

48^o CONGRESO INTERNACIONAL DE LA SEBBM

Libro de
Resúmenes

Book of
Abstracts



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Sociedad Española de
Bioquímica y Biología Molecular

#48congresoSEBBM

TARRAGONA

7-10 Septiembre 2026





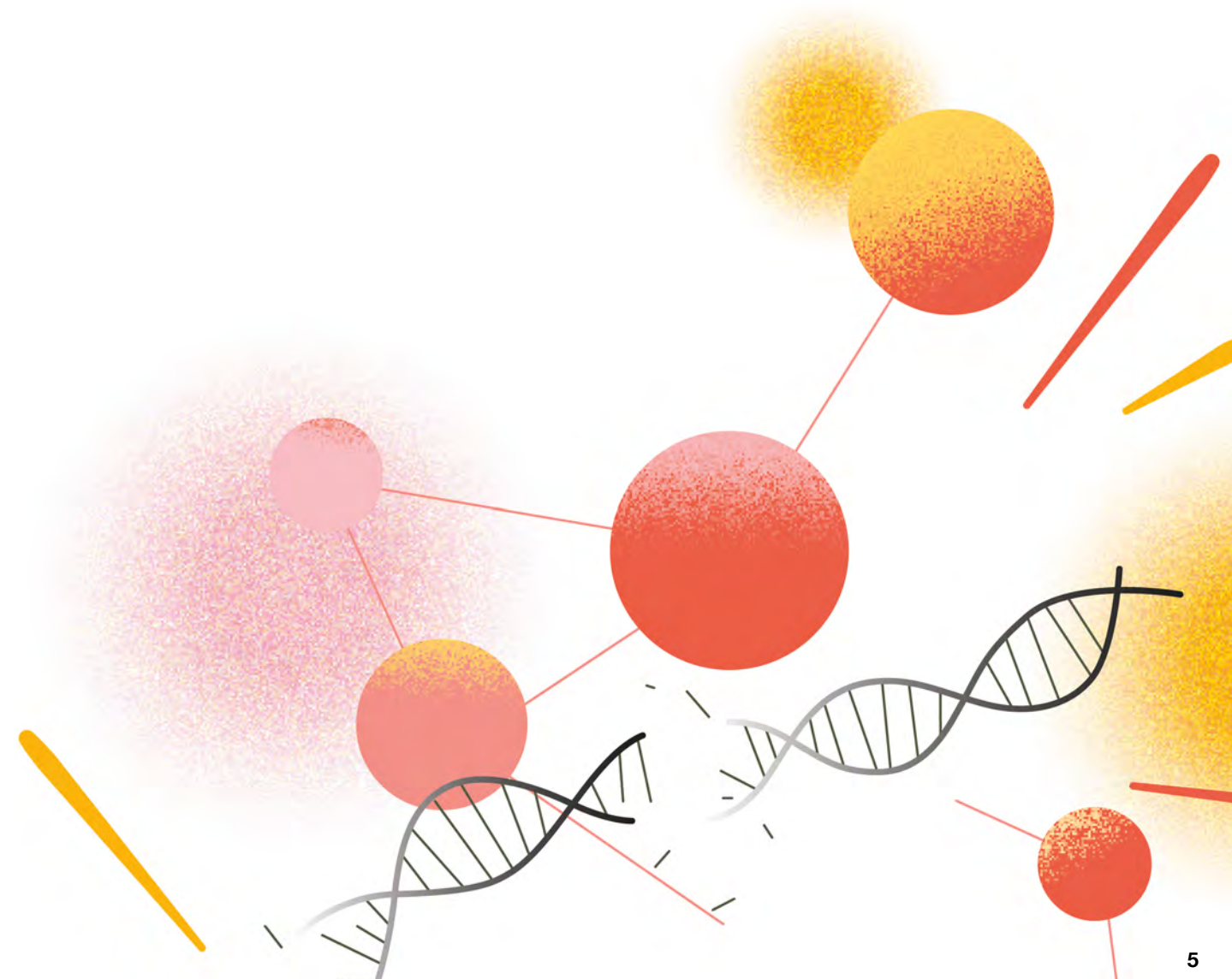
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BIENVENIDA

Queridos y queridas colegas, es un verdadero honor invitaros al 48º Congreso Internacional de la Sociedad Española de Bioquímica y Biología Molecular (SEBBM), que celebraremos en la ciudad de Tarragona del 7 al 10 de septiembre de 2026.

Tarragona, declarada **Patrimonio de la Humanidad por la UNESCO**, ofrece un marco excepcional para nuestro encuentro: una ciudad mediterránea, acogedora y vibrante, donde la historia, la ciencia y la cultura se entrelazan de forma única.

Este Congreso reunirá a investigadoras e investigadores de referencia nacional e internacional y ofrecerá un **programa científico de primer nivel**, que incluirá conferencias plenarias, simposios temáticos, sesiones de pósteres, actividades satélite y reuniones de los grupos de trabajo.

Tendremos el privilegio de contar con la conferencia inaugural de la **Dra. Isabel Fariñas**, así como con la Conferencia PABMB, la Conferencia Luis F. Leloir (SAIB) y la Conferencia H. Niemeyer (SBBMCh). Cerraremos el encuentro con la conferencia de clausura a cargo del **Dr. John F. Cryan**.

Como es tradición, también se convocarán **los premios y becas SEBBM**, que reconocen la excelencia y promueven el desarrollo de las nuevas generaciones de científicas y científicos.

En nombre del **Comité Organizador** y de la **SEBBM**, nos llena de ilusión poder dar la bienvenida a nuestra comunidad científica en Tarragona. Estamos convencidos de que el intercambio de ideas, resultados y experiencias en este entorno único no solo fortalecerá nuestra red de colaboración, sino que también inspirará nuevas líneas de investigación y proyectos conjuntos.

Os animamos a participar activamente y a vivir con nosotras y nosotros una edición que, sin duda, será inolvidable.

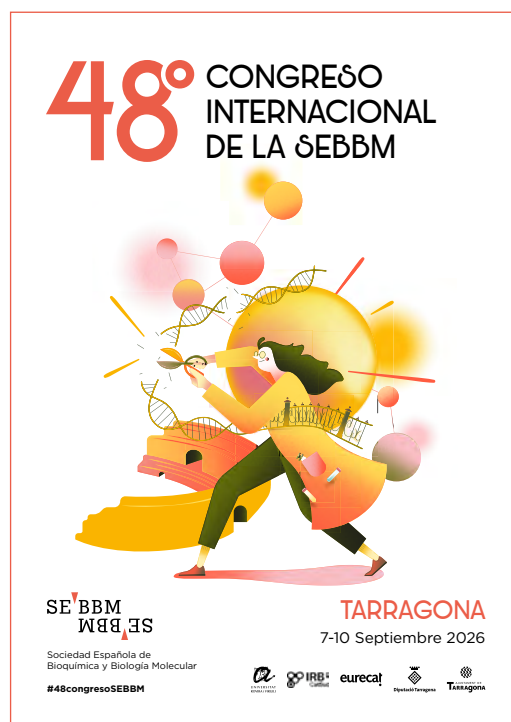
¡Os esperamos en Tarragona en septiembre de 2026!

Atentamente,



Anna Ardévol / Gerard Aragonès

Presidentes del Comité Organizador del 48º Congreso SEBBM



COMITÉ EJECUTIVO

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SOCIOS PROTECTORES Y ENTIDADES PATROCINADORAS

El Congreso internacional de la SEBBM es uno de los eventos científicos más importantes en nuestro país y ofrece un marco extraordinario para presentar tanto novedades científicas, como docentes y comerciales.

Socios protectores



Socios patrocinadores



Conferencias y premios



Stands / Expositores



Entidades patrocinadoras





PROGRAMA POR DÍAS

VIERNES, 4 DE SEPTIEMBRE

HORA	ACTIVIDADES SATÉLITE	SITIO
19:00h	Inauguración Exposición Arte y ciencia: La geometría de la vida	Centre Cultural El Castell del Cambrer (Reus)

LUNES, 7 DE SEPTIEMBRE

HORA	ACTIVIDADES SATÉLITE	SITIO
09:00h - 15:00h	Curso Iniciación a la investi- gación en Bioquímica y Biolo- gía Molecular	URV- Campus Sescelades (Sala de Graus ETSE)
09:00h - 13:00h	XVI Reunión de la Confe- rencia de Coordinadores de Grado y Máster en Bioquimi- ca y Biotecnología	URV-Campus Catalunya (Sala de Juntas)
09:00h - 13:00h	23 rd Conference on Trans-Pyrenean Investiga- tions in Obesity and Diabetes (CTPIOD Meeting)	URV-Campus Catalunya (Sala de Graus)

HORA	REUNIONES DE GRUPO	SITIO
16:00h - 18:00h	Educación	Sala Medusa
16:00h - 17:30h	Mujer y Ciencia	Sala Genius
17:30h - 18:30h	Emprendimiento e innovación	Sala Genius

HORA	SIMPOSIO	SITIO
16:30h - 18:15h	Simposio RAICEX (Red de Asociaciones de Investigadores y Científicos Españoles en el Exterior)	Auditorio Eutyches

HORA	ACTIVIDAD SATÉLITE	SITIO
19:00h	La bioquímica de Santa Tecla Conferencias científicas	Antic Ajuntament (Sala d'Actes)

HORA	CEREMONIA DE INAUGURACIÓN	
18:30h - 19:15h	Bienvenida institucional - <i>Autoridades</i>	Auditorio August
19:15h - 20:00h	Conferencia Inaugural - <i>Isabel Fariñas</i>	Auditorio August
20:00h - 20:30h	Exhibición Castellera - Xiquets de Tarragona	Auditorio August
20:30h - 22:00h	Cóctel de bienvenida	Vestíbulo El Palau

MARTES, 8 DE SEPTIEMBRE

HORA	SIMPOSIOS	SITIO
09:00h - 10:30h	S1.1 - When Metabolism Has a Clock: Biological Rhythms and Molecular Nutrition	Auditorio August
09:00h - 10:30h	S2.1 - Advances in Extracellular Vesicles for Therapeutic Applications	Auditorio Eutyches
09:00h - 10:30h	S3.1 - Fat Matters: Impact on Cancer, Obesity, and Liver Disease	Sala Genius
09:00h - 10:30h	S4.1 - From Structural Biology to Therapy: Rediscovering Amyloid Proteins	Sala Medusa

HORA	CONFERENCIA PLENARIA	SITIO
10:30h - 11:15h	FEBS National Lecture - <i>Henrik Oster</i>	Auditorio August

11:15h - 11:45h	Café, presentación pósteres y visita exposición comercial	
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HORA	CONFERENCIA PLENARIA	SITIO
11:45h - 12:30h	Conferencia Niemeyer - <i>Lorena De Lourdes Lobos González</i>	Auditorio August

HORA	CONFERENCIAS PATROCINADORES	SITIO
12:30h	BIO-RAD - Western Blot reproducible: integridad de datos, trazabilidad y cuantificación multiplex	Auditorio August
12:30h	ECOGEN - El fin de la Era Científico Artesano	Auditorio Eutyches
12:30h	AGILENT - 3D Biology 2.0: innovación, aplicaciones y ca- sos prácticos con Seahorse, xCELLigence eSight y Cytation	Sala Medusa
12:30h	CONDALAB - De biomarcadores a terapias: soluciones int egrales para la investigación traslacional en exosomas y vesículas extracelulares	Sala Minerva
12:30h	CONTROLTECNICA - Técnica y casos prácticos de apli- caciones de la electroforesis capilar con detección por fluorescencia	Sala Genius
12:45h	CULTEK - ON-TARGETplus™ 2.0: siRNA Design for the Modern Transcriptome	Sala Minerva
12:55h	PROQUINORTE - Linking Genotype to Transcriptional Phenotype at Single-Cell Resolution Using a Scalable RNA- DNA Co-Sequencing Platform	Sala Genius
13:00h	MEDCHEM - MCE One-Stop Compound Screening Plat- form for Basic Research and Early Drug Discovery	Auditorio Eutyches
13:00h	PHCBI - A Complementary Workflow for Dynamic Charac- terization of Cellular Function: Integrating Continuous Metabo- lic Monitoring with Advanced Live-cell Imaging	Sala Medusa
13:00h	LABCLINICS - Accelerating qPCR Success -- Reliable Solutions from Extraction to Detection	Sala Minerva
13:05h	CYMIT -De la poyata al mercado: cómo usar tu carrera científica fuera del laboratorio	Auditorio August
13:15h	LICOR- Simplifying Quantitative Multiplex Imaging from Western Blots to 3D Models	Sala Minerva

13:30h - 15:00h	Comida, presentación pósteres y visita exposición comercial	
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HORA	ACTIVIDAD SATÉLITE	SITIO
13:45h - 14:45h	Taller de electroforesis capilar en gel	Sala Genius

HORA	REUNIONES DE GRUPO	SITIO
15:00h - 17:30h	Biología molecular ómica y bioinformática	Auditorio Eutyches
15:00h - 16:30h	Química biológica	Sala Genius
15:00h - 16:30h	Parasitología molecular e infecciones emergentes	Sala Medusa
15:00h - 16:30h	Senescencia celular	Sala Minerva
16:30h - 19:00h	Biología sintética y biotecnología molecular	Sala Genius
16:30h - 19:00h	Mitocondria, comunicación celular y estrés oxidativo	Sala Medusa
16:30h - 19:00h	Biomembranas	Sala Minerva

HORA	ACTIVIDAD SATÉLITE	SITIO
17:30h - 18:30h	Sesión de Financiación Privada y Filantropía	Auditorio August

19:00h - 20:00h	Presentación pósteres y visita a exposición comercial	
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HORA	ACTIVIDADES SATÉLITE	SITIO
18:00h	La ciencia del chocolate (Taller infantil)	Biblioteca Pública
19:00h	La ciencia bien explicada: claves para decidir mejor Conversación científica con <i>Pere Estupinyà</i> y <i>Lluís Montoliu</i>	Antiga Audiència (Sala d'Actes)

MIÉRCOLES, 9 DE SEPTIEMBRE

HORA	SIMPOSIOS	SITIO
09:00h - 10:30h	S1.2 - Modulating the Biology of Ageing Through Nutrition: Molecular Mechanisms and Emerging Interventions	Auditorio August
09:00h - 10:30h	S2.2 - Microbiota Crosstalk with Peripheral Organs: From Liver Metabolism to Brain Function	Auditorio Eutyches
09:00h - 10:30h	S3.2 - Simposio Hispano- Mexicano. Computational Drug Design: Reality and Challenges in the Era of Artificial Intelligence	Sala Genius
09:00h - 10:30h	S4.2 - Transcription/mRNA decay coupling and its impact on gene expression	Sala Medusa

HORA	CONFERENCIA PLENARIA	SITIO
10:30h - 11:15h	Conferencia Luis F. Leloir - <i>Eduardo T. Cánepa</i>	Auditorio August

11:15h - 11:45h	Café, presentación pósteres y visita exposición comercial	
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HORA	CONFERENCIAS PLENARIAS	SITIO
11:45h - 12:25h	Mujer y Ciencia - <i>Sara Hernández Mejías</i>	Auditorio August
12:30h - 13:00h	Conferencia Premio 'Profesora María Teresa Miras' al Mejor Artículo de Jóvenes de la SEBBM <i>Naroa Goikoetxea-Usandizaga</i>	Auditorio August

HORA	CONFERENCIAS PATROCINADORES	SITIO
13:00h	PROMEGA - Salud celular en el ecosistema bioluminis- cente de Promega	Auditorio August
13:00h	EYOWN - Automatización de laboratorio orientada al proyecto: de la necesidad científica a la solución im- plantada	Auditorio Eutyches
13:00h	ABYNTEK - Optimización del flujo de trabajo en in- vestigación: Muestreo inteligente, reactivos robustos, resultados fiables	Sala Medusa
13:00h	CYTIVA - Plataformas de referencia para la Purificación y Caracterización de Proteínas	Sala Minerva
13:00h	BIOGEN - De lo convencional a lo innovador: cómo la imagen molecular está redefiniendo las aplicaciones en Biología Molecular	Sala Genius
13:15h	KUHNER - Hunting a 'ghost' with Kuhnner Shaker - the (mostly) forgotten cultivation parameter and its impact	Sala Minerva
13:25h	MACROGEN - Humanizando la genómica	Sala Medusa
13:25h	TETUBIO - Rethinking disease modeling: bridging can- cer, metabolism and liver pathology through integrated experimental workflows	Sala Genius
13:30h	PARALAB - Building Better Experiments: An Integrated Workflow for Next-Generation Bioscience	Sala Minerva
13:35h	PALEX - Tecnologías moleculares avanzadas: del reac- tivo de precisión hasta la NGS y ómicas	Auditorio Eutyches
13:40h	APLITECH - Hacia un laboratorio conectado: Automati- zando el flujo de trabajo desde la preparación de mues- tras hasta los bioprocesos	Sala Medusa

HORA	ACTIVIDADES SATÉLITE	SITIO
13:40h - 14:40h	Luminiscencia en tu bolsillo: MyGlo® y sus aplicaciones en salud celula	Auditorio August
13:50h - 14:50h	Sesión práctica en Seahorse, metabolómica y xCELLigence eSight	Sala Minerva

14:00h - 15:30h	Comida, presentación pósteres y visita exposición comercial	
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14:30h - 15:30h	Reunión de coordinadores de grupos SEBBM	Sala Genius
14:30h - 15:30h	Reunión de Cónsules SEBBM	Sala Medusa
14:30h - 15:30h	Reunión del comité editorial de la Revista SEBBM	Auditorio Eutyches

HORA	REUNIONES DE GRUPO	SITIO
15:30h - 18:00h	Bases moleculares de la patología	Auditorio Eutyches
15:30h - 18:00h	Estructura y función de proteínas	Sala Genius
15:30h - 18:00h	Señalización celular	Sala Medusa
15:30h - 18:00h	Matriz extracelular	Sala Minerva
		continúa ►

MIÉRCOLES, 9 DE SEPTIEMBRE (II)

18:00h - 19:30h	Café, presentación pósteres y visita a exposición comercial	
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18:00h	Asamblea General Ordinaria SEBBM	Sala Genius
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HORA	ACTIVIDAD SATÉLITE	SITIO
20:00h	Tarragona, Ciudad de Castells Actividad cultural	Pla de la Seu

21:00h	Cena de Gala	Casa Joan Miret
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JUEVES, 10 DE SEPTIEMBRE

HORA	REUNIONES DE GRUPO	SITIO
09:30h - 12:00h	Regulación de la expresión génica y dinámica del genoma	Auditorio Eutyches
09:30h - 12:00h	Regulación metabólica y nutrición	Auditorio August
09:30h - 12:00h	Neurobiología molecular	Sala Genius
09:30h - 12:00h	Muerte Celular e Inflamación	Sala Medusa

12:00h - 12:30h	Café, presentación pósteres y visita exposición comercial	
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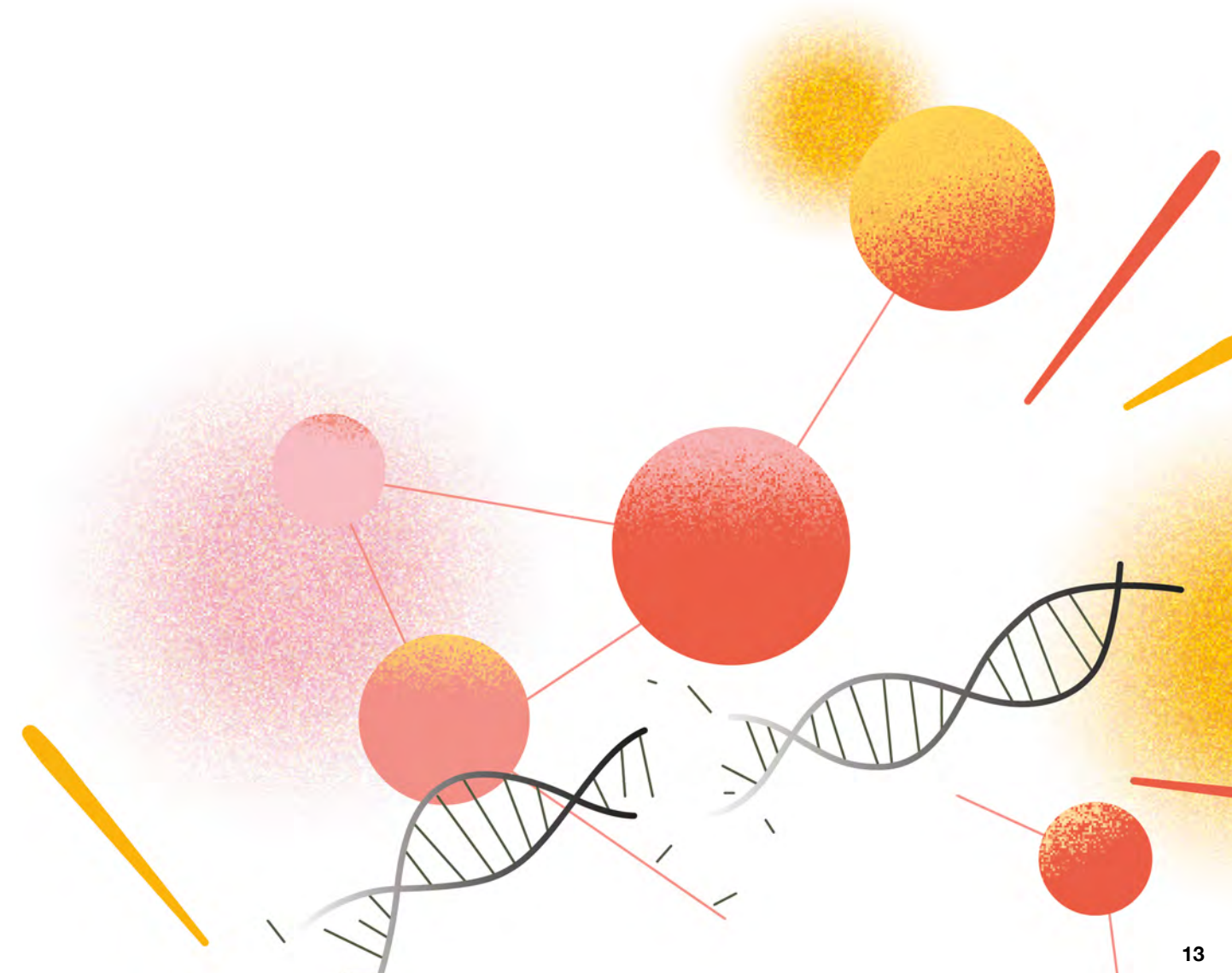
12.10h - 12.30h	Kahoot sobre nuestros patrocinadores	Auditorio August
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HORA	CONFERENCIA PLENARIA	SITIO
12:30h - 13:00h	Conferencia IBUB-SEBBM y entrega de premio - <i>Rubén Quintana-Cabrera</i>	Auditorio August

HORA	CEREMONIA DE CLAUSURA	SITIO
13:00h - 13:45h	Conferencia de Clausura - <i>John F. Cryan</i>	Auditorio August
13:45h - 14:15h	Ceremonia de entrega de medallas de Socios de Honor SEBBM y premios SEBBM y patrocinadores	Auditorio August
14:15h - 14:30h	Clausura institucional	Auditorio August



CONFERENCIAS PLENARIAS





LUNES, 7 DE SEPTIEMBRE

PL-01

Falling asleep: the regulation of stem cell quiescence in the adult brain

ISABEL FARIÑAS

Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED)

Departamento de Biología Celular y Biología Funcional

Instituto de Biotecnología y Biomedicina (BioTecMed), Universidad de Valencia, 46100 Burjassot, Spain.

New neurons that sustain the highly plastic olfactory circuitry are generated in the ventricular-subventricular zone (V-SVZ) of the adult mammalian brain. Neural stem cells (NSCs) within this niche are exposed to a broad array of regulatory cues that support lifelong neurogenesis while maintaining the stem cell reservoir. Adult NSCs originate from radial glial cells, the principal embryonic progenitors in the vertebrate brain, and retain key features of this lineage, including elements of their transcriptional program, a bipolar elongated morphology with apico-basal polarity enabling specialized interactions with neighboring cells, and expression of astrocytic markers. Unlike their fetal counterparts, however, most adult NSCs remain quiescent under physiological conditions. Transitions between quiescence and activation likely entail profound shifts in cellular physiology governed by tightly coordinated intrinsic and extrinsic mechanisms. We have found that entry into quiescence is accompanied by the deposition of specific extracellular matrix (ECM) components. Moreover, adhesion to ECM produced in response to pro-quiescent signals is sufficient to induce a quiescent-like state in proliferating NSCs. This transition requires RhoA-associated kinase (ROCK) activity and yes-associated protein (YAP)-dependent transcription. Deletion of YAP/TAZ in NSCs results in impaired ECM deposition and loss of quiescence in vivo, indicating that these factors orchestrate both the physical properties of the niche and a quiescence-associated transcriptional program in response to mechanical cues.

MARTES, 8 DE SEPTIEMBRE

PL-02

Circadian regulation of endocrine functions - from the brain and back

HENRIK OSTER

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Circadian clocks present in all tissues of our body regulate physiological functions across the day. The disruption of these rhythms – by genetics or external influences – is a major risk factor for the development of non-communicable diseases. Major outputs of the circadian system, and important mediators of internal synchrony between tissues, are hormonal rhythms that are ultimately controlled by the circadian pacemaker of the suprachiasmatic nucleus (SCN). We study how the SCN and endocrine tissue clocks interact at molecular and systemic levels to coordinate hormonal outputs and responses to environmental stimuli across the day. We also show how endocrine rhythms feed back on central circadian regulation in the SCN and other brain areas to modulate energy homeostasis, cognitive functions, and mood. The circadian coordination of the endocrine system provides an interesting framework and target to improve resilience against and optimise therapeutic strategies for some of the most prevalent diseases.

PL-03

Mammary tumour dynamics: a new perspective on the tumour microenvironment and therapeutics

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Tumor-derived small extracellular vesicles (sEVs) facilitate tumorigenic and metastatic processes in recipient cells through the transfer of bioactive molecular cargo. Although sEVs are increasingly recognized as key mediators of tumor-microenvironment communication, the specific molecules driving these effects remain incompletely understood. Lactadherin (MFG-E8), a glycoprotein associated with breast cancer (BC) progression, angiogenesis, and poor prognosis, has not previously been investigated as a

functional mediator of metastatic communication through tumor-derived sEVs.

This study evaluated the role of lactadherin-enriched sEVs secreted by metastatic MDA-MB-231 triple-negative breast cancer (TNBC) cells (sEV-MDA231) in promoting pro-metastatic properties in non-tumorigenic and non-metastatic recipient cells in vitro, as well as in a murine model of peritoneal carcinomatosis. Our results demonstrate that lactadherin is highly enriched in sEV-MDA231 and significantly enhances recipient cell migration and tumoroid formation. To therapeutically interfere with this signaling axis, lactadherin was blocked using both immunoneutralization strategies and specific anti-lactadherin DNA aptamers. Notably, both approaches significantly reduced the prometastatic effects induced by sEV-MDA231, highlighting lactadherin as a druggable extracellular target.

In vivo, administration of sEV-MDA231 promoted malignant ascites formation and increased tumor micronodule development, whereas lactadherin blockade markedly inhibited these pathological outcomes. Importantly, aptamer-mediated inhibition demonstrated therapeutic potential by suppressing key biological processes associated with metastatic dissemination.

Collectively, these findings provide the first evidence that lactadherin carried by metastatic BC-derived sEVs actively drives tumor progression and metastatic communication. Furthermore, they support the development of anti-lactadherin aptamers as a novel therapeutic strategy to disrupt extracellular vesicle-mediated tumor dynamics.

This work introduces a new perspective on mammary tumor biology. We propose that extracellular vesicle-associated lactadherin functions as a dynamic regulator of tumor-microenvironment communication, orchestrating metastatic reprogramming and representing a tractable therapeutic vulnerability in breast cancer.

Keywords:

Breast cancer, extracellular vesicles, lactadherin, metastasis, and therapeutic.

Founding:

Fondecyt 1261178 and ID25i10020 (LLG).

MIÉRCOLES, 9 DE SEPTIEMBRE

PL-04

Child maltreatment, epigenetics, and intergenerational transmission: biological mechanisms linking early adversity to mental health

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Child maltreatment and early adverse experiences represent one of the most significant and prevalent public health challenges worldwide. Exposure to abuse, neglect, and other forms of adversity during childhood is strongly associated with increased risk of mental and physical health problems across the lifespan with consequences that can extend to the next generation. Despite robust epidemiological evidence, the biological mechanisms through which these experiences leave lasting marks remain incompletely understood.

This lecture presents a research program investigating epigenetic mechanisms as mediators between maternal exposure to childhood maltreatment and its long-term biological and psychological consequences. Drawing on a human study that integrates retrospective measures of early adversity, psychological assessments during pregnancy, and large-scale epigenetic analyses in placenta and maternal blood, the talk will discuss how a history of maltreatment is associated with alterations in placental epigenetic maturation, changes in the epigenetic clock, and differentially methylated regions in genes linked to stress response and developmental regulation. The relationship between these biological alterations, the quality of mother-infant attachment, and the intergenerational transmission of vulnerability will also be addressed.

Beyond the molecular findings, the lecture will discuss the broader social and scientific context of child maltreatment research and its implications for designing biologically informed public health interventions. Understanding the mechanisms through which adversity leaves biological traces may contribute to developing strategies aimed at interrupting its intergenerational transmission, a challenge that is at once scientific and deeply relevant to public health policy.



PL-05

Proteins as active modulators of excited-state dynamics: biohybrid engineering toward quantum technologies

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Photoactive biohybrids, composed of proteins and synthetic chromophores, offer great potential for photonics by integrating the quantum control mechanisms of natural photo-systems into technological applications. However, designing such biohybrids remains challenging, particularly due to the difficulty of controlling the protein–chromophore interaction network, which can unpredictably influence the electronic and conformational states of the chromophores.^[1,2] In our lab, we have developed biohybrids based on optimized *de novo* proteins featuring well-defined cavities and flexible conformational states.^[3] This design enables precise tuning of the biohybrid's photoresponse through single-point mutations and allows us to investigate the fundamental roles of specific amino acids in chromophore relaxation. In particular, we have demonstrated the impact of polarized protein environments on chromophore relaxation and examined how conformational dynamics influence biohybrid behavior. We are also developing protein arrays to explore collective photoresponses.^[4] Our platform provides a powerful framework for engineering tunable photoactive systems and offers new insights for advancing bio-inspired photonic technologies.

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PL-06

The role of CNNM4 in the progression of cholangiocarcinoma: implications for ferroptosis and therapeutic potential

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Background and Aims: Cholangiocarcinoma (CCA) is a heterogeneous neoplasm of the biliary epithelium that easily infiltrates, metastasizes and recurs. Magnesium disbalance is a hallmark of CCA, being the magnesium transporter CNNM4 a key driver of various hepatic diseases. This study aims to unravel the role of CNNM4 in the initiation and progression of CCA.

Method: CNNM4 protein and gene expression were assessed *in vitro*, *in vivo* and in patients with CCA. Silencing of CNNM4 was effectively achieved by using siRNA or shRNA in CCA cell lines and GalNAc-conjugated siRNA in a transposon-based CCA mice model. The impact of CNNM4 on tumor cell proliferation, migration and invasion to the lungs was evaluated using the chicken chorioallantoic membrane model. Proteomic analysis was employed to elucidate the underlying molecular mechanisms.

Results: CNNM4 was upregulated in CCA samples from eight independent patient cohorts, comparing resected CCA samples (both iCCA and eCCA) with controls. Overexpression of CNNM4 was also confirmed in AKT/NICD, AKT/YapS127A and AKT/Fbxw7ΔF mouse models, as well as in human iCCA and eCCA cell lines, which also exhibited reduced intracellular Mg2+ levels, demonstrating a role for CNNM4 in Mg2+ extrusion in CCA. Functional studies showed that CNNM4 deficiency attenuated cell growth, chemoresistance, migration, invasion, tumorigenesis, cancer stem cell properties and the Warburg effect both *in vitro* and *in vivo*. Interestingly, proteomic analysis identified nuclear protein 1 (NUPR-1), an inhibitor of ferroptosis, as critical for the observed effects in CCA cells when CNNM4 levels are reduced. Knockdown of CNNM4 led to a significant reduction in NUPR-1 levels and increased iron accumulation and lipid peroxidation *in vitro* and *in vivo*. Furthermore, both the iron chelator deferiprone and overexpression of NUPR-1 were able to reverse the reduced proliferation induced by CNNM4 silencing, highlighting the specificity of ferroptosis in CNNM4-associated effects.

Conclusion: This study demonstrates that increased

CNNM4 expression drives CCA progression and malignancy and that its inhibition may be an effective therapeutic strategy to limit proliferation and metastasis in CCA patients.

JUEVES, 10 DE SEPTIEMBRE

PL-07

Mitochondria as drivers of intra and intercellular physiology

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Redox signaling, bioenergetics, metabolism, respiration, autophagy... It is well known that they are all processes essential for tissue physiology. Behind the scenes, mitochondria orchestrate this complex crosstalk, far beyond merely supplying energy.

Bearing all this in mind, our research aims to understand how redox signals from mitochondria arise and how they can be rewired towards tissue protection. We also study how mitochondrial shape, ultrastructure, and respiratory complexes coordinate respiration, or respond to its blockage following an insult or degenerative process. Finally, we evaluate how mitochondrial dynamics extend beyond the boundaries of individual cells to enable intercellular mitochondrial transfer, capable of reconfiguring the content, physiology, and metabolism of recipient tissues. With a special focus on the nervous system, here we recapitulate our findings towards a better understanding of mitochondrial biology as a master regulator of health and disease.

PL-08

Gut Feelings: Mining Microbes for Mental Health

JOHN F. CRYAN

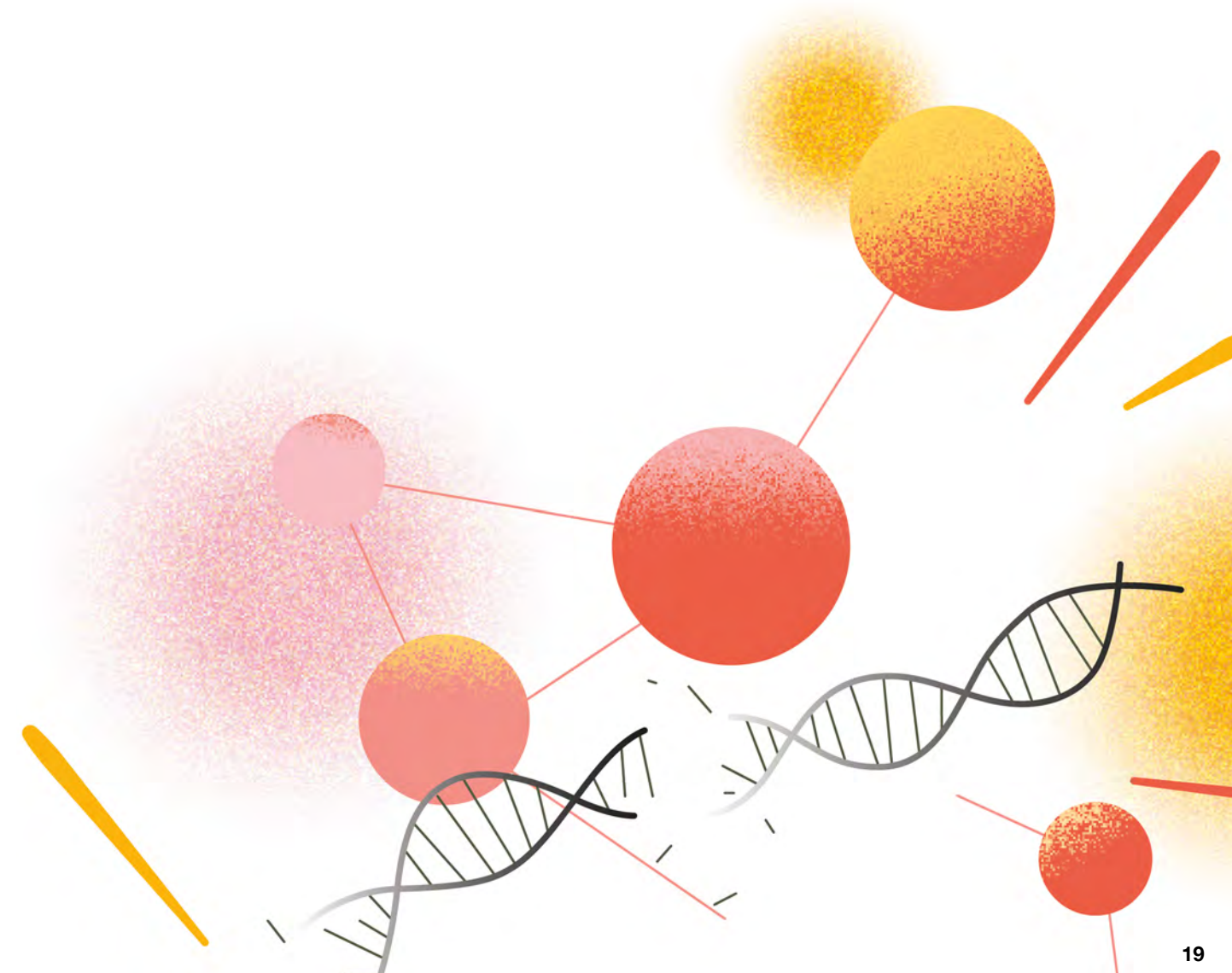
Dpto. Anatomy & Neuroscience, Principal Investigator, APC Microbiome Ireland

The microbiota-gut-brain axis is emerging as a research area of increasing interest for those investigating the biological and physiological basis of neurodevelopmental, age-related and neuropsychiatric disorders. The routes of communication between the gut and brain include the vagus nerve, the immune system, tryptophan metabolism, via the enteric nervous system or via microbial metabolites such as short chain fatty acids. Studies in animal models have been key in delineating that neurodevelopment and the programming of an appropriate stress response is dependent on the microbiota. Developmentally, a variety of factors can impact

the microbiota in early life including mode of birth delivery, antibiotic exposure, mode of nutritional provision, infection, stress as well as host genetics. Stress can significantly impact the microbiota-gut-brain axis at all stages across the lifespan. Moreover, animal models have been key in linking the regulation of fundamental brain processes ranging from adult hippocampal neurogenesis to myelination to microglia activation by the microbiome. Finally, studies examining the translation of these effects from animals to humans are currently ongoing. Further studies will focus on understanding the mechanisms underlying such brain effects and developing nutritional and microbial-based psychobiotic intervention strategies and how these interact with various systems in the body across the lifespan.



SIMPOSIO RAICEX





LUNES, 7 DE SEPTIEMBRE

S. RAICEX-1

Complementary preclinical in vivo cancer models for therapeutic evaluation and immunotherapy

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Lung cancer remains the leading cause of cancer-related mortality worldwide, emphasizing the need for robust pre-clinical models that faithfully reproduce tumor biology and treatment responses. The use of complementary syngeneic murine models provides a versatile platform for evaluating therapeutic efficacy and dissecting the mechanisms underlying antitumor immunity.

Subcutaneous, TC-1-Luc, and intracostal lung cancer models each address distinct aspects of disease progression and therapeutic evaluation. While subcutaneous tumors enable rapid and reproducible assessment of antitumor activity, the TC-1-Luc model allows longitudinal monitoring by bioluminescence imaging, and the intracostal model more closely recapitulates the tumor microenvironment and local disease progression.

These complementary models have been applied to evaluate the antitumor activity of a novel investigational compound administered intravenously, either alone or in combination with PD-1 immune checkpoint blockade. The contribution of adaptive immunity has been investigated through CD4⁺ and CD8⁺ T-cell depletion, providing mechanistic insight into the immune-mediated effects associated with treatment efficacy.

In parallel, increasing evidence identifies acyl-CoA-binding protein/diazepam-binding inhibitor (ACBP/DBI) as a regulator of cancer progression and antitumor immune responses, supporting its potential as a therapeutic target in immuno-oncology.

The integration of complementary murine models with pharmacological and immunological approaches provides a comprehensive framework for the preclinical evaluation of novel therapeutic strategies and for advancing the understanding of tumor-immune interactions in lung cancer.

S. RAICEX-2

Targeting the Glioblastoma Vascular Microenvironment: From Matrix Biology to Nanobody Therapeutics

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Despite decades of intensive research, glioblastoma (GBM) remains one of the most challenging cancers to treat. Its infiltrative nature, highly dynamic vascular microenvironment, and the blood-brain barrier collectively limit the efficacy of current therapeutic approaches. A hallmark of GBM is the development of a profuse and aberrant vascular network that promotes tumor progression. Understanding the molecular mechanisms governing this vascular microenvironment is therefore essential for the development of new therapeutic strategies.

Our work has focused on elucidating the molecular interactions within the GBM microenvironment that govern tumor vasculature. We have identified extracellular matrix regulators of GBM angiogenesis and elucidated their contribution to vascular dysfunction and their role in modulating endothelial cell-pericyte interactions. These findings have provided new insights into the molecular regulation of the GBM vascular niche and revealed previously unrecognized targets for therapeutic intervention.

These studies have led us to explore novel targeting approaches. We are developing engineered nanobodies targeting components of the tumor microenvironment as a new class of biologics for GBM. In this talk, I will discuss the rationale behind this strategy and present our recent progress toward the generation and functional characterization of nanobodies directed against vascular targets, highlighting their potential to modulate the GBM microenvironment and their use for future therapies.

S. RAICEX-3

Unravelling fibroinflammatory and immune signatures for PDAC early detection: a multi-omic approach

MARIA DEL PILAR ACEDO NÚÑEZ

University College London, Institute for Liver and Digestive Health, Royal Free Campus, London

Many upper gastrointestinal (UGI) malignancies are associated with late-stage diagnosis and poor patient prognosis. Pancreatic ductal adenocarcinoma (PDAC) has particularly high mortality rates, primarily due to the late onset of non-specific symptoms and aggressive nature of the disease. Treatment of early-stage PDAC correlates with better therapeutic responses and survival, therefore the development of improved diagnostic tools with the power to identify stage I-II patients is essential. Prolonged inflammation and immune dysregulation within the pancreas can stimulate the onset and promote the progression of PDAC. Peripheral blood mononuclear cells (PBMCs) are a population of circulating immune cells known to reflect some malignant changes that occur within solid tumours.

