether exposure to social pheromones throughout the life cycle mitigates isolation-induced changes in serotonin and dopamine.
Objectives:
The general objective is to evaluate whether simulating social presence through pheromone-impregnated swabs reduces neurochemical alterations caused by isolation at different life stages. Specific objectives are: (1) compare serotonin and dopamine levels among isolated larvae, isolated larvae with social simulation, and socially reared larvae; (2) determine if these differences persist or change in adulthood.
Method:
A quantitative experimental design with 144 Drosophila melanogaster Canton S was implemented. Larvae were distributed into three conditions: isolation without simulation (IWS), isolation with simulation (IWSim), and normal social condition (SC). Serotonin and dopamine levels will be measured at 72

and 480 hours, while developmental timing from larva to pupa and adult will also be recorded.
Expected Results:
At 72 hours, the IWSim group is expected to show serotonin and dopamine levels similar to the SC group, suggesting effective simulation of social presence. At 480 hours, a slight decline in the effect is anticipated, reflecting habituation. Developmental timing in IWSim individuals is predicted to resemble that of the SC group.
Discussion:
This design models the perception of companionship through chemical cues, offering new perspectives for studying sociability, social placebo effects, and symbolic substitution. The approach has implications for neuroscience, social psychology, life-cycle biology, comparative ethology, and mental health, particularly in contexts where isolation and perceived support have differential effects depending on species, sex, or developmental stage. Additionally, it provides a framework for exploring non-invasive interventions against isolation.

A novel clustering-based method for automated assignment of leaf epidermal cell types in the model plant *Arabidopsis thaliana*

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Leaves are essential organs for plant survival. In the leaf epidermis, stomata regulate transpiration and gas exchange, while puzzle-shaped pavement cells provide structural and mechanical support. A population of diverse stem cells collectively known as the stomatal lineage gives rise to all stomata and at least half of the pavement cells in the leaf epidermis. Therefore, the regulation of the stomatal lineage division and its differentiation into stomata and pavement cells is critical for leaf function. The current gold standard for tracking and studying stomatal lineage development in the model plant Arabidopsis thaliana involves live-imaging microscopy and fluorescent reporter lines specific to stomatal lineage cell types. However, live-imaging is technically demanding and generating reporter lines is extremely time-

consuming in plant models. An alternative strategy involves manually assigning cell types in images obtained from assays performed at a single endpoint, using cell size, morphology, and cellular context as criteria. Since this approach is labor-intensive, it limits the number of cells that can be analyzed. Additionally, it may introduce the observer bias. Here, we validate for the first time a cell-type assignment strategy that enables the automated and unbiased classification of the entire stomatal lineage population together with its early descendants, as well as the terminal cell types, stomata and pavement cells. Applied to confocal images of the Arabidopsis thaliana leaf epidermis from endpoint assays, this method relies on the classic k-means clustering algorithm, exploiting the morphological features and cellular context of epidermal cells, without the need for reporter lines or live-imaging microscopy.

Unfolded protein response transcription factors ATF6 and XBP1s shape the immunometabolism of dendritic cells

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Dendritic cells (DCs) are professional antigen presenting cells that, upon recognition of inflammatory stimuli, undergo profound metabolic and functional reprogramming to support immune activation. As secretory cells, activated DCs face substantial endoplasmic reticulum (ER) stress, engaging the unfolded protein response (UPR), a key regulatory network safeguarding proteostasis and organelle adaptation. While the UPR is implicated in the immunogenic functions of DCs, its precise role in metabolic rewiring and the contribution of specific UPR transducers in these cells remain insufficiently understood.
Here, we investigated the immunometabolic roles of two major UPR-associated transcription factors, ATF6 and XBP1s, using a novel conditional knockout mouse model targeting these factors specifically in DCs. Bone marrow-derived DCs (BMDCs) were exposed to saturated fatty acids (SFAs), in particular palmitic acid (PA), to mimic the metabolic stress conditions associated with obesity and metabolic syndrome. Using SCENITH, a cutting-edge flow cytometry assay for single-cell metabolic profiling, we found that both SFA