We hypothesised that the PBMCs of stage I/II PDAC patients mirror the dysregulated immune and inflammatory processes associated with pancreatic tumorigenesis and thus, exhibit differential gene expression patterns compared to control patients with benign UGI diseases. To validate our hypothesis, PBMCs were isolated from the peripheral blood of 51 PDAC patients (stage I/II n= 29, stage III/IV n= 22) and 48 high-risk control patients via a Ficoll gradient and total RNA was extracted for bulk RNA sequencing.

We identified 26 significantly differentially expressed genes (DEGs) ($p < 0.00001$, $\log_2 \text{fc} > 1$) of interest in stage I/II PDAC PBMCs relating to inflammatory, immune and oncological signalling pathways. Gene set enrichment analysis (GSEA) identified TNF- α signalling via NF κ B as the most highly enriched upregulated pathway (NES = 2.35, $\text{padj} < 0.001$). Logistic regression and ROC analysis revealed a high performing signature including 3 genes from the leading edge of this pathway (plus serum CA19-9) with an AUC of 0.94 (sensitivity=90%, specificity=90%).

The top 6 DEGs have been validated by qPCR, and we will evaluate protein abundance and cell type by flow cytometry in the coming months. In parallel, we have assessed the serum proteome of 55 stage I/II PDAC patients and 165 high-risk control patients by OLINK. We are currently performing spatial whole transcriptomics in human PDAC and chronic pancreatitis tissues using the Bruker GeoMx® Digital Spatial Profiler.

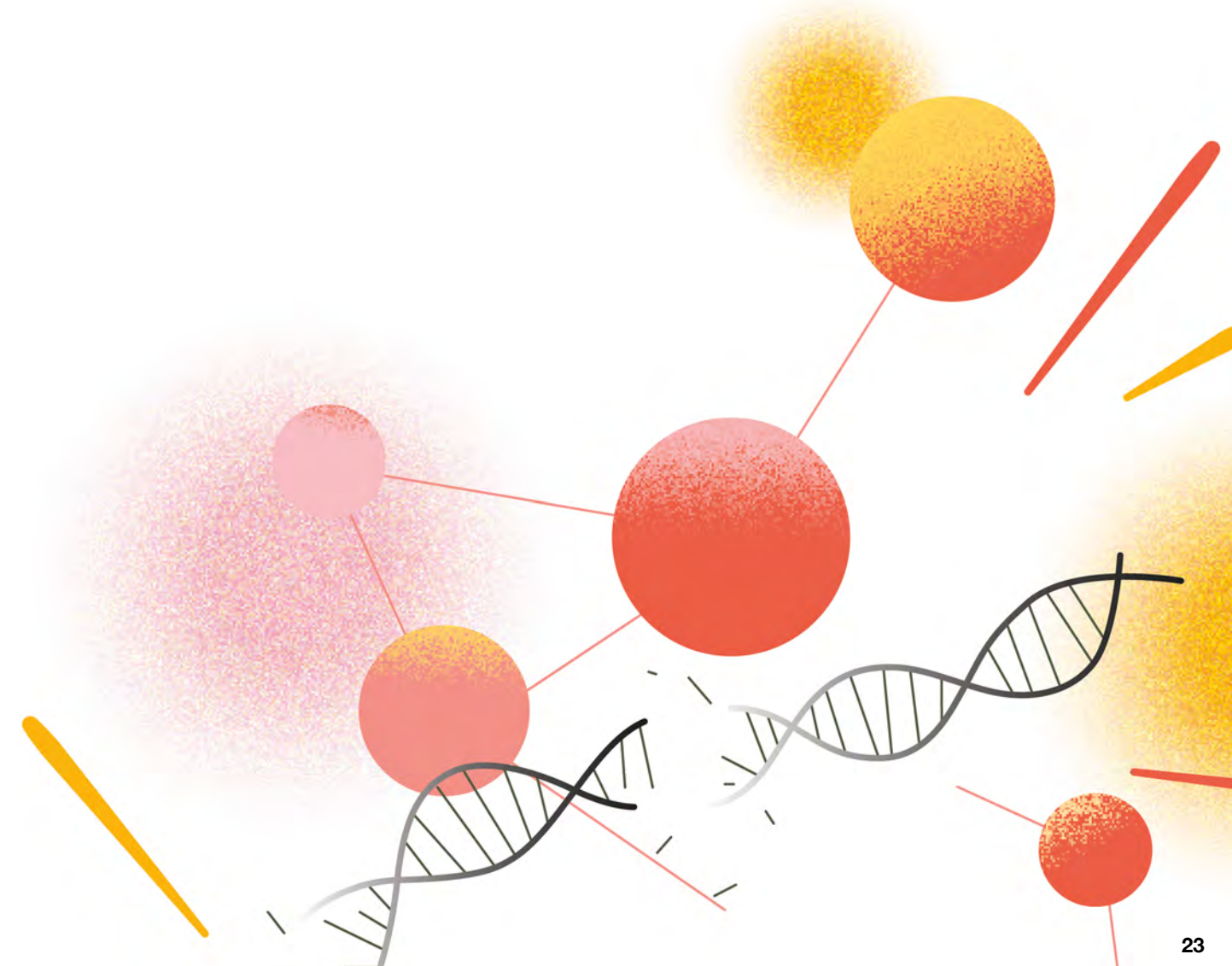
The multi-omic integration of these findings may offer an improved multidimensional view of the systemic and local

immune cell related changes that take place in pancreatic cancer initiation, facilitating its detection at the earliest stages of disease.



SIMPOSIOS

8 DE SEPTIEMBRE





MARTES, 8 DE SEPTIEMBRE

SIMPOSIO 1

S1.1. When Metabolism Has a Clock: Biological Rhythms and Molecular Nutrition

S1.1. - 1

It's all in the Seasoning: How Seasonal Timing Reprograms Metabolic Physiology

GISELA HELFER

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Metabolism is often considered in terms of nutrients, hormones, and energy balance, yet these processes do not occur in isolation from time. Across the animal kingdom, seasonal changes in day length provide a powerful environmental signal that reshapes physiology in anticipation of predictable fluctuations in food availability, temperature, and energetic demands. These adaptations influence body weight regulation, energy expenditure, glucose homeostasis, behaviour, cognition, and reproductive function, highlighting the remarkable plasticity of metabolic systems. Seasonal timing is encoded through neuroendocrine pathways that translate photoperiodic information into coordinated physiological responses. This process involves extensive remodelling of central and peripheral regulatory networks, allowing organisms to transition between distinct metabolic states across the year. Studies in seasonal species have revealed that many traits commonly associated with metabolic dysfunction can arise naturally as adaptive responses to environmental change, providing unique opportunities to understand the mechanisms governing metabolic flexibility and resilience. Growing evidence suggests that environmental timing also influences the way organisms respond to nutritional signals. The physiological effects of diet may vary according to biological context, raising important questions about how nutrition interacts with circadian and seasonal rhythms to shape health outcomes. Understanding these interactions may offer new perspectives on the increasing prevalence of metabolic disease in modern environments characterised by constant food availability and reduced exposure to natural temporal cues. Integrating chronobiology, neuroendocrinology, and nutritional science provides a framework for understanding metabolism as a dynamic process that changes not only according to what is consumed, but also when and under which environmental conditions those signals are received.

S1.1. - 2

Eating timing and metabolic health

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A growing body of evidence suggests that the endogenous circadian clock, the molecular machinery generating 24h rhythms in our body, tightly interacts with metabolic functions. Circadian rhythms are maintaining metabolic health and often disturbed by obesity, type 2 diabetes, and other metabolic diseases. We and others showed previously that the metabolic response to the same food differs in the morning and in the evening suggesting that food timing is an important factor of metabolic regulation. Further, food intake is an external zeitgeber which can entrain circadian rhythms. Therefore, chrononutrition, a novel discipline which investigates the relation between circadian clock, nutrition, and metabolism, has attracted increasing attention in recent years. This talk will present selected results of our research related to the eating timing effects.

Firstly, we demonstrated an association of eating timing parameters (calorie midpoint, timing and energy intake of the first and last meal, meal frequency etc.) with anthropometric measures as well as markers of glucose metabolism. In particular, the calorie midpoint showed robust positive correlations with body mass index and insulin sensitivity in a human cohort.

Secondly, we investigated effects of the time-restricted eating (TRE) which is a promising strategy to improve metabolic outcomes acting at least in a part via the circadian clock. To reveal which eating timing is more beneficial for metabolic health, we compared the impact of the early (eTRE) versus late TRE (lTRE) in overweight or obese women with an increased diabetes risk in a carefully controlled cross-over study. The trial was conducted upon nearly isocaloric calorie intake to separate the eating timing effects from the calorie restriction. Surprisingly, an isocaloric TRE shifted circadian clocks in blood monocytes but did not improve a glycaemic control and other cardiometabolic parameters, suggesting an importance of calorie restriction in TRE effects.

Thirdly, we demonstrated that changes of the diurnal macronutrient distribution in humans induces a marked remodelling of the oscillating and non-oscillating transcriptome related to lipid and glucose metabolism and inflammatory

response and, in this way, affects the whole-body metabolism. Using experiments in isolated human and mouse adipocytes, we showed that a direct entrainment of circadian clock in adipocytes by postprandial insulin might at least partly mediate this phenomenon, providing first evidence that and how the food timing can reprogram adipose tissue transcriptome in humans.

Taken together, our data suggest that eating timing-based strategies represent a promising non-pharmacological tool to restore circadian rhythms and affect metabolic in metabolic diseases, but their effects and mechanisms require further investigation.

S1.1. - 3

Potential role of phenolic compounds in the prevention of alterations caused by circadian disruption

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Circadian rhythms play a fundamental role in the regulation of metabolism and physiological homeostasis. Modern lifestyle factors, including shift work and social jetlag, frequently disrupt these rhythms, increasing the risk of metabolic syndrome and related chronic diseases. Phenolic compounds have emerged as promising bioactive molecules capable of modulating biological clocks and metabolic pathways. Previous studies from our group demonstrated that a grape seed proanthocyanidin extract (GSPE) exerts beneficial effects against several components of metabolic syndrome and influences the expression of clock genes involved in circadian regulation. To investigate the potential of phenolic compounds, specifically GSPE, to prevent or attenuate metabolic alterations induced by circadian disruption and to explore the mechanisms underlying these effects we carried out a study in animal model of chronodisruption. Circadian disruption was induced through alterations of the light-dark cycle, mimicking conditions experienced by shift workers and individuals with irregular schedules. The impact of chronodisruption on metabolic health, hormonal regulation, biological rhythms, and gut microbiota was evaluated. The effects of GSPE supplementation were assessed through physiological, biochemical, metabolomic, and gene expression analyses.

Circadian disruption induced increased adiposity, hormonal and metabolic alterations, and a loss of synchronization among biological systems, including the gut microbiota. These changes were associated with biomarkers indicative of increased cardiometabolic risk. GSPE supplementation partially restored circadian rhythmicity, improved several metabolic parameters, and reduced fat accumulation. Metabolomic and transcriptomic analyses identified novel biomarkers associated with chronodisruption and provided insights into the molecular pathways affected by circadian misalignment.

The findings support the concept that phenolic compounds can modulate circadian biology and may represent a promising nutritional strategy to counteract the adverse metabolic consequences of circadian disruption. Maintaining circadian homeostasis appears essential for metabolic health, and phenolic compounds such as GSPE could contribute to reducing the burden of chronodisruption-associated disorders.

Acknowledgments: Grant Project PID2021-128813OB-IO funded by MCIN/AEI/ 10.13039/501100011033 and by "ERDF A way of making Europe."

SIMPOSIO 2

S2.1. Advances in Extracellular Vesicles for Therapeutic Applications

S2.1. - 1

Extracellular Vesicles: Isolation Strategies, Functional Applications, and Therapeutic Potential

MARCEL-LA FRANQUESA

Group Leader of ENACT (Experimental Nephrology and Advanced Cell-based Therapies), Health Research Institute Germans Trias i Pujol (IGTP); President of GEIVEX.

Extracellular vesicles (EVs) have emerged as key mediators of intercellular communication, with growing relevance as biomarkers and therapeutic agents across diverse pathological settings. However, their nanoscale dimensions continue to pose significant challenges for isolation, characterization, and mechanistic study. In a rapidly expanding field, rigorous methodological standards and transparent reporting are essential to ensure reproducibility and meaningful biological interpretation.

This talk will provide an overview of foundational EV isolation and characterization strategies, highlighting both es-



established approaches and emerging flow-cytometry-based methods designed to improve analytical resolution. I will also present disease-specific functional assays developed to assess therapeutic potency of EV-based interventions, with a particular focus on applications in chronic kidney disease.

S2.1. - 2

Encapsulation of Therapeutics in Biological and Synthetic Vesicles: Engineering Approaches and Functional Advantages

CRISTINA FORNAGUERA

Universitat Ramon Llull, IQS, Barcelona, España

Extracellular vesicles (EVs) have emerged as promising delivery systems due to their intrinsic biocompatibility, low immunogenicity and natural ability to interact with biological tissues. However, their translation into effective therapeutic platforms requires engineering strategies that enable efficient cargo loading, improved transport across biological barriers and selective cellular targeting. In this presentation, I will discuss our work on the development of engineered EVs based on both mammalian and plant-derived EVs, using lemon-derived vesicles as a representative example of scalable and sustainable plant nanocarriers.

Our research focuses on transforming natural vesicles into programmable delivery systems for biomedical applications. We have developed strategies for the encapsulation of therapeutic mRNA and investigated how vesicle engineering can enhance cargo stability and intracellular delivery. In parallel, we have modified EVs surfaces with zwitterionic moieties to improve transport across physiological barriers, including the pulmonary mucus layer, enabling efficient delivery following inhalation. We have also incorporated targeting ligands to promote selective uptake by antigen-presenting cells, opening new opportunities for vaccination and immune modulation.

By combining cargo loading technologies with surface engineering approaches, we aim to establish a versatile platform capable of adapting natural vesicles to different therapeutic applications. The presentation will highlight the functional advantages of engineered biological vesicles, discuss key design considerations governing their performance, and compare their potential with synthetic vesicular systems for the next generation of nanomedicines.

S2.1. - 3

Encapsulation of Extracellular Vesicles in Biomaterials for Local and Sustained Release in Therapy

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Background: Postoperative recurrence remains a major challenge in Crohn's disease (CD) despite biologic therapies. Creeping fat is increasingly recognized as an immunometabolic driver of intestinal inflammation and disease progression and a promising therapeutic target. We developed VesicleX, an acellular extracellular vesicle (EV)-based platform targeting creeping fat to reprogram the inflammatory microenvironment.

Methods: EVs from subcutaneous adipose-derived mesenchymal stem cells were isolated by size-exclusion chromatography (SEC) and characterized by nanoparticle tracking analysis, flow cytometry and cryo-TEM. EVs were incorporated into a lyophilized alginate matrix for sustained local release. Immunomodulatory effects were evaluated *ex vivo* in human creeping fat and intestinal mucosa explants from CD patients and *in vivo* in a TNBS-induced rat colitis model with mesocolic adipose hyperplasia resembling human creeping fat. Inflammatory markers were ana-

lyzed by qPCR, ELISA and histology.

Results: EV treatment significantly reduced pro-inflammatory gene expression (TNF, IL1B, IL6, CCL2) and increased anti-inflammatory signalling (IL10/TNF ratio) in creeping fat and intestinal mucosa explants. EVs promoted macrophage polarisation towards an anti-inflammatory phenotype (IL10, CD163, MRC1). The lyophilised EV-alginate matrix preserved EV stability up to 12 months at room temperature. Release kinetics confirmed sustained EV release from day 1 to day 7, supporting prolonged local bioavailability. *In vivo*, local administration improved disease outcomes, including reduced disease activity index ($p=0.01$), increased colon length ($p=0.047$), improved endoscopic scores ($p=0.045$) and reduced LCN-2 ($p=0.02$), with enhanced mucosal healing.

Conclusions: The lyophilised EV-alginate matrix enables stable, localized and sustained immunomodulatory delivery, promoting reprogramming of creeping fat and intestinal immunity. This approach addresses an unmet need in preventing postoperative recurrence in CD and supports next-generation EV-based therapies.

SIMPOSIO 3

S3.1. Fat Matters: Impact on Cancer, Obesity, and Liver Disease

S3.1. - 1

Adipocytes in Action: Shaping the Tumor Microenvironment

AINA LLUCH BALAÑA

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Obesity and excess adiposity are associated with an increased risk of developing up to 18 different cancer types. Beyond serving as energy reservoirs, adipocytes actively contribute to tumor initiation and progression by promoting chronic inflammation, altering cellular signaling, and shaping a supportive tumor microenvironment (TME). In ovarian cancer (OC), the deadliest gynecological malignancy due to its late diagnosis, the omentum represents the first metastatic site, highlighting the central role of adipose tissue in disease progression.

Within the ovarian cancer TME, adipocytes undergo phenotypic and functional reprogramming in response to tumor-derived signals, giving rise to cancer-associated adipocytes (CAAs). These cells secrete a broad range of

bioactive molecules, including cytokines, adipokines, lipids, and extracellular vesicles (EVs), which contribute to tumor growth, metastatic dissemination, and immune modulation. Increasing evidence indicates that adipocytes can influence antitumor immunity, including the activity of natural killer (NK) cells, key effectors of immune surveillance. However, the crosstalk between adipocytes and NK cells in this scenario remains largely unexplored.

Using proteomic profiling of adipocyte-derived EVs and total secretomes from murine and human *in vitro* models, we identified multiple NK-cell receptor ligands associated with immune regulation. Notably, CAAs exhibited an enrichment of inhibitory NK-cell ligands within their secretome, including EV-associated proteins, suggesting a previously underappreciated mechanism by which adipocytes may suppress NK-cell cytotoxic activity and facilitate immune evasion in ovarian cancer.

These findings highlight adipocytes as active regulators of the ovarian cancer microenvironment and uncover adipocyte-NK cell crosstalk as a promising area of research. Understanding how CAAs reshape immune responses may reveal novel therapeutic opportunities to overcome immune suppression and improve outcomes for patients with ovarian cancer.

S3.1. - 2

Life of a Fat Cell in Health and Disease

FRANCISCO JOSÉ ORTEGA DELGADO

Institut d'Investigació Biomèdica de Girona Dr. Josep Trueta (IDIBGI), Gerona, España

Impaired adipose tissue function is a central mechanism whereby aging and excessive adiposity contribute to cardiometabolic complications and the risk of illnesses primarily driven by genetics, lifestyle, and/or environment. This relationship aligns with altered cellular programs within fat depots, particularly in adipocyte composition and phenotype, that can impair adipose synthetic and secretory functions. The adipose tissue is a pivotal metabolic and endocrine organ. Complex, plastic, and dynamic, it represents one of the most prominent defenses against inappropriate life habits. The quintessential adipose cell-type, the adipocyte, is a highly specialized but versatile and malleable cell. As custodian of the body's main energy stocks, its plasticity and endocrine communication shape adipose function to the point of explaining disease causation. With an average lifespan of about 10 years, those adipocytes, the most prevalent cell population in body fat, contribute to the homeostatic maintenance through both auto-paracrine and long-distance signaling. While exposure to calorie-dense diets, accompanied by infrequent or poor physical activity, results in an unremitting caloric surplus, enhanced adipogenesis not only





distributes energy among newly formed adipocytes (which is good) but also increases the number of hypertrophic adipocytes (which is bad). These large adipocytes release pro-inflammatory cytokines related to the hypoxic stress, followed by recruitment and activation of immune cells towards meta-inflammation, the chronic, low-grade systemic inflammation that is primarily triggered by nutrient excess and metabolic stress. The adipogenic niche can also compromise tissue adipogenic capability to a point at which adipocytes transdifferentiate back into mesenchymal precursor cells. Such plasticity is exemplified in pregnancy, when adipocytes located at the stromal compartment of mammary glands gradually disappear in response to proliferation of the ductal epithelium and formation of milk-secreting alveoli during lactation. These are just a few examples of the lesser known aspects of fascinating fat cells, which consistently still offer numerous opportunities for the discovery of new biomarkers and targets for pharmacological intervention in the field of lifestyle-related non-communicable diseases.

SIMPOSIO 4

S4.1. From Structural Biology to Therapy: Rediscovering Amyloid Proteins

S4.1. - 1

A Structure-Based Strategy to Target Pathogenic α -Synuclein in Parkinson's Disease

SALVADOR VENTURA

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α -Synuclein (aSyn) aggregation is a key factor in neurodegeneration in Parkinson's disease (PD). We have used the different structural properties of toxic oligomers and amyloid fibrils to identify a family of peptides that bind to these a-synuclein species with low nanomolar affinity without interfering with the monomeric, functional protein. This activity results in high anti-aggregation potency and the ability to prevent oligomer-induced neuronal damage. With a structure-function relationship established, we identified human candidates with similar binding, anti-aggregation, and detoxifying properties. Administration of the leading candidate in a PD animal model preserved the nigrostriatal pathway and completely prevented motor dysfunction.

Using a combination of structural methods, including cryo-EM, ssNMR, SAXS, XL-MS, and HXD-MS, we have delineated the interaction region between these peptides and aSyn in the context of oligomers. Deletion or mutation of this region abolishes both aSyn aggregation and neurotoxicity, validating it as a disease-relevant structural hotspot. This provided the foundation for generating conformation-specific nanobodies and human IgGs that selectively recognize toxic oligomers and suppress aSyn amyloid formation. Collectively, our findings define a new structure-based therapeutic paradigm for PD, providing both disease-modifying agents and conformation-specific tools with strong potential for diagnosis and intervention in synucleinopathies.

S3.1. - 3

The Magnesium Link: Connecting Micronutrient Balance to Cancer, Obesity, and Liver Dysfunction

MALU MARTINEZ CHANTAR

Centro de Investigación Cooperativa en Biociencias, CIC bioGUNE, Bilbao, España

Magnesium homeostasis is emerging as a critical regulator of metabolic and hepatic disease progression. Our work highlights the role of magnesium transport and signaling pathways, particularly the CNNM4 axis, in the transition from metabolic dysfunction-associated steatotic liver disease (MASLD) to liver injury and cancer. Through studies in alcohol-associated liver disease and cholangiocarcinoma, we demonstrate that altered magnesium balance is tightly linked to inflammation, mitochondrial dysfunction, metabolic stress, and tumor-promoting mechanisms. In parallel, our findings support the existence of a brain-liver communication axis in which micronutrient imbalance contributes to systemic metabolic dysregulation and hepatic pathology. Together, these studies position magnesium not only as a metabolic biomarker but also as a potential therapeutic target connecting obesity, liver dysfunction, and cancer development.

S4.1. - 2

Extracting mechanistic insights into amyloid formation by deep mutagenesis

BENEDETTA BOLOGNESI

Institute for Bioengineering of Catalunya, IBEC, Barcelona, España

Understanding how protein sequence determines amyloid formation remains a central challenge in molecular biology. While structural and biophysical approaches have provided detailed insights into mature amyloid assemblies, the transient molecular events that govern nucleation and early self-assembly are often difficult to access experimentally. Deep mutational scanning is a powerful route to interrogate amyloid formation at unprecedented scale and extract mechanistic information directly from sequence-function relationships. By systematically measuring the effects of thousands of mutations on amyloid nucleation and assembly, we can identify the sequence determinants that promote or slow down aggregation. We show how comprehensive mutational landscapes of amyloid proteins can aid the interpretation of human genetic variation by identifying pathogenic gain-of-function mutations. Beyond variant interpretation, large-scale measurements of interactions between mutations can be leveraged to probe the transition states of amyloid nucleation, capturing signatures of transient species that are otherwise challenging to characterize experimentally. Finally, extending these approaches to functional amyloids and broader sequence spaces enables the discovery of general principles governing amyloid assembly and function across biological systems. Together, our results demonstrate how large-scale exploration of sequence space can bridge human genetics, biophysics, and evolution to uncover the molecular principles governing amyloid formation.

S4.1. - 3

Amyloid assemblies as signaling platforms: insights from solid-state NMR spectroscopy

MIGUEL MOMPEÁN

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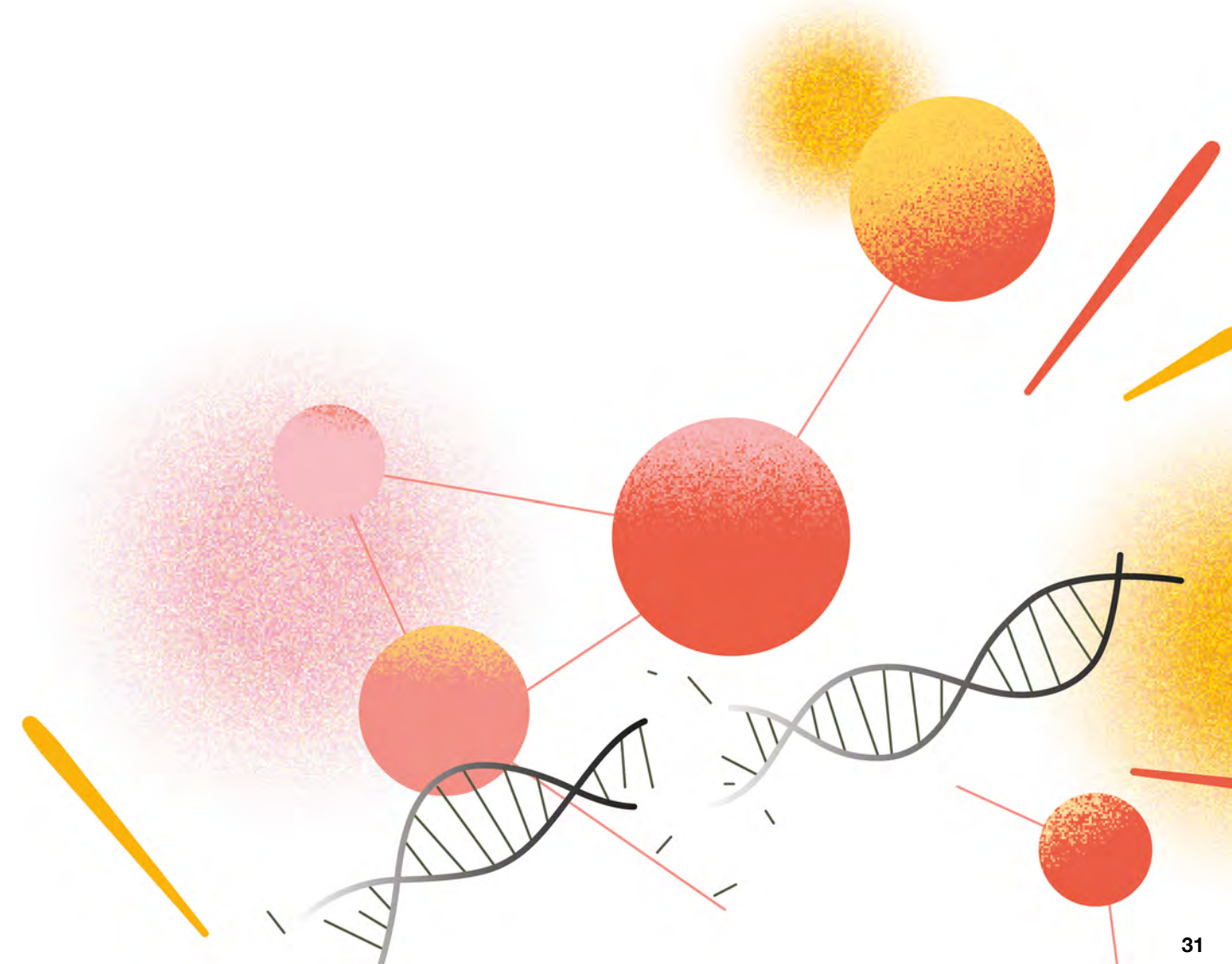
RIP homotypic interaction motif (RHIM)-containing proteins assemble into functional amyloids that act as signaling platforms in necroptosis and can be mimicked or rewired by viral factors. These systems illustrate how amyloid assembly can encode biological specificity rather than simply reflect generic fibril formation. Our work uses solid-state NMR spectroscopy, together with complementary structural and biophysical approaches, to investigate how signaling amyloids achieve selective self- and cross-assembly.

A central focus is the idea that determinants of specificity extend beyond the canonical RHIM tetrad. In particular, we are exploring the role of residues outside the core motif, both within the fibril-forming region and in the surrounding fuzzy coat, in shaping partner recognition and assembly outcome. Our ongoing results suggest that a conserved asparagine outside the tetrad contributes non-equivalently in human RIPK1 and RIPK3, pointing to an unexpected asymmetry in how these two RHIMs encode heteromeric assembly. Extending this analysis to additional host and viral RHIMs further suggests that variation at the equivalent position, including substitution by cysteine in ICP6-like motifs, may modulate compatibility and introduce additional regulatory features. In parallel, distinct RHIM proteins appear to sample different fuzzy-coat conformational ensembles, which may include extended polyproline II structure. Together, these observations support a broader view of signaling amyloids as structured yet tunable assemblies in which both the amyloid core and the dynamic periphery contribute to molecular recognition and functional outcome.



SIMPOSIOS

9 DE SEPTIEMBRE





MIÉRCOLES, 9 DE SEPTIEMBRE

SIMPOSIO 1

S1.2. Modulating the Biology of Ageing Through Nutrition: Molecular Mechanisms and Emerging Interventions

S1.2. - 1

The Bitter Side of Ageing: How TAS2R Signalling Shapes Gut Function and Systemic Ageing Biology

XIMENA TERRA BARBADORA

Universitat Rovira i Virgili, Tarragona, España

Ageing is accompanied by a progressive decline in physiological function and an increased susceptibility to metabolic and inflammatory disorders. A central feature of this process is immune dysregulation, which contributes to chronic low-grade inflammation, commonly referred to as inflammageing. The gastrointestinal tract plays a key role in this context, acting not only as a site for nutrient absorption but also as a major barrier against luminal antigens, microbial products and pro-inflammatory stimuli. Age-related alterations in intestinal epithelial integrity may therefore promote the translocation of molecules such as lipopolysaccharide (LPS), amplifying systemic inflammation and contributing to ageing-associated metabolic dysfunction.

Bitter taste receptors (TAS2Rs), originally described in the oral cavity, are now recognised as extra-oral chemosensory receptors involved in the regulation of gastrointestinal physiology, immune responses and epithelial barrier function. Nutritional bioactives, including grape-seed proanthocyanidin extract (GSPE) and other bitter compounds, may activate TAS2R-dependent pathways and contribute to protective effects in ageing.

This presentation will discuss recent findings on the expression and functional relevance of TAS2Rs in the gastrointestinal tract during ageing, with particular focus on their relationship with inflammation, intestinal permeability and microbiota-associated changes. Evidence from animal models of ageing will be integrated to illustrate how TAS2R expression and signalling are modulated in aged organisms and how these changes may relate to age-associated alterations in gut function and systemic homeostasis. In addition, the presentation will describe a strategy for identifying TAS2R-targeting bioactive compounds associated with metabolic protection, together with in vitro, ex vivo and in

vivo evidence supporting their effects on epithelial barrier integrity and inflammatory responses, including models of LPS-induced systemic inflammation.

Overall, these findings support TAS2Rs as functional nodes linking nutrient sensing, gut barrier homeostasis and immune regulation. Targeting bitter taste receptor signalling may therefore represent an emerging nutritional strategy to modulate gut function and systemic ageing biology.

S1.2. - 2

Energy Restriction via Time Restricted Feeding: Metabolic and Biological Impact

ANDRE SARMENTO-CABRAL, MARTA G. NOVELLE, LUZ MARINA SÁNCHEZ-MENDOZA, NATALIA HERMAN-SANCHEZ, SAMANTA LOZANO DE LA HABA, MARTA RODRIGUEZ-VAZQUEZ, PABLO ITURBE, EDUARDO CHICANO-GÁLVEZ, FRANCISCO JAVIER CUBERO, RAUL M. LUQUE JOSE CORDOBA-CHACON JUAN L. LOPEZ-CANOVAS, JOSE M VILLALBA, MANUEL D. GAHETE, **ALBERTO DIAZ-RUIZ**

IMDEA Nutrition

Moderate caloric restriction is reported as a robust nutritional intervention with the capacity to promote metabolic health and extend lifespan. Time-restricted feeding (TRF) is also a relevant dietary strategy to counteract obesity and metabolic disorders. Herein, we implemented more pragmatic TRF interventions in male mice with chronic metabolic dysfunction previously established by prolonged high-fat, high-cholesterol, high-fructose feeding. These interventions (i) elicited comparable and significant improvements in whole-body physiology, (ii) promoted key hallmarks of energy restriction, and (iii) induced a coordinated transcriptional and lipidomic remodeling. Despite this, the overall outcomes were less pronounced than those achieved via dietary normalization with standard chow, highlighting the need to combine TRF with complementary therapeutic approaches.

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S1.2. - 3

Extracellular Vesicles in Aging: Molecular and Cellular Mechanisms

CONSUELO BORRAS BLASCO

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Aging causes a progressive decline in tissue function through interconnected processes, including oxidative damage, chronic low-grade inflammation, cellular senescence, and a gradual breakdown of intercellular communication. Small extracellular vesicles (sEVs) have attracted increasing interest as natural carriers of paracrine signals between cells, and recent evidence suggests they may actively influence aging-related processes.

Our work explores this biology from two complementary angles. On one hand, we have examined how sEVs derived from young adipose mesenchymal stem cells (ADSC-sEVs) can counteract aging when administered systemically to old mice. Across multiple tissues, including skeletal muscle, kidney, heart, liver, and brain, ADSC-sEV treatment consistently reduced oxidative stress, inflammation, and senescent cell burden while promoting tissue-specific regeneration. Functionally, treated animals showed improvements in physical performance, frailty scores, cardiac diastolic function, metabolic flexibility, and neurobehavioral parameters, including motor coordination and memory. The metabolome of treated mice, both in plasma and heart tissue, shifted towards profiles more reminiscent of those of young animals. Mechanistically, we have identified the taurine transporter TauT as a cargo enriched in young ADSC-sEVs that is delivered to the aged brain in vivo, and whose blockade abolishes the neurological benefits of treatment, linking a specific molecular cargo to a defined functional outcome for the first time in this context.

On the other hand, to understand how EV biology changes in human aging, we have profiled the miRNA cargo of plasma-derived sEVs across four age-defined groups: young adults, centenarians, centenarian offspring, and non-centenarian offspring, stratified by frailty status. Centenarians and their offspring share a miRNA expression profile similar to that of young individuals, enriched in regulators of proteostasis, intercellular communication, and structural integrity, whereas frail individuals show a collapse of this protective landscape towards pro-inflammatory and pro-senescent signatures.

Together, these results support a model in which the quality of EV-mediated intercellular signaling is a key determinant of aging trajectories, and that restoring a youthful EV environment, either exogenously or as a feature of exceptional longevity, is a potential strategy to delay the functional decline associated with aging.

SIMPOSIO 2

S2.2. Microbiota Crosstalk with Peripheral Organs: From Liver Metabolism to Brain Function

S2.2. - 1

When gut viruses talk to the brain: Microviridae bacteriophages modulate food addiction

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Food addiction is a relevant contributor to the obesity pandemic, affecting approximately one in five individuals. However, the molecular mechanisms linking the gut microbiome to food addiction remain largely unclear. Using shotgun metagenomic analyses, we identified bacteriophages from the *Microviridae* family, particularly *Gokushovirus* WZ-2015a, as being associated with food addiction, assessed using the Yale Food Addiction Scale 2.0 (YFAS 2.0), and with obesity across multiple human cohorts.

Functional analyses revealed that food addiction and *Gokushovirus* are linked to serotonin and dopamine metabolism. Faecal microbiota transplantation (FMT) and faecal virome transplantation (FVT) from human subjects with a higher *Gokushovirus* load induced increased food addiction-like behaviour in mice, together with changes in tryptophan, serotonin and dopamine metabolism across different brain regions, as well as alterations in dopaminergic receptors.

Targeted analyses of tryptophan metabolism identified lower concentrations of anthranilic acid (AA) associated with *Gokushovirus*. AA supplementation in mice reduced food addiction-like behaviour and altered pathways related to neurotransmitter synthesis and release. In *Drosophila melanogaster*, AA supplementation regulated feeding behaviour and addiction-like ethanol preference, accompanied by changes in the dopaminergic system.

Overall, these findings suggest that bacteriophages within the gut microbiome may contribute to the regulation of food addiction by modulating tryptophan and tyrosine metabolism, revealing a microbiome-metabolite-brain axis relevant to obesity-associated addictive-like eating behaviour.



S2.2. - 2

Early life microbiota–diet interactions: Insights from cohort data to in vitro studies on health outcomes

MARIA CARMEN COLLADO

Instituto de Agroquímica y Tecnología de Alimentos, IATA-CSIC, Paterna, España

Early life period is critical for the interaction between diet and microbiome, which shapes immune, metabolic and neurodevelopmental trajectories with long-term health consequences. This presentation will provide an overview of the evidence obtained from a prospective mother–infant cohort and complementary in vitro and in vivo mechanistic studies, with the aim of improving our understanding of how early-life nutritional exposures influence microbiome development and function. Particular emphasis will be placed on breastfeeding, bioactive components of human milk, and microbial-derived metabolites as key modulators of host–microbiome interactions. Integrating clinical, multi-omics, and experimental approaches, this presentation will show how observational findings can be translated into mechanistic insights. This opens new opportunities for the development of microbiome-targeted nutritional strategies to promote lifelong health.

S2.2. - 3

Microbial Histidine Catabolism: Unlocking New Therapies for Metabolic Dysfunction

XAVIER ESCOTE

Universitat Rovira i Virgili, Tarragona, España

Obesity and its associated comorbidities, particularly Non-Alcoholic Fatty Liver Disease (NAFLD), represent a critical global health challenge. Recent research into the gut–liver axis has identified a significant link between the gut microbiota, histidine metabolism, and the progression of metabolic disorders. This work highlights that plasma histidine levels are negatively correlated with the degree of hepatic steatosis in human cohorts.

Metagenomic and transcriptomic analyses reveal that patients with advanced steatosis exhibit increased activity in microbial histidine catabolism pathways (the Hut pathway). Experimental evidence confirms that this relationship is causal: fecal microbiota transplantation (FMT) from low-histidine donors and mono-colonization with *Enterobacter cloacae* in model organisms lead to increased hepatic triglyceride accumulation and the upregulation of pathways favoring lipid storage.

Conversely, the study demonstrates the therapeutic potential of Histidine Amino Acid (HAA) supplementation. In *Drosophila melanogaster* and various animal models—including diet-induced, genetic, and surgical models—HAA supplementation significantly ameliorated the hallmarks of NAFLD. In addition, new results have highlighted the role of histidine in obesity, finding that histidine metabolism deregulation in adipose tissue is associated with increased adiposity.

In conclusion, these findings establish the gut microbiota–histidine axis as a key regulator of metabolic health. Restoring histidine levels through HAA supplementation offers a promising, multi-faceted therapeutic strategy for the management of obesity and NAFLD.

SIMPOSIO 3

S3.2. Simposio Hispano-Mexicano. Computational Drug Design: Reality and Challenges in the Era of Artificial Intelligence

S3.2. - 1

When Does Structure-Based Drug Design Really Work? Lessons, Limitations, and Good Practices

SANTIAGO GARCIA-VALLVÉ

Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia. Research group in Nutrigenomics. Cheminformatics & Nutrition Unit. Tarragona.

The rapid growth of artificial intelligence (AI) in drug discovery is expanding access to advanced computational tools, accelerating research while also increasing the risk of misuse when methods are applied without proper validation or critical interpretation.

The reliability of structure-based drug design depends first on the careful selection and validation of protein structures, particularly when multiple conformations are available for the same target. Structural quality and biological relevance must be critically assessed, and dedicated tools can assist in the systematic evaluation and comparison of available structures.

Equally important is the validation of computational methods such as molecular docking. Protocols should be evaluated through re-docking to assess pose prediction accuracy and through cross-docking to measure robustness across different protein conformations and to guide structure selec-

tion. Benchmarking using known active and inactive compounds is essential to ensure meaningful discrimination, while docking scores should be interpreted cautiously, as their correlation with experimental activity is often limited.

Recent advances in structure prediction and AI-based approaches provide powerful new opportunities, but their applicability remains context-dependent and requires careful validation. Overall, computational approaches are best viewed as tools for prioritization and hypothesis generation rather than definitive predictors. While AI is contributing to the democratization of drug discovery, it also reinforces the need for methodological rigor and critical assessment. Experimental validation remains the ultimate benchmark, and the primary goal of computational workflows is to support the efficient identification of the most promising candidates for testing.

S3.2. - 2

Chemical Space Characterization and Activity Cliffs: Insights for Reliable Virtual Screening and Predictive Modeling

JOSÉ L. MEDINA-FRANCO

DIFACQUIM research group, Department of Pharmacy, School of Chemistry, National Autonomous University of Mexico, Mexico City, Mexico

Computational drug discovery increasingly relies on virtual screening and machine learning approaches to prioritize compounds and guide decision-making. However, the reliability of these methods strongly depends on the quality, diversity, and biological relevance of the underlying chemical data. In this lecture, I will discuss how chemical space characterization and activity cliff analysis can provide key insights for improving the interpretation and predictive power of computational models. Emphasis will be placed on the systematic characterization of compound libraries employed in virtual screening, including the assessment of structural diversity, molecular representation, and the coverage of biologically relevant regions of chemical space. The lecture will also examine activity and property cliffs, pairs or groups of structurally similar molecules displaying large differences in biological activity, as valuable sources of mechanistic insight and critical benchmarks for predictive modeling. Through representative case studies, I will illustrate how small structural modifications may profoundly alter biological response and model performance. Finally, the talk will discuss the importance of high-quality experimental data for training, validation, and interpretation of predictive models, emphasizing best practices for more reliable and biologically meaningful computational drug discovery.

S3.2. - 3

Harnessing AI to Discover a Chemical Probe for Every Human Protein

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Vall d'Hebron Institute of Oncology, VHIO, Barcelona, España

Despite remarkable advances in precision medicine, approved drugs currently modulate only a small fraction of the human proteome, leaving thousands of proteins without chemical tools to study their biology or evaluate their therapeutic potential. This limited coverage represents one of the major bottlenecks in drug discovery and restricts the ability of artificial intelligence (AI) methods to generalize beyond well-studied targets.

In this lecture, I will discuss the challenges and opportunities of applying AI to computational drug discovery in an era characterized by unprecedented volumes of biological, chemical and structural data. I will highlight how the success of modern AI approaches is critically dependent on the availability of high-quality experimental data, particularly for understudied proteins where ligand information remains scarce. In this context, I will present recent international open-science initiatives, including Target 2035, MAINFRAME and the Innovative Health Initiative (IHI) project LIGAND-AI, which aim to generate and openly share large-scale protein–ligand interaction datasets to accelerate the development and benchmarking of next-generation AI models.

I will also discuss emerging opportunities enabled by these resources, including the development of foundation models for hit identification and the systematic exploration of ultra-large chemical spaces. Finally, I will illustrate how the integration of AI, systems chemical biology and experimental validation can reveal previously unrecognized therapeutic opportunities through the characterization of drug metabolites, expanding both the druggable proteome and our current pharmacological arsenal.

Together, these efforts illustrate how multidisciplinary collaboration, open science and AI-driven approaches are transforming the discovery of small-molecule modulators and bringing us closer to the long-term goal of developing a chemical probe for every human protein.



SIMPOSIO 4

S4.2. Transcription/mRNA decay coupling and its impact on gene expression

S4.2. - 1

Gene-Specific Transcript Buffering Through Coupled RNA Synthesis, Export and Decay

FAEZEH FOROUZANFAR, FANNY LEBOS, AUDREY FURST, DAVID MORENO, DAMIEN PLASSARD, BERNARDO REINA-SAN MARTIN, LASZLO TORA, NACHO MOLINA AND **MANUEL MENDOZA**

Institute of Genetics and Molecular and Cellular Biology (IGBMC), Strasbourg, France

Maintaining appropriate RNA levels is essential for cellular homeostasis despite fluctuations arising from intrinsic and environmental perturbations. Transcript buffering, whereby changes in RNA synthesis are compensated by opposing changes in RNA turnover, has traditionally been viewed as a global phenomenon acting across the transcriptome. However, the mechanisms that enable buffering at the level of individual genes remain poorly understood.

Using acute depletion of the transcriptional coactivator TIP60/KAT5 in mouse embryonic stem cells, we previously demonstrated that transcript buffering operates in a gene-specific manner. By combining measurements of newly synthesized, nuclear and cytoplasmic RNA with quantitative modeling, we found that changes in transcription are accompanied by compensatory alterations in RNA export and stability. As a result, many transcripts maintain relatively stable steady-state levels despite substantial changes in synthesis rates. These findings revealed that RNA export and decay are dynamically coordinated with transcription to preserve transcript homeostasis.

Building on these findings, I will present new evidence that transcript buffering extends beyond post-transcriptional regulation. Ongoing work indicates that TIP60 promotes recruitment of RNA polymerase II to active genes, but that reduced polymerase recruitment can be compensated within the transcription process itself, thereby sustaining RNA synthesis despite decreased polymerase occupancy. Together, these observations suggest the existence of multiple successive buffering layers acting along the gene expression pathway. A first layer operates within transcription to maintain RNA synthesis output in the face of altered polymerase recruitment, while a second layer couples RNA synthesis to export and decay to stabilize transcript abundance. These

findings support a model in which gene expression robustness emerges from nested buffering mechanisms acting sequentially from transcription initiation to RNA turnover.

S4.2. - 2

Co-transcriptional licensing of cytoplasmic mRNA decay controlling inflammation

PAVEL KOVARIK

University of Vienna, Vienna, Austria

AU-rich element (ARE)-mediated mRNA decay (AMD) is a key driver of regulated degradation of unstable mRNAs. Most prominent mRNAs targeted by AMD include those coding for cytokines and growth factors, highlighting the essential function of this degradation pathway in control of inflammation and cell growth. Although AMD takes place in the cytoplasm, surprisingly, the process is licensed in the nucleus, as revealed in our recent study. AMD is dependent on RNA-binding proteins (RBPs) which serve as adaptors connecting the target mRNA with the deadenylation and decapping enzymes. We showed that AMD driven by the RBP tristetraprolin (TTP, Zfp36), an essential suppressor of inflammation, is licensed in the nucleus through TTP binding to pre-mRNA, which we unexpectedly found to be the principal TTP target rather than the mature mRNA. Following processing of TTP-bound pre-mRNAs to mRNAs and nuclear export, the TTP-mRNA complex recruits the cytoplasmic RNA degradation machinery. These findings establish that the fate of TTP targets is decided already at the level of pre-mRNA, hence before the spliced and mature mRNA reaches the cytoplasm. The consequence of this hierarchical regulation is that TTP-bound RNAs are degraded, not translated, once they enter the cytoplasm, thereby preventing hyperinflammation. We are currently following the hypothesis that TTP loading onto target RNA occurs co-transcriptionally and that only AREs in nascent transcripts can be recognized as binding sites by TTP and other AMD-active RBPs. Data supporting the existence of this fate decision step in the mRNA life cycle will be presented.

S4.2. - 3

Sfp1: a zinc-finger protein that couples transcription elongation to mRNA decay regulation

SEBASTIÁN CHÁVEZ¹, LOLA DE MIGUEL¹, ANTONIO JORDÁN-PLA², XENIA PEÑATE¹, M^ªCRUZ MUÑOZ-CENTENO¹, JOSÉ E. PÉREZ-ORTÍN²

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The yeast protein Sfp1 is a member of the zinc-finger transcription factor family, traditionally known for stimulating the synthesis of ribosomal proteins and ribosome biogenesis factors. However, our recent research demonstrates that Sfp1 is a multifaceted crosstalk factor that bridges the gap between nuclear transcription and cytoplasmic mRNA decay.

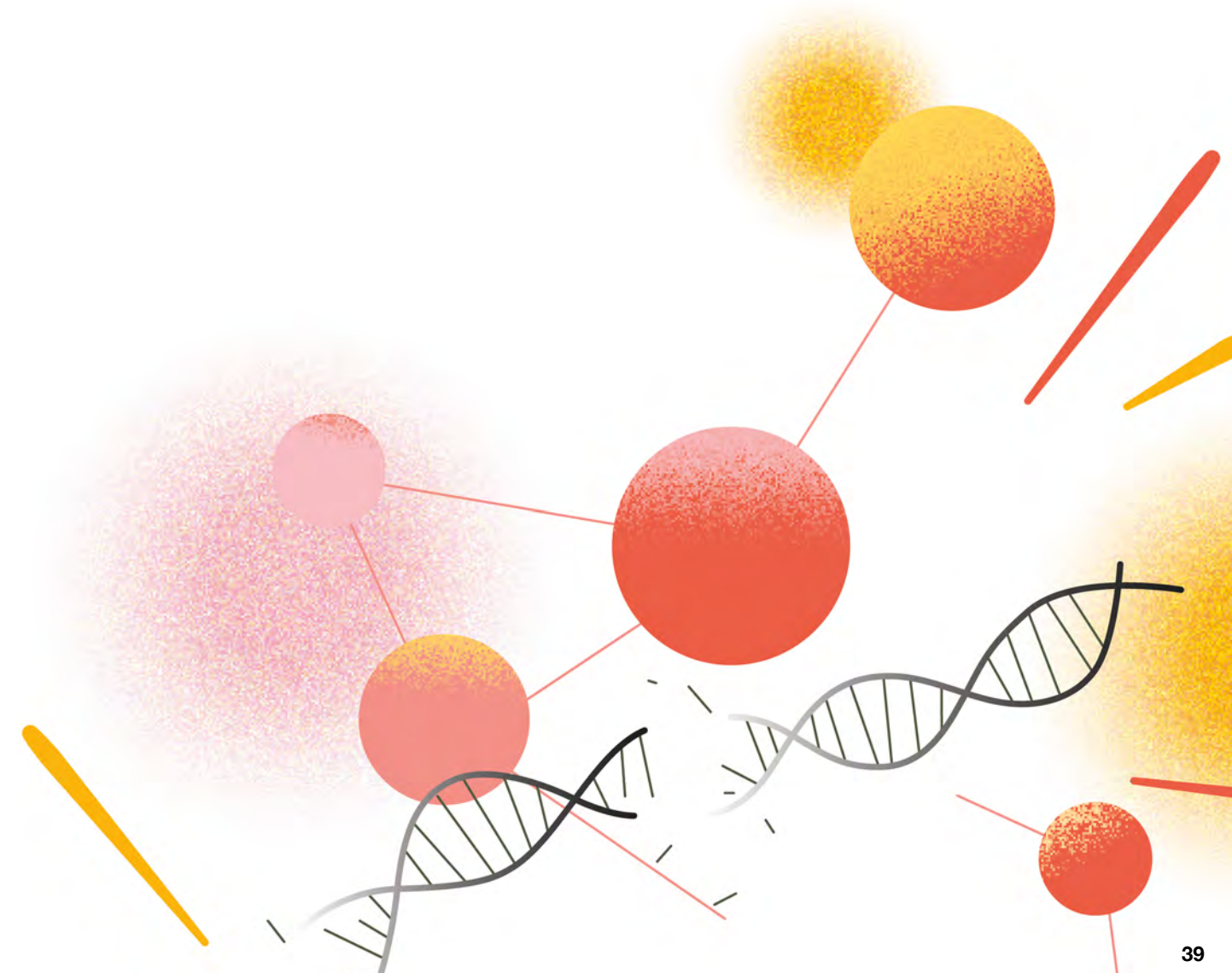
Sfp1 utilizes its unique structural properties to “imprint” mRNAs, ensuring that the nuclear history of a transcript dictates its cytoplasmic fate. A central clue of the mechanistic link between transcription elongation and imprinting is the physical interaction of Sfp1 with RNA polymerase II (Pol II), specifically with its Rpb4 subunit. This association alters the elongating Pol II configuration, increasing backtracking—a process where the polymerase moves backward along the DNA template. It is proposed that this backtracked state creates a kinetic window that facilitates the “partner switch” of Sfp1 from the polymerase to the nascent mRNA.

This co-transcriptional imprinting is highly specific and governed by promoter elements, particularly Rap1-binding sites, which determine which transcripts Sfp1 will accompany to the cytoplasm. Once exported, Sfp1 stabilizes its “client” mRNAs by slowing down the deadenylation-dependent decay pathway.

In contrast to other transcription/decay cross-talk factors that buffer gene expression to maintain constant mRNA levels, Sfp1 acts as an enhancing gene expression driver, stimulating synthesis while simultaneously repressing decay to rapidly increase mRNA abundance in response to growth cues. Ultimately, Sfp1 serves as a paradigm for how many zinc-finger proteins coordinate the entire life cycle of mRNAs to facilitate integrated gene regulation.



CONFERENCIAS DE EMPRESAS





MARTES, 8 DE SEPTIEMBRE

CP-01 BIORAD

Western Blot reproducible: integridad de datos, trazabilidad y cuantificación multiplex

MARC MARTIN

Product Specialist

El western blot sigue siendo una técnica central para el análisis de proteínas, pero su valor científico depende cada vez más de la trazabilidad de la imagen, la transparencia en el procesado y la elección adecuada de la estrategia de detección y normalización. Esta charla abordará la integridad de los datos en western blot desde una perspectiva práctica: cómo adquirir, archivar y documentar imágenes originales; cómo aplicar ajustes de presentación sin comprometer la cuantificación; y cómo reportar de forma clara los parámetros de captura, el procesado y los controles utilizados.

A partir de este marco, se discutirá el impacto de la elección del método de detección en la calidad del dato, comparando quimioluminiscencia y detección fluorescente en términos de linealidad, reproducibilidad y capacidad de multiplexación. En particular, la detección fluorescente permite la adquisición simultánea de múltiples dianas en una misma membrana, reduce la variabilidad asociada a *stripping & reprobing*, y facilita enfoques cuantitativos más robustos.

El objetivo es mostrar cómo un workflow integrado puede reducir variabilidad técnica, conservar evidencias primarias y reforzar la reproducibilidad. También se discutirán sus limitaciones, destacando la necesidad de validar la normalización en cada sistema biológico y de mantener el análisis cuantitativo sobre imagen cruda. La sesión combinará criterios de buenas prácticas con ejemplos aplicados para situar la captura de imágenes como un elemento crítico en la calidad del dato.

CP-02 ECOGEN

El fin de la Era Científico Artesano

LAURA SANZ-SÁNCHEZ

PhD, Scientific Sales Manager

La evolución en la extracción de ácidos nucleicos durante las últimas cuatro décadas ha transformado la biología molecular y la biotecnología. Históricamente, el aislamiento del material genético dependía de protocolos engorrosos, largos y peligrosos. Estos requerían reactivos tóxicos como el fenol o el cloroformo, y presentaban riesgos físicos y químicos para el operador. Además, los resultados dependían de la destreza manual del operador. La revolución tecnológica de los últimos años ha acelerado los diagnósticos clínicos y por tanto resultados en biomedicina mejorando la reproducibilidad experimental y disminuyendo drásticamente los tiempos de procesamiento. La automatización integral ha permitido procesar múltiples muestras de manera simultánea, minimizando el error humano en el pipeteo. Sin embargo, esta transición plantea nuevos retos y desafíos para la comunidad científica. Al delegar la labor técnica en nuevos equipos de procesamiento y extracción, el científico asume un rol de supervisor y analista. El éxito en la ciencia moderna dependerá en no sólo aceptar ciegamente los resultados emitidos por el equipo sino en mantener el espíritu crítico que siempre ha acompañado al método científico. La identificación de posibles sesgos o fallos en el sistema automatización serán clave para una correcta interpretación y la validación de los datos obtenidos.

CP-03 AGILENT

3D Biology 2.0: innovación, aplicaciones y casos prácticos con Seahorse, xCELLigence eSight y Cytation

MIRIAM GUADALUPE CONTRERAS MOSTAZO

PhD. Product Specialist CMR Agilent Technologies

En los últimos años, la transición desde los modelos celulares 2D convencionales hacia sistemas tridimensionales (3D) ha transformado profundamente la investigación biomédica, aportando modelos más fisiológicamente relevantes y predictivos. Sin embargo, este cambio también ha planteado una complejidad biológica y nuevos retos analíticos, tecnológicos y de interpretación de datos. Tras una primera aproximación a las novedades en tecnología 3D presentadas el año pasado, esta ponencia "3D Discovery 2.0" presenta una actualización centrada en cómo las últimas innovaciones están impulsando nuevas aplicaciones y capacidades analíticas.

En esta sesión se mostrará cómo las plataformas de Agi-

lent —Seahorse, xCELLigence y Cytation— están evolucionando para abordar la complejidad de modelos como esferoides, organoides y co-cultivos. Se destacarán avances en protocolos, consumibles, instrumentos, adquisición de datos y análisis que permiten obtener resultados reproducibles y relevantes en entornos tridimensionales.

Se revisarán aplicaciones clave del análisis metabólico con Seahorse en 3D, evidenciando su valor en áreas como oncología e inmunología, así como la capacidad de xCELLigence para monitorizar procesos dinámicos en tiempo real (proliferación, citotoxicidad, etc.), sin necesidad de marcadores. Complementariamente, se explorará el papel de Cytation en la caracterización estructural y funcional mediante imagen multimodal.

La presentación pondrá un énfasis especial en aplicaciones prácticas, incluyendo estudios de eficacia farmacológica, toxicidad y modelos más predictivos para drug discovery. También se abordarán aspectos críticos como la estandarización, la reproducibilidad y la integración de datos.

Dirigida a investigadores que buscan avanzar en el uso de modelos 3D, esta sesión ofrecerá una visión clara y aplicable de cómo las tecnologías actuales permiten obtener resultados más relevantes y acelerar la toma de decisiones en investigación.

Esta ponencia conectará directamente con el symposium asociado (actividad satélite), donde estos conceptos se llevarán a la práctica en una sesión más interactiva y aplicada.

CP-04 CONDALAB

De biomarcadores a terapias: soluciones integrales para la investigación traslacional en exosomas y vesículas extracelulares

LAURA FERNÁNDEZ, ELENA MORENO

Jefas de Producto en Condalab

Los exosomas y otras vesículas extracelulares (VEs) contienen proteínas, mRNA, miRNAs y otros elementos bioactivos que reflejan el estado fisiológico o patológico de las células de origen, convirtiéndolas en biomarcadores de interés para medicina de precisión. Estas vesículas también actúan como mensajeros intercelulares y pueden modular procesos como la regeneración tisular, la respuesta inflamatoria o la angiogénesis, por lo que también son muy atractivas para el desarrollo de terapias avanzadas. Sin embargo, la obtención de resultados reproducibles y biológicamente relevantes depende de la calidad de cada etapa del flujo de trabajo, desde la preservación o producción hasta el aislamiento y análisis molecular de las VEs.

En esta sesión abordaremos la producción eficiente de

VEs a partir de células madre mesenquimales mediante medios especializados, así como la preservación de exosomas en biofluidos con kits que mantienen la integridad de estos biomarcadores durante la recogida, transporte y almacenamiento. Además, revisaremos tecnologías para el aislamiento de exosomas a partir de diferentes matrices biológicas y la posterior purificación y caracterización de RNA y miRNAs asociados.

Una oportunidad para conocer enfoques prácticos y soluciones escalables que permitan acelerar la investigación en exosomas y vesículas extracelulares, desde la muestra hasta el dato biológico.

CP-05 CONTROLTECNIA

TÉCNICA Y CASOS PRÁCTICOS DE APLICACIONES DE LA ELECTROFORESIS CAPILAR CON DETECCIÓN POR FLUORESCENCIA

LOLA LLORENTE ORTEGA

PhD, Life Science Product Specialist

Capillary electrophoresis is a technique that allows different molecules to be separated according to their mass/charge ratio, across a small diameter capillary by subjecting them to a high voltage. The *Qsep1* and *Qsep100* Bio-Fragment analyzer are automated equipments based on capillary electrophoresis technology and fluorescence detection. These equipments unify the process of gel preparation, sample loading, electrophoresis and imaging in a single step, providing all the information related to the samples such as concentration and integrity in an electropherogram and gel. The advantages of using these bioanalyzers over the conventional electrophoresis method are multiple: they require low sample volume, offer high resolution and reproducibility of results, and save valuable time and money. The fields in which this technique is commonly used are biotechnology and molecular biology, the pharmaceutical industry, clinical diagnosis, and forensic laboratories. Among the numerous applications of the equipment are the typing of the human papillomavirus (HPV), animal and plant genotyping, microsatellites detection, quality control post-PCR, quality control of library preparation for sequencing, microdeletions diagnosis, visualization of PCR amplifications with heterodimers or quality evaluation of DNA/RNA samples prior to sequencing, among others.



CP-06 CULTTEK

ON-TARGETplus™ 2.0: siRNA Design for the Modern Transcriptome

JOHANNA DE CASTRO ARCE

PhD, Global Field Application Scientist, Dharmacon Research Reagents

Revvity

RNA interference (RNAi) using chemically synthesized siRNAs remains a cornerstone of gene perturbation studies. Dharmacon™ ON-TARGETplus™ (OTP) siRNAs combine algorithm-driven design and chemical modifications to deliver potent, specific gene silencing. The rapid expansion of the human transcriptome through long-read sequencing has revealed extensive isoform diversity, necessitating comprehensive siRNA redesign. ON-TARGETplus™ 2.0 (OTP 2.0) siRNAs target nearly all protein-coding genes in RefSeq v231 and are optimized for broad isoform coverage, high predicted knockdown efficacy, and target specificity. RNA-Seq analyses demonstrate potent gene silencing while reducing newly annotated and global off-target effects compared to OTP 1.0 siRNAs and alternative products, establishing OTP 2.0 as a next-generation solution for high-confidence functional genomics screening.

CP-07 PROQUINORTE

Linking Genotype to Transcriptional Phenotype at Single-Cell Resolution Using a Scalable RNA–DNA Co-Sequencing Platform

ROBERT WEREN

*PhD, Sr. Business Development Manager Atrandi Biosciences
www.atrandi.com*

Single-cell RNA sequencing is widely used to profile cellular states and CRISPR perturbations, yet it only captures transcribed regions and cannot confirm whether editing has occurred at the intended genomic locus. Detection is further constrained by expression sparsity, limiting the resolution of genotype-driven heterogeneity.

We present a high-throughput single-cell DNA and RNA co-assay based on Semi-Permeable Capsule (SPC) technology, which enables multi-step processing of single cells at scale. Whole-transcriptome profiling is combined with targeted genotyping by multiplex PCR amplicon sequencing in the same cell, directly mapping genotype to transcriptional state and validating CRISPR edits at their genomic targets — independent of gene expression level.

We applied this workflow to both healthy and malignant

human cells, profiling primary samples with multiplexed amplicon panels targeting SNP-containing loci alongside whole-transcriptome capture. Genotypes were recovered from most captured cells, enabling donor and clonal deconvolution and robust mapping of genetic background onto cell-state heterogeneity across normal and disease contexts. The assay supports user-defined PCR panels spanning transcribed and non-transcribed regions and scales readily in both cell number and panel breadth. We will discuss how this dual-modality approach advances the dissection of genotype–phenotype relationships at single-cell resolution in health and disease.

CP-08 MEDCHEM

MCE One-Stop Compound Screening Platform for Basic Research and Early Drug Discovery

IAIN WANG

Product specialist

Compound libraries, virtual screening, high-throughput screening and biophysical binding assays are increasingly important tools in modern biochemistry, molecular biology and early drug discovery. These approaches help researchers move from biological hypotheses to experimentally testable chemical tools, supporting target discovery and validation, mechanism-of-action studies, hit identification and lead optimisation.

In this talk, we will introduce the MedChemExpress (MCE) One-Stop Compound Screening Platform, which integrates compound screening services with MCE Bioactive/Diversity Compound Libraries, Target protein production, and virtual screening resources. The platform supports researchers working across basic, translational and early-stage drug discovery projects by combining access to diverse, well-annotated compounds with screening and validation technologies, including virtual screening, high-throughput screening and molecular interaction assays such as SPR, MST, BLI and ITC.

The presentation will also highlight how academic researchers have used MCE products and services to support different research goals, including molecular mechanism studies, inhibitor and activator discovery, phenotypic study and PROTAC design. Through selected published example case studies, we will show how an integrated screening workflow can help accelerate the identification of bioactive molecules, validate compounds–target interactions and generate useful chemical starting points for further biological investigation.

CP-09 PHCBI

A Complementary Workflow for Dynamic Characterization of Cellular Function: Integrating Continuous Metabolic Monitoring with Advanced Live-cell Imaging

ADRIAN BAUMANN

Product specialist del LicellMo en PHCbi.

Cellular metabolism is a key regulator of cell function, adaptation and differentiation, yet its dynamic nature is often difficult to capture using conventional endpoint analyses. To address this challenge, we present an integrated workflow combining the LiCellMo™ Live Cell Metabolic Analyzer (PHCbi) and the Cell3iMager NX (SCREEN Holdings) for comprehensive characterization of cellular activity in 2D and 3D culture systems.

LiCellMo™ provides continuous, non-invasive monitoring of glucose consumption and lactate production, enabling real-time assessment of cellular metabolic activity throughout culture. Complementary imaging analyses with Cell3iMager NX, performed at media changes and key experimental time points, allow quantitative evaluation of cell growth, morphology, confluence and differentiation status.

By integrating continuous metabolic measurements with imaging-based phenotypic characterization, this workflow delivers a more complete picture of cellular behaviour than either technology alone. Imaging data help contextualize metabolic changes by linking them to cell growth and morphological transitions, facilitating interpretation of cellular activity on a per-cell basis.

This complementary approach enables dynamic characterization of cellular function and plasticity while overcoming the limitations of isolated snapshot measurements, supporting applications in basic research, regenerative medicine and advanced cell therapy development.

CP-10 LABCLINICS

Accelerating qPCR Success -- Reliable Solutions from Extraction to Detection

JAOUHARA EL MAKHLOUFI

Scientific expert / International Technical Support Specialist

Despite the emergence of new technologies, quantitative PCR (qPCR) remains essential across diverse fields, including clinical diagnostics, food safety, basic research, and agriculture. However, researchers frequently encounter

significant bottlenecks throughout the standard qPCR workflow, such as time-consuming and toxic nucleic acid extraction methods, long reverse transcription (RT) protocols with genomic DNA (gDNA) contamination, and unstable real-time amplification in complex templates.

This presentation will explore a comprehensive “Sample to Result” strategy designed to overcome these hurdles and deliver fast, sensitive, and reproducible outcomes. We will introduce streamlined solutions, including safe, rapid, and automated magnetic extraction systems that eliminate toxic reagents like Trizol. Furthermore, we will demonstrate how to accelerate the workflow using an innovative 5-minute, all-in-one RT supermix with robust gDNA elimination. Finally, the session will cover advanced real-time PCR technologies, featuring ultra-sensitive master mixes with visual tracking dyes and a smart, rapid quantification system that halves standard run times. By optimizing each step from extraction to data analysis, laboratories can significantly improve throughput and reliability.

CP-11 CYMIT

De la poyata al mercado: cómo usar tu carrera científica fuera del laboratorio

LIA AVILA CAÑO

CYMIT QUIMICA, S.L. Product Manager

Durante la carrera o el doctorado en ciencias, parece que solo existe un camino: el laboratorio. Durante la universidad la academia se presenta a menudo como la única opción válida, lo que puede generar la falsa sensación de que salir de ella implica que los conocimientos adquiridos no sirven para nada fuera del entorno experimental.

En esta charla, a través de la experiencia real de varios profesionales de CymitQuimica —un marketplace que conecta laboratorios con fabricantes de productos químicos y biológicos—, mostraremos que el sector privado ofrece un amplio abanico de oportunidades donde el perfil científico está muy demandado.

Explicaremos en qué consisten puestos clave de los que rara vez se habla en las facultades, pero que requieren obligatoriamente una sólida base técnica: desde la gestión de grandes cuentas (*Key Account Management*) o el desarrollo de negocio (*Business Development*), hasta el marketing científico y el soporte técnico especializado. Con ello, queremos visibilizar que la trayectoria científica no termina necesariamente en la poyata o tras defender la tesis, sino que existen alternativas profesionales muy estimulantes para seguir vinculados al avance de la ciencia



CP-12 LICORBIO

Simplifying Quantitative Multiplex Imaging from Western Blots to 3D Models

LEA NÄSTLE

Senior Field Applications Scientist

Modern life science research demands imaging technologies that adapt to increasingly diverse experimental models and workflows. From traditional Western blotting to advanced cellular assays and tissue imaging, researchers require solutions that deliver quantitative, reproducible data while minimizing the need for multiple specialized instruments. A versatile imaging platform not only streamlines laboratory workflows but also enables scientists to transition seamlessly between applications as research questions evolve.

This presentation explores how the LICORbio Odyssey® imagers support the entire research pipeline, from early discovery experiments through validation studies, without compromising image quality or quantitative performance. Attendees will discover how one platform accommodates a broad range of sample types, including membranes, cultured cells, tissue sections, and three-dimensional models such as spheroids and organoids. By integrating multiple imaging modalities and multiplex fluorescence within a unified workflow, researchers can generate richer datasets while simplifying data analysis. Through representative application examples, this session will demonstrate how a versatile imaging platform enables researchers to move efficiently from hypothesis generation to biological validation while maintaining consistent quantitative performance across assay formats. Participants will gain practical insights into designing flexible imaging workflows that increase laboratory efficiency, expand experimental possibilities, and help future-proof research programs. Whether your work focuses on protein analysis, cell biology, or tissue-based research, this presentation will demonstrate how versatility can accelerate discovery, enhance confidence in experimental results, and unlock new opportunities for scientific innovation.

MIÉRCOLES, 9 DE SEPTIEMBRE

CP-13 PROMEGA

Salud celular en el ecosistema bioluminiscente de Promega

JAVIER ALVAREZ

PhD, Digital Marketing and Communication Manager Promega Biotech Ibérica

En el laboratorio, las preguntas son siempre múltiples e inherentes al proceso de descubrimiento. Mientras se evalúa si una célula está viva, el investigador ya se está preguntando si se está dividiendo, qué vía está activada o por qué responde de esa manera. Durante 25 años, CellTiter-Glo® ha sido el standard para responder a la primera pregunta: ¿Vive? Miles de publicaciones la citan como referencia, y equipos de investigación en todo el mundo lo eligen porque saben que los datos que genera son reproducibles y de calidad. La investigación no se detiene en los estudios de viabilidad, y la siguiente pregunta surge de manera natural: ¿Se divide? Y aquí es donde la narrativa luminiscente continúa aportando valor. El nuevo Lumit® Cell Proliferation Assay (Human Ki-67)—una forma luminiscente de responder esa pregunta en ~2 horas y sin lavados. Y desde la base de la viabilidad y la proliferación, el ecosistema bioluminiscente continúa expandiéndose a análisis complejos de función mitocondrial, glucólisis o citoquinas, permitiendo estudios metabólicos, inmunológicos y de procesos inflamatorios en este contexto bioluminiscente.

Para quienes necesitan responder a estas preguntas en paralelo, los ensayos multiplex en el mismo pocillo son posibles empleando iluminómetros GloMax®. Para laboratorios que comienzan o buscan una solución compacta, MyGlo® proporciona la misma confianza luminiscente con un instrumento de pequeño tamaño y muy asequible. En esta charla haremos una revisión de la tecnología Promega para responder preguntas complejas en salud celular con metodología luminiscente.

CP-14 EYOWN

Automatización de laboratorio orientada al proyecto: de la necesidad científica a la solución implantada

ENRIQUE ORTUÑO

Business Development Manager

La automatización de laboratorio se ha convertido en una herramienta clave para mejorar la reproducibilidad, la trazabilidad, la eficiencia y la calidad de los procesos experimentales en bioquímica, biología molecular, biotecnología y diagnóstico. Sin embargo, automatizar no consiste únicamente en adquirir un robot o incorporar instrumentación avanzada. El verdadero valor de la automatización aparece cuando la solución se diseña a partir de las necesidades reales del laboratorio, del flujo de trabajo, del tipo de muestra, de los reactivos, de los volúmenes, de la variabilidad del proceso y de los objetivos científicos o productivos del proyecto.

Desde Eyown, abordamos la automatización de laboratorio desde una perspectiva de consultoría independiente, centrada en el análisis previo de cada aplicación antes de recomendar una tecnología o marca concreta. Se revisarán los criterios que deben considerarse para seleccionar la marca, el modelo y la configuración instrumental más adecuados: capacidad de pipeteo, compatibilidad con consumibles, integración con equipos periféricos, gestión de líquidos complejos, escalabilidad, flexibilidad, facilidad de programación, mantenimiento, soporte técnico, costes operativos y posibilidades de validación.

Además, se destacará la importancia de acompañar la elección del instrumento con una implantación completa: instalación, puesta en marcha, adaptación del sistema al flujo de trabajo real, programación de protocolos, optimización de métodos, pruebas de robustez y entrenamiento de los usuarios finales.

La presentación incluirá ejemplos de decisiones habituales en proyectos de automatización, mostrando cómo distintas aplicaciones pueden requerir soluciones muy diferentes: desde plataformas abiertas y flexibles para investigación hasta sistemas más cerrados, robustos o altamente integrados para entornos regulados o de alta productividad. El objetivo final es mostrar que una automatización bien diseñada no sustituye el conocimiento científico del laboratorio, sino que lo potencia, reduce errores operativos y libera tiempo para tareas de mayor valor añadido.

CP-15 ABYNTEK

Optimización del flujo de trabajo en investigación: Muestreo inteligente, reactivos robustos, resultados fiables

VANESA GÓMEZ

PhD

Abyntek es una empresa biotecnológica española con más de 20 años de experiencia apoyando la investigación y el diagnóstico mediante el suministro y desarrollo de reactivos de alta calidad. Nuestra misión es simplificar los flujos de trabajo en el laboratorio proporcionando herramientas fiables y soporte técnico especializado en cada etapa del proceso de investigación.

En esta presentación mostramos soluciones integradas diseñadas para mejorar la eficiencia, la reproducibilidad y la calidad de los datos, desde la recogida de muestras hasta la validación *in vivo*. Comenzamos con la obtención de muestras a través de nuestra colaboración con DNA Genotek, cuyos sistemas para ADN, ARN, microbioma y metabolómica garantizan una alta estabilidad a temperatura ambiente, mejoran la adherencia del donante mediante métodos no invasivos y optimizan los flujos de trabajo con formatos compatibles con automatización, reduciendo limitaciones logísticas.

A continuación, nos centramos en los flujos de trabajo *in vitro*, donde la reproducibilidad y el rendimiento analítico son clave. A través de Abylabel, ofrecemos proteínas, anticuerpos, ensayos ELISA/CLIA y kits multiplex para citometría de flujo que respaldan estrategias experimentales consistentes y escalables. Además, presentaremos formatos innovadores como los Abypanels que permiten el cribado en paralelo de varios anticuerpos en volúmenes reducidos, y los kits multiplex, que facilitan la cuantificación simultánea de biomarcadores en una única muestra, de manera personalizable.

Finalmente, abordamos la investigación *in vivo* con los anticuerpos de Bio X Cell, estándar de referencia en estudios preclínicos, con alta pureza, validación y más de 30.000 citas en la literatura.

En conjunto, estas soluciones demuestran cómo un enfoque integral, puede reducir la complejidad y permitir a los investigadores generar resultados fiables de forma eficiente. Esta es la misión de Abyntek.



CP-16 CYTIVA

Cytiva: Plataformas de referencia para la Purificación y Caracterización de Proteínas

NEREA BERNARDO

Imaging Sales Specialist

Desde la purificación hasta la caracterización funcional, Cytiva ofrece tecnologías avanzadas para acelerar la investigación en proteínas y otras biomoléculas. En esta charla se presentarán los sistemas ÄKTA para purificación automatizada y en paralelo, los equipos de imagen de alta sensibilidad que permiten la detección y cuantificación de proteínas de baja abundancia y la plataforma Biacore para el análisis preciso y en tiempo real de interacciones biomoleculares, incluyendo el uso de un kit universal que simplifica el desarrollo experimental.

CP-17 BIOGEN

De lo convencional a lo innovador: cómo la imagen molecular está redefiniendo las aplicaciones en Biología Molecular

ESTER ABARQUERO DIEZHANDINO

PhD, especialista de producto en Biogen Científica.

Las tecnologías de imagen han evolucionado desde herramientas destinadas a la simple documentación de ácidos nucleicos y proteínas hasta convertirse en plataformas capaces de proporcionar información cuantitativa, funcional y espacial sobre procesos biológicos complejos. Esta transformación ha impulsado nuevas estrategias experimentales en investigación básica, traslacional y biomédica.

Los recientes avances en sistemas de fluorescencia multi-canal, quimioluminiscencia e imagen molecular in vivo han ampliado de forma significativa la sensibilidad, la capacidad de multiplexación y el alcance de los estudios biológicos. Estas tecnologías permiten detectar señales débiles, monitorizar eventos biológicos de manera no invasiva y obtener información dinámica sobre la distribución y evolución de biomoléculas, células y procesos fisiopatológicos.

La aplicación de estas herramientas abarca desde el análisis de expresión génica y proteica hasta el estudio de biomarcadores, mecanismos de enfermedad, biodistribución de vectores y seguimiento de terapias avanzadas. En particular, la imagen molecular se ha consolidado como una tecnología de gran valor para el desarrollo de terapias génicas y celulares, facilitando la evaluación de la localización, persistencia y actividad biológica de las estrategias terapéuticas en modelos preclínicos.

La integración de tecnologías de imagen cada vez más sensibles y versátiles está contribuyendo a una comprensión más profunda de los sistemas biológicos, acelerando la investigación traslacional y ampliando las posibilidades experimentales para abordar los desafíos actuales de la biología molecular y la biomedicina.

CP-18 KUHNER

Hunting a 'ghost' with Kuhner Shaker - the (mostly) forgotten cultivation parameter and its impact

GUILLEM HERNANDEZ

Sales Manager Kuhner Shaker SAU

Shake-flask cultivation is a standard procedure in wet laboratories to produce many products, from small molecules (e.g.: antibiotics) to proteins, antibodies, DNA/RNA, viruses, cells...

Despite its common use, there is still a cultivation parameter, key for the cultivation's respiration and aeration/ventilation, that remains forgotten by most of the scientific community. But it is still there, like a ghost, haunting down on the cultivation, causing huge potential impacts in process' yields. Have you ever heard "my cells grow better in this or that flask", or even a "My cells only grow in x or y liter flasks"? But when wanting to know why that is happening, the answer you mostly got was (and still is) "that's something empirical"? This talk is for you. Together, we will bring the phantom parameter in shake-flasks cultivations under the spotlight, and we will explore its impact while going through who Kuhner Shaker is and what can offer as a leading company in the shaking technology field.

CP-19 TEBUBIO

Rethinking disease modeling: bridging cancer, metabolism and liver pathology through integrated experimental workflows

CHRISTELLE CATONE

Ph.D.

Summary: We present an integrated workflow combining human-relevant 3D models, RNA-based tools and advanced readouts to study cancer, obesity and liver disease. This approach enables mechanistic insights and improves translational relevance by bridging experimental models with clinical biology. Applications across multiple disease areas will demonstrate how unified pipelines can accelerate discovery and therapeutic development.

CP-20 MACROGEN

Macrogen: Humanizando la genómica

IRIA LAURA MARTÍNEZ GARCÍA, CELIA LÓPEZ GÓMEZ

NGS Consultants and Application Specialists in Macrogen

Macrogen Inc., fundada en Seúl en 1997, es hoy uno de los referentes globales en servicios genómicos. Bajo su filosofía "Humanizing Genomics", la compañía impulsa desde hace casi tres décadas la misión de transformar la genómica en valor real para la investigación, la clínica y la sociedad. Con presencia en más de 150 países y una red internacional de laboratorios y centros operativos, Macrogen da soporte a más de 18.000 clientes activos en todo el mundo. En este contexto, Macrogen España actúa como hub estratégico para la Península Ibérica e islas, combinando cercanía científica, soporte personalizado y acceso directo a infraestructura de secuenciación de escala global. Esta integración permite responder tanto a proyectos locales como a grandes consorcios internacionales con la misma robustez tecnológica y calidad operativa. La propuesta tecnológica de Macrogen se estructura en dos grandes pilares complementarios: la genómica de precisión basada en metodologías consolidadas como la secuenciación Sanger y la síntesis de oligonucleótidos, y las plataformas de descubrimiento a gran escala basadas en tecnologías NGS.

1. Genómica de Precisión: Sanger & Oligos

La secuenciación Sanger continúa siendo el gold standard para validación molecular. Macrogen ofrece soluciones rápidas y robustas para verificación de clones, productos de PCR, identificación microbiana y análisis de fragmentos. En paralelo, la síntesis de oligonucleótidos permite la producción personalizada de ADN, ARN, péptidos modificados y genes sintéticos bajo un sistema integrado de fabricación "one-roof", con control de calidad total mediante MALDI-TOF MS en cada lote.

2. Genómica de nueva generación: NGS

2.1 Transcriptómica (RNA-seq)

Análisis global de la expresión génica mediante estrategias de mRNA-seq y total RNA-seq, así como small RNA-seq. Permite estudiar regulación génica, rutas biológicas y dinámicas celulares con alta resolución.

2.2 Exoma Completo (WES)

Enfoque optimizado para la detección de variantes en regiones codificantes. Compatible con múltiples tecnologías de captura (Agilent SureSelect, Twist Bioscience), adaptándose a objetivos clínicos y de investigación: enfermedades raras, oncología y estudios poblacionales.

2.3 Genoma Completo (WGS)

Máxima resolución genómica para capturar variantes estructurales, CNVs y regiones no codificantes. Combina plataformas de alto rendimiento como Illumina NovaSeq

X Plus con tecnologías de lectura larga (PacBio HiFi y Oxford Nanopore) para análisis estructural avanzado y ensamblajes de novo.

2.4 Metagenómica y Microbioma

Caracterización de comunidades microbianas mediante Amplicon sequencing (16S/ITS/18S) para perfil taxonómico preciso y Shotgun metagenomics para un análisis funcional y resolución a nivel de especie o cepa. Aplicaciones en salud humana, microbioma animal, agricultura, industria alimentaria y vigilancia ambiental.

Macrogen integra todas estas tecnologías en un ecosistema único de genómica escalable, diseñado no solo para generar datos, sino para acelerar descubrimiento, habilitar medicina de precisión y transformar ciencia en impacto real. Invitamos a los asistentes a descubrir cómo esta visión se traduce en práctica diaria y cómo la genómica, cuando se escala correctamente, deja de ser solo tecnología para convertirse en decisión, conocimiento y futuro.

El valor diferencial de Macrogen radica en la convergencia de tres factores: el soporte técnico especializado y cercano en español, el cumplimiento estricto de las normativas de calidad y protección de datos europeas (RGPD), y una política de precios competitiva que democratiza el acceso a la genómica de vanguardia.

CP-21 PARALAB

Building Better Experiments: An Integrated Workflow for Next-Generation Bioscience

AMARLIG FERRIGNI

Product Specialist BIO

Advances in cell biology, tissue engineering and imaging technologies are transforming experimental design, enabling researchers to generate more physiologically relevant, quantitative and reproducible data. Rather than relying on isolated techniques, modern bioscience increasingly benefits from integrated workflows that connect complementary technologies across multiple stages of the research process.

This presentation follows the workflow of a contemporary research project, from cell preparation and quality assessment to advanced in vitro model development, live-cell monitoring, high-resolution imaging, and single-cell characterization. The discussion will highlight how selecting the appropriate technology at each experimental stage can improve data quality, reproducibility and biological insight. Key technologies will include automated cell counting, perfusion-based bioreactors, multimaterial 3D bioprinting, long-term live-cell imaging, super-resolution microscopy, quantitative whole-slide fluorescence imaging and spectral flow cytometry.

Using examples from cancer biology, neuroscience, stem cell research and regenerative medicine, this talk will illustrate how integrating complementary technologies enables researchers to build more predictive experimental models, better understand cellular complexity and accelerate scientific discovery.

CP-22 PALEX

Tecnologías moleculares avanzadas: del reactivo de precisión hasta la NGS y ómicas

ROCÍO CAMPO

Marketing Manager Life Science

La investigación actual en bioquímica y biología celular —especialmente en campos con alta heterogeneidad como la patología molecular, la senescencia y el metabolismo— exige niveles críticos de reproducibilidad y sensibilidad. La transición exitosa desde los modelos *in vitro* hacia la caracterización a resolución unicelular depende de la eliminación de sesgos metodológicos. En este escenario, Palex Medical se consolida no solo como proveedor, sino como un *partner* tecnológico estratégico para la comunidad científica, impulsando el avance de la ciencia mediante un acompañamiento integral que abarca desde la consultoría preventiva y el diseño experimental hasta el soporte técnico postventa y la optimización de protocolos por parte de un equipo especializado de aplicaciones.