exposure and the combined loss of ATF6 and XBP1 significantly reduced global protein synthesis in DCs.
Importantly, in wild-type DCs, PA exposure led to reduced glycolytic capacity and glucose dependence, accompanied by increased metabolic dependence for energy production, a metabolic shift absent in ATF6/XBP1 deficient DCs. These results indicate that a functional UPR is required for the metabolic flexibility of DCs under lipotoxic conditions. On functional level, gene expression and cytokine profiling revealed that UPR activity enhances the production of pro-inflammatory cytokines in DCs, particularly under high- SFA conditions, linking ER stress to inflammatory outputs.
Together, our findings uncovered an unappreciated role for ATF6 and XBP1s in integrating lipid-induced stress signals into the metabolic and immune programming in DCs. These insights open new avenues for targeting the UPR in DCs as a potential strategy to modulate inflammation in metabolic disorders.

XBP1s controls fatty acid oxidation and mitochondrial metabolic programs in dendritic cells and macrophages

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Professional antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, play critical roles in shaping immune responses. Thus, understanding the molecular mechanisms regulating their activation and function is of significant biomedical relevance in several diseases. Interestingly, these cells must dynamically adjust their metabolism upon recognition of pathogens or inflammatory stimuli to activate effectively, yet the molecular pathways coordinating metabolism and activation remain incompletely understood. In this regard, the unfolded protein response (UPR), particularly the IRE1/XBP1s axis, has been shown to contribute to their activation, although the functional link between IRE1/XBP1s activation and metabolism in immune cells remains poorly explored.
In this study, we identified the transcription factor XBP1s as a key regulator of the metabolic state in these immune cells. To investigate this, we analyzed their metabolic profiles at the single-cell level using SCENITH technology. Our data indicate that cells lacking XBP1s exhibit a mitochondria-independent phenotype, accompanied with a significant reduction in fatty acid oxidation

(FAO) compared to control cells. Pharmacological activation of XBP1s using the selective activator IXA4 in control cells shifted their metabolism toward enhanced FAO, along with a reduction in intracellular neutral lipid accumulation. These findings demonstrate a direct mechanistic link between XBP1s activity and FAO. Notably, this FAO-associated metabolic signature driven by XBP1s correlated with an upregulation of pro-inflammatory cytokine gene expression, thereby functionally coupling XBP1s-dependent metabolic reprogramming to inflammatory effector functions.
Overall, our results reveal a complex connection between IRE1/XBP1s and cellular metabolism in this immune cell subset, expanding our understanding of immunometabolism and proteostasis, and opening new avenues for therapeutic strategies targeting the UPR in immune-related diseases.

Optimization of metabolic networks in *Acidithiobacillus caldusT* for production of extracellular polysaccharides (EPS)

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Acidithiobacillus caldus DSM 8384T is a moderately thermophilic (37°C-45°C) Gram-negative acidophilic bacterium that lives in extremely acidic environments (pH 1 to 3), chemolithoautotrophic microorganism that plays a key role in bioleaching (Valdés et al., 2009). It obtains its energy through the oxidation of elemental sulfur (S°) compounds (RISCS) and fixates carbon through the Calvin-Benson-Bassham (CBB) cycle. To date, the complete carbon metabolism of At. caldus has not been characterized.
Genome-scale models (GEMs) describe the set of reactions that can be carried out by an organism based on information encoded in its genome. For each reaction, they include stoichiometry and gene-protein-reaction (GPR) associations, which are formulated based on genome annotation data and experimental evidence (Thiele et al., 2010). A GEM allows for the prediction of metabolic flux distributions using optimization techniques (Orth et al., 2010).