Metodología y Soluciones Tecnológicas: presentamos un ecosistema integrado de herramientas avanzadas diseñadas para optimizar la cadena de valor del dato científico. Entre nuestras soluciones destacamos la caracterización celular, cuantificación de senescencia y estrés oxidativo, las plataformas multiplexadas por citometría de flujo para perfilado de citocinas inflamatorias, la validación IHC en tejidos complejos y la supresión de autofluorescencia, entre otros. Además, la tecnología de nanobolas de ADN para democratizar la NGS y nuestras tecnologías Ómicas que permiten mapear el tejido, para obtener ensayos robustos, reproducibles y de alto impacto.

CP-23 APLITECH

Hacia un laboratorio conectado: Automatizando el flujo de trabajo desde la preparación de muestras hasta los bioprocesos.

ELISABETH CASADO

Product and Quality Manager, Aplitech Biolab

En el entorno actual de la investigación biotecnológica, la automatización ha dejado de ser una opción para convertirse en una necesidad crítica para garantizar la reproducibilidad y la eficiencia. Sin embargo, la implementación de equipos aislados a menudo crea nuevos “silos” de información y cuellos de botella operativos que limitan el potencial experimental.

Esta presentación explora la transición desde la automatización de tareas individuales hacia la creación de un Laboratorio Conectado. Se analizará cómo la integración técnica entre los sistemas de Liquid Handling de Analytik Jena, los Bioreactores de Getinge-Applikon, y otros equipos de análisis, permiten establecer un flujo de trabajo continuo, desde la preparación de las muestras o un inóculo hasta el control exhaustivo del cultivo celular o microbiológico.

A través de soluciones de integración desarrolladas por Aplitech Biolab, demostraremos cómo esta sincronización no solo minimiza la variabilidad introducida por la manipulación manual, sino que garantiza una trazabilidad total del dato, permitiendo al investigador centrarse en el análisis científico y la toma de decisiones. Analizaremos casos prácticos donde la estandarización del proceso experimental ha permitido reducir los tiempos de ciclo y mejorar significativamente la consistencia de los resultados.

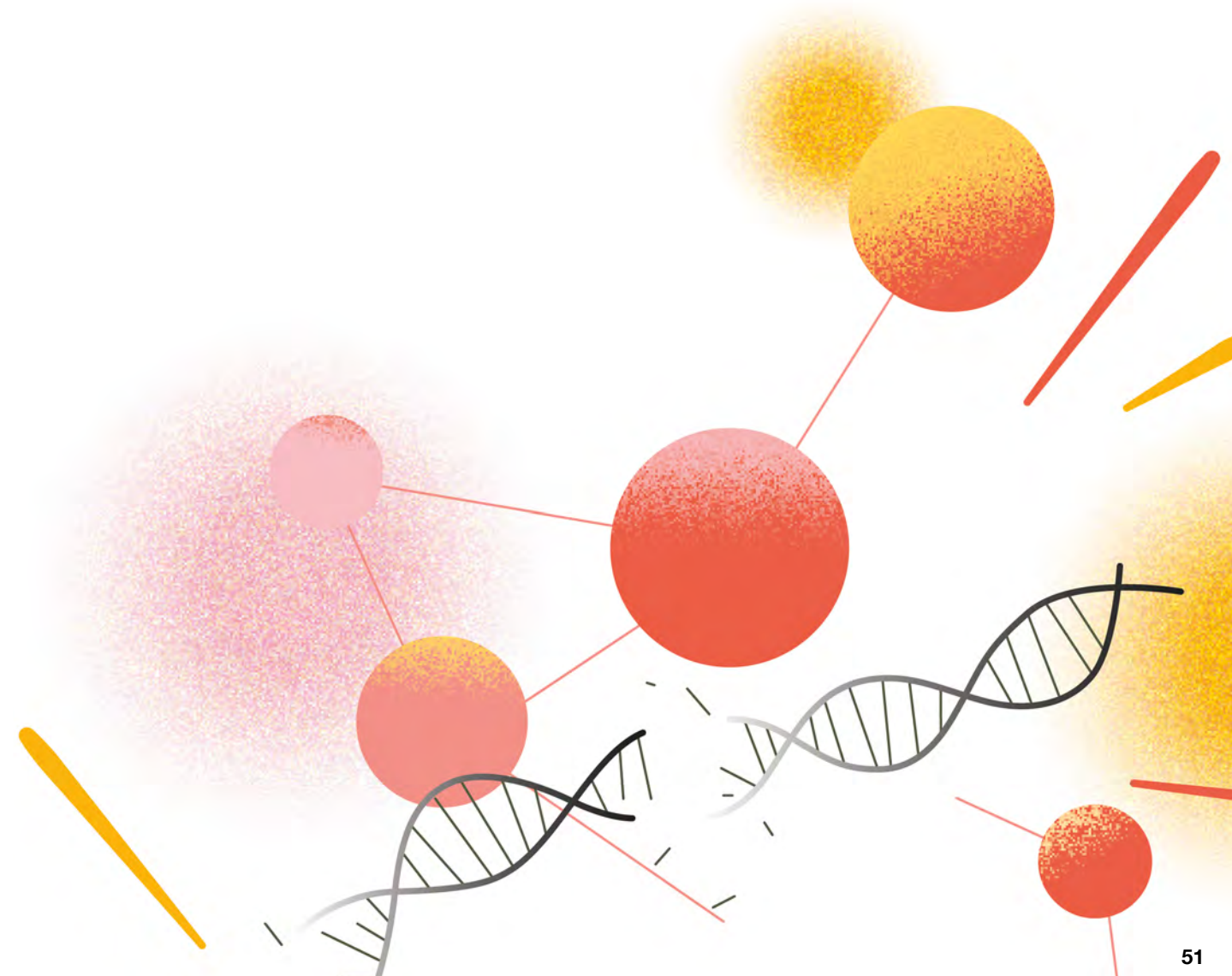




GRUPOS CIENTÍFICOS DE LA SEBBM:

EDUCACIÓN

7 DE SEPTIEMBRE





O-001

Impacto De La Inteligencia Artificial Generativa En El Rendimiento Y Satisfacción Del Alumnado: El Caso De PARTICIP-AI

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El Aprendizaje Basado en Problemas (ABP) es una metodología activa fundamental en la formación médica, aunque presenta desafíos en la participación equitativa y la personalización del aprendizaje. El proyecto PARTICIP-AI integra herramientas de Inteligencia Artificial (IA) en las sesiones de Bioquímica y Biología Molecular de primer curso de Medicina (URV) para potenciar la preparación previa, la interacción en el aula y la retroalimentación continua.

Se diseñó un estudio comparando dos sesiones ABP (PBL1 sin IA vs. PBL2 con soporte de IA). Los estudiantes (n=102) utilizaron IA para formular hipótesis y explorar un caso clínico sobre hipercolesterolemia antes de la sesión presencial. Se analizaron las respuestas correctas, tiempo de respuesta, puntuación y satisfacción mediante cuestionario Likert.

La integración de IA mejoró significativamente el rendimiento académico: las respuestas correctas globales aumentaron del 61,88% (PBL1) al 78,08% (PBL2). Las mejoras más destacadas se observaron en Q2 (respuestas correctas: 27,72%→72,12%) y Q6 (54,46%→83,65%) con una puntuación media superior (6613,3 vs. 4783,66). El tiempo de respuesta se redujo drásticamente en todas las preguntas (ej. Q1: 10,58s→3,62s) con una media PBL1: 9,54s vs. PBL2: 8,59s. La satisfacción fue elevada facilitando la comprensión (media 4,30, con el 64,4% otorgando la máxima puntuación), recomendando el método (media 4,18) y mejorando la participación (media 4,13).

PARTICIP-AI demuestra que la IA estructurada potencia el ABP, mejorando resultados académicos, eficiencia cognitiva y satisfacción estudiantil. La metodología es transferible a otras asignaturas y promueve un aprendizaje activo, personalizado y colaborativo en la formación médica.

Keywords:

Inteligencia Artificial; Aprendizaje Basado En Problemas; Educación Médica; Rendimiento Académico; Satisfacción Estudiantil

O-002 / P-001

Del Aula A La Divulgación: Un Proyecto Europeo Que Forma Estudiantes De Grado Como Facilitadores Científicos

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La implicación de la sociedad con la ciencia es una misión fundamental de las universidades. Inspirar vocaciones científicas en jóvenes contribuye a una sociedad más crítica y equitativa. Para ello, es clave formar facilitadores científicos capaces de acercar la ciencia al público mediante actividades prácticas y accesibles. Sin embargo, esta formación apenas está integrada en los planes de estudio universitarios.

Cell Explorers es un programa irlandés de educación y divulgación científica de gran difusión y éxito, con más de 10 años de recorrido.

Con el objetivo de trasladar este modelo a otras universidades de la Alianza Europea ENLIGHT, personal investigador y docente de la Universidad de Galway (UoG), la Universidad de Burdeos (UoB) y la Universidad del País Vasco (EHU) colaboraron en el proyecto SHARE.

En noviembre de 2024, miembros de la UoB y la EHU visitaron la UoG para formarse en la metodología Cell Explorers. Posteriormente, entre marzo y mayo de 2025, se desarrolló un estudio piloto en la EHU con estudiantes voluntarios de grado y máster formados como facilitadores científicos mediante módulos online y talleres prácticos. Estos estudiantes llevaron a cabo una actividad educativa para jóvenes de 8 a 17 años de cuatro centros escolares del País Vasco, replicando el taller "Fantastic DNA".

Los resultados indicaron un aumento de la curiosidad científica y la confianza de los jóvenes en la ciencia, además de mejorar las competencias comunicativas del alumnado universitario. Los próximos pasos incluyen consolidar un modelo sostenible de divulgación científica y formación en facilitación dentro de la red ENLIGHT.

Financiación:

"SHARE: supporting Higher Education and Research through Engagement", convocatoria Enlight+ 2024

Keywords:

Habilidades Blandas, Vocaciones STEM, Divulgación

P-002

Competency Based Integration of Molecular and Clinical Skills in Undergraduate Biomedicine Education

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Integrated Biomedicine II is a second year course within the Bachelor's Degree in Biomedicine at Universidad Europea de Madrid. This 3 ECTS module articulates theoretical foundations with the acquisition of practical and clinical competencies through active learning and performance based evaluation. Its curriculum builds upon prior training in biostatistics, immunology, virology, microbiology, genetic engineering, medical genetics, pathophysiology, and structure-function subjects, fostering interdisciplinary integration and promoting a coherent, clinically oriented understanding of biomedical knowledge.

During the 2025–2026 academic year, a competency based practical assessment model was implemented, combining an Objective Structured Practical Examination (OSPE) with an Objective Structured Review Examination (OSRE). The assessment consisted of three work-stations: DNA isolation and qPCR setup, microscopic evaluation of pulmonary histopathology, and quantitative analysis and interpretation of experimental data. All stations were contextualized within clinical scenarios involving patients with diverse pulmonary infections. Performance outcomes were compared with those from the previous academic year to determine the impact of the new methodology. Results demonstrated that the incorporation of OSPE/OSRE enhanced students' experimental proficiency, analytical capacity, and clinical reasoning. Learners exhibited greater autonomy in laboratory procedures, improved data interpretation skills, and overall superior performance. Integrating biomedical content with competency based methodologies promotes a deeper learning and strengthens the application of biochemical and molecular principles to clinical contexts, offering a transferable model for other life science degrees.

Keywords:

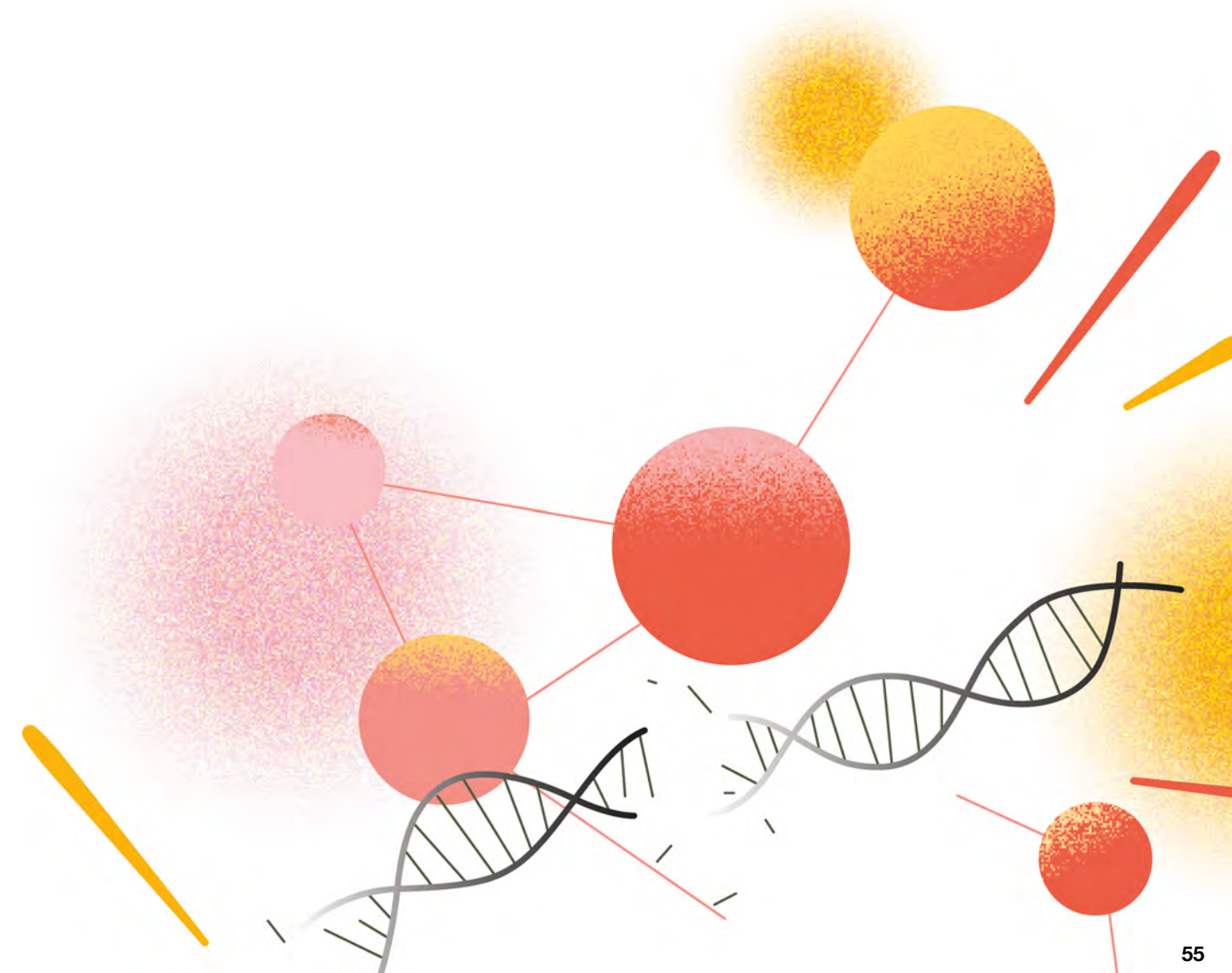
Integrated Biomedicine, Competencies, Objective Structured Practical Examination, OSPE, Objective Structured Review Examination, OSRE



GRUPOS CIENTÍFICOS DE LA SEBBM:

MUJER Y CIENCIA

7 DE SEPTIEMBRE





O-003/P-003

From biochemical foundations to cancer research: building leadership in biomedical science

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My scientific trajectory reflects a progression from biochemical training to translational cancer research, shaped by interdisciplinary formation and engagement in initiatives promoting women in STEM. My career is driven by scientific curiosity and a commitment to increasing the visibility and leadership of women in biomedical research.

I trained in Biochemistry, which provided the basis for my specialization in Cellular and Molecular Biology and Cancer Research. Since my early experience as an undergraduate intern in the Department of Biochemistry and Molecular Biology, I have been involved in research through my Bachelor's and Master's theses, focused on natural bioactive compounds with anticancer and antiangiogenic properties. These studies provided me with experience in cell culture models and functional assays of proliferation, migration, angiogenesis, and oxidative stress. Currently, my PhD research focuses on triple-negative breast cancer, aiming to characterize natural compound derivatives that modulate tumor progression and metastasis within the tumor microenvironment.

Alongside research, I have been recognized through initiatives promoting excellence and leadership in STEM as a young woman researcher, including the Soroptimist Excellence Women in STEM Award, the Soroptimist International Leadership Academy, and the Girls in STEM Educathon at the University of Málaga. I also participate in outreach activities such as the European Researchers' Night.

My training is complemented by an expert course in clinical trial methodology, bioinformatics, and translational research, and a competitive grant for the Organoids and 3D Models Summer Course in Bologna 2026, strengthening my expertise in advanced experimental models. This reflects my commitment to bridging basic research with clinical application in oncology.

Overall, my career integrates research in triple-negative breast cancer with leadership development and active con-

tribution to the visibility of women in STEM, shaping my goal to advance translational biomedical science.

Keywords:

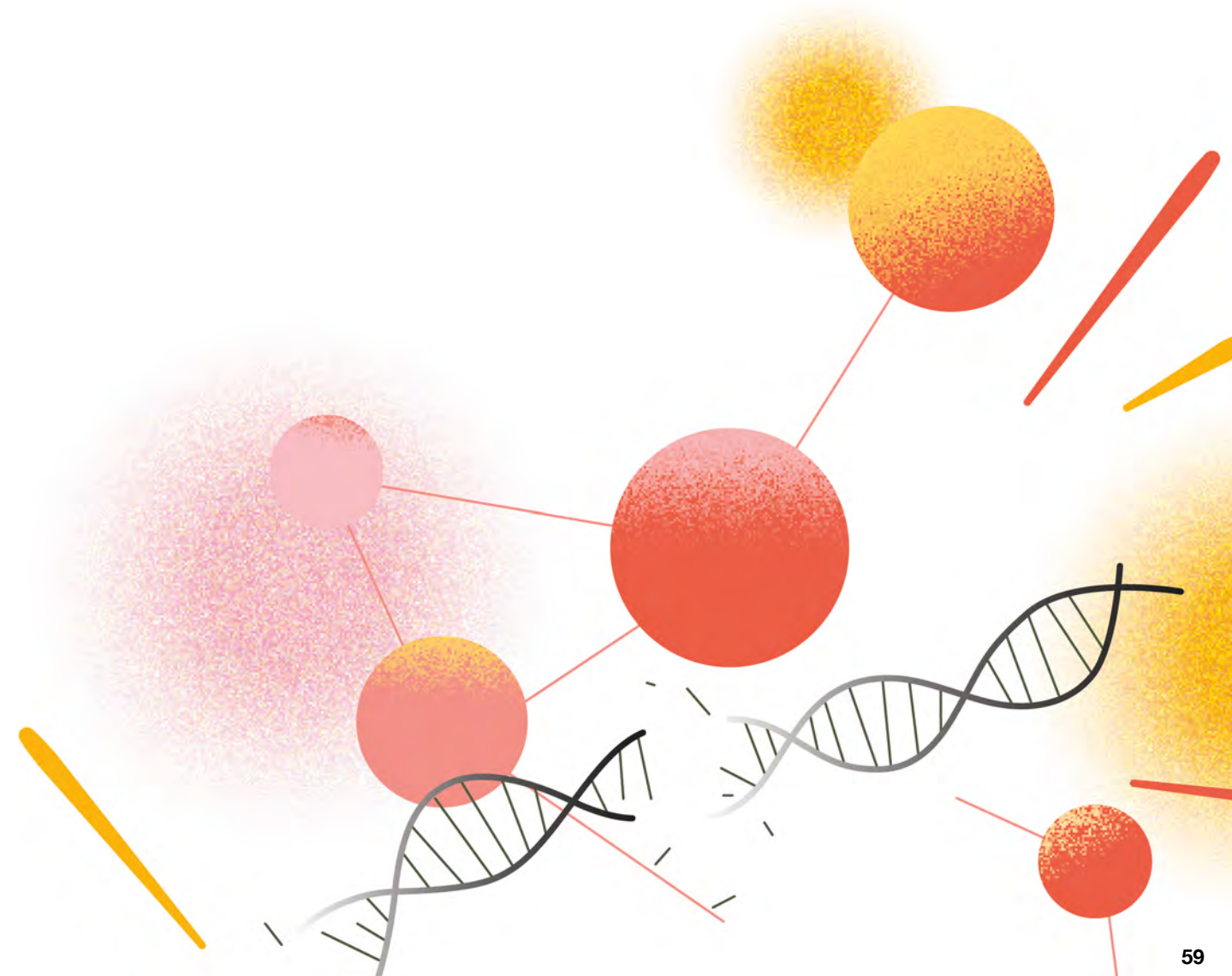
Women, STEM, Leadership, Cancer, Biomedical, Translational, Research



GRUPOS CIENTÍFICOS DE LA SEBBM:

EMPRENDIMIENTO E INNOVACIÓN

7 DE SEPTIEMBRE





O-004

Telara Pharma: From Scientific Discovery To Neuroprotective Therapies For Glaucoma

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Telara Pharma is a Spanish biotech company born from translational research and a clear unmet medical need: preventing vision loss in glaucoma. While current treatments focus on lowering intraocular pressure, disease progression often continues, leaving millions of patients at risk of irreversible blindness.

The company originated from over a decade of academic research exploring the protective potential of cilastatin in kidney injury, which later revealed wider applications in neuroprotection. This scientific insight laid the foundation for Telara's entrepreneurial journey: transforming a known, clinically used molecule into a novel therapeutic approach for ocular diseases.

Telara is now developing a first-in-class neuroprotective therapy for glaucoma, repurposing cilastatin as an eye drop to protect retinal cells and complement existing treatments. By focusing on neuroprotection, rather than only symptom control, the company aims to redefine the standard of care in a large and growing market projected to reach approximately \$8.8 billion by 2030.

From its origins as an spin-off to securing intellectual property, early funding, and strategic partnerships, Telara illustrates the challenges and opportunities of biotech entrepreneurship. Its journey highlights the importance of scientific differentiation, capital efficiency, and a licensing-driven business model to accelerate development and maximize impact.

This talk will share how Telara Pharma navigates the path from discovery to clinical development, turning research excellence into a scalable venture with the potential to change how neurodegenerative eye diseases are treated.

Keywords:

Glaucoma, Neuroprotection, Neuroinflammation, Spin-Off, Entrepreneurship, Eye Drop, Ophthalmology, Clinical Trial, Biotechnology

O-005

Where Science Meets Courage: Building A Drug From Nothing

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Academic research often generates discoveries with clear translational potential, yet the path from an early scientific insight to a tangible therapeutic product remains long, complex, and rarely straightforward. This journey requires addressing a wide range of challenges that extend far beyond experimental science: intellectual property strategy, regulatory frameworks, legal considerations, funding constraints, and the assembly of the right multidisciplinary team.

This talk will reflect on the early stages of transforming a scientific concept into the foundation of a drug development effort, emphasizing the realities of working with limited resources and incomplete information. In this context, progress is rarely linear; instead, it is characterized by continuous iteration, reassessment, and adaptation. Decisions must often be made under uncertainty, balancing scientific rigor with strategic considerations.

Ultimately, this process demands not only strong science but also resilience and courage. Navigating setbacks, redefining directions, and maintaining momentum are essential components of innovation in biomedicine. By sharing lessons learned from this journey, this presentation aims to provide a realistic perspective on the challenges and opportunities at the interface of academia and drug development, and to encourage scientists to engage with the translational potential of their work.

Keywords:

Entrepreneurship, Technology Transfer

P-004

Structure-Dependent Immunomodulatory Activity Of Pectins From Chilean Papaya And Flaxseed Seed Mucilage

PABLO SEPÚLVEDA ORELLANA, SUSANA SAEZ AGUAYO, CAROLINA OTERO ACUÑA

Universidad Andrés Bello, Santiago, Chile

Pectins are plant polysaccharides generally recognized as safe and widely used in the food and cosmetic industries. Their bioactivity is linked to molecular architecture, and domains such as homogalacturonan (HG) and rhamnogalacturonan I (RG-I) have been associated with immunomodulatory effects. However, their potential from agro-industrial waste remains poorly explored. This study evaluated pectins extracted from seed mucilage residues of Chilean papaya (*Vasconcellea pubescens*) and flaxseed (*Linum usitatissimum*) as bioactive compounds capable of modulating cellular and immune responses.

Native and structurally modified extracts were obtained through non-enzymatic physicochemical treatments that induced demethylation, fragmentation, and changes in functional groups. Structural characterization included sugar composition, pectic epitope detection, and fragmentation analysis. Biological activity was assessed by viability assays and immunomodulatory parameters, including NO release, endocytic activity, and immune gene expression by RT-qPCR in RAW 264.7 macrophages.

So far, our results indicate that native papaya pectins are enriched in highly methyl-esterified HG, whereas flaxseed pectins are enriched in branched RG-I. Structural modifications generated distinct patterns in both samples. Papaya pectins tended to increase cell viability, whereas flaxseed pectins showed moderate cytotoxicity. In macrophages, some samples increased NO release. In addition, papaya pectins increased the expression of TNF- α , iNOS, IL-6, and IL-12b, whereas flaxseed pectins strongly induced iNOS and IL-10, revealing distinct immunomodulatory responses.

These findings suggest that agro-industrial residues are a promising source of immunomodulatory compounds with biotechnological potential.

Keywords:

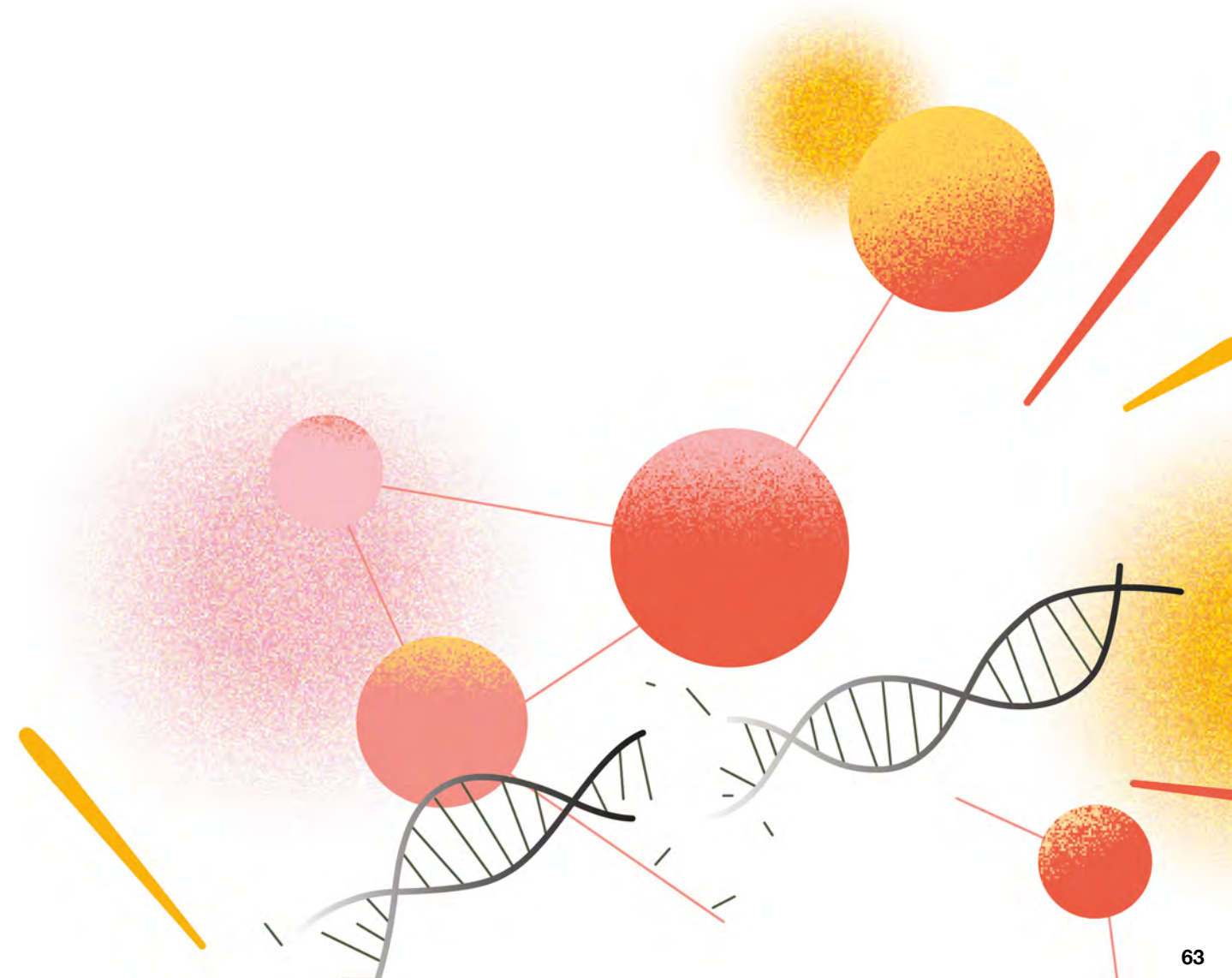
Pectins, Immunomodulation, Macrophages, Agro-Industrial Waste



GRUPOS CIENTÍFICOS DE LA SEBBM:

BIOLOGÍA MOLECULAR ÓMICA Y BIOINFORMÁTICA

8 DE SEPTIEMBRE





O-006

Fine-Tuning Biological Foundation Models For Anticancer Drug Target Discovery And Protein-Drug Network Refinement

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Defining the precise molecular targets for anticancer therapeutics remains a critical challenge in computational oncology. While conventional data-driven networks provide valuable biological insights by integrating drug-derived omics data (e.g., the NCI-60 panel) with topological metrics of the drug interactions (e.g., the B-index) [1], their predictive value can be significantly enhanced.

Recent breakthroughs in AI-based Biological Foundation Models and Large Language Models (LLMs) offer an unprecedented opportunity to optimize these drug-target networks [2].

In this study, we propose an integrative framework that bridges network biology and generative AI via link prediction and knowledge graph completion. By mapping established clinical databases such as DrugBank [3] onto our functional, omics-based protein-drug networks, we construct a unified biomedical knowledge graph. We use state-of-the-art foundation models (such as Transformer-based protein and chemical encoders) to extract high dimensional embeddings from protein sequences and drug structures (SMILES) [4, 5]. This dual-input architecture is fine-tuned using calculated weights as a functional prior, training the model to predict the most probable missing vertices in the network [6].

This pipeline aims to filter out experimental noise and rank novel, structurally non-obvious drug-target associations with high probability. Ultimately, this paradigm shift demonstrates that combining omics-derived networks with fine-tuned biological LLMs allows for active, mechanistically driven anticancer drug target discovery and drug-protein network refinement.

Keywords:

Computational Oncology, Drug-Target Interaction Prediction, Biological Foundation Models, Large Language Models, Knowledge Graphs, Link Prediction, Network Biology, Multi-Omics Integration, Transformer Models, Anticancer Drug Discovery

O-007

Multi-Omic Data Integration And Analysis Using Bioinformatic Protocols: Application To Discover Gene Markers Of Prognosis In Lung Cancer

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The analysis of large-scale multi-omic and longitudinal clinical data provides new opportunities to identify prognostic biomarkers in cancer. In this study, we present an integrative bioinformatics workflow to analyse multi-omic datasets. The proposed workflow aims to integrate and analyse combination of molecular profiles derived from primary tumors with pathological and survival data, with special focus on key oncogenes. Lung adenocarcinoma (LUAD) is used as a case study, with particular emphasis on the role of key oncogenes.

Datasets were downloaded from publicly available repositories, including The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). As a key objective of this work, we study several multi-omic data analysis and integration methods recently developed in the bioinformatics field. Many methods have been developed over the last decade, such as the well-known MOFA (Multi-Omics Factor Analysis) [1], and MOFA+ [2]. All these initial methods, rely mainly on classical statistical frameworks as it can be seen in the reviews by Heo et al. (2021) [3] and Duan et al. (2021) [4]. Recently, advances in artificial intelligence (AI) have made it possible to develop Deep Learning (DL) and Neural Networks (NN) based methods for integrative analyses. Thus, in our study we focus on the use and evaluation of modern methods like those based on graphs [5], autoencoders [6] and multi-kernel learning [7].

By comparing classical and modern approaches, we can get a better understanding of the strengths and weaknesses of the current multi-omic integration methodologies, and their potential to discover clinically relevant biomarkers and molecular signatures associated with disease progression and patient survival.

Keywords:

Multi-Omics Integration, Lung Adenocarcinoma, Prognostic Biomarkers, Deep Learning, Neural Networks, Survival Analysis

O-008/P-005

De Novo Design of Selective Focal Adhesion Kinase Modulators

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Advances in deep learning have reshaped structural biology by enabling highly accurate prediction of protein structures directly from amino acid sequences (AlphaFold and RoseTTAFold). Beyond structure prediction, computational strategies now allow the de novo design of proteins with customized functions, including specific binding and catalytic properties. Among these innovations, denoising diffusion probabilistic models (DDPMs), RFdiffusion, generate realistic protein backbones by iteratively refining random noise under minimal structural constraints.

In this work, we employed RFdiffusion to design de novo protein binders ("deepbinders") targeting the kinase domain of focal adhesion kinase (FAK), a target in cancer therapy. Using five crystallographic structures of FAK as templates, we generated 30,000 backbone conformations, followed by sequence assignment with ProteinMPNN and structural refinement using Rosetta. Designs were filtered based on AlphaFold2 confidence metrics, resulting in 117 candidates. Experimental validation identified 50 FAK-binding proteins, including 20 inhibitors.

The natural substrate of FAK, ATP, binds within a cleft between the N- and C-lobes of the kinase domain, enabling catalytic activity. Experimental analyses revealed that different deepbinder can induce specific N/C-lobe conformations which allosterically affect ATP binding, resulting either in kinase inhibition or activation. Since ATP binding is highly conserved, yet binder specificity is high, our results suggest that by generating binders that target specific kinase conformations, the activity of any kinase can be modulated, ranging from inhibition to activation.

Overall, AI-driven protein design enables rapid generation of stable, high-affinity, and selective protein modulators.

Keywords:

FAK, Inhibitors, Binders, RFdiffusion

O-009/P-006

Integrated Analysis Of Nucleolar Proteome And Morphology Uncovers Metastasis-Related Remodeling In Colorectal Cancer

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The **nucleolus** is a membraneless nuclear organelle in eukaryotic cells, best known for its central role in ribosome biogenesis. Although its association with cancer was first described in the 19th century, recent studies have expanded its functional relevance, implicating the nucleolus in key processes as stress response, transcriptional control, and cell proliferation. Meanwhile, **colorectal cancer (CRC)** ranks as the third most frequently diagnosed malignancy and the second leading cause of cancer-related deaths worldwide.

In this study, we investigated nucleolar remodeling and its functional contribution to CRC metastasis. First, nucleolar structure was assessed using high-content imaging in isogenic CRC cell lines exhibiting distinct metastatic tropisms: highly metastatic variants targeting the liver (KM12SM), liver and lung (KM12L4a), and lymph nodes (SW620), as well as their poorly metastatic counterparts (KM12C and SW480, respectively). Observed morphological alterations prompted us to further characterize the isolated nucleoli using label-free quantitative (DIA-LFQ) proteomics. Differential analysis identified metastasis-associated protein changes, mainly enriched in RNA metabolism and nucleolar regulatory pathways. Key candidate proteins were validated through Western Blot, immunofluorescence, and immunohistochemistry. Functional relevance was confirmed by transient loss-of-function assays performed *in vitro* and *in vivo*, demonstrating their role in promoting metastatic dissemination. Overall, our findings reveal novel molecular drivers linked to nucleolar function in CRC metastasis and highlight the nucleolar proteome as a promising source of prognostic markers and therapeutic targets.

Keywords:

Nucleolus, Colorectal Cancer, Cancer, Metastasis, Biomarker Discovery, Proteomics, LFQ-DIA



O-010/P-007

Candidate Gene Panel In Breast Cancer: Differential Expression And Association With Clinical Variables And Survival

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Universidad Libre, Barranquilla, Colombia

Objective: To evaluate the expression of a candidate gene panel in breast cancer and its association with clinical and demographic variables using bioinformatics analyses.

Materials and Methods: A cross-sectional, descriptive, bioinformatics-based study was conducted using tumor data from The Human Protein Atlas (HPA). Eight genes (CITED2, COL4A6, FHL2, LCP2, LRP1B, SLITRK6, TBX-A2R, and TRIP10) were analyzed in relation to age, race, tumor stage, vital status, and survival. Gene expression was assessed as a continuous variable. Statistical analyses included descriptive methods, Mann–Whitney U and Kruskal–Wallis tests, correlation analyses, and Benjamini–Hochberg FDR correction.

Results: High interindividual variability was observed across the gene panel. CITED2 showed progressively higher expression with age, while SLITRK6 and LCP2 displayed age-dependent patterns. CITED2 and FHL2 differed significantly according to race. No significant associations were found with tumor stage or vital status after multiple-testing correction. Only CITED2 showed a weak inverse correlation with follow-up time among living patients.

Conclusions: The gene panel exhibited marked heterogeneity in breast cancer. CITED2 emerged as the most consistent age-associated gene and the strongest candidate for further validation. Overall, the panel showed limited prognostic value but may help identify biologically relevant targets for future studies.

Keywords:

Breast Cancer, Gene Expression, Bioinformatics, The Human Protein Atlas, CITED2, Biomarkers, Survival Analysis, Transcriptomics, Precision Oncology, Prognostic Markers.

O-011/P-008

Depot-Specific Circadian Transcriptomic Signatures In Human Subcutaneous And Visceral Adipocytes From Subjects With Obesity

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Circadian rhythms are crucial for metabolic functions in adipose tissue (AT), whereas circadian disruption is strongly linked to obesity and metabolic disorders. However, despite its importance, and given the intrinsic heterogeneity of AT depots, the molecular mechanisms regulating these rhythmic patterns remain poorly defined. Thus, the aim of this study was to assess the endogenous circadian transcriptomic profiles of human SAT- and VAT-derived adipocytes. Preadipocytes were isolated from SAT and VAT collected during bariatric surgery from severely obese donors and differentiated *in vitro* into mature adipocytes. After forskolin synchronization, *Bmal1-luc* bioluminescence was continuously recorded, confirming functional circadian clocks in SAT and VAT adipocytes. In parallel, cells were collected every 4h over 24h for RNA-seq analysis. Circadian analysis identified 2413 oscillatory genes. Most transcripts maintained the same rhythmicity in both depots (1978), while 357 lost rhythmicity and 77 gained it in VAT, only *PER1* displayed a changed oscillatory pattern between SAT and VAT. Depot-specific differences were also observed in non-oscillatory transcripts, with higher expression of *HSD11B1*, *LEPR*, *STAR*, *SLC2A1* and *OLR1* in VAT, and *IRS1*, *CD36*, *DGAT2* and *CIDEA* in SAT. Functional enrichment analyses highlighted pathways that differed between adipocyte types, such as PI3K-Akt and MAPK signaling, cytokine-cytokine

receptor interaction, calcium and hormone signaling. Overall, our results showed that SAT and VAT adipocytes display distinct circadian transcriptomic signatures, suggesting that circadian regulation contributes to the depot-specific molecular identity of AT. Further studies are needed to clarify how the adipocyte clock interacts with AT metabolism in obesity.

Keywords:

Circadian Clock, Adipocytes, White Adipose Tissue, Metabolism, Obesity, Cosinor, Chronobiology

O-012/P-009

Multi-Omic Profiling Of The Gut Microbiome In Cow's Milk-Allergic Infants

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Cow's milk protein allergy (CMPA) is one of the most prevalent food allergies in early infancy, and alterations in the gut microbiota and its metabolic activity have been proposed as contributors to disease development. We hypothesised that infants with IgE-mediated CMPA display a distinct fecal microbial-metabolic profile compared with milk-tolerant non-allergic controls. The study population comprised 69

infants aged 0-6 months: 46 allergic infants and 23 controls. Fecal samples were analysed using a multi-platform metabolomics approach alongside gut microbiota profiling. Multi-omics integration was performed using the DIABLO framework within mixOmics to identify coordinated metabolite, taxonomic and functional signatures associated with CMPA and feeding status. Metabolomics analysis revealed slight differences between allergic and control infants, with feeding emerging as a relevant factor linked to allergic status. Allergic infants showed elevated faecal levels of serine, proline and valine, and diminished lysine levels. Conversely, short-chain fatty acids exhibited no significant disparities between the groups. Microbiota analyses indicated compositional differences associated with CMPA, including taxa linked to both allergy and dietary patterns. In addition, shotgun metagenomics pointed to alterations in lipid-related microbial pathways. Diet-based comparisons highlighted changes in saturated fatty acids and tricarboxylic acid cycle metabolites, particularly in formula-fed infants. The findings suggest that early-life CMPA is associated with subtle but biologically relevant alterations in host–microbiota co-metabolism. Integrating metabolomic, taxonomic, functional, and dietary data may improve the characterisation of allergic phenotypes during infancy.

Keywords:

Gut Microbiota, Metagenomics, Metabolomics, Food Allergy

O-013/P-010

Single-Cell RNA Sequencing Reveals Cellular And Transcriptional Heterogeneity In Pediatric Medulloblastomas

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Medulloblastoma is a malignant pediatric brain tumor classified into four molecular groups—WNT, SHH, G3, and G4—each exhibiting high cellular and transcriptional heterogeneity. This diversity drives complex clinical behavior and underscores the need for single-cell resolution characterization of the tumor microenvironment (TME), including



its cellular composition and gene expression profiles. This study aimed to evaluate cellular and transcriptional heterogeneity in G3 and G4 medulloblastomas using single-cell RNA sequencing (scRNA-seq). Six patient samples (2 G3, 4 G4) obtained between 2016 and 2024 at Hospital Infantil de México Federico Gómez were analyzed. Dissociated tissues were processed using the Chromium 10X system, and libraries were sequenced on a NextSeq 2000 platform. Data analysis was performed in R using Cell Ranger and Seurat. Partial results identified 740–7,800 individual cells per sample, corresponding to 14 distinct cell types within the TME. Molecular subtypes were confirmed in all six cases. Quantitative analysis revealed a TME dominated by astrocytes in both subgroups, comprising >75% of non-neoplastic cells. However, significant differences emerged in minor populations. Group 3 exhibited a more immature profile, with higher proportions of neurons and primitive neuroepithelial cells. In contrast, Group 4 showed a more diverse stromal niche, enriched for endothelial/epithelial cells, as well as immune precursors (T cells and promyelocytes). These findings suggest that while glial support is a conserved feature, tumor molecular identity differentially modulates the recruitment and complexity of other lineages within the pediatric TME.