A draft genome-scale model for A. caldus DSM 8384T was built with PathwayTools (Karp et al., 2010) with a refined PROKKA (Seemann T., 2014) genome annotation as input. The obtained draft was then complemented by an orthology-based reconstruction generated in AuReMe (CreativeLabs, 2013) with Acidithiobacillus ferrooxidans (Campodónico et al., 2016) as a reference. Both drafts were merged and curated semi-automatically retrieving a model that contains 1486 metabolites, 1153 reactions, and 796 genes. Simulations of different scenarios where biomass or EPS synthesis are being prioritized allow to retrieve new insights on carbon distribution in these bioleaching bacteria and complement these simulations with in-vivo results

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Under pressure: effects of psychological stress on B cells

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Psychological stress triggers the release of effector hormones such as adrenaline and cortisol, whose impact on immune responses is increasingly recognized. However, the cellular mechanisms by which these signals alter immune cell function remain unclear. B cells are central to humoral immunity: beyond antibody production, they regulate other immune cells, and their dysfunction contributes to inflammatory and immune imbalances often linked to mental health. During B cell activation, antigen recognition triggers the formation of an immune synapse, a specialized structure that enables antigen extraction and processing for presentation to T cells, required for full B cell activation. A critical event in this process is the spreading and remodeling of the actin cytoskeleton, which occurs concomitantly with microtubule and lysosomal polarization to the synaptic membrane, facilitating antigen extraction and presentation. In this study, we aimed to characterize how stress influences B cell activation, focusing on the cytoskeletal dynamics underlying immune synapse formation. Using the murine A20 cell line, we modeled acute and chronic stress through exposure to adrenaline and hydrocortisone. RT-qPCR showed that chronic stress did not significantly modify the expression of Prkaca, Nr3c1, or Fkbp5, genes involved in adrenergic and glucocorticoid pathways. By contrast, immunofluorescence imaging revealed that acute stress induces rapid, transcription-independent alterations: reduced actin spreading, impaired MTOC and lysosome polarization toward the immune synapse, thereby decreasing antigen

extraction capacity. These results suggest that psychological stress does not require long-term gene reprogramming to negatively affect B cells; instead, it directly alters cytoskeletal architecture and dynamics critical for immune synapse formation. In conclusion, this work provides novel evidence that psychological stress compromises immune synapse formation and B cell functions by destabilizing cellular pathways involved in organelle and cytoskeleton remodeling. Such perturbations may raise their activation threshold and consequently weaken humoral response, which may have an impact on mental health-related diseases.

Cross-species network analysis identifies GBF3 as a conserved drought regulator in tomato and Arabidopsis through DAP-seq profiling

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Drought stress profoundly reshapes plant transcriptional programs through complex gene regulatory networks (GRNs). To uncover conserved regulatory components, we integrated publicly available RNA-seq data from four phylogenetically distant species — Arabidopsis thaliana, Solanum lycopersicum, Oryza sativa and Zea mays — and standardized experimental metadata to enable direct cross-study comparisons. Differential expression analysis under drought identified species-specific sets of responsive genes, which were then intersected to define a robust core of conserved drought-induced genes. Using chromatin accessibility data and gene co-expression profiles, we predicted GRNs for each species and extracted transcription factors consistently positioned as central regulators of these core genes across all species.
This multi-layer network approach highlighted the bZIP G-box Binding Factor GBF3 as a highly connected and conserved regulator. To experimentally define its DNA-binding landscape in tomato, we performed DNA affinity purification sequencing (DAP-seq). GBF3 bound canonical G-box motifs (CACGTG) with clear enrichment near transcription start sites, and its targets substantially overlapped with those reported for GBF3 in A. thaliana. At the same time, each species showed unique target genes and functional enrichments, pointing to

conserved modules in abscisic acid signaling and drought-related transcriptional cascades, together with lineage-specific adaptations.
By combining cross-species GRN inference with experimental profiling, this study details the conserved and divergent features of GBF3-mediated transcriptional control during drought stress, providing a framework for leveraging conserved cis-regulatory modules in crop improvement.