Keywords:

Pediatric Medulloblastoma, ScRNAseq, Transcriptional Heterogeneity

O-014/P-011

Identifying New Metabolic Targets In FOLFOX Resistant Colorectal Cancer Via A Comprehensive Multi Omics Systems Biology Workflow

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Colorectal cancer (CRC), the second leading cause of cancer-related mortality worldwide, remains a major clinical challenge despite advances in targeted therapies. FOLFOX is widely used as frontline treatment, but its efficacy is limited by chemoresistance and progression. Tumor metabolism is a key driver of therapeutic response, yet subtype-specific metabolic vulnerabilities are poorly understood. Here, we applied an integrative multi-omics systems biology approach to identify metabolic targets to enhance FOLFOX efficacy in CRC.

We analyzed transcriptomics, targeted metabolomics, and nutrient exchange fluxes, including glucose, lactate, amino acids, and oxygen consumption, in eight CRC cell lines under control and FOLFOX-treated conditions. These data were integrated into contextualized genome-scale metabolic models using the CORDA algorithm, enabling subtype-specific network reconstruction and flux analysis.

This framework revealed distinct metabolic rewiring across CRC subtypes in response to FOLFOX, affecting central carbon and amino acid metabolism, suggesting adaptive strategies that support survival under chemotherapeutic stress. Importantly, subtype-specific synthetic lethal metabolic targets were identified whose inhibition may sensitize cells to FOLFOX.

Overall, this integrative approach provides a predictive framework to translate complex molecular data into actionable insights. It supports the development of metabolism-informed combination therapies in CRC and may be extended to other solid tumors.

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Keywords:

Systems Biology, Metabolism, Bioinformatics, Cancer, Quimiotherapy

O-015/P-012

Analysis Of The Involvement Of GLG1 And BAIAP2 In Colorectal Cancer By Functional Proteomics

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Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide and the second leading cause of cancer-related death, mainly due to late detection and met-

astatic dissemination. Improving early diagnosis and understanding the molecular mechanisms driving tumor progression are therefore essential to increase patient survival, highlighting the need for novel biomarkers with diagnostic, prognostic and therapeutic potential. In this study, we investigated the functional relevance of GLG1 and BAIAP2 in CRC progression, two proteins previously reported to be overexpressed in aggressive CRC phenotypes. Isogenic CRC cell models with different metastatic abilities were used to represent progressive states of tumor dissemination. Loss-of-function cell-based assays were performed using stable shRNA-depleted cells to evaluate the biological role of both proteins in the tumorigenic and metastatic properties of CRC cells. After confirming efficient depletion, *in vitro* functional assays were conducted to assess the impact of GLG1 and BAIAP2 silencing on cell proliferation, adhesion, invasion, migration and colony formation. *In vivo* murine models allowed evaluating tumor growth, liver metastasis formation and survival in a physiological context. Additionally, quantitative LC-MS/MS proteomic analysis was performed in silenced CRC cells to identify differentially expressed proteins and altered signaling pathways. Selected candidates were subsequently validated to identify proteins implicated in CRC progression and metastasis. Overall, GLG1 and BAIAP2 depletion induced marked alterations in metastatic-associated phenotypes, supporting their functional involvement in CRC progression and dissemination, and highlighting their potential as prognostic biomarkers of metastasis.

Keywords:

Colorectal Cancer, Proteomics, Metastasis, Biomarkers

O-016/P-013

AI-Driven Hit Discovery Against SARS-CoV-2 Mpro: A Boltz-2 Integrated Workflow

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Identifying viable drug candidates from large compound libraries remains a major bottleneck in early drug discovery. Traditional docking approaches can underperform when targeting challenging binding sites, such as large, shallow, or highly flexible pockets, limiting their reliability as standalone tools. We present an integrated virtual screening workflow incorporating Boltz-2 to prioritize small-molecule hits against the SARS-CoV-2 Main Protease (M-pro), a well-validated antiviral target with a structurally characterized binding site.

Starting from 200,000 commercial compounds, OMEGA

was used to remove molecules with undefined chirality. A LGBM machine learning model reduced the library to 40,000 candidates, which were evaluated using Boltz-2. Detailed knowledge of the M-pro binding pocket guided characterization of key interactions across subpockets, including hydrophobic contacts and hydrogen bonds critical for potency.

Validation using PDB crystal structures and COVID Moonshot compounds showed a meaningful correlation between Boltz-2 predicted values and experimental pIC50 data. Drug-likeness filtering with OpenEye FILTER, combined with SAR studies using the pICkit library, yielded 20 high-confidence hits.

This workflow demonstrates how combining AI/ML prioritization, structure-based pose prediction, and rational SAR filtering effectively reduces large libraries to tractable candidate sets, mitigating the risks of relying solely on AI predictions. Selected compounds are being acquired for experimental inhibition assays in collaboration with a medicinal chemistry group.

Keywords:

AI, Virtual Screening, Machine Learning, Structure-Based Drug Discovery, SARS-CoV-2, Main Protease, Boltz-2

O-017/P-014

Network-Based Analysis Of Collateral Sensitivity In Antifungal Resistance

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Fungal infections affect millions annually, and antifungal resistance is an increasing biomedical concern. Collateral sensitivity (CS), where resistance to one drug creates vulnerability to another, has emerged as a potential therapeutic strategy in bacteria but remains poorly characterized in fungi. Our project proposes that resistance-conferring genetic alterations impose network-level constraints that generate predictable collateral sensitivities.

To address this, we propose a systems biology framework integrating a large-scale *S. cerevisiae* chemical genomics dataset comprising ~4,800 gene knockouts and ~500 histone PTM mutants evaluated across ~120 conditions. This framework will systematically identify CS interactions. CS-associated genes will be integrated with protein-protein and genetic interaction networks to identify functional modules and vulnerability pathways. Selected subnetworks will then be characterized using RNA-seq and transcription



factor activity inference to identify candidate regulatory drivers, which will be experimentally tested through epistasis or KO-rescue assays in yeast, with potential conservation assessed in clinically relevant fungal pathogens.

Preliminary results suggest that CS events are widespread and highly structured, with human drugs and food-related compounds found strongly enriched, suggesting that known treatments may function to exploit resistance-associated vulnerabilities. By integrating phenotype profiles with network biology and regulatory inference, this project aims to generate mechanistically grounded and predictive models of fungi vulnerabilities and identify novel therapeutic targets and combination strategies against antifungal-resistant infections

Keywords:

Antifungal, Gene Regulatory Networks, Collateral Sensitivity, Chemical Genomics, Yeast, *Saccharomyces Cerevisiae*, Omics.

P-015

Transcriptional And Proteomic Profiling Of Microglia Under Physiological And Pathological Conditions

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Aging drives microglial cells toward a pro-inflammatory, neurodegenerative state characterized by upregulation of inflammatory mediators and loss of synaptic regulatory functions. Galectin-3 (Gal3), a carbohydrate-binding protein markedly elevated in microglia during aging and neurodegenerative disease, has emerged as a key modulator of this pathological shift.

This study performed integrated transcriptomic and proteomic profiling of microglia from wild-type (WT) and Gal3 knockout (KO) mice at 6 and 24 months of age. In aged WT animals, transcriptomic analysis revealed upregulation of pro-inflammatory genes—including TNF, IL-1 β , and S100A8/A9—and enrichment of IL-17, NOD-like receptor, and osteoclast differentiation pathways. Concurrently, genes governing synaptic structure, calcium signaling, and cholinergic neurotransmission were significantly downregulated. Proteomic data corroborated these findings, demonstrating loss of lipid metabolism functions and accumulation of lipid droplets, hallmarks of age-related neurodegeneration.

In Gal3 KO mice, transcriptomic profiling showed partial restoration of synaptic remodeling genes, reduced cytokine

and chemokine signaling, and a qualitatively distinct IL-17 pathway output favouring regulatory mediators (IKKi, MMP9, LCN2) over neurotoxic effectors. Proteomics confirmed recovery of actin binding, energy metabolism, and lipid biosynthetic processes.

These findings identify Gal3 as a critical age-responsive regulator linking neuroinflammation, lipid metabolism, and synaptic maintenance. Its deletion promotes a homeostatic microglial phenotype, positioning Gal3 as a promising therapeutic target for age-associated neurodegeneration.

Keywords:

Microglia, Galectin-3, Neuroinflammation, Aging, Transcriptomics, Proteomics, Neurodegeneration, Lipid Metabolism, Synaptic Remodeling, Knockout

P-016

Interrogating Histone PTM Function Through Chemical Genomics

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Histone post-translational modifications (PTMs) regulate chromatin dynamics and gene expression. Dysregulation of these modifications, as well as the enzymes that write, erase, and recognize them, has been linked to numerous human diseases. Despite their importance, the functions of most histone PTMs, their interactions (crosstalk), and their regulators remain poorly understood.

While histone point mutant libraries have been instrumental in uncovering the roles of individual PTMs, a systematic and high-throughput approach is needed to comprehensively map their functional relationships.

In this project, we have expanded a large-scale strategy developed in our laboratory to investigate histone PTM function using *Saccharomyces cerevisiae*. By combining reverse genetics with chemical genomics, we are assessing the fitness phenotypes of approximately 600 histone point mutants spanning all four core histones (H2A, H2B, H3, and H4). These mutants are designed to either mimic or prevent phosphorylation, acetylation, and methylation events. In parallel, we are analyzing approximately 5,000 gene deletion mutants of the yeast across 151 diverse stress conditions, including environmental stresses, nutrient limitations, and exposure to human drugs. This large-scale screen generates a phenotypic fingerprint for each mutant.

By comparing these phenotypic profiles, we are identifying functional associations between histone PTM mutants and

their potential regulators. These findings will expand our understanding of the histone code and provide a foundation for mechanistic studies of newly discovered chromatin regulatory pathways.

Keywords:

Histone, PTM, Chemical Genomics, Crosstalk, Chromatin, *Saccharomyces Cerevisiae*, Epigenetics

P-017

Spatial Proteome Reorganization During Influenza A Virus Infection

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Internal compartmentalization is a defining feature of cellular organization, creating distinct biochemical environments and enabling regulation through dynamic relocalization of macromolecules. Viruses, as obligate intracellular parasites, exploit and remodel host organelles to complete their replication cycles, yet the mechanisms underlying these processes remain incompletely understood. A comprehensive understanding of viral infection thus requires mapping dynamic changes in protein localization across the cell.

Here, we applied differential centrifugation coupled with mass spectrometry to generate proteome-wide maps of subcellular protein localization during influenza A virus (IAV) infection. Using correlation profiling, we quantified protein distribution patterns across subcellular fractions and identified widespread, time-resolved changes in protein localization. Our analysis reveals extensive and dynamic remodeling of the host spatial proteome, uncovering previously unrecognized pathways affected by infection and highlighting novel functional associations among host factors.

This dataset provides a comprehensive resource for studying host-virus interactions and offers new insights into the spatial organization of the IAV life cycle, with potential implications for the development of antiviral strategies.

Keywords:

Influenza, Spatial Proteome, Virus-Host Interactions, Subcellular Localization, Differential Centrifugation, DIANN

P-018

Human RNase 2 Is Essential For Macrophage Response To Viral RNA. Generation Of tRNA-Derived Small RNAs By Selective Cleavage At Anticodon tRNA Loops And CCA Ends

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RNase 2 is the most abundant human RNase A member in macrophages. In our previous work, we reported how THP-1 cells-derived macrophages infected by RSV activated RNase 2 expression and how the protein gene knock-out impaired significantly the cell survival to infection. We characterized the RNase 2 endonuclease cleavage products by comparison of tRNA population between wild-type (WT) and RNase 2 knock-out (KO) THP-1-derived macrophage cells. The following study confirmed the preferred cleavage sites and structural determinants of RNase 2 selective on tRNAs.

Here, we explored the protein role by co-transcriptomics of WT and KO macrophages in absence/presence of a virus-derived single-stranded RNA (ssRNA40). Results revealed that RNase 2 is key for maintaining cell homeostasis. RNase 2 deletion induced the expression of stress-response markers and abolished the antiviral response. In contrast, the up-regulated genes in WT macrophages participate in pro-inflammatory response through TLR8-dependent pathways and antiviral immunity, with activation of MAPK and JAK-STAT pathways. We also identified five top tRNA-derived small RNAs (tDRs) in response to ssRNA40 related to RNase 2, showing preferential cleavage at CA and uridine rich regions of anticodon loops. Another conserved target in all RNase 2-generated 3'tDRs was found at the CCA end, releasing truncated 3'-CC. Among tDRs unique for WT exposed to RNA40, tRNA-LysTTT 3'-half stands out with the highest significant sequence coverage difference. Last, we demonstrated how tRNA-LysTTT fragments generated *in vitro* by recombinant RNase 2 cleavage can recover by themselves the immune response of RNase 2-KO cells.

Results highlight the essential role of RNase 2 selective



tRNA cleavage in antiviral response and inflammation.

Keywords:

RNases, NcRNA, TRNA-Derived Small RNAs (TDRs), Endonuclease Cleavage, Innate Immunity, Antiviral Response, Inflammation

P-019

Towards The Functional Characterization Of A Lankacidin-Like Polyketide Cluster In *Pseudomonas Ogarae* F113

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The rhizosphere is a complex microbial niche where specialized metabolites contribute to microbial competition, plant colonization and community assembly. *Pseudomonas ogarae* F113 is a plant growth-promoting rhizobacterium with strong biotechnological potential. Its genome contains a poorly characterized biosynthetic gene cluster predicted to encode a lankacidin-like polyketide/macrolide, referred to here as LkcA. However, this cluster appears to be silent under standard laboratory conditions, making its biological function and chemical identity largely unknown.

This project proposes a synthetic biology-based framework to study the LkcA cluster. The strategy includes heterologous expression in *Pseudomonas putida* KT2440, promoter-reporter assays to identify potential inducing signals, and microbiological tests to explore the activity spectrum of the putative macrolide. In parallel, the ecological role of LkcA will be investigated through comparative rhizosphere colonization assays using the wild-type strain and an LkcA-deficient mutant, combined with microbiome and proteomic analyses.

This work aims to connect cryptic specialized metabolism with rhizosphere function in *Pseudomonas*, providing a basis to understand how polyketide-mediated interactions may influence microbial competition and plant-associated bacterial fitness.

Keywords:

Lankacidin, *Pseudomonas Ogarae* F113, Polyketide

P-020

Mapping Host Cell Phenotypes Under Bacterial Infection And AMP Treatment Using A Cell Painting Approach

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Antimicrobial resistance (AMR) is a major global health concern driven by the increasing prevalence of infections with insufficient therapeutic options. In this context, antimicrobial peptides (AMPs) represent promising alternatives due to their structural diversity and broad spectrum of antimicrobial mechanisms. However, their impact on host-pathogen interactions and infection-associated cellular phenotypes remain poorly understood.

In this work, we developed a Cell Painting-based high-content imaging approach to map host cell phenotypic responses to bacterial infection and evaluate AMP anti-infective mechanisms. Human cell lines A549, MRC-5 and HepG2 were infected with four clinically relevant bacterial pathogens associated with severe infections: *Pseudomonas aeruginosa*, *Salmonella enterica*, *Staphylococcus aureus* and *Listeria monocytogenes*. Infection-associated phenotypes were analyzed at early and prolonged stages (30 min and 3 h), while a panel of 30 AMPs with distinct mechanisms of action was assessed for its ability to modulate host cellular responses. Multiparametric fluorescence staining targeting nuclei, endoplasmic reticulum, actin cytoskeleton, Golgi apparatus, plasma membrane and lysosomes enabled comprehensive morphological profiling. Images acquired using an Operetta CLS confocal high-content platform were analyzed with CellProfiler to generate quantitative phenotypic signatures.

This pipeline enabled the identification of pathogen- and host-specific morphological fingerprints and provides a framework to discriminate AMP-induced anti-infective responses, expanding the application of Cell Painting to systems biology of infection and biomedicine, characterizing therapeutic mechanisms, and phenotypic screening of novel anti-infective compounds.

Keywords:

Cell Painting, Antimicrobial Resistance (AMR), Antimicrobial Peptides (AMPs), High-Content Imaging, CellProfiler, Host-Pathogen Interactions, Phenotypic Profiling, Bacterial Infection

P-021

VEGF-A Modulates Fibroblast Migration And Integrin Nanoscale Organization: Insights From Super-Resolution Microscopy And Hippo Signaling

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Vascular endothelial growth factor-A (VEGF-A) is a vital growth factor acting as a chemoattractant during wound healing. While the Hippo pathway is a known regulator of migration through YAP/TAZ transcription factors, the interaction between VEGF-A and Hippo signalling in non-endothelial cells remains poorly understood. We investigated the effect of VEGF-A on human primary dermal fibroblasts using a multiscale approach. Migration experiments on cell monolayers and individual cells were complemented by single particle tracking and super-resolution microscopy experiments of the $\alpha_5\beta_1$ integrin. To quantify receptor organization at the nanoscale, we applied HDBSCAN clustering analysis to evaluate differences in cluster area, shape, and density. These parameters were analysed inside and outside focal adhesions, at the leading edge versus the cell centre, and under VEGF-A treated versus untreated conditions.

Our results revealed that VEGF-A treatment increases individual cell migration velocity while slowing down collective migration. Furthermore, super-resolution imaging demonstrated that VEGF-A produces a nontrivial effect on the nanoscale organization of integrin clusters. These changes in area and density varied significantly, especially outside the focal adhesions. Notably, we established a correlation between these receptor clustering organization and the cellular localization of YAP/TAZ in relation to the Hippo pathway. Our study underscores the intricate interplay between VEGF-A signalling, migration, and $\alpha_5\beta_1$ organization, shedding light on the role of the Hippo pathway in non-endothelial cells. These findings reinforce the importance of understanding the nanoscale spatial organization of cell surface receptors in physiological processes.

Keywords:

Migration, SPT, Super-Resolution, VEGF, Integrin A5b1, Hippo Patway, Protein Clusters

P-022

Separating Signal From Leakage: A New Framework For Natural Antisense Transcripts Discovery

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Natural antisense transcripts (NATs) constitute an important layer of gene regulation; however, their identification remains challenging due to technical artifacts inherent to RNA sequencing. We found that a putative NAT was previously annotated in the maize lignin biosynthesis gene *COMT1* locus based on full-length cDNA (flcDNA) data. This NAT has a predicted open reading frame, suggesting it can code for a protein (annotated in UniProt under accession C4J6W8). We used targeted proteomics and generated transgenic plants overexpressing the *COMT1* NAT gene, and our data strongly suggests that this protein is not produced *in vivo*. Detailed analysis revealed that the predicted transcript likely resulted from technical artifacts, including strand misassignment (mirror effects) or library preparation leakage. This prompted us to reassess NAT annotations genome-wide in maize. Thus, using NASTIseq, we identified candidate NAT loci along the genome. Although NASTIseq reliably identifies loci with antisense transcription, downstream transcript reconstruction using StringTie was frequently misled by strand leakage, leading to misannotation of antisense transcripts. To address this, we developed a correction pipeline leveraging strand-specific RNA-seq signal. Genome-wide coverage tracks were corrected by subtracting signal from the opposite strand using empirically derived leakage factors. Corrected profiles were used to define high-confidence transcriptional regions, and transcript assembly was constrained to these regions using filtered alignment files. This approach provides a new framework for RNAseq analyses, removing leakage-driven artifacts and improving antisense transcript reconstruction. This new computational pipeline will be publicly available in online repositories.

Keywords:

Natural Antisense Transcripts, Transcriptomics, Strand Leakage, Bioinformatics



P-023

Identification Of Differential TRNA Species And Their Derivatives In Cell Cycle Of *Saccharomyces Cerevisiae*

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Transfer RNAs (tRNAs), the major transcript population of RNA polymerase III, play important roles in cellular homeostasis, as the composition of the tRNA pool is a key determinant of translational output and, consequently, of the proteome composition. Given that proteome composition is dynamically remodelled throughout the cell cycle, we hypothesize that the tRNA pool — composed of distinct combinations of tRNA isoacceptors and isodecoders — undergoes analogous changes to meet the shifting translational demands of each cell cycle phase, specifically focusing on phases G1 and S. Here, we investigated the differential accumulation of tRNA species and their derivatives — including tRNA-derived fragments (tRFs) and halves (tiRNAs) — throughout the cell cycle of the model organism *Saccharomyces cerevisiae*. Using synchronized yeast cultures and a tRNA sequencing procedure established by us, we profiled tRNA pool composition at cell cycle phases G1 and S and, in addition, developed a statistical methodology for successfully identifying those tRNA derivatives. Our results reveal phase-specific changes in the abundance of particular tRNA isoacceptors and isodecoders, suggesting a coordinated regulation of the tRNA pool that may support the translational demands of each cell cycle stage. Furthermore, we identified differentially expressed tRNA-derived fragments which could have potential regulatory roles, expanding the functional landscape of tRNA biology beyond their canonical role in translation. Taken together, these findings suggest that tRNA pool remodelling is an active and regulated process during cell cycle progression in *S. cerevisiae*, with implications for the understanding of translational control mechanisms in eukaryotic cell division.

Keywords:

Transfer RNA, Cell Cycle, TRF, TiRNA, Bioinformatics

P-024

Identification Of Gut Microbiota Changes And Predictive Microbial Signatures Throughout The Development Of Pulmonary Fibrosis In Aged Mice

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Introduction: Pulmonary fibrosis (PF) is a progressive disease with an initial inflammatory response. Gut microbiota (GM) changes have been linked to experimental PF, but the preceding microbial profiles are unclear. We hypothesize that GM changes precede and predict PF development, and that a high-fat high-carbohydrate (HFHC) diet may modulate these alterations.

Methodology: Aged female mice were fed a control chow or a HFHC diet and instilled with PBS or bleomycin (BLM). Faecal samples were collected on days -1,3,7 and 14. GM profiles were analysed by 16S rRNA amplicon gene sequencing. PF was assessed using Masson's Trichrome staining, bronchoalveolar lavage (BAL) leukocytes were quantified by flow cytometry, gene expression by RT-qPCR, and plasma D-lactate by an enzymatic assay.

Results: HFHC diet did not affect BLM-induced Ashcroft score, fibrosis and inflammation markers, or BAL cell counts, but HFHC diet alone induced the expression of *Cxcl5*, *Ccl12* and *Il17a* in BAL cells. GM α -diversity differed at day 7 in response to BLM and diet, while diet was the primary driver of compositional variation. D-lactate was detectable only in HFHC-fed mice. At day 3, ANCOM-BC detected *Clostridium_sensu_stricto1*, *Enterorhabdus* or *Odoribacter* as BLM-enriched taxa, the latter being positively correlated with the expression of inflammatory genes. At day 7, *Christensenellaceae_R-7_group* increased and positively correlated with *Mcp-1*, while *Akkermansia* decreased and inversely correlated with *Il-6*. Notably, LEfSe identified *Parabacteroides* as a discriminant taxon and Random Forest classification ranked it as a top predictive feature.

Conclusion: Aged mice developing PF show time-dependent GM changes associated with inflammation, which may serve as predictive signatures of PF development.

Keywords:

Pulmonary Fibrosis, Gut Microbiota, Bleomycin, Bronchoalveolar Lavage Fluid, Candidate Microbial Signature.

P-025

Spheroids As An In Vitro Model Of Endometriosis For Biomarkers And Therapeutic Targets Validation

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Endometriosis is a chronic inflammatory gynaecological condition that affects more than 10% of the female population worldwide. It is characterised by the accumulation of functional endometrial tissue outside the uterine cavity, known as endometriotic lesions. This disease remains poorly understood, with an uncertain aetiology, heteroge-

neous clinical presentation, delayed diagnosis, and limited treatment options.

For these reasons, it is necessary to investigate new therapeutic targets and new non-invasive diagnostic methods for early detection. We analysed the proteome of tissue samples from endometriotic lesions and healthy endometrial tissue. The shotgun proteomic study identified a total of 7,039 proteins contained in the tissue samples studied, of which 134 showed significant differential expression in samples from endometriotic lesions compared with samples from healthy endometrium.

In order to do a functional validation of these potential therapeutic targets, it is necessary to develop a robust *in vitro* model of endometriosis that replicates the disease genotype. We are currently establishing a 3D model using mesenchymal stem cells and an endometrial fibroblast line cultivated in Matrigel using different expansion media over a period of 21 days. After this period, the resulting spheroids are collected and endometriosis markers are validated at the transcriptomic level (*RAD51*, *TIMELESS*, *NLK* and *BCL6*).

The proteomic analysis identified several candidate biomarkers and therapeutic targets for endometriosis. The establishment of this 3D endometriosis model provides a robust platform for their functional validation, supporting the development of novel non-invasive diagnostic strategies and more effective therapeutic approaches.

Keywords:

Endometriosis, Proteomic Study, 3D Model, Therapeutic Targets, Biomarkers

P-026

KLF2 Modulates Stretch-Induced Transcriptional Mechanoresponses In Endothelial Cells

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Vascular endothelial cells (ECs) are key regulators of vascular tone, tissue homeostasis, and organ regeneration. As highly mechanosensitive cells, ECs convert hemodynamic forces —such as shear stress and cyclic stretch— into biochemical signals via mechanotransduction. The transcription factor KLF2, induced by laminar shear stress, maintains the endothelium in a quiescent, anti-inflammatory, and anti-thrombotic state, yet its role in stretch-induced mechanotransduction remains unexplored. Here, we in-



vestigated KLF2 function in stretch-induced transcriptional modulation using gain- and loss-of-function approaches in primary human umbilical vein ECs (HUVECs). KLF2 was overexpressed via lentiviral transduction or simvastatin treatment, and knocked down by siRNA transfection, including in simvastatin-treated cells. Cells were kept static or subjected to cyclic stretch, followed by bulk RNA-seq. Our results revealed that KLF2 acts as a bidirectional regulator of stretch-induced transcriptional responses, simultaneously enabling and repressing distinct gene programs. KLF2-enabled programs were dominated by stress-protective and anti-proliferative responses, while KLF2-repressed programs included endothelial activation and pro-inflammatory mediators. In sum, this work uncovers a previously unrecognized role for KLF2 in stretch-induced mechanotransduction, which could inform therapeutic strategies targeting KLF2 to mitigate maladaptive endothelial responses in vascular diseases driven by pathological mechanical stress.

Keywords:

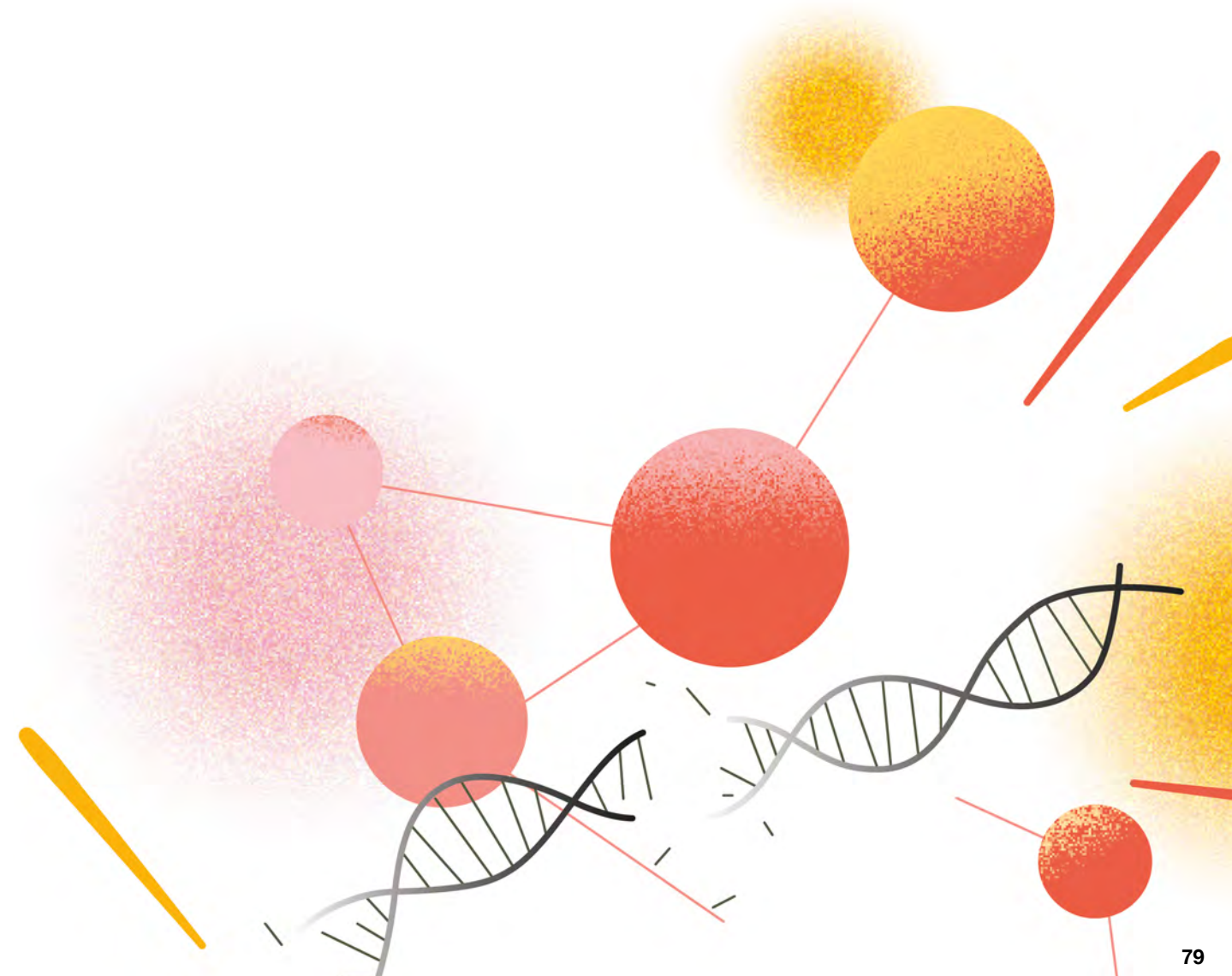
KLF2, Endothelial Cells, Mechanotransduction, Cellular Stretch, Bulk RNA-Seq.



GRUPOS CIENTÍFICOS DE LA SEBBM:

QUÍMICA BIOLÓGICA

8 DE SEPTIEMBRE





O-018

Photoswitchable Small Molecules To Restore Visual Acuity And Visually Guided Behavior In Animal Models Of Blindness

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Blinding diseases due to photoreceptor (PhR) degeneration like age-related macular degeneration (AMD) and retinitis pigmentosa (RP) leave the rest of the retinal circuitry largely intact, albeit unable to respond to light. Gene therapy can revert PhR degeneration, but it can only be applied to a small subset of RP patients. Alternatively, implanted electronic retinal prostheses aim at a larger population by electrically stimulating the surviving neurons. However, the treatment is invasive, costly, and provides limited resolution. Photopharmacology can develop photoswitchable small molecules to restore vision impairment by conferring light sensitivity to ion channels that are widely expressed in the remaining inner retinal neurons, and a first-in-human clinical trial is ongoing. Here, we have developed novel photoswitchable small molecule ligands of metabotropic glutamate 6 (mGlu₆) receptors, which are located exclusively at the dendrites of ON bipolar cells (OBCs, postsynaptic to PhRs) and can leverage a privileged position to mimic physiological signals in the remnant retinal circuit. These photoswitchable ligands (prosthe6) thus act as 'molecular prostheses' that can restore the light input to the retina *via* upstream-targeted control of the circuit after PhRs degeneration. Prosthe6 compounds are allosteric, drug-like, water soluble, and display outstanding *in vitro* properties including full efficacy, nanomolar potency, fast deactivation in ambient white light, and fast reactivation in the dark. *In vivo* experiments show that they readily recover the visual acuity and restore the innate light avoidance behavior in mouse models of blindness (AMD and RP). These effects are mediated by mGlu₆ receptors *in vivo* and can also be achieved by topical administration.

Keywords:

Photopharmacology, Photochromism, Photoswitch, Azobenzene, Push-Pull, Allosteric Modulator, Metabotropic Glutamate Receptor, mGlu₆, Optokinetic Reflex Retinitis Pigmentosa (RP), Age-Related Macular Degeneration (AMD)

O-019

Chemical Modulation Of Microtubules Structure As A Pharmacological Target

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Microtubules are dynamic cytoskeletal polymers whose structural organization regulates intracellular transport, force generation, and recognition by motor proteins and microtubule-associated proteins (MAPs). Microtubule-stabilizing agents (MSAs), widely used in cancer therapy and increasingly explored in neurodegeneration, suppress depolymerization but often at the cost of structural perturbations that may contribute to secondary toxic effects.

Understanding how MSAs remodel the microtubule lattice is therefore essential to define their functional impact on the cytoskeletal machinery. Using an integrated structural and functional approach, we show that microtubule lattice architecture can be chemically modulated and this is a key regulator of MAP recognition and intracellular transport. Drug-imposed lattice states, involving both longitudinal spacing and lateral protofilament contacts, encode distinct functional outputs. Using Tau as a structurally sensitive neuronal MAP, we demonstrate that compact lattices promote rapid and homogeneous Tau binding, whereas expanded lattices favour patch-like condensate formation. Lattice expansion also reduces dynein contact time without compromising processivity, while kinesin-1 motility is more complexly regulated by the combined effects of axial and lateral conformations.

Using medicinal chemistry, we show that MSAs can be modified to avoid adverse structural perturbations. Our lead compound retains stabilizing activity while preserving a native-like lattice architecture, resulting in more physiological Tau dynamics and transport behaviour. This demonstrates that microtubule stabilization and lattice remodelling are separable pharmacological properties, opening new therapeutic opportunities in several diseases.

Keywords:

Microtubules, Cancer, Neurodegeneration, Paclitaxel

O-020/P-027

1,6-Diazapyrene As A Novel Blue-Light-Activated Photosensitizer For Antibacterial Photodynamic Therapy

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The growing threat of antimicrobial resistance is steadily undermining the effectiveness of current antibiotic treatments for bacterial infections, highlighting the need for alternative strategies. Antibacterial photodynamic therapy (aPDT) has emerged as a promising approach to treat topical infections through the light-induced generation of reactive oxygen species (ROS) by photosensitizer (PS) compounds. A recently synthesized diazapyrene isomer, 1,6-diazapyrene (DAP16), has been proposed to undergo a photooxidative reaction with molecular oxygen producing singlet oxygen, a well-characterized ROS. Here, we investigated the photooxidative mechanism of DAP16 and evaluated its potential as a new PS for aPDT. Using *Escherichia coli* as a model organism, we demonstrated that DAP16 exhibits bactericidal activity upon blue-light irradiation (430 nm LED), supporting the proposed photooxidative mechanism. Several methylated derivatives of DAP16 were employed to further elucidate the chemical properties required for light-mediated singlet oxygen production. Furthermore, fluorescence microscopy confirmed cellular uptake of DAP16 through its intrinsic fluorescence. In addition, using multiple indicators of ROS-induced damage, including DNA cleavage, and membrane integrity, we showed that photoexcited DAP16 causes oxidative damage simultaneously affecting diverse essential structures. Finally, combining photoactivated DAP16 with antibiotics enhanced its bactericidal effect. Altogether, these results demonstrate antibacterial activity of DAP16 under blue-light irradiation and support its potential as a novel PS, expanding the set of available antimicrobial tools.

Keywords:

Photosensitizer, Photodynamic Therapy, Singlet Oxygen, Diazapyrene, Blue Light

O-021/P-028

The Intrinsically Disordered Protein NUPR1 Is A Target Of Salvianolic Acid A In Pancreatic Cancer Cells

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Nuclear protein 1 (NUPR1) is an intrinsically disordered protein (IDP) that plays a central role in the cellular stress response and cancer progression. Previous studies show that small molecules can disrupt NUPR1 biomolecular interactions by engaging two key hotspot regions around Ala33 and Thr68.

In this study, we identify the natural compound salvianolic acid A (SAA) as a modulator of NUPR1. SAA is a plant-derived bioactive molecule with reported anti-inflammatory and anticancer properties. Binding was characterized using fluorescence spectroscopy ($K_d = 10 \pm 2 \mu\text{M}$) and isothermal titration calorimetry (ITC) ($K_d = 39 \pm 5 \mu\text{M}$). NMR analysis indicated that SAA was bound to multiple regions of NUPR1, while preserving its intrinsically disordered conformational ensemble. Molecular docking simulations further supported an atomistic model of interaction.

In MIA PaCa-2 pancreatic cancer cells, SAA exhibited an IC_{50} of approximately $20 \mu\text{M}$, in agreement with biophysical binding data. Importantly, SAA inhibited stress granule formation induced by NUPR1, suggesting functional disruption of stress response pathways associated with this IDP.

Overall, these findings demonstrated that natural products can target an IDP involved in cancer with low micromolar affinity. This supported the potential use of bioactive plant-derived compounds as modulators of disordered proteins and their pathological functions.

Keywords:

Intrinsically Disordered Proteins, Nuclear Protein 1, Pancreatic Cancer, Protein-Drug Interactions, Salvianolic Acid A, Stress Granules



O-022/P-029

Combating Fungal Phytopathogens In Horticultural Crops Through Bioactive Agents

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The intensive use of synthetic fungicides and plastic mulch is resulting a challenging concern in agriculture due to their environmental impact. Thus, the BioBIVE project is developing biodegradable mulching systems for the controlled release of bioactive agents to manage fungal phytopathogens in horticultural crops.

BioBIVE is evaluating 3 bioactive agent types: basic substances, microbial antagonists and seaweed phlorotannins against 12 relevant phytopathogenic fungi, including *Fusarium*, *Botrytis*, *Verticillium* and *Phytophthora* species. In all cases, growth inhibition bioassays were used to detect the most effective agents.

First, the antifungal effect of 13 basic substances from several commercial brands approved under Regulation (EC) No 1107/2009 was evaluated. Their chemical composition and the absence of common synthetic pesticides was determined. Besides, their thermal stability was verified, allowing the incorporation into biodegradable polymer matrices. The strongest basic substances were found to be nettle, horse-tail and chitosan.

Second, 51 bacterial strains were screened as microbial antagonists leading to the selection of 5 isolates belonging to the *Bacillus* and *Streptomyces* genera. Their genomes were sequenced to identify biosynthetic gene clusters potentially associated with antifungal activity.

Finally, biomass sourced from a range of wild harvested and cultivated seaweeds was subjected to different extraction protocols, composition analyses and antifungal assays. Production of the most potent extract from *Ascophyllum nodosum* was upscaled.

Currently, the functionalisation of the release platforms and their efficacy, using the best selected bioagents, are being carried out to identify the most promising candidates for subsequent field application.

Keywords:

Basic Substances, Biocontrol, Microorganisms, Phlorotannins, Fungal Phytopathogens, Horticultural Crops

O-023/P-030

Development Of A Synbiotic Beverage Using The Prebiotic Potential Of *Palmaria Palmata* And The Fermentative Capacity Of *Lactobacillus Plantarum*

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Palmaria Palmata, also known as “Dulse”, is a marine macroalga with prebiotic, antioxidant capacity, rich in nutrients such as unsaturated fatty acids and essential amino acids. This has positioned it as a functional food of interest due to its health benefits. Among its main components, xylan can be found, from which xylo-oligosaccharides (XOS) can be obtained. These compounds act as prebiotics with the ability to selectively modulate the gut microbiota and confer several health benefits.

On the other hand, *Lactobacillus plantarum* is a lactic acid bacterium with probiotic capacity, given its resistance to gastric transit, bacteriocin production against pathogenic bacteria, and immunomodulatory capacity. It has also been widely used in the food industry as a starter culture in yogurt, cheese, and fermented beverages.

The objective of this study is the development of a synbiotic fermented beverage, encompassing the extraction of XOS from *P. palmata* through environmentally friendly methods that optimize their release in order to achieve a high effective prebiotic concentration at the end of the process. A fermentation with *L. plantarum* was carried out using the XOS-enriched algal extract, and the antioxidant, antidiabetic, and immunomodulatory properties of the beverage were evaluated before and after fermentation, to determine the added value conferred by the fermentation process to assess its role as a functional probiotic in the intestine, and short-chain fatty acid levels were determined due to their association, with metabolic and immune benefits.

Keywords:

Xylo-Oligosaccharides, Synbiotic Beverage, Prebiotic, Gut Microbiota, Antioxidant Activity, *Lactobacillus Plantarum*

P-031

Impact Of Extraction Methodology On Algae Xylo-Oligosaccharides Properties

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Prebiotics are defined as substrates that can be utilized by beneficial microorganisms present in our microbiota to either grow or to enhance their beneficial effects. With this broad definition many substances can be considered as prebiotics, although the most known ones are non-digestible fibres.

Xylo-oligosaccharides (XOS) are non-digestible fibres obtained from the hydrolysis of vegetable cell walls. Terrestrial sources, namely corn or rice, have been extensively studied in the past decade. Meanwhile, novel raw material sources such as algae XOS are gaining interest due to the different structure of these anhydrosugars and the low recalcitrance of the starting material. It has been reported that the origin and the method of obtention can impact the effect of these beneficial compounds.

For all these reasons, we studied the differential effects of XOS rich extracts obtained by enzymatic hydrolysis of commercialised *Palmaria palmata* xylan and *P. palmata* algae, as well as by acid hydrolysis of *Caulerpa lentillifera*.

Results show that enzymatically derived extracts obtained directly from the algae exhibit higher antioxidant and antidiabetic activities than those derived from commercially purified xylan. In contrast, their prebiotic effects are comparable. However, XOS obtained by acid hydrolysis of *C. lentillifera* display markedly lower antioxidant activity than enzymatically produced *P. palmata* XOS. These findings highlight the significant impact of the processing method on the functional properties of these prebiotics.

Keywords:

Prebiotics, Algae, Gut Microbiota, Xylo-Oligosaccharides

P-032

Influence Of CYP3A4 And CYP3A5 Genetic Variants On Atorvastatin And 2-Hydroxyatorvastatin Plasma Levels

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BACKGROUND/OBJECTIVE

Atorvastatin is primarily metabolized in the liver by cytochrome P450 enzymes. CYP3A4 and CYP3A5 are the leading enzymes that synthesize active metabolites such as 2-hydroxyatorvastatin (2-OH). Genetic polymorphisms in CYP3A4 and CYP3A5 may influence enzyme activity and contribute to interindividual variability in atorvastatin metabolism. The aim of this study was to evaluate the association between genetic variants in these genes and plasma levels of atorvastatin and its main metabolite.

METHODS

This study analysed blood samples from 54 patients medicated with atorvastatin. Atorvastatin and 2-OH plasma levels were analysed using liquid chromatography with tandem mass spectrometry (LC-MS/MS). Genes CYP3A4 (rs2740574 and rs35599364) and CYP3A5 (rs776746) were genotyped analysed using TaqMan Drug Metabolism Genotyping Assay. Statical analyses were performed using the SPSS Statistics 29.0 software (SPSS Inc., Chicago, IL, USA), where the significance was set at p<0.05.

RESULTS

Carriers of the CYP3A4 (rs2740574) variant tended to exhibit lower 2-OH plasma levels compared to wild-type in-



dividuals, suggesting a potential association between this polymorphism and reduced metabolite formation. However, this trend did not reach statistical significance ($p=0.066$).

CONCLUSIONS

Atorvastatin and its main metabolite levels show a strong correlation ($p<0.001$), supporting the role of CYP3A-mediated metabolism. Although no statistically significant associations were observed between the studied genetic variants and drug/metabolite levels, a trend was identified for CYP3A4 (rs2740574), suggesting a possible influence on atorvastatin metabolism. Studies including larger patient populations may improve the robustness and specificity of these findings.

Keywords:

Atorvastatin, 2-Hydroxyatorvastatin, CYP3A4, CYP3A5, Pharmacogenetics, Drug Metabolism, Genetic Polymorphism

P-033

Exploring SARS-CoV-2 PLpro Inhibition Through Docking-Based Activity Prediction And Structure-Based Pharmacophore Modeling

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SARS-CoV-2 papain-like protease (PLpro) is an essential enzyme for viral replication and immune evasion, making it an attractive therapeutic target for COVID-19 treatment. However, current PLpro inhibitors are limited by low binding affinity and/or poor ADMET properties, highlighting the need for more effective PLpro inhibitors. In this work, the structural features of the PLpro binding pocket were first characterized through the identification of key residues involved in ligand recognition and the analysis of protein-ligand interactions observed in crystallographic complexes using the pICkIT library. Then, redocking and cross-docking experiments were performed with different crystallized PLpro structures to assess their suitability for virtual screening. A dataset comprising crystallized and non-crystallized ligands with known inhibitory activity was used to correlate docking scores and experimental pIC50 values, enabling the development of a predictive model capable of estimating ligand activity with an error of ± 1 log unit and correctly predicting 98.99% of the compounds included in the dataset. In parallel, a pharmacophore model conformed by 6 sites (2 aromatic rings, 2 hydrophobic, 1 hydrogen bond acceptor and 1 hydrogen bond donor) was generated based

on the most relevant binding interactions and validated using a set of active compounds and decoys, demonstrating its ability to distinguish active from inactive molecules. The combined predictive model and pharmacophore approach provide a validated platform for virtual screening of large chemical libraries and prioritization of novel PLpro inhibitors for further experimental evaluation.

Keywords:

SARS-CoV-2, PLpro, Virtual Screening

P-034

Adaptation Of Inguinal Adipose Tissue To Short Photoperiod Exposure In Male And Female Fischer 344 Rats

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Background: Photoperiod (PP) regulates energy homeostasis and adipose tissue function, but the time required for adipose tissue adaptation to PP changes remains unclear. This study evaluated whether one week of exposure to a short photoperiod (L6) following four weeks under a standard photoperiod (L12) is sufficient to induce molecular and morphological adaptations in inguinal white adipose tissue (iWAT).

Methods: Male and female Fischer 344 rats were maintained under L12 conditions for four weeks and then either remained under L12 or were transferred to L6 for one additional week. Adipocyte number, area and volume were quantified in iWAT, and the expression of Ppar γ , C/ebp α , Fasn, Cpt1b, Lpl, Lep, Adipoq and Sucnr1 were analysed.

Results: Histological analysis revealed marked sex-related differences but no effect of PP change. Females displayed a higher number of adipocytes, whereas males showed larger adipocyte area and volume, irrespective of PP. No significant differences in adipocyte morphology were detected between L12 and L6 within either sex. In contrast, gene expression responses were sex dependent. In males, L6 exposure increased Ppar γ , Cpt1b, Lep, Adipoq and Sucnr1 expression, whereas in females only C/ebp α and Fasn were upregulated.

Conclusions: A change to a L6 exposure modulates the expression of genes related to lipid metabolism in iWAT, particularly in males. However, these transcriptional alterations are not accompanied by any noticeable changes in adipocyte morphology. This suggests that molecular adaptations may precede structural remodelling of adipose tissue. Overall, these findings contribute to a better understanding

of sex-specific differences in the adaptation to PP changes, highlighting their potential impact on metabolic health.

Keywords:

Adipose Tissue, Female, Male, Fischer 344 Rats, Photoperiod

P-035

Validation Of Phosphatidylcholine-Interacting Ubiquitinated Proteins

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Post-translational modifications (PTMs) and protein-lipid interactions act together to control numerous cellular and molecular processes, yet the mechanistic connection between these two regulatory layers remains largely unexplored. In particular, it is unclear how lipid binding might modulate ubiquitination, or conversely, how ubiquitination could influence protein association with specific membrane lipids. Progress in this area has been hampered by the lack of methods capable of simultaneously probing ubiquitinated proteins and their lipid interaction partners *in vivo*. In this work, we have established a chemical biology approach to map the ubiquitinated protein-phosphatidylcholine (PC) interactome in living cells. We have combined an *in vivo* ubiquitin biotinylation strategy based on the *Escherichia coli* biotin ligase BirA, which enables selective enrichment of ubiquitin conjugates, with a bifunctional, clickable and photoactivatable PC analogue (pacPC) that allows visualization and identification of PC-binding proteins under physiological conditions. Integration of these complementary tools has revealed the ubiquitinated protein-PC interactome and has identified LYRIC, SEC22b and Emerin as robust PC-interacting ubiquitinated proteins, which have been validated in this study. This dual approach provides a platform for the purification and characterization of ubiquitinated proteins that specifically interact with PC and offers a framework to dissect the crosstalk between PTMs and membrane lipids and its impact on cellular function in health and disease.

Keywords:

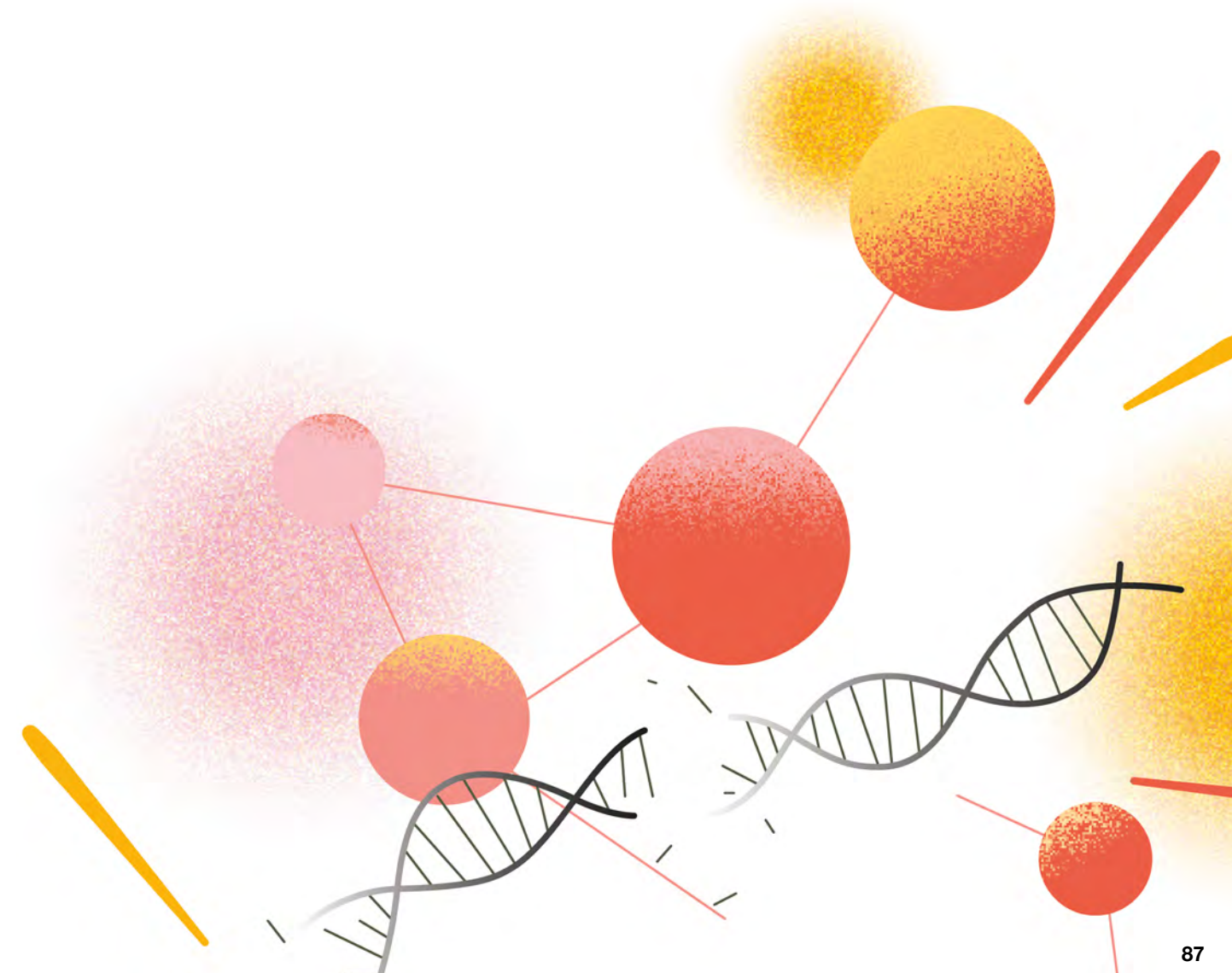
Post-Translational Modifications, Ubiquitination, Protein-Lipid Interactions, Bifunctional Phosphatidylcholine, Click Chemistry, BioUb Strategy, Interactome



GRUPOS CIENTÍFICOS DE LA SEBBM:

SENESCENCIA CELULAR

8 DE SEPTIEMBRE





O-024

Senolytics In Alzheimer's Disease: Insights From Preclinical Models

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Cellular senescence is a hallmark of aging and has been increasingly implicated in brain aging and Alzheimer's disease (AD). Given that aging is the strongest risk factor for AD, the accumulation of senescent cells and their pro-inflammatory secretome (SASP) may contribute to neuroinflammation and neurodegeneration, positioning senescence as a potential therapeutic target.

Our research program aims to define the contribution of cellular senescence to neurodegeneration and cognitive decline. Building on evidence supporting the efficacy of senotherapies in age-related contexts, we investigate the impact of senolytic interventions in preclinical models of AD and age-associated cognitive impairment. We examine how senescent cells influence brain pathology and function, focusing on neuroinflammatory and neurodegenerative outcomes as well as cognitive performance.

This work integrates fundamental aging biology with translational neuroscience and provides insight into whether targeting cellular senescence with senolytics may offer a disease-modifying strategy for neurodegeneration.

Keywords:

Senolytics, Alzheimer's Disease, Neuroinflammation

O-025

Therapy-Induced Senescence As A Driver Of Drug Tolerance And Phenotypic Adaptation In Melanoma

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While immunotherapy and targeted therapies have revolutionized advanced melanoma, their long-term success is fundamentally limited by therapeutic resistance, with ~50% of patients not responding and 20–30% of initial responders eventually relapsing without novel genetic aberrations. Our research focuses on the critical window where drug-tolerant persister (DTP) cells adapt and survive initial treatment, and we reposition **therapy-induced senescence (TIS) not as a terminal endpoint but as an adaptive, reversible mechanism that actively drives drug tolerance and cell adaptation**. To model this, we selected three BRAF^{V600E} mutant patient-derived melanoma models (MM074 melanocyt-

ic-like, MM099 mesenchymal-like, and MM383 neural-crest stem cell-like) and established a live-cell genetic reporter system to identify cells that regain proliferation under therapeutic pressure, characterizing non-cycling DTP and cycling DTP-C cells at the multiomic level. Our findings reveal that each model follows a distinct path to resistance: MM074 DTP-C cells are genetically driven by chromosomal rearrangements; **MM099 DTP cells deploy therapy-induced senescence as an active adaptive mechanism** that promotes sustained survival and drug tolerance under continuous pressure; and MM383 cells exhibit remarkable non-genetic plasticity, where DTP-C cells revert to a drug-naïve morphology upon treatment withdrawal, demonstrating a reversible phenotypic memory. By identifying TIS as a central mechanism of drug tolerance and cell adaptation rather than a mere bystander effect, our work opens the door to targeting senescent DTP cells—using senolytics or SASP modulators—to abrogate the tolerant state and prevent the critical switch to irreversible resistance in melanoma.

Keywords:

CANCER PLASTICITY, MELANOMA, SENESCENCIA, INTRATUMOR HETEROGENITY, DRUG RESISTANCE

O-026/P-036

Targeting RhoA Nuclear Mechanoactivity Rejuvenates Aged Hematopoietic Stem Cells

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Mechanical alterations contribute to the decreased regenerative capacity of hematopoietic stem cells (HSCs) upon aging. RhoA is a key regulator of mechanosignaling, but its role in mechanotransduction in stem cell aging remains unclear. Here we demonstrate that RhoA is activated by increasing nuclear envelope (NE) tension by cell confinement and by osmotic shock. Interestingly, our data show that aged HSCs experience physiologically higher intrinsic NE tension and RhoA activation. We show that pharmacological inhibition of RhoA activity lowers NE tension in aged HSCs. Feature image analysis of HSC nuclei reveals that an aged dependent chromatin remodeling is responsible of higher NE tension levels upon aging. Moreover, our data show that RhoA inhibition restores youthful levels of the heterochromatin marker H3K9me2 in aged HSCs and decreases chromatin accessibility and transcription at retrotransposons. Finally, we demonstrate that RhoA inhibition in aged HSCs upregulates Klf4 expression and transcriptional activity, improving aged HSC regenerative capacity and lympho-myeloid skewing in vivo. Together, our data outline an intrinsic RhoA-dependent mechanosignaling axis in HSCs, which can be pharmacologically targeted to restore aged stem cell function.

O-027/P-037

A Novel Combinatorial Therapeutic Strategy To Treat Pseudomyxoma Peritonei

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Pseudomyxoma peritonei (PMP) is a rare mucinous neoplasm characterized by progressive mucin accumulation in the peritoneal cavity. Although cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is the current standard treatment, many patients eventually relapse due to the lack of effective therapies.

Recent studies show that over 70% of PMP cases harbor activating KRAS mutations, mainly KRASG12D. We previously demonstrated that pharmacological inhibition of KRASG12D with MRTX1133 suppresses tumor growth, although adaptive EGFR signaling limits its efficacy. In addition, the PMP microenvironment is highly hypoxic, promoting tumor survival through HIF-1α-dependent pathways.

Based on these observations, we evaluated a combined therapeutic strategy targeting KRASG12D (MRTX1133), EGFR (cetuximab) and HIF-1α signalling (digoxin). In 3D organoid cultures under hypoxic conditions, the triple drug combination markedly reduced cell viability and organoid size compared with controls and single or double-drug treatments. Importantly, these findings were recapitulated in a PMP patient-derived xenograft (PDX) model, where the triple combination completely prevented tumour growth throughout the 16-week follow-up, outperforming all other treatment groups.

To decipher the mechanisms underlying this response, we are applying a global phosphoproteomics strategy to PDX-Os exposed to the different treatments.

Overall, our results demonstrate that simultaneous targeting of KRASG12D, EGFR and hypoxia-driven signalling produces a durable antitumour response in preclinical PMP models, supporting this combinatorial strategy as a potential therapeutic approach for KRASG12D-mutant PMP.

Keywords:

Pseudomyxoma Peritonei, KRASG12D, Targeted Therapy, Hypoxia, Combination Therapy



O-028/P-038

Orai1 Regulates Extracellular Vesicle-Mediated Communication In Cellular Senescence

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Cellular senescence is one of the hallmarks of aging and is associated with tissue deterioration and decline functional capacity. Senescent cells are characterized by a secretory phenotype known as the senescence-associated secretory phenotype (SASP), which is capable of transmitting senescence in a paracrine manner to neighbouring cells. SASP is composed of signalling molecules, like interleukins and cytokines, as well as extracellular vesicles (EVs). The aim of this study was to prevent the ability of the SASP to propagate senescence, with a particular focus on the role of EVs.

For that, we performed a shotgun proteomic analysis that identified several proteins as potential targets involved in the transmission of senescence through EVs. To validate these proteins, we employed siRNA-mediated knockdown combined with high-content phenotypic analyses using the Operetta system, assessing key senescence-associated features such as reduced proliferation and increased β -galactosidase activity. We further investigated whether the validated protein was associated with aging *in vitro* and *in vivo* and evaluated its short-term inhibition in cellular models could prevent the onset of paracrine senescence.

Among the proteins identified, ORAI1 emerged as a particularly relevant candidate. We observed that its expression was significantly increased across different models of aging and senescence. Notably, short-term inhibition of ORAI1 in cellular models of senescence reduced the number of EVs released and decreased the propagation of paracrine senescence.

In conclusion These results identify ORAI1 as a key regulator of EV-mediated intercellular communication during senescence, opening new therapeutic opportunities to limit the progression of aging and its associated pathologies.

Keywords:

SASP, Senescence, Extracellular Vesicles, ORAI1

O-029/P-039

A Role For GRK2 In Cellular Senescence Of Normal And Breast Tumor Cells

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Cellular senescence is a stable cell-cycle arrest with a pro-inflammatory senescence-associated secretory phenotype (SASP). Although senescence initially acts as a tumor-suppressive mechanism, the persistence of SASP-producing cells can drive cancer recurrence, therapy resistance, and tumor invasiveness.

Estrogen deprivation (ED) therapy is a key treatment for estrogen receptor-positive (ER+) breast cancer (BC). Beyond antiproliferative effects, ED promotes cellular senescence, although the mechanisms remain poorly understood. In this context, we investigated the role of G protein-coupled receptor kinase 2 (GRK2), a key regulator of cellular homeostasis that modulates both GPCR and non-GPCR type-specific effector interactomes.

Our results show that GRK2 downregulation promotes premature senescence in several non-tumoral contexts. In ER+ BC cells, GRK2 loss enhances ED-induced senescence and SASP production, suggesting that elevated GRK2 levels, commonly observed in BC, may act as a barrier to this response. Consistently, estrogen deprivation reduces GRK2 levels while increasing the abundance of p53, a central regulator of senescence.

Because the E3 ubiquitin ligase MDM2 regulates GRK2 and p53, we explored their functional interplay. GRK2 promotes MDM2-dependent p53 downregulation and decreases sensitivity to p53-reactivating MDM2 inhibitors. Importantly, GRK2 phosphorylates MDM2 at multiple sites across its regulatory and structural domains. In MDM2-silenced cells rescued with wild-type or mutant MDM2, GRK2-dependent phosphorylation modulates ligase activity and substrate specificity, altering stress-response pathways linked to senescence.

The GRK2-MDM2 signaling axis emerges as a potential therapeutic target in ER+ breast cancer to improve endocrine therapy efficacy

Keywords:

Senescence, GRK2, MDM2, p53

Cellular Senescence, G-Protein-Coupled Receptor Kinase 2, MDM2 Ligase, Ubiquitome, Estrogen Deprivation, Breast Cancer

P-040

Hydroxytyrosol Supplementation Modulates Thymic Output In Individuals With Overweight And Prediabetes In A Randomized, Double-Blind, Placebo-Controlled Parallel Trial

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B/A: Hydroxytyrosol (HT) is an olive-derived phenolic compound with antioxidant and anti-inflammatory properties. The thymus plays a key role in T-cell production but undergoes age-related involution, which may be accelerated by oxidative stress, chronic low-grade inflammation and metabolic conditions. We explore the effect of chronic supplementation (16 weeks) with an HT-rich extract (15 mg/day) in individuals at risk (overweight with prediabetes) on immune homeostasis, focusing on thymic output.

M: A randomized, double-blind, placebo-controlled parallel trial was conducted in adults (40–70 years). Participants received HT (n=24) or placebo (n=25) 16 weeks. Signal joint TRECs (sj-TRECs) and sj/ β -TRECs ratio were quantified by droplet digital PCR in PBMCs. Relative Leukocyte Telomere Length (rLTL), a marker of cellular replicative history and biological aging, was assessed by qPCR from the same PBMCs samples. Analyses were performed using

linear mixed-effects models.

R: Thymic output remained stable in the HT group, whereas a significant decline was observed in the placebo group, with between-group significant differences confirmed (B=0.366; 95% CI 0.054–0.678; p=0.023). A similar trend was observed for the sj/ β -TRECs ratio (p=0.093). The decline was more pronounced in males. rLTL showed a decreasing trend in the placebo group, with no changes in the HT group.

C: HT supplementation may exert a protective effect on thymic function, preventing the decline in T-cell output observed in the placebo group. The absence of changes in rLTL supports a limited short-term modulation, consistent with a preventive rather than restorative effect. Overall, results support a role for HT in preserving immune homeostasis, potentially through modulation of redox and inflammatory pathways.

Keywords:

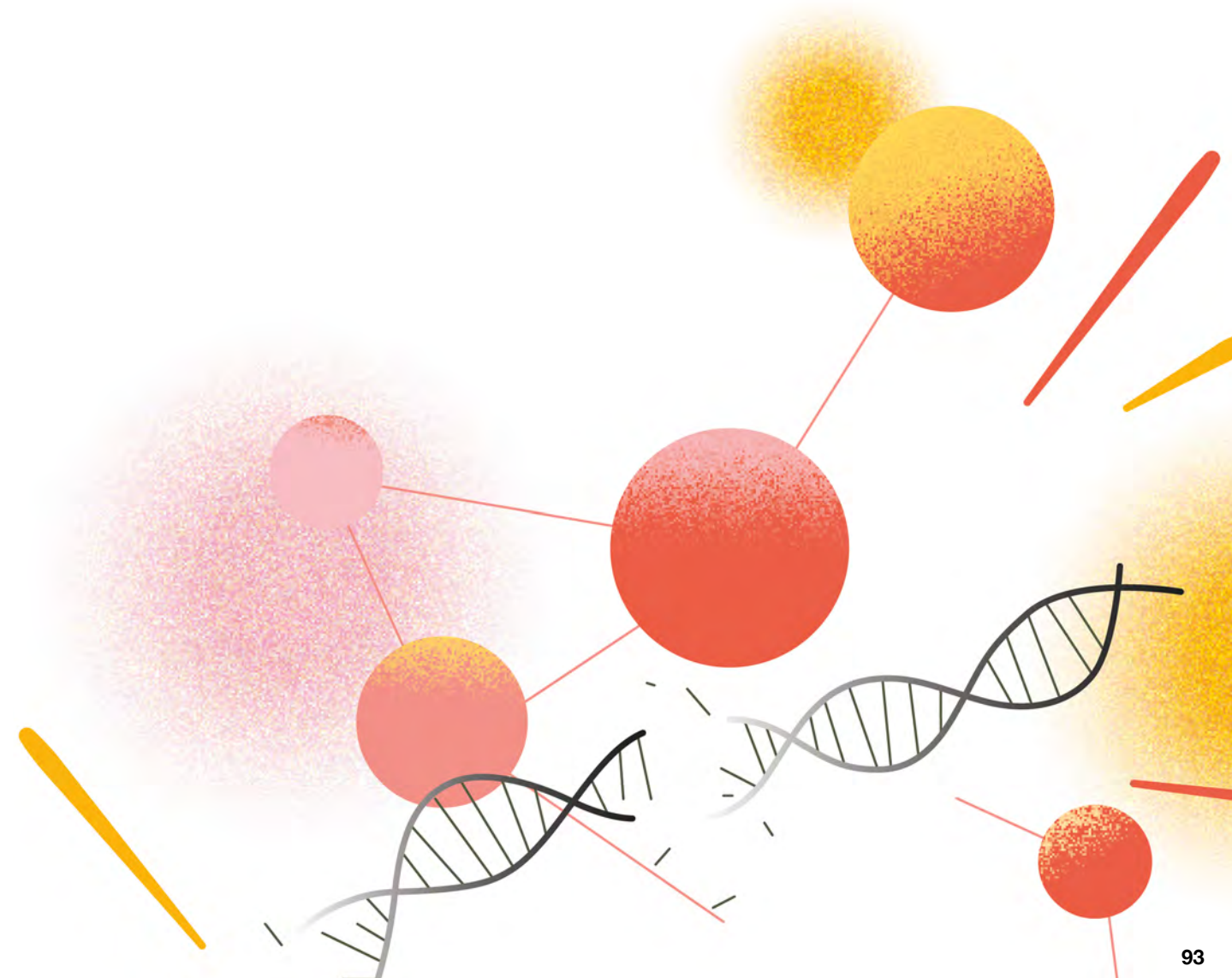
Hydroxytyrosol, Thymic Output, TRECs, Telomere Length, LTL, Trial, Supplementation, Immune Homeostasis



GRUPOS CIENTÍFICOS DE LA SEBBM:

PARASITOLOGÍA MOLECULAR E INFECCIONES EMERGENTES

8 DE SEPTIEMBRE





O-030

Rewiring Malaria Parasite Development: SIRT1 Activation Links Cell-Cycle Delay With Antigenic Variation In Plasmodium Falciparum

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Malaria is an infectious disease caused by protozoan *Plasmodium* parasites and transmitted through *Anopheles* mosquitoes. Widely endemic of tropical and subtropical regions of the world, malaria coexists with nutritional and endocrine disturbances, including iodine deficiency-associated hypothyroidism, which has raised interest in whether host metabolic status may modulate disease outcomes.

Pharmacological strategies that reproduce aspects of a hypothyroid-like state have been investigated, including compounds targeting SIRT1, a NAD⁺-dependent human deacetylase. In this framework, SIRT1 activation has been associated with reduced severity in experimental malaria models, suggesting an interplay between host metabolic signalling and parasite biology.

In this study, we have established a time-resolved RNA sequencing strategy covering 48 hours of *in vitro* culture of intraerythrocytic *Plasmodium falciparum* under SIRT1 activation. This design allowed a systematic assessment of dynamic transcriptional changes across the parasite's blood-stage cycle.

The integration of bioinformatic analyses revealed widespread transcriptional remodelling linked to perturbations in cell cycle progression and to genes associated with antigenic variation. These effects indicate a coordinated alteration of developmental timing together with shifts in expression programs involved in immune evasion.

Overall, our results support that SIRT1 not only impacts host environment but also exerts a direct and broad influence on *Plasmodium falciparum* transcriptome, delaying para-

site maturation and reshaping antigenic variation dynamics, which may ultimately affect host-parasite adaptation.

Keywords:

Malaria, Hypothyroidism, Transcriptomics

O-031

Immunochemotherapy For Cutaneous Leishmaniasis: Combining Topical Amphotericin B With The HisAK70 Vaccine

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Cutaneous leishmaniasis (CL) is a neglected tropical disease for which current treatments remain limited by toxicity, cost, and variable efficacy, particularly in endemic regions with limited healthcare resources. In this context, the development of safer, accessible, and translational therapeutic strategies remains a major challenge. Here, we investigated an immunochemotherapy approach combining topical amphotericin B (AmB) with the therapeutic DNA vaccine HisAK70 in a murine model of *Leishmania major* infection. BALB/c mice were subcutaneously infected and treated with topical AmB alone, AmB plus HisAK70, or paromomycin as a reference therapy. Therapeutic efficacy was evaluated through lesion progression, parasite burden in draining lymph nodes and spleen, and key immunological markers associated with parasite control.

The combined AmB + HisAK70 treatment significantly reduced lesion progression and markedly decreased parasite burden compared with infected controls, demonstrating effective control of both local infection and systemic dissemination. This effect was associated with reduced arginase activity in infected tissue and an increased IFN- γ /IL-4 ratio, indicative of a shift toward a protective Th1 immune response. Notably, the combination therapy enhanced the efficacy of AmB alone, supporting a synergistic interaction between direct antiparasitic activity and immune modulation.

Overall, these findings support immunochemotherapy as a promising strategy to improve therapeutic outcomes in CL by integrating topical drug delivery with targeted immune activation. This approach may contribute to the optimization of safer and more accessible translational therapies for endemic settings with limited resources.

Keywords:

Cutaneous Leishmaniasis, HisAK70, Amphotericin B, Immunochemotherapy

O-032/P-041

Aptamer Selection Targeting Conserved Regions Of The Respiratory Syncytial Virus F Protein

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Respiratory Syncytial Virus (RSV) is a negative-sense single-stranded RNA virus belonging to the *Pneumoviridae* family and represents one of the leading causes of acute lower respiratory tract infections worldwide. It is estimated to cause 3.6 million hospitalizations and approximately 100,000 deaths annually in children under five years of age, with 97% of these deaths occurring in low- and middle-income countries. Although infants constitute the highest-risk population, older adults and individuals with comorbidities are also susceptible to severe disease.

Currently, several safe and effective vaccines and immunoprophylactic therapies have been approved for infants to protect against the most severe forms of the disease. All these strategies target the viral fusion (F) protein because of its role in viral entry. However, the potential emergence of resistance-associated and escape mutations, together with the limited implementation of these strategies in low- and middle-income countries, highlights the need for novel therapeutic approaches. In this study, highly conserved regions within the F protein were identified as targets for aptamer selection using the SELEX methodology. After the selection process and analysis of different SELEX rounds by next-generation sequencing (NGS), six candidates were identified.

Functional assays demonstrated that one candidate exhibited strong neutralizing activity against both RSV-A and RSV-B strains in HEp-2 cells. Furthermore, the aptamer showed no neutralizing activity against human metapneumovirus (hMPV), demonstrating specificity for RSV over other members of the same viral family. These findings position this aptamer as a promising candidate for the devel-

opment of specific and cost-effective therapeutic interventions against RSV.

Keywords:

Aptamers, Respiratory Syncytial Virus (RSV), Fusion Protein, Neutralization

O-033/P-042

DNA Vaccine Against Blood-Stage Plasmodium Falciparum To Prevent Severe Malaria

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Malaria remains a critical global health threat, with *Plasmodium falciparum* causing over 600,000 deaths annually, primarily among children in sub-Saharan Africa. Current vaccines focus on pre-erythrocytic stages; however, parasite escape remains frequent, highlighting the urgent need for effective blood-stage vaccines to complement existing strategies. This study integrates the pPAL DNA platform, an antibiotic resistance-free vector authorized by the European Medicine Agency (EMA/CVMP/858971/2022), with the selection of six immunodominant blood-stage antigens containing epitopes with dual immunological IgM+IgG immunological reactivity associated with protection from clinical malaria in asymptomatic individuals with submicroscopic infection.

Three chimeric immunogens, prioritized as promising candidates cloned into the pPAL vector were evaluated for immune response in C57BL/6J mice, focusing on antibody titers (IgG1, IgG2a, IgG2c and IgM), *in vitro* growth inhibition assays (GIA), and deep characterization of major cell lines by intracellular cytokine staining using spectral flow cytometry (CD3, CD4, CD8a, CD107 and the cytokines IFN γ , IL-10, TNF α , IL-4).

The results demonstrate all three DNA vaccine candidates elicit complementary immunogenicity profiles in C57BL/6J mice, with detectable antigen-specific cellular and humoral responses. To date, one candidate has shown *in vitro* para-



asite-neutralizing activity. The next step will be to develop a multigene DNA vaccine combining the three candidates to target blood-stage antigens relevant to severe malaria.

Keywords:

Malaria; Plasmodium Falciparum; Immunoproteomics; IgM; IgG; DNA Vaccines; PPAL

via vesicles exhibited a synergistic potential with the LACK gene, significantly enhancing the immunogenic response. LACK itself was also present in EVs. These findings highlight the potential role of EVs in pathogenesis.

Keywords:

Leishmania Infantum, Extracellular Vesicles, Neoleish, LACK, PPAL, Vaccines, Vaccine Candidates, Drug Targets

O-034/P-043

Extracellular Vesicles From Leishmania Infantum Contain Immunogenic Proteins

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Neoleish® is a DNA vaccine against canine leishmaniasis developed over the last two decades. This vaccine is based on the activated protein kinase C receptor analog (LACK) antigen gene from *Leishmania infantum* and the antibiotic resistance-free mammalian expression plasmid vector pPAL. The vaccine was developed in the Molecular Parasitology and Vaccines lab (PMV) at CIB-CSIC and authorized by the European Commission (Reg. No. 2/22/290), according to the positive opinion emitted by the European Medicines Agency. Simultaneously to the development of this vaccine, the PMV lab integrated integrating omics approaches for differential gene expression analysis and other selection criteria to identify and validate a library of vaccine candidates and potential drug targets. The objective of the present study was to characterize the protein cargo of *Leishmania infantum* extracellular vesicles (EVs).

EVs from promastigotes and intracellular amastigotes, the latter obtained through *in vitro* infections of the PMA-stimulated U937 cell line, were isolated and their protein cargo identified using LC-MS/MS proteomics. Vaccine candidates were assayed in murine models to evaluate immunogenicity and efficacy. Some were also found to be potential therapeutic targets.

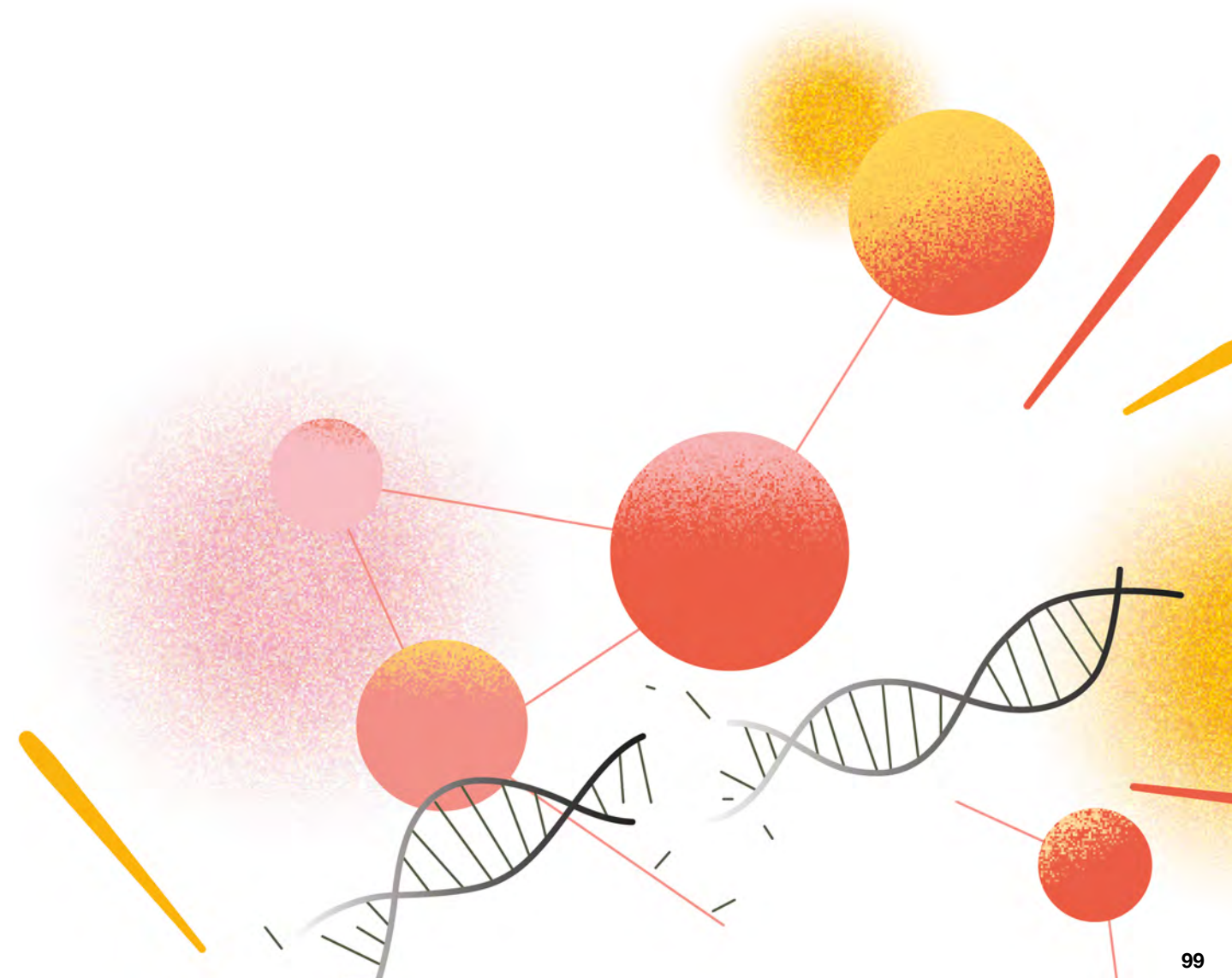
L. infantum EVs contained EV markers such as gp63 and HSPs. Surprisingly, EV samples contained the validated vaccine candidates and the potential drug targets previously found with the differential gene expression profiling-based screening strategy. Furthermore, these proteins exported



GRUPOS CIENTÍFICOS DE LA SEBBM:

BIOLOGÍA SINTÉTICA Y BIOTECNOLOGÍA MOLECULAR

8 DE SEPTIEMBRE





O-035

Characterising TraC As A Functional Pore-Forming Protein Within The PKM101 Conjugative Machinery

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Type IV secretion systems (T4SSs) are complex nanomachines that span the entire cell wall of Gram-positive and Gram-negative bacteria. Upon donor-target cell contact, T4SSs are able to act as protein translocators but also mediate DNA transfer in a process called conjugation. For this purpose, they elaborate conjugative pili or surface adhesins to promote attachment with recipient bacteria. Among the diverse T4SSs, the one derived from the pKM101 conjugative plasmid is of great interest as it represents a system minimized enough to accomplish the interchange of genetic material. The pKM101-derived pilus is composed of a minor subunit, TraC, which is positioned at the tip of the pilus and it is hypothesized to establish the first donor-recipient interaction during bacterial conjugation.

To unravel the role of TraC, we used proximity labelling as a new approach to study the interaction characteristics of TraC with the recipient bacteria. Nevertheless, we found that this soluble protein was unable to biotinylate target proteins as it spontaneously inserts in the outer membrane fraction of target cells. So, we hypothesized that TraC may be forming pores upon outer membrane contact, potentially undergoing structural rearrangements from a monomeric to an oligomeric state. By using calcein-loaded liposomes, we discovered that negatively charged lipids are susceptible to membrane permeabilization upon TraC contact in a concentration and charge dependent manner. Moreover, single-channel recording using negatively charged droplet bilayers demonstrate open state events related to pore formation. These results not only provide insights into the specific function of pKM101-encoded TraC, but will also improve our current understanding of the conjugation process in minimized T4SSs.

Keywords:

Proximity Labelling, Conjugation, T4SS, Outer Membrane, Pore-Forming Protein

O-036/P-044

Ancestral Cas Proteins Reveal Latent Catalytic Diversity And Modular Architecture

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RNA-guided CRISPR-Cas nucleases underpin genome engineering, yet most advances focus on a small set of highly efficient enzymes, especially Cas9 and Cas12. This focus has provided deep insight into selected systems, while the broader evolutionary diversity of CRISPR enzymes across all domains of life remains less explored. Whether hallmark features of modern nucleases, such as PAM dependence, substrate specificity, and guide RNA recognition, arose from more flexible ancestral states is still unclear. Ancestral sequence reconstruction (ASR) provides access to these early forms and reveals biochemical properties that have since been refined or lost.

Here, we study FCA-anCas, a reconstructed Cas9-like nuclease estimated to date back ~2.6 billion years, as a model of ancestral functional diversity. Although it showed no detectable activity in cells, it exhibited intrinsic nickase activity *in vitro*. By tailoring experimental conditions, we demonstrated that FCA-anCas functions in eukaryotic cells as a PAM-independent nickase capable of genome editing via paired-guide strategies. This activity was also validated in zebrafish embryos, where efficient editing was achieved even with single guide RNAs, including at sites poorly targeted by near-PAMless variants such as SpRY.

Biochemically, FCA-anCas processes dsDNA, ssDNA, and ssRNA through both targeted and collateral cleavage, combining features typically associated with Cas9, Cas12, and Cas13 systems. Its modular architecture is highly amenable to recombination, allowing the generation of chimeric nucleases that remain active *in vivo*. Together, these results support a model in which ancestral CRISPR-Cas enzymes were more flexible than modern counterparts and highlight ASR as a route to expand the genome engineering toolkit.

Keywords:

CRISPR-Cas, ASR, Genome Engineering, Zebrafish Embryos, Chimeric Nucleases

O-037/P-045

Harnessing Bacteria As Living Builders Of Reusable Multi-Enzymatic Nanoreactors For Textile Waste Biorecycling

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The accumulation of textile waste is a growing global concern, with fiber production exceeding 100 million tons annually. Enzyme-based biodegradation has emerged as a sustainable strategy for recycling polyethylene terephthalate (PET), a recalcitrant polymer widely used in textile industry. However, scaling-up these technologies faces several challenges, including biocatalysts reusability and stability. Here, we present an “in-cellulo” platform for the one-step immobilization of PET-degrading enzymes. To this end, we used bacteria as a host “builder”, capable of self-assembling enzymes into protein-based nanospheres.

Initially, we immobilized the benchmark hydrolase LCC^{ICCG}, increasing its thermal stability and reusability, achieving near-complete degradation (>90%) of three consecutive batches of textile PET in 72h. To further improve the degradation efficiency, we designed and immobilized a two-enzyme architecture comprising LCC^{ICCG} and a MHETase-like enzyme. The multi-enzyme nanoreactor proved to be highly active and reusable, efficiently degrading challenging colored PET textiles. Additionally, we demonstrate the integration of these nanoreactors in the degradation of blended cotton/PET textile waste, where cotton is completely degraded using cellulases cocktails and the remaining PET is then treated with immobilized enzymes. Finally, we report the use of our nanoreactors as a promising nonspecific “scavenging tool” for the removal or reutilization of textile dyes after enzymatic degradation.

Our findings, combined with straightforward purification of immobilized enzymes, highlight our platform as a powerful tool to support the industrial translation of textile biorecycling. Current work focuses on the upcycling of PET monomers using immobilized enzymatic cascades.