Functional specialization of human U5 snRNA variants controls alternative splicing and cellular phenotypes in cancer cells

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RNA splicing is essential for gene expression, enabling intron removal from precursor messenger RNAs (pre-mRNAs) to form mature mRNAs. Alternative splicing significantly expands transcriptomic diversity, affecting approximately 95% of human genes with multiple exons. Central to this process is the spliceosome, a complex molecular machine composed of small nuclear RNAs (snRNAs; U1, U2, U4, U5, and U6) and protein factors. Although protein splicing factors' roles in controlling splicing specificity are well-documented, the functional relevance of RNA components—particularly snRNAs—remains largely unexplored.
Unlike other snRNAs that have dominant variants, human U5 snRNA exists as five major variants (U5A, U5B, U5D, U5E, and U5F) with subtle sequence differences transcribed from distinct loci. Through analysis of publicly available eCLIP and RNA-seq datasets, including TGIRT-seq, we identified variant-specific interactions with RNA-binding proteins and differential expression patterns. Notably, U5D, U5E, and U5F are significantly upregulated in diverse cancer cell lines relative to normal adult tissues, suggesting preferential utilization of these variants in malignant contexts.
We hypothesized that U5 snRNA variants confer functional specialization to spliceosomes, promoting distinct splicing programs rather than functioning as interchangeable components. Using CRISPR-Cas9, we generated individual knockouts of each major U5 variant in triple-negative breast cancer cells (BT-549) and performed comprehensive transcriptomic analysis. Each U5 variant knockout produced distinct transcriptional signatures affecting hundreds of genes, demonstrating non-redundant functions. RNU5D and RNU5F knockouts

showed similar profiles, consistent with their cancer co-upregulation. Most remarkably, RNU5E knockout dramatically suppressed MYC transcriptional activity while activating interferon signaling and viral defense pathways. Alternative splicing analysis revealed variant-specific patterns, with phenotypic characterization confirming differential impacts on cell proliferation and resistance to chemotherapeutic agents.
Our findings provide compelling evidence that U5 snRNA variants confer specialized functional roles in spliceosomal regulation, directly impacting gene expression programs and cellular phenotypes relevant to cancer biology, identifying U5E as a potential therapeutic target.

Casein kinase 1 activation loop govern a conserved phosphoswitch mechanism regulating the circadian period in Eukaryotes

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The regulation of circadian period in eukaryotes relies on multisite phosphorylation of negative clock components by Casein Kinase 1 (CK1). However, how CK1 achieves substrate specificity to control timing independently of degradation remains unclear. Here, we describe a spontaneous Neurospora crassa mutant, clock-time modification (ctm), carrying a single H165D substitution in CK1a at the conserved anion-binding site 3. This mutation leads to a ~6-hour period lengthening without altering general kinase activity or stability of its negative clock component FRQ. Molecular dynamics simulations reveal that H165D disrupts activation loop dynamics, destabilizing the “up” configuration and affecting the architecture of the catalytic cleft. In vivo and in vitro assays show that CK1actm selectively impairs phosphorylation at two FRQ phospho-regions: the PEST-1 and C-terminal domains, which act as circadian “phospho-switches” analogous to the FASP and degron regions in mammalian PER2. Mutation of a single residue within PEST-1 (S538A) and C-terminal strongly synergizes with CK1actm, while their phosphomimetic versions rescue the period defect, demonstrating that phosphorylation at these sites sets the circadian period. Introduction of the CK1actm analog (H162D) into human CK1 recapitulates the substrate selectivity defects in PER2-derived peptides, indicating that this phosphoswitch mechanism is evolutionarily conserved. Altogether, our findings establish that a conformational change in the catalytic cleft of CK1a due the mobility in the activation loop modulates the substrate recognition at specific timing regions

of negative clock component proteins, revealing a conserved regulatory axis that govern the circadian period from fungi to mammals

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The v-SNARE VAMP8 protein participates in the secretion of chemo-exosomes in A2780cis ovarian cancer cells

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Introduction: Ovarian cancer (OvCa) is the most lethal gynecological malignancy, with cisplatin (CDDP) as the standard treatment. High mortality is largely due to CDDP resistance and metastasis, where exosomes play a key role. Exosomes are extracellular vesicles (EVs) generated in multivesicular bodies (MVBs) within the endosomal pathway, requiring fusion with the plasma membrane for release. Our group demonstrated that CDDP-resistant ovarian cancer cells A2780cis secrete pro-tumorigenic EVs in response to CDDP, named chemo-exosomes, but its mechanism of release remains unknown. Transcriptomic analysis of A2780cis cells shows upregulation of VAMP8, a v-SNARE protein involved in membranes fusion, after CDDP treatment, suggesting its role in chemo-exosomes release.
Methods: A2780cis cells were treated with CDDP for 72 hours. VAMP8 abundance, distribution, and colocalization with Rab7 and Rab27a were evaluated via immunofluorescence. VAMP8-knockdown (VAMP8-KD) using shRNA was performed to assess exosome secretion and lysosomal status, given the balance between both elements.