Keywords:

Bacteria, Nanoreactors, Enzymes, Immobilization, Textile Waste, PET Biorecycling, Textile Dyes

O-038/P-046

Decoding Lipid Membrane Repair: Real-Time Dynamics Of The ESCRT Nanosealer

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The integrity of the cell membrane is fundamental to life, yet it is constantly challenged by diverse environmental stressors. From mechanical tension and osmotic shifts to emerging threats like nanoplastic-induced perforation, membrane lesions represent a critical point of vulnerability.

Long before the emergence of complex eukaryotes, the Last Universal Common Ancestor (LUCA) faced a fundamental biophysical challenge: maintaining lipid membrane integrity. To survive, early life developed a highly versatile *Hair-Pin α-helical protein* module capable of remodeling lipid bilayers.

Today, this ancient blueprint survives as the ESCRT superfamily: a universal ‘nanosealer’ shared by bacteria, plastids, archaea, and mammals. With this machinery now recognized as a primary mediator of membrane repair across all domains of life, our work dissects its biophysical continuum. Unlike the multi-subunit ESCRT complexes required in mammals and Asgard archaea, PspA and Vipp1¹ act as self-sufficient, single-protein engines capable of executing the entire membrane remodeling process. We demonstrate how these proteins sense and respond to mechanical and topographical cues on the membrane.

For the first time, using advanced biophysical techniques such as Fast-AFM, Cryo-EM and combined with Deep-learning analysis, we are able to visualize these processes in real time at molecular resolution. This reveals how these proteins change their conformation to execute membrane repair under various conditions, allowing us to quantitatively compare their functional efficiency in closing membrane lesions.

Keywords:

Membrane Repair, ESCRT-III, Lipid Membrane Damage, Fast-AFM, Cryo-EM



O-039/P-047

A Novel LncRNA In White Adipose Tissue Of Children With Obesity

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Background: According to the WHO's 2024 report, 160 million children and adolescents (ages 5–19) were living with obesity. Spain is the leading country in Europe in childhood obesity. Importantly, 80% of the children with obesity will remain with obesity until the adulthood facing risks of chronic diseases. Effective treatment strategies are urgently needed to improve public health. Long non-coding RNAs (lncRNAs) have emerged as key regulators of metabolic homeostasis. However, little is known about the role of lncRNAs in children's adipose tissue.

Methods & Results: Our previous KIDSADIPOSEQ transcriptomic analysis identified a significant upregulation of CYTOR in the subcutaneous white adipose tissue (scWAT) of children with obesity. To explore its mechanism in pediatric adipose tissue, we computationally predicted its primary transcript, murine ortholog, and SNPs within transcription factor binding sites. In addition to bioinformatic prediction of its upstream regulators, we validated a dramatic overexpression of CYTOR in an *in vivo* childhood obesity model, established by feeding 3-week-old C57BL/6 mice with HFD for 4 weeks. *In vitro*, CYTOR expression increased time-dependently during 3T3-L1 adipocyte differentiation. These *in vivo* and *in vitro* results confirm the involvement of the lncRNA in obesity metabolism. Subsequent analysis of differentially co-expressed genes between children with or without obesity, GO and PPI networks revealed that this gene participates in regulation of transcription and protein-containing complex.

Conclusion: Our results indicate that the CYTOR is a functional mediator of metabolic adaptation in obesity. In future, targeted knockdown of CYTOR will be used to validate these predictions and explore the underlying molecular mechanisms.

Keywords:

Childhood Obesity, LncRNA, White Adipose Tissue

O-040/P-048

MiST-IC Tagging: Self-Assembling Protein-Only Nanospheres With Tunable Surfaces For Therapeutic And Industrial Applications

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The IC-Tagging system enables the intracellular production of nanospheres (NS) encapsulating proteins of interest, providing a protective environment that preserves their native folding and functional activity. This system has recently been applied to vaccine development, the stabilization of therapeutic proteins with particular interest in oral enzyme delivery, and also enzymatic biorecycling of plastic. In this work, we expanded this tool to enable simple, covalent, and targeted attachment of diverse components (small molecules, fluorescent probes, peptides, entire proteins and enzymes, antibody derivatives, etc.) to the NS surface through sortase-mediated ligation. This new technology, termed MiST-IC, builds on the strengths of IC-Tagging to streamline the rational design and production of proteins of therapeutic or industrial interest. It also broadens the platform's applicability to diagnostics, targeted therapies and construction of enzymatic nanoreactors. The resulting technology combines efficient one-step production with high structural and functional adaptability, positioning it as a promising tool in biotechnology and biomedicine. Overall, MiST-IC Tagging represents an innovative strategy for generating highly functionalizable novel protein nanomaterials.

Keywords:

Protein Nanoparticles, Protein Stabilization, Enzymes, Surface Modification

O-041/P-049

Design Of Multi-Functionalized Main Vault Protein-Based Structures For Smart Delivery Of Anticancer Proteins

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Most chemotherapeutic drugs have low bioavailability or are rapidly cleared from the body, creating great interest in developing effective drug delivery systems (DDS). Previously, different groups have produced protein nanoparticles based on the eukaryotic major vault proteins (MVP) to create vault-like void structures. This structure can encapsulate virtually any cargo protein by fusing it to the INT peptide of the inner vault VPARP component and can be used as DDS. Vault-like structures were originally produced in insect cells, but the production yield was low and required tedious purification. To address these issues, we have investigated the production of MVP in *Escherichia coli* followed by purification under denaturing conditions and subsequent protein refolding. We have also designed a model cargo consisting of a modified green fluorescent protein (GFP). Nanostructure formation has been checked by transmission electron microscopy (TEM) and dynamic light scattering (DLS). Functionality of these nanostructures has been checked by pull-down analysis. We have optimized MVP variants production in form of inclusion bodies to maximize their expression. Denaturing conditions allowed purification of MVP variants in an unassembled form simplifying the protocol and increasing the yield. MVP do not refold forming the vault structure but a spherical structure of similar dimensions as analyzed by TEM and DLS. We have demonstrated with pull-down experiments that these structures encapsulate the model GFP-derived cargo. Our production system allows to refold different MVP variants in a single structure each one being decorated with a different functional peptide and therefore we can reconstitute smart DDS structures with precise proportions of each of these peptides.

Keywords:

Cancer, Drug Delivery System, Pharmacokinetics, Refolding, Vault

O-042/P-050

ASR-Guided Development Of A Fully Synthetic Base Editor With Enhanced Targeting Flexibility

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Gene therapy has emerged as a promising strategy for treating genetic diseases by directly correcting their molecular causes. Unlike conventional lifelong treatments, genome editing offers the possibility of definitive and precise therapeutic interventions. However, current editing tools still present important limitations regarding specificity, safety, target accessibility, and delivery efficiency.

Most genome editing technologies are based on CRISPR/Cas systems, originally evolved as bacterial defense mechanisms and later adapted for programmable genome editing. Despite their versatility, Cas nucleases require protospacer adjacent motifs (PAMs) near the target site, limiting the accessibility of many pathogenic mutations. In addition, double-strand DNA breaks may induce insertions or deletions (indels), chromatin stress, and altered reading frame.

Second-generation CRISPR-derived systems such as Base Editing were developed to overcome these limitations. Since many genetic disorders are caused by single nucleotide polymorphisms (SNPs), Base Editors enable precise nucleotide conversion without generating double-strand breaks, reducing indel formation and associated toxicity. Nevertheless, these systems still present drawbacks, including bystander edits, Cas-independent deamination, sequence-context dependency, and large construct size, which complicates viral delivery.

Previously, our laboratory developed ancestral near-PAM-less Cas nucleases with reduced immunogenicity through Ancestral Sequence Resurrection (ASR). Here, we propose the development of a fully synthetic ancestral Base Editor combining improved targeting flexibility, reduced immunogenicity, and optimized editing properties.

Keywords:

CRISPR, Base Editing, Synthetic Biology, Genenome Editing



O-043/P-051

Identification Of Selective Peptide Binders For Structurally Homologous Proteins Using ECPX Bacterial Surface Display Screening

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Peptide display systems enable the screening of large peptide libraries for a wide range of biotechnological applications. Among these systems, eCPX bacterial surface display employs the eCPX protein scaffold to express peptides on the surface of *Escherichia coli*. 1

The eCPX system enables both the quantification of individual peptide binding and the screening of large peptide libraries against purified target proteins by flow cytometry and pulldown assays, respectively.

In this work, the binding of a previously characterized 23-mer peptide to two mammalian proteins, A and B, which share structural homology, was validated and quantified using this system. To identify peptide variants with selective binding toward each target protein, a theoretical library containing 64 million sequences was designed and cloned into the eCPX system. This library was generated by introducing all 20 amino acids at 6 selected positions within the original peptide sequence. The library was expressed in *E. coli*, and following screening against proteins A and B, candidate peptides showing selective binding to each target protein were identified.

Finally, the interaction between these candidate peptides and their target proteins was validated in HEK293T cells using a bimolecular fluorescence complementation (BiFC) assay. 2

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Keywords:

ECPX, Bacterial Display, Peptide Library Screening, Selective Binding, BiFC

O-044/P-052

Functional Validation Of Transposable Elements Of *Pseudomonas Putida* As “Bridge Editing” Tools In Eukaryotic Cells

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CRISPR-Cas gene-editing tools have revolutionized biology since their discovery in 2012. However, the generation of large insertions, deletions, or inversions (involving thousands, tens of thousands, or hundreds of thousands of bases), associated with congenital diseases such as Phelan-McDermid syndrome (which corresponds with a deletion of the end of chromosome 22), remains a significant challenge for research and treatment. Recently, mobile prokaryotic elements (IS, insertional sequences) have been described in both *Escherichia coli* (PMID: 40997214) and *Citrobacter rodentium* (PMID: 41642947) that contain a small recombinase and an RNA with two domains complementary to the origin and destination sites of the insertion sequence. These elements have been shown to be programmable, thus possessing the potential to act as genome editors through a mechanism entirely different from that used by the popular CRISPR-Cas tools. In both cases, the laboratories involved have demonstrated the successful use of these bridge-editing systems with large genomic sequences. In this work, we aim to evaluate the activity of two of these IS systems: ISPpu9 and ISPpu10, derived

from *Pseudomonas putida* (PMID: 40705920), in eukaryotic cells, both mouse and human, with the goal of enabling their future use in the treatment of human genetic diseases and disorders. This research consortium, funded by the Community of Madrid's technology grant program, seeks to perform insertions, deletions, and inversions extending up to large segments of the genome.

Keywords:

Bridge, Genome Editing, Recombinase, Gene Therapy, Deletion, Insertion, Inversion, Prokaryotes, Eukaryotes

O-045/P-053

Sustainable Enzymatic Production Of Carbon-Based Conductive Inks For Printable RFID Antennas

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Printed electronics demand conductive inks that combine low cost, mechanical flexibility, and compatibility with scalable manufacturing processes. However, most existing formulations rely on metallic components or harsh processing conditions, limiting their sustainability and safety. In this work, we develop fully carbon-based conductive inks by exfoliating graphite through the use of enzymatically derived cellulose and chitin nanocrystals (CNCs and ChNCs). These nanocrystals are produced using engineered ancestral enzymes, eliminating the need for acid hydrolysis and avoiding unwanted structural modifications and environmental drawbacks.

To enhance chitin nanocrystal production, a pretreatment with the loosenin-like protein PcaLOOL7 was introduced. Loosenins are non-catalytic accessory proteins that disrupt the hydrogen-bonding network within polysaccharide structures, thereby enhancing enzymatic accessibility. This strategy led to an approximately threefold increase in yield while

maintaining physicochemical properties. The resulting nanocrystal-assisted exfoliation generates graphene inks with excellent dispersion stability and suitable rheological behavior for screen printing on both paper and polycarbonate substrates. In particular, ChNC-based formulations show improved adhesion on polymer surfaces. The inks reach conductivities above 10^4 S m^{-1} and enable the fabrication of UHF RFID antennas with reliable read ranges of 5–6 m. Overall, this approach provides an enzyme-enabled, acid- and metal-free route toward sustainable, high-performance conductive inks for printed electronics.

Keywords:

Synthetic Biology, Carbon-Based Inks, Conductive Inks, RFID Antennas

P-054

Functional Study Of CRISPR-Associated Mu-Type Transposons For The Targeted Integration Of Large DNA Sequences

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CRISPR-based genome editing has transformed molecular biology; however, its reliance on double-strand breaks (DSBs) raises concerns regarding genomic instability and limits precision. Although base and prime editing technologies circumvent DSBs, they are not suitable for the insertion of large DNA sequences, which are often required for therapeutic applications. CRISPR-associated transposase (CAST) systems have emerged as promising tools for programmable, DSB-free DNA integration (1).

In this project, we investigate *CasMuV*, a novel and compact CAST system identified through bioinformatic analysis that combines a Cas12 nuclease with MuA/MuB transposase components from bacteriophage Mu (2). Preliminary evidence indicates that CasMuV enables targeted DNA integration in bacteria without generating DSBs.

The main objective of this thesis is to explore the potential of CasMuV for genome engineering in mammalian cells. To this end, we aim to: (i) characterize the molecular determinants governing its integration mechanism; (ii) reconstitute and optimize the system in human cells, assessing its efficiency and specificity; and (iii) validate the targeted insertion of therapeutically relevant DNA sequences.



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Keywords:

CRISPR-Associated Transposase (CAST), DSB-Free DNA Integration

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Keywords:

CRISPR, Genome Editing, CRISPR-Associated Transposon

P-056

Purification And Characterization Of A Mu-Like CRISPR-Associated Transposon System

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CRISPR-associated transposases (CASTs) enable programmable DNA integration and hold great potential for genome engineering. Here, we study CasMuV, a rare CAST system composed of a catalytically inactive Cas12, the MuB ATPase, and the MuA transposase. Our aim is to purify and reconstitute the complex to investigate RNA-guided transposition in vivo and in vitro, and to facilitate structural studies by electron microscopy. Initial expression in *E. coli* using 10×His tags resulted in poor affinity purification and low soluble yield, with most protein forming inclusion bodies. Heparin chromatography reduced nucleic acid contamination but led to protein instability. Fusion to a 6×His-SUMO tag significantly improved solubility and purification efficiency, enabling better recovery of soluble proteins, although stability remained limiting. For catalytic inactive Cas12, refolding from inclusion bodies followed by guide RNA addition successfully stabilized the protein. SEC purification and RNA gel analysis confirmed proper folding and formation of a Cas12-RNA complex. Current work extends these refolding and stabilization strategies to MuA and MuB by incorporating their substrates. These results establish a foundation for assembling CasMuV and advancing mechanistic and structural studies of RNA-guided transposition.

Keywords:

CAST, CRISPR

P-055

Functional Characterization Of Novel Mu-Like CRISPR-Associated Transposons

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The development of CRISPR-Cas technologies has been a turning point for genome editing. However, their dependence on double-strand breaks (DSBs) constrains precision and can lead to undesired outcomes such as deletions, insertions, and genomic rearrangements. While base and prime editing approaches avoid DSBs, their therapeutic application remains limited for diseases driven by heterogeneous mutations that require large DNA insertions or genotype-independent strategies. In contrast, CRISPR-associated transposons (CASTs) have recently emerged as a promising alternative for genome editing that enables RNA-guided integration of multi-kilobase DNA payloads without inducing DSBs¹.

Among CAST systems, type V variants employing catalytically inactive Cas12 effectors offer a compact and programmable platform for directional DNA insertion, yet their broader application is hindered by the occurrence of RNA-independent transposition events².

Here, we present the functional characterization of CasMu-V, a novel and rare Mu-like CAST system identified through large-scale bioinformatic mining³. CasMu-V consists of a nuclease-deficient Cas12 effector associated with MuA, a DDE transposase, and MuB, an ATPase associated with Mu transposition, forming a compact genetic module capable of guide-dependent, DSB-free DNA integration. Given the intrinsic efficiency of Mu transposases and the compact size of the system, it represents a promising candidate for programmable genome editing and delivery applications.

These findings expand the functional diversity of CAST systems and establish a foundation for the development of next-generation genome editing technologies.

P-057

Decoupling Detoxification From Assimilation In Furanic Compound Metabolism. Biotransformation Of HMF By *E. Oleovorans* CECT 5344

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Bioconverting 5-hydroxymethylfurfural (HMF) into 5-hydroxymethyl-2-furoic acid (HMFA) is crucial for sustainable bio-polymers. However, biocatalysts often suffer from furanic toxicity or lose yield through substrate mineralization. This study uses in-line NMR, genomic synteny, and RNA-Seq to contrast the wild-type assimilator *Stutzerimonas nitritolerans* 4A and the biocatalyst *Ectopseudomonas oleovorans* CECT5344 R1D. Both strains share a conserved primary detoxification mechanism: massive induction of the *hmfABCDE* operon. This rapidly oxidizes HMF's toxic aldehyde group to HMFA, defending against cellular damage. Beyond this, their pathways diverge. Strain 4A uses downstream TRAP transporters and a UbiD/UbiX decarboxylase complex to integrate furanic carbon into the TCA cycle for biomass. Conversely, R1D harbors an *IS1106* transposon-mediated deletion that eliminates HMFA dehydrogenase and its transporters. This prevents TCA entry, forcing 100% stoichiometric extracellular accumulation of HMFA. To survive this bottleneck, R1D activates lateral compensatory pathways. It cross-induces the *liu/mcc* aliphatic operon to process ring-cleaved intermediates, up-regulates the homogentisate pathway (*hpd, hmgA*) to depolymerize cytotoxic humins, and recruits ATP-independent CoA-transferases (*scoA/B*) to counter chemiosmotic stress. This evolutionary divergence uncouples detoxification from assimilation. Together with its remarkable metabolic plasticity, R1D stands out as a robust cellular chassis for the production of high-value polymer precursors.

Keywords:

Bioetanol, 5-Hidroximetilfurfural (HMF), *Ectopseudomonas Oleovorans*, Biorremediación.

P-058

ReChb Overcomes Molecular Constraints Of CRISPR Systems For Expanded Targeting Of Pathogenic Mutations

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The development of precise and versatile genome editing tools remains a central challenge in the treatment of genetic diseases defined by molecular causes¹. Here, we present the therapeutic implementation of ReChb, a synthetic nuclease reconstructed from an ancient Cas12a lineage², as a platform for the correction of pathological mutations in mammalian cells. ReChb overcomes key limitations of modern CRISPR nucleases, including strict PAM requirements and restricted substrate range, displaying broad target accessibility, guide RNA flexibility across species, and the ability to process both single- and double-stranded DNA and RNA substrates².

In this work, the versatility of ReChb has been evaluated across multiple platforms and diverse genomic contexts, demonstrating robust editing activity at disease-relevant loci. Notably, ReChb retains efficient activity across distinct therapeutic strategies and achieves editing at pathogenic sites inaccessible to modern Cas12a orthologs due to PAM constraints, expanding the repertoire of treatable mutations.

These findings position ancestral sequence reconstruction (ASR) as a strategy to unlock therapeutic targets previously beyond the reach of contemporary genome editing tools, consistent with previous reports on other ASR-derived nucleases³.

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Keywords:

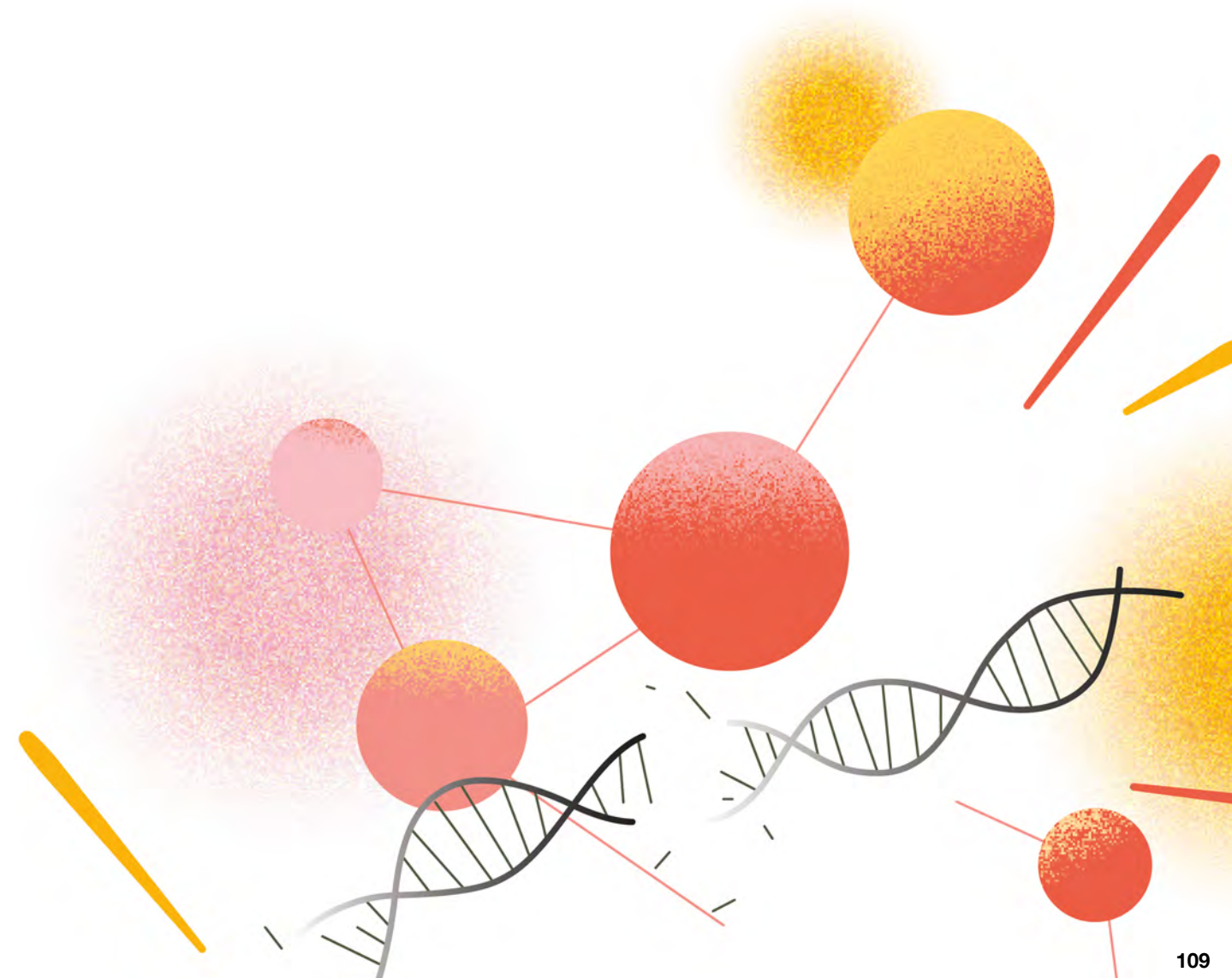
CRISPR, Synthetic Nucleases, ASR, Genome Editing, Therapeutic Applications



GRUPOS CIENTÍFICOS DE LA SEBBM:

MITOCONDRIA, COMUNICACIÓN CELULAR Y ESTRÉS OXIDATIVO

8 DE SEPTIEMBRE





O-046

Cellular Context As A Determinant Of Mitochondrial Regulation

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Mitochondria are central regulators of cellular metabolism and stress adaptation, integrating signaling pathways that coordinate energy production with cellular and tissue-specific demands. Emerging evidence indicates that mitochondrial gene expression is dynamically modulated by signaling networks, including reversible phosphorylation pathways and stress-responsive mechanisms that shape mitochondrial function under physiological and pathological conditions.

This presentation will explore current advances in the regulation of mitochondrial gene expression and translation, with particular emphasis on how these processes contribute to metabolic adaptation and tissue-specific vulnerability in mitochondrial diseases. Special attention will be given to the role of reversible phosphorylation and integrated stress response (ISR) signaling as modulators of mitochondrial activity, cellular bioenergetics, and organ-specific phenotypes.

Understanding how distinct tissues respond to mitochondrial dysfunction through differential signaling and stress adaptation programs may provide new insights into the molecular basis of mitochondrial pathologies and identify novel therapeutic opportunities targeting mitochondrial communication pathways.

Keywords:

Mitochondria, OXPHOS, Cellular Integration, MtDNA

O-047

Uncovering The Role Of NDUFS4 Ser173 Phosphorylation In Mitochondrial Complex I

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Mitochondrial complex I (CI) is the first and largest OXPHOS complex, key in cellular energy production. Complex-I-deficiency represents the most frequent pathogenetic cause of human mitochondriopathies. Structurally, CI is L-shaped and consists of 45 subunits: 14 core-subunits, essential for catalysis, and 31 supernumerary-subunits. Among these subunits, NDUFS4 is one of the most evolutionary conserved and has been identified as a mutational hotspot in patients with Leigh or Leigh-like syndromes. In mammals, NDUFS4 harbors a canonical PKA phosphorylation site at Ser173 which is thought to participate in the mitochondrial import and/or processing of the precursor protein. Additionally, NDUFS4-phosphorylation has been suggested to contribute to the stability and proper assembly of the CI N-module. However, the phosphorylation of this buried residue (and its physiological relevance) remains debated, as it has not yet been observed in any resolved CI structure to date. To address this question and to investigate the impact of NDUFS4-Ser173 phosphorylation in vivo, we have generated a novel genetically modified mouse line carrying a targeted allele lacking the essential phosphorylation site for PKA(Ser173Ala) in exon 5 of the *Ndufs4* gene. This mouse model also carries a wild-type exon 5 of *Ndufs4* (*Ndufs4m-Cherry*), enabling controlled re-expression of the WT protein. The ongoing characterization of this mouse model is providing a unique framework to dissect the functional relevance of NDUFS4 phosphorylation, allowing us to elucidate its role both in vivo and at a molecular level, and to uncover how this putative modification contributes to the regulation and integrity of mitochondrial CI.

Keywords:

Complex I, NDUFS4 Phosphorylation, Leigh Syndrome, Mitochondria

O-048/P-059

SIRT3 Restrains Mitochondrial DNA-driven CGAS-STING Activation And Type I Interferon Responses To Control Autoimmune Inflammation

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Mitochondria regulate innate immunity by releasing damage-associated molecular patterns such as mitochondrial DNA (mtDNA). Sirtuin 3 (SIRT3), a mitochondrial deacetylase, controls mitochondrial homeostasis, reactive oxygen species (ROS), and inflammation. Here, we show that Sirt3 deficiency in macrophages increases cytosolic mtDNA, activating the cGAS-STING pathway and enhancing IFN- β and interferon-stimulated gene expression, thereby promoting resistance to vesicular stomatitis virus. Paracrine IFN- β further amplifies antiviral defenses. Using mtDNA-deficient cells, we demonstrate that intact mtDNA is essential for this response. Elevated mitochondrial ROS drive mtDNA leakage and STING activation, which is reversed by MitoTEMPO. Importantly, in vivo, Sirt3 deficiency in mice exacerbates STING-dependent peritoneal fibrosis, increasing macrophage infiltration and fibrotic remodeling. Supporting clinical relevance, transcriptomic analyses from patients with lupus nephritis and rheumatoid arthritis reveal reduced SIRT3 expression, suggesting that its downregulation may promote pathological Type I interferon responses and chronic inflammatory disease.

Keywords:

Mitochondria, SIRT3, MtDNA, Inflammation, CGAS-STING

O-049/P-060

Role Of The Mitochondrial Sodium/Calcium Exchanger NCLX In Ferroptosis, Cell Viability And Brain Injury After Ischemic Stroke

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Ischemia-reperfusion (IR) injury, as occurs in recanalized ischemic stroke, induces oxidative stress and iron accumulation, key drivers of ferroptotic cell death. We investigated whether inhibition of the mitochondrial Na⁺/Ca²⁺ exchanger NCLX modulates ferroptosis-related pathways in cellular and murine models of cerebral IR.

In human neuroblastoma SK-N-DZ cells, IR increased lipid peroxidation, reactive oxygen species (ROS), free iron levels, and expression of transferrin receptor 1 (TfR1) and iron regulatory protein 1 (IRP-1), indicating adaptive regulation of iron metabolism under oxidative stress. Pharmacological inhibition of NCLX, similarly to the ferroptosis inhibitor ferrostatin-1 (Fer-1), reduced ROS, lipid peroxidation and free iron accumulation. However, neither SK-N-DZ cells nor primary neurons showed improved viability after NCLX inhibition; in primary cortical neurons, viability was reduced, suggesting cell-type-dependent vulnerability under IR conditions.

In mice subjected to transient middle cerebral artery occlusion (tMCAO), the NCLX inhibitor ITH12575 significantly reduced infarct volume, brain iron accumulation and neuronal TfR1 upregulation in the peri-infarct region, supporting attenuation of ferroptosis-associated pathways. However, treated animals displayed increased brain edema, higher mortality, and elevated expression of inflammatory and blood-brain barrier disruption markers.

These findings indicate that NCLX inhibition modulates iron homeostasis and molecular hallmarks of ferroptosis after IR, but also raises important safety concerns related to neuronal viability and neuroinflammatory responses that must



be addressed before considering this strategy for ischemic stroke therapy.

Keywords:

Mitochondria, Ferroptosis, Ischemic Stroke, Neuroprotection, Mitochondrial Sodium, Iron Regulation, Brain Injury

O-050/P-061

DNA Binding Properties Of Mitochondrial Transcription Factor A, The Protein That Compacts MtDNA

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Mitochondrial transcription factor A (TFAM) is a 29-kDa protein composed of two HMG-box domains separated by a flexible linker. It is essential for the transcription and compaction of human mitochondrial DNA (mtDNA), a 16.5-kbp circular double-stranded molecule. The scarcity of viable TFAM mutations underscores its critical role and limited tolerance for sequence variation. We have extensively characterized the structural basis of TFAM function by X-ray crystallography. The mechanism of DNA compaction by TFAM is reflected in the crystal structure, which shows several protein-protein interfaces between TFAM/DNA crystallographic mates. We investigated the P178L mutant, associated with mtDNA depletion, neonatal liver failure, and early death, and found that the complex with DNA behaved similarly to the wild-type protein in solution but failed to crystallise, likely owing to increased flexibility. We also studied TFAM bound to the LSP2 promoter, which exhibited a distinct binding mechanism that may be related to promoter regulation. These and other features of TFAM binding to DNA will be presented.

Keywords:

TFAM/MtTFA, MtDNA Transcription And Compaction, Mitochondrial Rare Disease

O-051/P-062

Mitochondrial Alterations And Impaired Mitophagy In The Development Of Insulin Resistance: Insights From Muscle Models

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Autophagy is a process responsible for degrading and recycling damaged organelles. When altered, cellular waste triggers oxidative stress, inflammation, and organelle dysfunction. Mitophagy, the selective autophagic clearance of damaged mitochondria, can be compromised in obesity and diabetes (T2D). However, the mechanism underlying these mitochondrial alterations remains unclear. A central hypothesis is that dysregulation of the process leads to the accumulation of damaged mitochondria, which in turn exacerbates mitochondrial damage and insulin resistance (IR). To investigate this further, we utilized both in vitro and in vivo models. To mimic lipid overload, C2C12 myotubes were treated with palmitate to induce IR and mitochondrial stress. In our model, palmitate reduced mitophagic flux, mitochondrial function, and lysosomal function, correlating with IR. To explore mitophagy's role in IR development, we employed three approaches: silencing the key mitophagy protein BNIP3, selective lysosomal activation (C381 compound), and pharmacological mitophagy activation (Urolithin A). While C381 and UroA reversed lysosomal degradative capacity, all three approaches—including genetic inhibition of BNIP3—worsened mitochondrial dysfunction and IR. For in vivo studies, male Mito-QC mice (C57BL/6J background) were fed either a control or high-fat diet (HFD) for 8 weeks. HFD-fed mice developed a clear IR profile. Furthermore, our data showed that HFD increased mitolysosome number while markedly reducing lysosomal proteolytic efficiency. These findings suggest that obesity impairs mitophagy, which is key in the development of insulin resistance. More efforts are required for a better understanding of T2D pathogenesis, and this will direct future research towards new target therapies.

Keywords:

Insulin Resistance, Mitophagy, Mitochondrial Dysfunction, Obesity, Type 2 Diabetes, Lysosomal Function

O-052/P-063

Redox Dynamics During Adipogenesis In The Tumour Microenvironment

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Emerging evidence indicates that hormonal therapies can remodel the tumour microenvironment (TME), particularly its adipose compartment which actively regulates tumour biology. Using a murine prostate cancer model, we demonstrated that androgen deprivation therapy (ADT) induces profound TME remodelling enriching a brown adipose-like component. We investigated whether ADT promotes redox alterations in the adipose compartment and whether these changes contribute to TME remodelling during mesenchymal-to-adipose transition. To this end, we analysed the effects of antiandrogen-induced browning on redox balance during adipogenesis in 3T3-L1 preadipocytes. Cells were treated with the antiandrogens bicalutamide or enzalutamide and β -adrenergic agonists isoproterenol and mirabegron were used as a positive control. Adipogenic differentiation was confirmed by NileRed lipid staining. We evaluated redox status, mitochondrial dynamics, lipid peroxidation and antioxidant enzyme expression by confocal microscopy and Western blotting. Additionally, we also measured the GSH/GSSG ratio by isotope-dilution LC-MS/MS. Antiandrogens reduced cell size, enhanced mitochondrial function and increased antioxidant enzyme levels. In contrast, β -adrenergic agents increased cell size, promoted lipolysis and reduced mitochondrial mass. Although both strategies increased mitochondrial membrane potential and GSH levels, β -adrenergic agonists induced a more oxidative intracellular environment. Importantly, ADT modulates redox balance while improving mitochondrial function and promoting adipose remodelling within the prostate TME. However, both browning strategies display distinct molecular signatures. Work was supported by AEI/SEKUEENS Grants (PID2023-151750NB-I009, PREP2023-000432, SEK-25-GRU-GIC- 24-080)

Keywords:

Adipogenesis, Tumour Microenvironment, Redox, Antiandrogens.

O-053/P-064

Bilirubin Decreases Mitochondrial Protein Translation Through Altering Ribosome Content And Maturation Decreasing Oxidative Phosphorylation Capacity

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The exact role of bilirubin in the development of metabolic diseases is still unclear. Bilirubin can scavenge lipophilic reactive oxygen species and is produced from the direct product of heme catabolism biliverdin (Baranano et al., PNAS 2002). Bilirubin synthesis occurs in the cytosol of all cells and is catalysed by biliverdin reductase A (BLVRA). Previous studies showed that increased bilirubin production, fueled by an elevation of biliverdin transported from the mitochondria into the cytosol, caused beta cell dysfunction and hepatic insulin resistance (Shum M, et al., Science Translational Medicine 2021; Molecular Metabolism, 2022). However, the exact mechanism by which bilirubin decreases mitochondrial oxidative phosphorylation (OXPHOS) and the consequences of inducing bilirubin synthesis inside the mitochondria on metabolic diseases remain undefined. Thus, our aims are:

i) Determine the mechanism by which decreased bilirubin production elevates mitochondrial function, by generating BLVRA KO HepG2 cells and ii) to determine the effects of locating BLVRA inside the mitochondrial matrix, to effectively induce a primary increase in bilirubin synthesis inside the mitochondria.

To obtain an increase in bilirubin inside mitochondria, we have expressed an engineered form of Biliverdin Reductase A that contains a mitochondrial matrix targeting sequence in its N-Terminus (mito-BLVRA). This construct has been expressed in hepatocytes and pancreatic islets. We have observed that increasing bilirubin in mitochondria causes a defective respiration and reduced glucose stimulated insulin secretion. These changes could be explained by an increased supercomplex assembly and increased maturative state of mitochondrial ribosome that induce increased mitochondrial translation.

Keywords:

Mitochondria, Metabolism, OXPHOS, Bilirubin, BLVRA, Mitochondrial Translation,



O-054/P-065

Cell-Type Specific Differences In Human Mitochondrial Oxidative Phosphorylation System Levels And Functionality

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Mitochondrial disorders are among the most common in-born errors of metabolism and are primarily caused by defects in the oxidative phosphorylation system (OXPHOS). OXPHOS comprises the electron transport chain (ETC), formed by four multimeric complexes (complexes I-IV) and two mobile electron carriers, together with ATP synthase (complex V). OXPHOS biogenesis requires the coordinated expression of mitochondrial and nuclear genes, as well as the assembly of respiratory complexes and supercomplexes. Although mitochondria are present in practically all cell types, disease manifestations are often restricted to a few organs, and the mechanisms behind this tissue-specificity are still unknown.

With the aim of setting the grounds to understand how OXPHOS dysfunction might affect different human cell types, we have assessed the amounts and function of the OXPHOS complexes, with a special emphasis on complex III, the central element in the ETC, in four different human cell lines: SH-SY5Y neuroblastoma cells, HepG2 hepatic cells, human embryonic kidney cells (HEK293T) and MO3.13 oligodendrogloma cells.

We have measured the steady-state levels of OXPHOS subunits as well as the amounts of fully assembled mature complexes and supercomplexes in the different cell lines, using denaturing and native protein electrophoresis, respectively. In addition, we have determined the enzymatic activity of complexes I-IV in all four cell lines.

This comparative study has revealed remarkable differences in the amounts, stoichiometry and activity of the ETC complexes across these commonly used human cell models.

Keywords:

Mitochondria, OXPHOS, Disorder

O-055/P-066

Loss Of Mitochondrial Plasticity Negatively Impacts On HCC Development In The Context Of MASLD

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Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) can progress to Hepatocellular Carcinoma (HCC), but the mechanisms driving this transition are unclear and the condition does not have effective treatment options. Given the role of mitochondrial dysfunction and oxidative stress in MASLD, we studied their contribution to the progression of HCC using wild-type (WT) and PGC-1 α knock-out (KO) mice, a model of impaired mitochondrial metabolic plasticity. Mice were fed a normal or high-fat diet (HFD) and treated or not with teratogens (T) for 24 weeks.

KO mice showed reduced hepatic lipid accumulation compared with WT animals. However, they developed a significantly higher tumor burden, especially under combined HFD and teratogen treatment. This increase was not linked to higher proliferation, inflammation, or fibrosis. Despite greater tissue damage, KO mice failed to properly activate apoptosis, likely due to impaired NRF2- and p53-mediated oxidative stress and DNA damage responses. Instead, they displayed increased activation of alternative cell death pathways, with elevated p-RIPK3 and GSDMD and reduced Gpx4 and UCP-2 levels under HFD plus teratogens.

To investigate mechanisms, FaO hepatocytes were used. Oxidative phosphorylation was enhanced by replacing glucose with galactose, and lipid accumulation was induced with palmitic acid. Cells were exposed to H₂O₂ to assess oxidative stress responses. Galactose-grown cells showed greater resistance to oxidative stress and more efficient apoptosis than glucose-grown cells.

Overall, these results indicate that mitochondrial dysfunction plays a central role in HCC development. PGC-1 α deficiency increases oxidative stress while impairing protective pathways, thereby promoting hepatocarcinogenesis.

Keywords:

Mitochondria, Metabolic Plasticity, Oxidative Stress, Hepatocellular Carcinoma, PGC-1 α , Metabolic

Dysfunction-Associated Steatotic Liver Disease (MASLD)

O-056/P-067

Hepatic Mitochondrial Bioenergetics And Redox Status In Obese Rats: Sex-Specific And Photoperiod-Dependent Effects Of (Poly)Phenol-Enriched Seasonal Fruit Extract Mixtures

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Dietary polyphenol-rich fruits are known to modulate redox homeostasis and mitochondrial function, but whether their effects in obesity depend on sex and environmental photoperiod remains largely unexplored. In this study, we investigated how a five-week supplementation with the combination of seasonal polyphenol-rich extracts (winter and summer fruits) influences hepatic antioxidant capacity and mitochondrial bioenergetics in cafeteria diet-induced obese rats exposed to either a short (6-h light; L6) or long (18-h light; L18) photoperiod for eight weeks. Supplementation with these polyphenol combinations significantly increased hepatic antioxidant responses and upregulated the protein expression of mitochondrial respiratory complexes in both sexes. However, the subsequent increases in the enzymatic activity of these respiratory complexes were much more modest. Notably, the therapeutic effects of the polyphenol mixes were markedly more pronounced in males than in females. This sexual dimorphism is likely explained by the higher baseline redox and bioenergetic state of females, who already exhibited enhanced antioxidant defences and elevated respiratory complex activities compared to males. Together, these findings demonstrate that polyphenol supplementation improves mitochondrial and redox profiles in obesity, while highlighting that biological sex is a crucial determinant of the hepatic responsiveness to seasonal dietary bioactive compounds.

Keywords:

Sexual Dimorphism, Photoperiod, MASLD, Polyphenols, Mitochondrial Bioenergetics, Oxidative Stress, Cafeteria Diet

O-057/P-068

Iron-Induced Oxidative Stress Promotes Adipose Tissue Remodeling And Adipocyte Lipolysis

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Oxidative stress (OS) has emerged as an important regulator of adipocyte metabolism; however, the mechanisms linking reactive oxygen species (ROS) to lipid turnover remain incompletely understood. Using complementary *in vivo* and *in vitro* models of iron (Fe)-induced OS, we found that Fe overload increased lipid peroxidation and additional OS markers in adipose tissue, accompanied by reduced triacylglycerol, diacylglycerol, and monoacylglycerol content, consistent with enhanced lipolysis. Histological analyses revealed smaller adipocytes, reduced adipose tissue volume, fibrosis, and substantial tissue remodeling. In parallel, β -catenin expression was markedly increased in gonadal adipose tissue from Fe-overloaded mice.

In differentiated adipocytes, Fe increased ROS production, lipid peroxidation, membrane permeability, extracellular glycerol release, and expression of the lipolytic enzymes adipose triglyceride lipase and hormone-sensitive lipase, while reducing lipid droplet size. Similar effects were observed with menadione, a distinct oxidative stressor, suggesting that the observed response was driven by OS rather than iron *per se*. OS was also associated with decreased phosphorylation of acetyl-CoA carboxylase and Akt, and increased ERK1/2 phosphorylation. Importantly, the induction of *Pnpla2* and *Lipe* by Fe was abolished in β -catenin-deficient adipocytes, suggesting that β -catenin signaling is required for OS-induced activation of the lipolytic program.

These findings identify β -catenin as a key mediator linking OS to adipocyte lipolysis and reveal a mechanism through which OS drives adipose tissue remodeling. Ongoing studies are aimed at elucidating the signaling pathways and molecular mechanisms underlying β -catenin-dependent activation of the lipolytic program.