Results: In A2780cis cells, cisplatin reshapes vesicular trafficking by increasing and redistributing VAMP8, altering its association with lysosomal (LAMP1), late endosomal (Rab7), and secretory (Rab27a) compartments, while VAMP8 knockdown counteracts these effects by preventing cisplatin-induced exosome release and related processes.

Acute ketamine application inhibits optogenetic activation in murine hippocampal slices

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Introduction: Psychosis is a clinical construct and a symptom of multiple mental disorders, characterized by features that can impair development of a normal life. This condition is hypothesized to involve glutamatergic dysregulation, in particular a decrease in NMDAR function that disrupts the hippocampal excitation-inhibition balance by decreased activation of the GABAergic interneurons in the hippocampus. While the NMDAR nonselective antagonist, ketamine is used to model of psychotic-like behavior in animals, it also affects other molecular pathways by activating other receptors, and its precise effect in neural activation of different hippocampal subregions remain unclear due to limitations of traditional techniques. Methods: To analyze the differential effects of acute ketamine application in various hippocampal nuclei, we used an all-optical neurophysiology approach in acute mouse brain slices. We delivered AAV by stereotactic injection to express an orange calcium indicator and a blue light-activated cation channel. Under the microscope, slices were stimulated with an optogenetic protocol, and we measured neuronal activation in baseline condition and upon application of pharmacological perturbations. We further characterized neuronal response types by applying synaptic blockers, including the selective NMDAR antagonist AP5. Results: There was a differential activation of neurons in the subregions of the hippocampus. The application of different concentrations of Ketamine decreased the activity in all the subareas of the hippocampus in contrast to the application of AP5 that shows that the activity increases. Also, it was compared to the application of a GABAa blocker, and it has the opposite effects in the neural activation. Conclusions: The different activation in the subregions was expected and is due to the different types of neurons. The application of AP5 and Ketamine might be different due to an acute mechanism of Ketamine different from the NMDAR blocker function that needs to be studied, like the effect in calcium response related proteins.

Nitrate modulates pectin metabolism and cell wall mechanical properties during cell expansion and cotyledon growth in Arabidopsis

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Nitrate is one of the most relevant nitrogen sources for plants. Besides its key nutritional role, nitrate acts as a signal molecule that regulates plant gene expression, metabolism, physiology, growth and development. In cotyledons and true leaves, nitrate promotes growth via cell expansion and endoreplication. Integrative bioinformatics analysis of transcriptome data indicated cell wall organization is a relevant biological process among differentially expressed genes by nitrate. However, there is scant information on the influence of nitrate on cell wall composition and properties during cell expansion and growth. Here, we explore the interaction between nitrate-induced growth and cell wall metabolism with emphasis on the role of the pectin matrix. We evaluated changes in cell wall monosaccharide profile and methylesterified pectin content of cotyledons grown under contrasting nitrate conditions. We also analyzed pectin methylesterase activity and characterized cell wall elasticity changes during nitrate-induced cell expansion using atomic force microscopy (AFM) and automated confocal microextensometry (ACME). Finally, we explored pectin-related processes that respond to nitrate to identify candidate genes involved in these interactions. Taken together, our results support a model in which pectin methylesterification is associated with cell expansion in nitrate-mediated cotyledon growth in Arabidopsis thaliana. We integrate genomics, bioinformatics and cell biology approaches to provide insights into the interplay between nitrate nutrition, cell wall metabolism, and biomechanical properties for cell expansion.
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Larval social isolation induces lifespan-long motivational deficits in *Drosophila melanogaster*: A comparative model of apathy

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Introduction: Apathy and motivational deficits are core symptoms of mood and neurodegenerative disorders, yet their developmental origins and behavioral biomarkers remain poorly understood across species. Comparative models are essential to elucidate how early-life experiences shape long-term motivational traits.
Methods: This study examined the effects of larval social isolation on motivational behavior in Drosophila melanogaster. Third-instar larvae were reared in either isolated or social conditions. Behavioral assays assessed re-ingestion latency (time to return to food after disengagement), feeding duration, and locomotor activity. The same individuals were tracked into adulthood (days 20–25 post-eclosion) and tested under food-deprived conditions for latency to approach novel food stimuli and general exploratory behavior.
Expected results: It is expected that larval social isolation will lead to a significant increase in re-ingestion latency and a reduction in exploratory behavior, both during the larval stage and in adulthood. These behavioral outcomes are anticipated to reflect a stable phenotype of reduced motivational drive, consistent with apathy-like or anhedonic traits across the lifespan.
Discussion: Findings indicate that early-life social deprivation induces enduring motivational impairments, likely reflecting disruptions in conserved neurobehavioral circuits. This supports the utility of Drosophila melanogaster as a tractable model to investigate the developmental roots of apathy and motivational decline. The model provides insight into prodromal behavioral markers relevant to human conditions such as depression and early-stage Alzheimer’s disease.

Modulation of the effects of social isolation in adult *Drosophila melanogaster*: a behavioral and neurochemical study

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Social isolation (SI) represents a significant environmental stressor affecting behavioral and neurochemical functioning across species. In humans, chronic isolation associates with cognitive deterioration, increased dementia risk, and mental health problems, particularly in older adults. Animal models demonstrate that SI induces neuroplasticity alterations and maladaptive behaviors including increased aggression and social avoidance. However, emerging evidence suggests prior positive social experiences can foster behavioral and neural resilience against future social challenges. Drosophila melanogaster serves as an ideal experimental model due to its simple nervous system, functional homology with human neurotransmitters, and complex behavioral repertoires. Objective: To determine whether prior socialization modulates SI effects in adult Drosophila melanogaster, both behaviorally (locomotion, aggression) and in stress-related neurochemical marker expression, specifically dopamine and octopamine. Methodology: Between-groups experimental design with N=60 Drosophila melanogaster (Canton-S line) divided into three conditions (n=20 each): A) Isolated from eclosion; B) Socialized during larval stage, isolated in adulthood; C) Socialized throughout life cycle. Dependent variables: locomotor activity, aggression measures, and dopamine/octopamine levels. Experimental procedures included behavioral evaluations in aggression and neurochemical analysis Expected Results: Individuals with prior socialization are expected to exhibit lower aggression and hyperactivity levels, with more stable dopamine and octopamine concentrations, compared to those isolated from eclosion. These differences may indicate a protective effect of early socialization, activating social resilience mechanisms similar to mammals. Behavioral and neurochemical differences are anticipated to become more pronounced in late adulthood, suggesting cumulative effects of prolonged isolation. Conclusion: This study aims to provide evidence on social resilience mechanisms in simple animal models, supporting the hypothesis that early social experiences can buffer

against chronic social stress. Findings could have translational implications for preventive interventions in human mental health, particularly populations like older adults or individuals subjected to prolonged confinement, strengthening Drosophila melanogaster as a valid model for investigating protective factors against SI.

Impact of social isolation across the lifespan of *Drosophila melanogaster* on the expression of spatial neophobia towards unfamiliar environments

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Background:
The social environment plays a crucial role in neurobehavioral development, as individual behavior is shaped by the context in which organisms develop. In Drosophila melanogaster, social interactions during the larval stage influence neural development and result in behavioral modifications. Neophobia, an instinctive fear of unfamiliar environments, must be overcome by organisms to effectively access resources.
Objective:
The general objective of this study is to analyze how social isolation throughout the developmental cycle (egg to adult) affects spatial neophobia expression in Drosophila melanogaster.
Specific Objectives:
(1) To evaluate behavioral differences between isolated, socially reared, and progressively integrated groups;
(2) To identify critical developmental periods sensitive to social isolation;
(3) To explore potential sex-related differences in neophobic behavior.
Methods:

We conducted a quantitative experimental study with three groups: (A) flies reared in complete isolation, (B) flies reared socially, and (C) flies progressively integrated at 24h, 48h, and 96h intervals. Each group includes 20–30 individuals, kept at 24–25°C under a 12-hour light/dark cycle. Behavioral responses were evaluated using spatial neophobia tests. Statistical analyses include ANOVA, Tukey post hoc comparisons, and sex-stratified analysis.
Expected Results:
We expect isolated flies to display the highest neophobic behavior, while progressively integrated ones will show intermediate responses. This would support the hypothesis that social isolation impairs exploratory behavior and affects neural plasticity. These findings align with Cohen et al. (2015), who reported asymmetric responses to novelty in Drosophila.
Conclusions:
This study may reveal a direct relationship between social isolation and spatial neophobia in adult Drosophila melanogaster, offering insight into how social contexts shape neural circuits and adaptive behavior, with parallels in human development.
Keywords: Social isolation, spatial neophobia, Drosophila melanogaster, neurobehavioral development, early-life experience, exploratory behavior.

Spreading light-sheet microscopy in Chile and South America

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Light sheet Imaging Universidad Mayor Chile (LiSIUM-Chile) is a local initiative to spread the knowledge and use of light sheet microscopy (LSM) in Chile and South America.
Currently, the microscopy unit of the Universidad Mayor (UM) has the only commercial LSM of intensive use in Chile and is the first of its kind in all South America. At UM, we obtained, in 2021 – (thanks to a government grant for advanced research equipment, FONDEQUIP) –a ZEISS LSM7 raising significant interest among our collaborators seeking to implement LSM bioimaging. Currently, our LSM is used in regular investigation, PhD thesis and training with different kind of fixed, clarify and alive samples. Thanks to funding from the Chan Zuckerberg Initiative (CZI) to Expand Global Access to Bioimaging (2022) and Advancing Imaging Through Collaborative Projects (2023) we expanded our possibilities to spread the knowledge about this technology from our country to all South America. The aim of them is to connect several labs at the UM with other institutions in Chile and abroad to build a hub for LSM in Latin America, and to Bringing Flamingo Light Sheet Microscopes to South

America to increase our capacities. The last one, is an international collaboration between 3 Bioimaging hub of South America (Brazil, Uruguay and Chile), and Jan Huisken's Lab in Germany, to build and bring to our region 3 Flamingo LSM.
We have conducted more than 8 international activities, including in-person LSM workshops, with over 50 participants, with diverse backgrounds and academic stages, from 8 countries across our continent. Additionally, we have supported the training of microscopy staff in Chile and abroad, along with providing ongoing assistance to researchers in their scientific challenges.

Plant calcium signaling: A mechanistic modeling perspective

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Calcium (Ca2+) is an ubiquitous second messenger. It plays a pivotal role in both long-term processes such as plant growth and development, as well as short-term responses to various environmental stresses. Each stimulus induces a specific Ca2+ signal, that is decoded by a network of calcium binding proteins (CBPs) that in turn modulate target proteins (TPs). We propose a multi-level theoretical approach to understand the basis and principles of Ca2+ signature decoding. The mathematical model is based on biochemical and thermodynamic solid first principles, with interactions between Ca2+, CBPs and TPs at the atomic level. This model considers different scenarios, including modulation by rapid direct binding of Ca2+ to the TP with a slower subsequent modulatory effect (as ion channels with EF hands), modulation by the catalytic activity of a CBP on the TP (as kinase activity), and modulation by the binding of a CBP to the TP (as calmodulin activity).
The differences in free energy provides the basis for mechanistic models, describing initial steps of Ca2+ signaling cascades by activation/inactivation of CBPs using chemical kinetics and the Eyring rate theory. Furthermore, we identify a group of macroscopic parameters that provide valuable information on changes in the relative activity of CBPs and TPs during calcium oscillations. The relations between Ca2+, CBPs and TPs are then implemented as a network of basic Ca2+-CBP-TP modules that can be combined to increasingly complex networks. As an example, our approach can explain the long-standing question why Ca2+-dependent protein kinases show substrate-depended

differences in their Ca2+-sensitivity. Linking the theory presented here with physiological wet-lab analyses may offer unprecedented opportunities to address fundamental biological and agronomical issues such as plant responses to diverse environmental stresses.

TC-NER and replication stress: A critical link for genomic stability

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Introduction: Replication stress (ER) can cause DNA damage, mutations, genomic instability, and contribute to the development of diseases such as cancer. R-loops, DNA-RNA hybrid structures, can induce ER. These are repaired by the transcription-coupled nucleotide excision (TC-NER) mechanism. In this work, the effect of TC-NER deficiency on DNA repair and response to hydroxyurea (HU)-induced ER was evaluated. Methods: Transformed fibroblasts deficient in ERCC6 (GM16095, ERCC6_p.Lys337Ter) and wild-type (GM00637, ERCC6_WT) were used. Cells were exposed to 2mM HU for 1, 4, and 24 hours, followed by a recovery time of 1,4,24,48, and 96 hours, depending on the experiment. ER was assessed by indirect immunofluorescence (IIF) of RPA/pRPA and BrdU. γH2AX and 53BP1 were assessed as surrogate markers of DNA damage and repair response. Colorimetric and caspase 3/7 activation assays were used to quantify viability and apoptosis. Mutational profiling and transcriptional activity were assessed in ERCC6_p.Lys337Ter cells. Following 4-hour HU exposure and a 72-hour recovery, RNA and DNA were extracted for RNA-seq and WES, respectively. Results: HU-induced ER correlates with an increase in double-strand-breaks (DSBs), an increase in non-homologous end-joining (NHEJ) repair, decreased viability, and increased apoptosis in both cell lines. The magnitude of this response was dependent on the time of exposure to HU and the time of recovery. Interestingly, ERCC6_p.Lys337Ter cells presented higher levels of 53BP1 after short-term exposure to HU (1, 4 hours) while ERCC6_WT cells showed lower levels of 53BP1, suggesting that during ER, ERCC6_p.Lys337Ter cells activate the NHEJ repair pathway. RNAseq results show that there are significant differences in basal gene expression. Furthermore, senescence-associated pathways were enriched in ERCC6_p.Lys337Ter cells exposed to HU.

In ERCC6_WT cells, mutagenesis only occurs in protein-coding genes, unlike ERCC6_p.Lys337Ter, which occurs independently of the type of expression.
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Born to be wired: How maternal nutrition programs the neurovascular brain and behavior

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Early-life nutrition is a pivotal determinant of both immediate survival and long-term vulnerability to metabolic and psychiatric disorders. Epidemiological studies link gestational caloric restriction (CR) with an increased incidence of psychotic disorders in adulthood, yet the underlying cellular mechanisms remain poorly understood. Epigenetic programming during gestation is thought to establish enduring transcriptional trajectories across neural, glial, and vascular compartments, potentially leading to impaired cerebral perfusion and long-lasting neuropsychiatric consequences. Here, we investigated adult offspring of dams exposed to either ad libitum (AL) feeding or 60% CR during pregnancy. From weaning, all offspring were maintained on AL diet, with a subset exposed to an additional week of CR. Adult animals were subjected to behavioral testing and whole-brain RNA-seq. Computational deconvolution of transcriptomic profiles revealed a striking imbalance in endothelial cell gene expression, more pronounced than in neuronal or glial cell types. Endothelial and vascular smooth muscle cells displayed profound transcriptional dysregulation, with enrichment of pathways implicated in vascular function and cerebral blood flow regulation. Moreover, endothelial transcriptional markers significantly correlated with maternal weight gain during pregnancy as well as with adult anxiety- and boldness-related behaviors.
These findings provide compelling evidence that developmental nutritional stress programs persistent transcriptional alterations in the cerebral vasculature, establishing a mechanistic link between gestational environment, neurovascular integrity, and adult behavioral vulnerability. By identifying endothelial dysfunction as a key driver of neurovascular uncoupling, our study highlights the vasculature as a critical yet underexplored contributor to the developmental origins of psychiatric disease.