Keywords:

Oxidative Stress, Adipose Tissue, Adipocyte, Lipolysis



P-069

ROS Induced Mitochondrial Hormesis Partially Protects From SGAs Mitochondrial Toxicity And Cardiovascular Disease

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The chronic intake of second-generation antipsychotic drugs (SGAs) has been shown to increase cardiovascular disease (CVD) risk. SGAs are lipophilic polar molecules that can accumulate in mitochondrial membranes and thus interfere with normal mitochondrial functions. Since mitochondrial dysfunction is a relevant event on CVD development, we evaluated the contribution of SGAs mitochondrial interference to the associated increased of CVD risk. To that end, we tested the SGAs Olanzapine (Ola), that induces weight gain, and Aripiprazole (Ari), that does not, in Primary bovine aortic endothelial cells (BAEC) and in WT and PGC-1 α knockout mice, a model of mitochondrial dysfunction. We found that both SGAs reduced mitochondrial respiration, but acutely, Ola triggered reactive oxygen species (ROS) production more significantly than Ari. This response to Ola led to the activation of adaptive responses, including increased antioxidant defenses, enhanced glycolytic flux and maintenance of mitochondrial volume, thus enabling redox and metabolic homeostasis. In contrast, Ari failed to activate these compensatory mechanisms. In fact, Ari long-term treatment suppressed stress responses and reduced metabolic plasticity, promoting more pronounced and sustained CV damage than Ola, particularly under conditions of mitochondrial dysfunction or dependence on oxidative metabolism. These findings indicate that the interference with mitochondrial activity and oxidative stress, along with the capacity of the subject to activate hormetic responses, play a key role in the CVD risk associated with chronic SGA treatment.

Keywords:

Mitochondria, ROS, Oxidative Stress, SGAs, Cardiovascular Disease

P-070

HEPATOCYTE GROWTH FACTOR (HGF) CONTRIBUTES TO THE DEVELOPMENT OF NITROSO-REDOX IMBALANCE IN THE HUMAN PLACENTA

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Hepatocyte growth factor (HGF), an adipokine linked to metabolic disorders, has been proposed as an "energy modulator" in the placenta, reducing fatty acid oxidation and promoting triglyceride accumulation. This lipotoxic context may contribute to nitroso-redox imbalance and placental dysfunction yet to be confirmed. In this study, placental explants from term cesarean deliveries (n=5) were cultured *ex vivo* with increasing HGF concentrations. Oxidative and oxidative and nitrosative stress markers (protein carbonyls, NADPH oxidase activity, nitrosothiols levels) and antioxidant responses (SOD, catalase, total antioxidant capacity) were measured. HGF exposure led to increased oxidative/nitrosative damage and decreased antioxidant activity. These findings suggest that elevated HGF levels may induce placental nitroso-redox dysregulation which could be implicated in the early stages of placental dysfunction and altered fetal metabolic programming.

Funding:

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Keywords:

Pregnancy, Hepatocyte Growth Factor, Placenta, Oxidative Stress, Inflammation

P-071

The Role Of GRIM-19 In Metformin-Induced Changes In The Redox State Of Leukocytes In Patients With Type 2 Diabetes

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Introduction: Type 2 diabetes mellitus (T2D) is associated with mitochondrial dysfunction, oxidative stress, and chronic low-grade inflammation. STAT3 phosphorylation at Ser727 links energy metabolism and inflammation. Metformin, the first-line treatment for T2D, may exert beneficial extraglycaemic effects on mitochondrial and inflammatory pathways.

Objective: To evaluate the effects of metformin on mitochondrial mass, redox status, GRIM19, p-STAT3 (S727), leukocyte-endothelial interactions, and inflammatory markers in T2D patients.

Methodology: The study included 74 healthy controls, 26 T2D patients without metformin, and 91 T2D patients treated with metformin. PBMCs and PMNs were isolated from blood samples. Mitochondrial and cytosolic parameters were analyzed by flow cytometry, protein expression by Western blot, leukocyte-endothelial interactions using a parallel flow chamber, and inflammatory molecules by Luminex.

Results: No differences were observed in glucose or HbA1c between T2D groups. Patients without metformin showed reduced mitochondrial mass (p<0.01), while metformin restored these levels. GRIM19 and p-STAT3 (S727) expression increased in metformin-treated patients (p<0.01), suggesting activation of mitochondrial signaling pathways. Leukocyte-endothelial interactions maintained the proinflammatory profile of T2D, without changes after metformin treatment. TNF α , myeloperoxidase, and VCAM-1 were elevated in T2D patients vs. controls and significantly reduced with metformin.

Conclusion: Metformin improves mitochondrial function and modulates the GRIM19-p-STAT3 (S727) pathway and inflammatory markers in T2D, supporting its role beyond glycemic control.

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Keywords:

Mitochondria, Type 2 Diabetes, Redox State, GRIM-19

P-072

3R And 4R Tau Differentially Alter Mitochondrial Function

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Tauopathies are a heterogeneous group of neurodegenerative disorders characterized by the pathological accumulation of misfolded tau protein in brain aggregates. Within this framework, a disrupted balance between 3R and 4R tau isoforms and/or impaired tau's physiological function is known to be sufficient to drive neurodegeneration. Elucidating whether distinct tau alterations promote shared or isoform-specific neurotoxic mechanisms is essential for the development of targeted therapeutic strategies. In this regard, previous data from our group revealed that an increased 4R/3R tau ratio disrupts mitochondrial function, affecting bioenergetics and calcium homeostasis. The present work evaluates whether overexpression of different tau isoforms similarly affects cellular homeostasis. To this end, we employed an SH SY5Y cell model overexpressing 3R and 4R tau isoforms. Our results indicate that both isoforms, besides presenting different expression and secretion profiles, impair mitochondrial function in different ways. Specifically, under high levels of 3R or 4R tau, several features related to bioenergetics are altered, including Complex I activity, Mitochondrial Membrane Potential, ATP production and glucose uptake. In addition, tau overexpression compromises mitochondrial redox processes, including antioxidant defense and ROS production, which in turn initiate cell death pathways. All observed effects showed isoform-specific patterns. These findings indicate that the development of disease-modifying therapies for tauopathies should be tailored to specific tau isoforms to achieve optimal therapeutic efficacy.

Keywords:

Tauopathies, Tau Isoforms, Mitochondrial Dysfunction, Bioenergetics, Oxidative Stress, Neurodegeneration



P-073

A Cluster Of Conserved Amino Acids Enhances The Thermal Stability Of Frataxin, An Antioxidant Mitochondrial Protein Mitochondria, comunicación celular y estrés oxidativo / Estructura y función de proteínas

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Friedreich ataxia is a rare cardio-neurodegenerative disease caused by mutations in the frataxin gene. Frataxin is a mitochondrial protein that plays key roles in iron homeostasis and antioxidant protection. Recent sequence analyses identified a cluster of four residues (Y143, S158, S161, and E189 in human frataxin) highly conserved in eukaryotic frataxins and CyaY proteins from the *Rickettsia* genus. To investigate their role in frataxin stability and function, we generated and purified mature wild-type frataxin (WT) and the variants E189A, S158A, S161A, Y143I, and Y143I E189A. Intrinsic fluorescence measurements showed similar profiles for all proteins at 20 °C, whereas proteins containing the E189A mutation exhibited markedly reduced fluorescence intensity at 45 °C. Thermal denaturation assays revealed lower melting temperatures and faster unfolding kinetics in all variants compared with WT, with E189A mutants being the most destabilized. Baker–Hubbard algorithm predicted that these residues form a hydrogen-bonding network linking the α 2 helix to the central β -sheet, with E189 as the only α -helical residue. This structural arrangement explains the pronounced destabilizing effect of the E189A mutation. Given the potential antioxidant role of tyrosine residues, we further assessed the protective capacity of frataxin variants against metal-catalyzed oxidation. Our results confirmed the antioxidant and iron-binding properties of frataxin and indicated that the residues investigated were not required for these properties.

Keywords:

Friedreich Ataxia, Iron, Oxidative Stress, Mitochondria, Metal-Catalyzed Oxidation

P-074

Differential Effects Of 3R And 4R Tau On Calcium Dynamics And Cell Death In Differentiated SH-SY5Y Cells

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Tauopathies are a heterogeneous group of neurodegenerative diseases characterized by abnormal tau protein accumulation. A strict balance between the main tau isoforms, 3R and 4R, is required in the healthy adult brain, with distinct tauopathies characterized by the selective accumulation of specific isoforms. Previous data working with iPSC neurons with the MAPT 10+16 mutation, that specifically accumulates 4R tau isoform and leads to frontotemporal dementia, revealed mitochondrial stress and aberrant calcium handling. However, the precise molecular mechanisms driving this toxicity and whether these effects are specific to the 4R isoform or shared with 3R tau remain unclear.

Using a differentiated human neuroblastoma cell line (SH-SY5Y) that differentially overexpresses tau 3R and 4R isoforms, we performed cell viability and excitotoxicity assays, and live fluorescence microscopy to evaluate the impact of tau overexpression on cell survival and calcium dynamics. Our results revealed a significant reduction in cell viability, driven by an increase in both apoptotic and necrotic cell death following tau overexpression. Furthermore, we observed a dysregulation of calcium homeostasis, which led to an increased vulnerability to both excitotoxicity and apoptotic cell death following an exogenous calcium overload, with distinct profiles emerging between the overexpressed isoforms. Finally, the expression levels of several proteins involved in calcium signaling were assessed without significant variations.

In conclusion, tau isoform-specific overexpression disrupts calcium homeostasis and drives cell death. These findings highlight how each isoform triggers distinct molecular mechanisms leading to neuronal loss and neurodegeneration.

Keywords:

Tau, Frontotemporal Dementia, Mitochondria, Calcium, 3R Tau, 4R Tau

P-075

The Dysregulation Of The Endocannabinoid System And The Increase In Antioxidant Defenses At The Gene Expression Level Are Associated With Increased Apoptosis In Cytotrophoblasts From Placentas Of Pregnancies With Preeclampsia

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Preeclampsia (PE) is a severe pregnancy disorder characterized by hypertension and frequently proteinuria, affecting 2–3% of pregnancies in our population. PE is associated with increased oxidative stress and mitochondrial dysfunction in the placenta. In parallel, modulation of the endocannabinoid system (ECS) is linked to multiple pathophysiological processes, including inflammatory diseases. The ECS is composed of enzymes involved in the synthesis and degradation of endocannabinoids, as well as their receptors, which are present in the placenta and participate in its development, uterine implantation, and maintenance of pregnancy and parturition.

Our results show increased expression of genes related to antioxidant defenses in placental trophoblasts in PE. We observed a 2-fold increase in COQ2 expression, involved in coenzyme Q biosynthesis. Antioxidant enzymes such as catalase, SOD2, and thioredoxin 2 (2-fold increase), glutathione peroxidase 1 (6-fold increase), and Nrf2 (4-fold increase) were also upregulated. In contrast, thioredoxin-interacting protein was markedly increased (30-fold). However, we observed a 33% increase in apoptosis in placental cytotrophoblasts from PE compared to controls. This is accompanied by dysregulation of ECS-related genes, with a 3-fold increase in CB1 receptor expression, increased NAPE-PLD (>3-fold), a key enzyme in anandamide synthesis, and a 2.5-fold increase in ABHD6, involved in endocannabinoid degradation.

These preliminary data suggest that in PE there is a dysregulation of the ECS that may impair trophoblast homeostasis, together with activation of antioxidant defense mechanisms that attempt to counteract oxidative stress; however, these

responses are insufficient to prevent increased apoptosis in placental cytotrophoblasts.

Keywords:

Mitochondria, Oxidative Stress, Endocannabinoid System, Preeclampsia

P-076

Characterization Of Exosomes From Hepatocarcinoma Cells: Implications Of PRDX6 In Tumor Communication

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Exosomes are small extracellular vesicles (30–200 nm) that play a central role in intercellular communication. Tumor cells are known to secrete more exosomes than normal cells, driving disease progression by transferring oncogenic factors, proteins, microRNAs, and other bioactive molecules to the tumor microenvironment.

Among the factors implicated in tumor progression, peroxiredoxin 6 (PRDX6) has gained considerable attention due to its multifunctional nature and its involvement in cellular redox homeostasis. Furthermore, recent studies highlight its enrichment in macrophage-derived extracellular vesicles. PRDX6 is the only member of the Prdx family exhibiting peroxidase, phospholipase A2, and lysophosphatidylcholine acyltransferase activity; therefore, in addition to regulating oxidative stress, it participates in phospholipid metabolism and membrane repair processes.

In this study, exosomes from HepG2 and SNU475 hepatocarcinoma cell lines containing or not PRDX6 were isolated using various methodologies. Characterization of these vesicles was performed by identifying canonical exosome markers and PRDX6 by Western blot. Vesicle size distribution and particle concentration were assessed using NanoSight NS300, while their morphology and ultrastructural features were examined by transmission electron microscopy, revealing the typical structures consistent with exosomes. Additionally, PRDX6-deficient cells were treated with exosome-enriched media derived from PRDX6-expressing cells. Our results demonstrate that exposure to these media significantly increases the proliferative and migratory capacities of recipient cells, while upregulating migration-related markers. Altogether, these results suggest that PRDX6 plays a key role in exosome-mediated tumor communication.



Keywords:

Exosomes, Peroxiredoxin 6, Tumor Communication, Hepatocarcinoma

P-077

Nrf2 Activation By Omaveloxolone: Implications For Neuroprotection In A Parkinsonian Murine Model

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Parkinson's disease (PD) is characterised by the gradual loss of dopaminergic neurons in the substantia nigra (SN) and the accumulation of α -synuclein deposits. At the molecular level, neuroinflammation, oxidative stress and mitochondrial dysfunction are key pathological mechanisms in neurodegeneration. All these processes are regulated by the Nrf2 pathway, a central transcription factor involved in cellular defense.

In this study, we assessed the neuroprotective effects of Omaveloxolone (Oma), a potent activator of the Nrf2 pathway, in a murine PD model. To this end, C57BL/6 WT mice received a unilateral stereotaxic injection of mutant α -synuclein (A53T) into the SN using an AAV9- α -SYNA53T viral vector. Animals were treated with Oma (10 mg/kg) via daily intraperitoneal injections for 14 days. Motor behavioral tests confirmed hemiparesis. Activation of the Nrf2 pathway was validated by increased levels of its target Nqo1, along with a reduced proinflammatory response in peritoneal macrophages. Oma exerted neuroprotective effects, significantly counteracting the loss of dopaminergic neurons in the SN. It also reduced glial reactivity, leading to changes in their morphology towards less inflammatory phenotypes. Its effects on mitochondrial metabolism were assessed by measuring NADH and ATP levels, as well as complex I activity in the striatum and prefrontal cortex. Furthermore, we conducted

an array-based analysis of electron transport chain subunits. Although alterations were detected in several of these parameters, the results remain not yet conclusive.

In summary, Oma prevents neuronal loss in our synucleinopathy model, but further studies are needed to understand if mitochondrial function modulation is contributing to the neuroprotective effects.

Keywords:

Parkinson's Disease, Omaveloxolone, Nrf2, Neuroinflammation, Oxidative Stress, Dopaminergic Neurons, Mitochondria, Mice, Alpha-Synuclein

P-078

Molecular And Functional Cardiac Alterations In The Friedreich Ataxia FXN151F Mouse Model

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Friedreich ataxia (FA) is an inherited neuro-cardiodegenerative disorder caused by homozygous GAA repeat expansions in the FXN gene that result in decreased levels of frataxin. This mitochondrial protein is required for iron-sulfur cluster biogenesis and energy metabolism. Frataxin deficiency disrupts mitochondrial function, leading to oxidative stress and impaired cellular bioenergetics. Cardiac complications are the leading cause of mortality in patients with FA.

In this study, we used the FXN^{I151F} mouse model, which harbors the pathogenic human point mutation I154F in the FXN gene. These mice exhibit low frataxin protein levels in all the tissues, resembling FA patients. FXN^{I151F} mice were examined at 21 weeks of age, prior to the onset of neurological symptoms, to investigate cardiac alterations.

Our results demonstrated an increase in markers of cardiac stress and fibrosis. Concomitantly, we observed increased translocation of the nuclear factor of activated T-cells 3 (NFAT3), a transcription factor implicated in the regulation of genes associated with cardiac hypertrophy. In addition, functional alterations were evaluated by echocardiography and electrocardiography.

In assessing mitochondrial impairment, our results revealed a decrease in the NAD⁺/NADH ratio, leading to reduced ac-

tivity of the NAD⁺-dependent deacetylase sirtuin 3 (SIRT3), along with an increase in mitochondrial protein acetylation in FXN^{I151F} heart. Simultaneously, we observed activation of the mitochondrial integrated stress response (ISRmt), an adaptive mechanism triggered in the context of mitochondrial dysfunction.

Altogether, these findings provide insights into the mechanisms underlying cardiac complications associated with systemic frataxin deficiency.

Keywords:

Friedreich Ataxia, FXN151F Mouse Model, Cardiomyopathy, Hypertrophy, Fibrosis, Mitochondrial Dysfunction, Mitochondrial Integrated Stress Response (ISRmt)

P-079

Cytotoxic And Phototoxic In Vitro Studies Of Cyclometalated Pt(II) Complexes With Phenylpyridinato-Based Ligands

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Emissive cyclometalated Pt(II) complexes have attracted considerable attention due to their remarkable photophysical properties and potential biomedical and optoelectronic applications. Following a literature-reported procedure, a new family of cyclometalated dipyrinato Pt(II) complexes of general formula [Pt(C^N)(N^N)], where C^N = dfppy **1**, ppy-CHO **2**, piq **3** and N^N = phenylpyridinato (dipy-Ph, **a**) or 3,4,5-trifluorophenylpyridinato (dipy-F₃Ph, **b**), was synthesized. The new complexes were characterized by spectroscopic techniques, and their optoelectronic properties were studied both experimentally and theoretically. All compounds were able to generate singlet oxygen (¹O₂) and their ability of NADH photo-oxidation was evaluated under green light irradiation and in the dark. The cytotoxicity of these complexes was assessed in A549 cancer cells, revealing remarkable baseline toxicity (IC₅₀ of 3.48–13.04 μ M) for all but one non-toxic complex, indicating promising anticancer potential. Upon exposure to green LED light for 15 minutes, the complexes exhibited significantly enhanced photo-toxicity, yielding IC₅₀ values even lower than those observed at 72 hours. Furthermore, light irradiation induced an increase in intracellular reactive oxygen species (ROS). Electrophoresis studies indicated that none of the complexes interacts

with DNA. Confocal microscopy revealed that while the compounds differentially alter cell morphology, they show no obvious signs of tubulin depolymerization. However, JC-10 assays demonstrated that they induce mitochondrial damage by mitochondrial membrane depolarization. Finally, uptake dynamics and intracellular localization studies confirmed efficient internalization with selective accumulation of specific complexes within lysosomes.

Keywords:

Cyclometalated Pt(II) Complexes, Cytotoxicity, Phototoxicity, Reactive Oxygen Species (ROS), Mitochondrial Membrane Depolarization, Cancer, Confocal Microscopy, Cancer Cell Lines

P-080

Kinase-Dependent Regulation Of Mitochondrial Translation Impacts Mitochondrial Function And Cellular Growth

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Mitochondria play a central role in cellular energy production through oxidative phosphorylation (OXPHOS), a process that relies on the coordinated assembly of multiprotein complexes composed of both nuclear- and mitochondrial-encoded subunits. Among these, thirteen essential components are encoded by mitochondrial DNA (mtDNA) and synthesized within the organelle, placing mitochondrial translation at the core of mitochondrial function and cellular homeostasis. Recent high-throughput studies have identified multiple kinases as potential regulators of mitochondrial translation, suggesting the existence of signaling networks that integrate mitochondrial activity with cellular demands.

To explore the functional relevance of these pathways, candidate kinases previously associated with mitochondrial translation were silenced in HEK293T cells. Kinase depletion resulted in distinct effects on cellular proliferation, mitochondrial protein expression, and respiratory capacity, indicating differential impacts on mitochondrial performance. Respiratory activity was further evaluated under glycolytic and OXPHOS-reliant conditions, revealing condition-dependent alterations in oxygen consumption profiles.

These findings support a model in which kinase-dependent regulation of mitochondrial translation contributes to the maintenance of mitochondrial function and shapes cellular growth behavior, providing further insight into the mechanisms that coordinate mitochondrial activity with cellular adaptation processes.





Keywords:

Mitochondrial Translation, Protein Kinases, Oxidative Phosphorylation, Bioenergetics, Mitochondrial Function

P-081

Mitochondrial DNA Variation Shapes Tumor Phenotypes In Lung Adenocarcinoma

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Mitochondrial metabolism is controlled by two genomes: the nuclear genome and mitochondrial DNA (mtDNA). Variation in mtDNA has been associated with differences in cancer risk and clinical outcomes, yet its contribution to tumor phenotypes remains poorly understood. Compared with nuclear DNA, mtDNA is more susceptible to inherited variation and somatic mutations. In addition to its metabolic role, mtDNA can also act as a signaling molecule influencing cellular stress and inflammatory responses.

Here, using lung adenocarcinoma (LUAD) cell models together with analyses of human cohorts, we investigated how mitochondrial genetic variation influences tumor behavior. We combined in vitro approaches, including cell cultures and tumor spheroids, with in vivo xenograft analyses to assess how differences in mtDNA background shape cancer phenotypes. mtDNA variation led to significant remodeling

of tumor cell features, including mitochondrial dynamics, spheroid organization, cell morphology, and inflammatory signaling associated with epithelial–mesenchymal transition (EMT). In vivo, these differences were associated with changes in tumor growth, spontaneous metastatic potential, and sensitivity to therapy.

Together, these findings identify mitochondrial genetic variation as an important determinant of tumor plasticity and progression in LUAD and support mtDNA as a potential contributor to oncogenesis and therapeutic response.

Keywords:

MtDNA, Mitochondrial Haplogroups, LUAD, Inflammation

P-082

Placental Nitroso-Redox Dysregulation In Maternal Obesity And Gestational Diabetes Mellitus: A Preliminary Proteomic Study

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Oxidative stress results from an imbalance between reactive oxygen species (ROS) and the antioxidant defense. In this context, nitrosative stress, caused by reactive nitrogen species (RNS), induces protein alterations through processes such as S-nitrosylation and tyrosine nitration. During pregnancy, especially in maternal obesity and gestational diabetes mellitus (GDM), inflammation, hyperglycemia and hyperlipidemia increase ROS/RNS production and consequently, may cause changes in redox homeostasis

that remain to be clarified. The main objective of this study was to obtain a differential profile based on the presence of NO-induced post-translational modifications in placental proteins from pregnancies complicated by pregestational obesity and/or GDM. To this end, human placental samples (trophoblastic villi) obtained a term and by scheduled cesarean section were analyzed and classified according to maternal body mass index and presence of GDM. Markers of oxidative and nitrosative stress were determined using techniques such as Western blot, OxyBlot, Biotin-Switch assay, and specific immunodetection. The results showed a significant increase in oxidative and nitrosative damage in placentas from women with pregestational obesity and/or GDM, along with a decrease in antioxidant capacity, suggesting an insufficient antioxidant response to redox imbalance. In conclusion, nitrosative stress emerges as a key factor in placental redox dysregulation in pregnancy-related disorders, highlighting the need for more in-depth studies based on -omics technologies such as redox proteomics.

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Keywords:

Placenta, Pregnancy, Oxidative Stress, Nitrosative Stress, Pregnancy-Related Disorders And Proteomic Analysis

P-083

Comparison Of MtDNA Instability Features In Tumor And Normal Mucosa Of Colorectal Cancer (CRC) Show Distinct Features For Subjects With Early-Stage (I-II) And Advance-Stage (III-IV) Tumors That Can Be Identified In CfDNA From Plasma Samples

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Colorectal cancer (CRC) is the third most commonly diagnosed cancer. Early diagnosis is crucial, but current screen-

ing methods are insufficient. Metabolic dysfunction is a risk factor, and mitochondrial DNA (mtDNA) instability is a well characterized feature. Thus, plasma cell free DNA (cfDNA) may be a relevant source of biomarkers. We analyzed tissue and blood samples in 60 CRC patients. We found that subjects with advanced stage tumors had in their intestinal mucosa more mitochondria than those bearing early-stage tumors, but these were more fragmented and perinuclear in subjects with advanced tumors. Analysis of mtDNA stability showed a reduced *MT-ND4/MT-ND1* ratio in the normal mucosa of subjects with advanced tumors, suggesting that mitochondrial structural alterations may be related to disease development. The observation that similar trends could be noted in PBMCs and immune-metabolic expression patterns in PBMCs were also different between early and advanced subjects, supports the relevance of these alterations. In the tumors, mtDNA analysis showed that the instability in the region between *MT-COX3* and *MT-ND4*, detected by qPCR with the oligonucleotide primer set *ND1v2* was higher in subjects with advance-stage tumors. Importantly, in plasma the levels of *MT-ND4/nuDNA* and *ND1v2/nuDNA* were also lower in advance-stage subjects, suggesting that their determination could be a relevant biomarker of disease development. Therefore, these results suggest that mtDNA alterations are strongly linked to CRC development. Early loss of *MT-ND4* in the mucosa could be a key event, driving the extension of the mtDNA stability beyond *MT-ND4* that can be detected in advanced tumors. Importantly, these features can be identified in cfDNA from plasma samples and may serve as biomarkers.

Keywords:

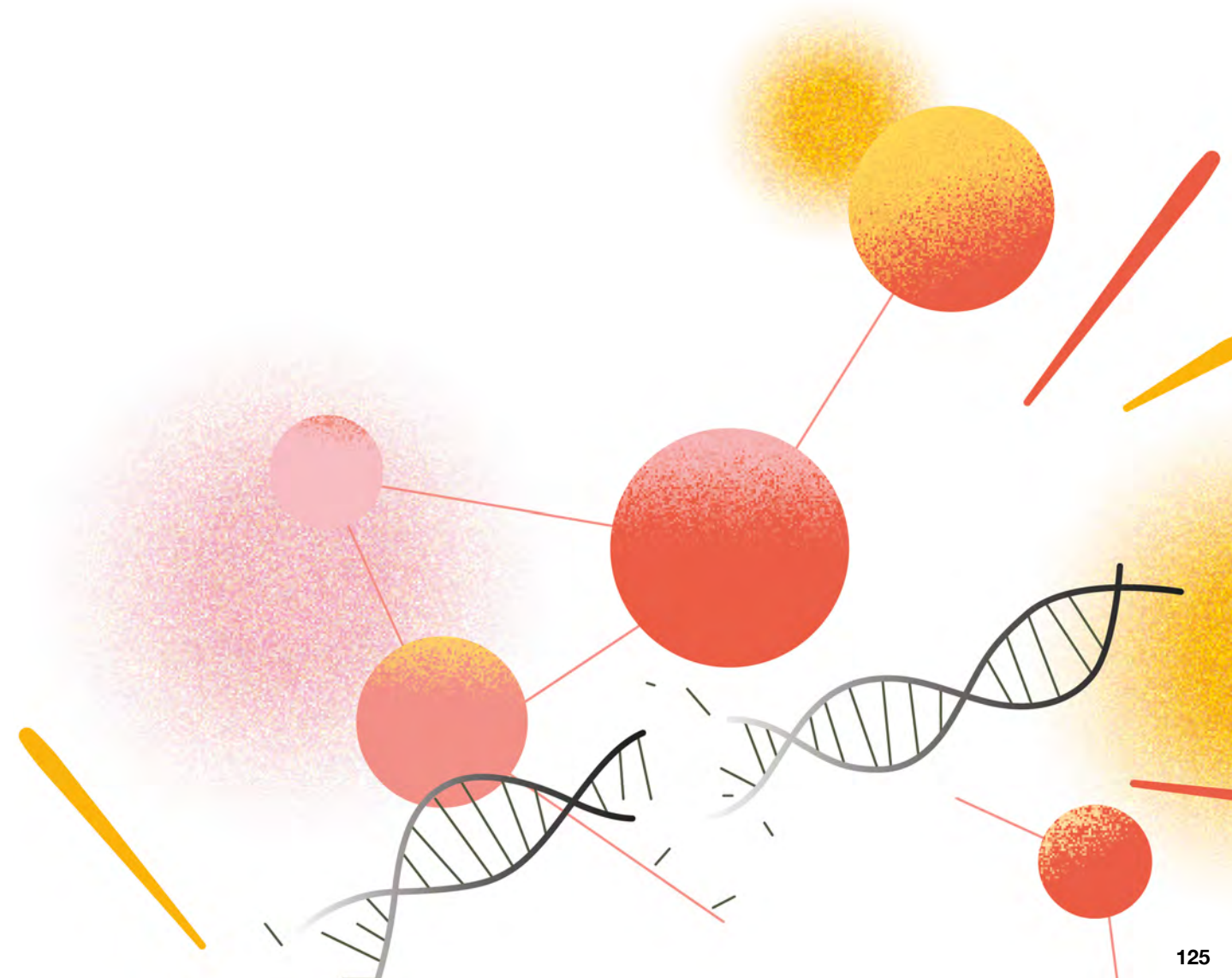
Colorectal Cancer, Mitochondria, CfDNA, Metabolism, MtDNA, OXPHOS, Oxidative Stress



GRUPOS CIENTÍFICOS DE LA SEBBM:

BIOMEMBRANAS

8 DE SEPTIEMBRE





O-058

Role Of Very Long-Chain Acyl-Ceramides In Endocytic Uptake

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Specialized endoplasmic reticulum (ER) subdomains termed ER sterol exit sites (ERSES), which contain a subset of sterol biosynthetic enzymes, transiently contact endocytic sites to locally supply sterols. Sterols at endocytic sites then contribute to initiate actin polymerization and drive membrane invagination. Osh2, an oxysterol-binding protein-related protein (ORP), interacts both with the sterol biosynthetic and endocytic machineries and mediates the non-vesicular sterol transfer at ER-endocytic contact sites (ER-ECS). Searching for other ERSES components, we identified Fat1, a fatty acid transporter and acyl-CoA synthetase with specificity for very long-chain (VLC) fatty acids (C20–C26). Analysis of VLC acyl-CoAs anabolic and catabolic pathways revealed a specific requirement for VLC acyl-ceramides (VLCA-Cers) in the constriction of endocytic invaginations. Further, we found that the ceramide synthase physically interacts with several BAR-domain-containing endocytic proteins involved in constriction and that Osh3, another ORP localized at ER-ECS, contributes to Cer extraction from the ER, monitored with a luminal Cer fluorescent probe. The data demonstrate a direct and local function of VLCA-Cers in endocytic budding.

Keywords:

Ceramides Endocytosis Yeast Lipid-Transport-Protein Membrane-Contact-Sites

O-059

Molecular Shaping Of The Elasticity And Strength Of Biomembranes

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The ability of cellular membranes to sense, contain, and adapt to stress through changes in shape and topology, without rupturing, is fundamental to life. Although the generation of and response to membrane stress are often associated with dedicated protein machinery, the material properties of the lipid bilayer underpin the most basic and likely primordial mechanisms by which membranes respond to diverse stresses, including tensile, bending, and electrical stresses. Here, we discuss how the elastic properties and molecular shapes of the constituents of cellular membranes, lipids and proteins, govern membrane responses to stress. We focus specifically on stress-driven deformations of membrane

geometric composites. We show that the stress-induced lateral redistribution of molecular shapes constitutes an independent mode of membrane deformation with complex rheological properties. This mode governs both mesoscale membrane deformations and the resulting accumulation of elastic stress, a key trigger of membrane poration, fusion, and fission. We further demonstrate that the combination of molecular shapes within a simple biomimetic lipid bilayer determines not only the corresponding stress thresholds but also the location and pathways of membrane failure under stress. These findings suggest that membrane stress responses can be rationally programmed at the level of the lipid matrix itself.

Keywords:

Membrane Nano Mechanics, Lipids, Molecular Shape, Curvature

O-060/P-084

De Novo Design Of An Apoptotic Membrane Protein Inhibitor

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Resistance to apoptosis is a hallmark of cancer and contributes to tumour cell survival, making apoptosis regulation an attractive therapeutic target¹. However, current strategies to inhibit apoptosis regulators often show limited clinical efficacy and adverse effects. Recent studies indicate that transmembrane (TM) interactions are essential for the activity of apoptosis regulators, and their disruption can restore apoptosis and promote cell death². Despite this potential, targeting TM domains remains challenging because membrane-embedded interfaces are difficult to modulate selectively with antibodies or small molecules³, while peptide-based TM mimetics usually suffer from poor solubility and suboptimal pharmacological properties.

In this study, we combined state-of-the-art computational design and protein engineering to generate a *de novo* triple-transmembrane protein capable of selectively binding to a target TM helix and suppressing its function. To this end, four-helix bundle scaffolds were generated using coiled-coil Crick parameterization⁴, selecting the most designable architectures. Then, LigandMPNN was used to design sequences predicted to fold into the target structure⁵.

Functional characterization demonstrated that the designed

binders selectively interact with the target membrane protein and induce apoptosis in cancer cells via TM binding.

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Keywords:

De Novo Design, Membrane Protein, Apoptosis, Protein Design

O-061/P-085

Pro-Inflammatory Cytokines And Alzheimer's-Related Proteins Disrupt Astrocytic Calcium Homeostasis Via PMCA Upregulation In Glioblastoma U-251 Cells

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Astrocytes play a central role in maintaining brain homeostasis, including the regulation of intracellular calcium dynamics. In the context of neuroinflammation and Alzheimer's disease (AD), astrocytes undergo reactive changes that may profoundly alter calcium signalling pathways.

Here, we investigated how pro-inflammatory cytokines and AD-related proteins, amyloid- β (A β) and tau, modulate the expression and activity of plasma membrane Ca²⁺-ATPases (PMCAs) in astrocytic cells. Using U-251 astrocytoma cells, we analysed PMCA isoform expression and Ca²⁺ extrusion activity following exposure to cytokines (IL-1 α , TNF- α , and C1q), A β , and tau. Flow cytometry, immunological and kinetic assays revealed that all PMCA isoforms are expressed in these cells and differentially regulated depending on the stimulus. Notably, cytokines and AD-related proteins induced a selective increase of specific PMCA isoform expression, accompanied by a significant upregulation of Ca²⁺-ATPase activity, while SERCA expression and activity remained unchanged.

These findings suggest that inflammatory and neurodegenerative signals converge to selectively modulate PMCA expression and function in astrocytes, identifying PMCA as a key component of astrocyte reactivity and a potential therapeutic target in Alzheimer's disease.

Funding:

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Keywords:

A β , Tau, Cytokines, PMCA, Astrocytes, Calcium

O-062/P-086

Adaptative Response Of Pyrimidine Transporters HCNT1 And HCNT3 To Nucleoside Levels

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Considering that pyrimidine nucleotides are mainly salvaged from nucleosides, this study aims at determining the role of high affinity pyrimidine nucleoside transporters in sensing and regulating pyrimidine salvage. Concentrative



nucleoside transporters (CNTs) mediate unidirectional sodium-coupled uptake of nucleosides. Here we examined the function of sensing nucleoside changes of hCNT1, which is pyrimidine-specific, and hCNT3, which can translocate purines and pyrimidines.

Under nucleoside depletion, hCNT1 and hCNT3 behave differently. RNA expression analysis revealed that among all nucleoside transporters, including the equilibrative ones, only hCNT1 was upregulated in different cell models. This unique regulation was also observed in presence of inhibitors of nucleoside uptake (NBTI) or nucleotide *de novo* biosynthesis, with no major changes in nucleotide salvage or *de novo* synthesis genes, suggesting a hCNT1-specific effect. On the other hand, nucleoside absence dramatically reduced hCNT3 presence at the plasma membrane, which was reversed by adding NBTI. Our results revealed a link between Akt pathway and hCNT3 subcellular localization.

Given the homotrimeric structure of hCNT3, we explored whether hCNT1 was also an homotrimer. PDBePISA analysis and AlphaFold modelling unveiled that hCNT1 could form an homotrimer, which was validated by NanoBRET assay. The oligomers presented almost no alterations when glycosylation or trafficking were inhibited, suggesting that they are stable since early maturation. Intriguingly, we detected for the first time that hCNT1 and hCNT3 can form heteromeric complexes in basal conditions, such as differentiated CaCo-2 cells.

Overall, this study unveiled for the first time a substrate regulation of concentrative pyrimidine transporters.

Keywords:

Pyrimidines, Nucleosides, CNT1, CNT3

O-063/P-087

Glycation Of Synaptic Vesicles And α -Synuclein: A Potential Molecular Link Between Diabetes And Neurodegeneration

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Type 2 diabetes mellitus (T2DM) is increasingly recognized as a major risk factor for Parkinson's disease, potentially through mechanisms involving impaired glucose metabolism and elevated methylglyoxal (MG) levels. MG promotes the formation of Advanced Glycation End-products (AGEs), which accumulate in Lewy bodies and are associated with neurodegeneration. Among the affected proteins, α -synuclein (α S), a key regulator of synaptic vesicle (SV) trafficking and dopamine neurotransmission, is highly susceptible

to glycation and oxidative stress. These modifications may disrupt α S-membrane interactions and contribute to synaptic dysfunction.

This work aims to elucidate how glycation alters α S interactions with synaptic vesicles. To address this, we combine experimental and computational approaches using native and modified α S together with biomimetic SV models. Native and MG-modified vesicles and proteins are characterized using biophysical techniques including dynamic light scattering, microscopy, and mass spectrometry. In parallel, all-atom molecular dynamics simulations are performed on neuronal-like lipid membranes containing cholesterol to investigate α S-membrane interactions under native and modified conditions.

As preliminary progress, a simplified SV model has been developed and subjected to MG-induced glycation. Importantly, the formation of the crosslinking AGE MOLD was detected in glycated vesicles, together with measurable alterations in vesicle physicochemical properties. These glycated vesicles will be used to study their interaction with both native and glycated α S. In addition, the first all-atom simulations of neuronal-like membranes have been completed using GROMACS, establishing a framework for future analyses of α S binding and membrane perturbation.

Keywords:

Glycation, Synaptic Vesicles, Alpha-Synuclein, Methylglyoxal, Neurodegeneration

O-064/P-088

Melithery-Mediated Lipid Modulation As A Novel Approach Against Cancer Progression

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Background and Aims:

Melithery is an emerging therapeutic strategy based on bioactive lipids to modulate the structure and functionality of the cell membrane. Since the plasma membrane is the first element in contact with the cell's environment, controlling its composition could allow us to modulate key cellular functions such as adhesion, communication, migration,

and even cell proliferation or viability. This project aims to evaluate new bioactive lipids as potential agents with anti-proliferative and antimetastatic properties against different cancer cell types.

Methods:

This study evaluated the potential of melithery in two lung cancer cell lines: A549 and H1299. Cell viability was evaluated by flow cytometry using Sytox Green, while wound-healing and transwell assays were performed to assess cell migration and invasion after treatment. Wound closure and cell motility were monitored and quantified using the Incucyte live-cell imaging system. Chemotactic capacity was quantified using Ibidi chambers after 24 hours of pretreatment for 16 hours.

Results:

Treatment induced a dose-dependent decrease in cell viability within 24 hours, even at low concentrations. In addition, transwell and wound-healing assays demonstrated a significant reduction in migratory and invasive capacity in both lung cancer cell lines, particularly after treatment with one of the tested compounds. Furthermore, Ibidi chamber assays revealed altered displacement dynamics and impaired chemotactic response following compound pretreatment.

Discussion:

Our preliminary results suggest the effectiveness of melithery depends on the specific lipid composition, providing new insights into membrane-targeted strategies as innovative approaches to limit motility of lung cancer cells.

Keywords:

Lipid, Migration, Viability, Cancer, Invasion, Motility

O-065/P-089

PADI4 Inhibition By Small Extracellular Vesicles As A New Therapeutic Approach In Glioblastoma

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Glioblastoma (GBM) is the most aggressive primary brain cancer, characterized by rapid growth and infiltration into surrounding tissues. Current treatment protocols, including

cytotoxic chemotherapy, effectively target localized tumors but are limited by severe systemic side effects due to high dosing requirements. In this study, we observed a significant interpatient variability in PADI4 protein levels of patient derived GBM cell lines. When investigating GSK484, we observed that its encapsulation in small EVs derived from GB-39 cells (GB-39 EVs^{GSK484}) led to an increased cytotoxicity at lower drug concentrations compared to direct application. GB-39 EVs^{GSK484} also reduced the interaction between MDM2 and PADI4, further supporting its specific action of interfering with downstream signaling pathways involved in tumor progression and chemoresistance. Consistent with this, GB-39 EVs^{GSK484} also impaired wound closure, suggesting reduced migratory capacity of GBM cells. These findings highlight not only the importance of citrullination as a therapeutic target in cancer but also the relevance of GBM-derived small EVs as a promising and versatile drug delivery system that can minimize the potential toxicity. As GSK484 is more than 400 times more efficient than its direct application, this work opens the way for further preclinical exploration to optimize GBM therapy and explore its applicability in other malignancies. This innovative approach may pave the way for more effective and personalized cancer treatments.

Keywords:

Glioblastoma; PADI4; Drug Delivery; Extracellular Vesicles, PLA



P-090

Understanding Glioblastoma Resistance To Radiotherapy: Metabolomic And Transcriptomic Study Of Cells, Culture Media And Small Extracellular Vesicles

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Glioblastoma (GBM) is the most aggressive primary brain tumor, characterized by tumor heterogeneity, poor prognosis, profound metabolic reprogramming and resistance to therapy. Understanding how metabolic alterations contribute to treatment response and interact with the tumor microenvironment (TME) remains a major challenge. Here, we aimed to characterize the metabolic adaptations underlying radiotherapy response in GBM.

We performed an integrative multi-omics study combining transcriptomic profiling and nuclear magnetic resonance (NMR)-based metabolomics in seven patient-derived GBM cell lines with differential radiosensitive. Metabolite composition was analyzed in GBM cells, small extracellular vesicles (EVs) and culture media to capture both intracellular metabolic states and extracellular metabolic exchange.

Metabolomic profiling revealed distinct signatures associat-

ed with radiotherapy response, including alterations in lactate, glutamate, glucose, branched-chain amino acids and TCA cycle intermediates. GBM-derived EVs were enriched in lipids, amino acids and metabolites supporting their role in metabolic adaptation under nutrient-limited conditions.

Transcriptomic analysis showed widespread gene expression changes, including coordinated downregulation of genes involved in central metabolic pathways and upregulation of adaptive and stress-related processes. Integration of transcriptomic and metabolomic data provided insight into metabolic rewiring associated with radiotherapy resistance and identified candidate metabolic regulators involved in this process.

These findings highlight the relationship between cancer cell metabolism and the TME and support the potential of EV-associated metabolites as biomarkers for patient stratification and therapeutic targeting.

Keywords:

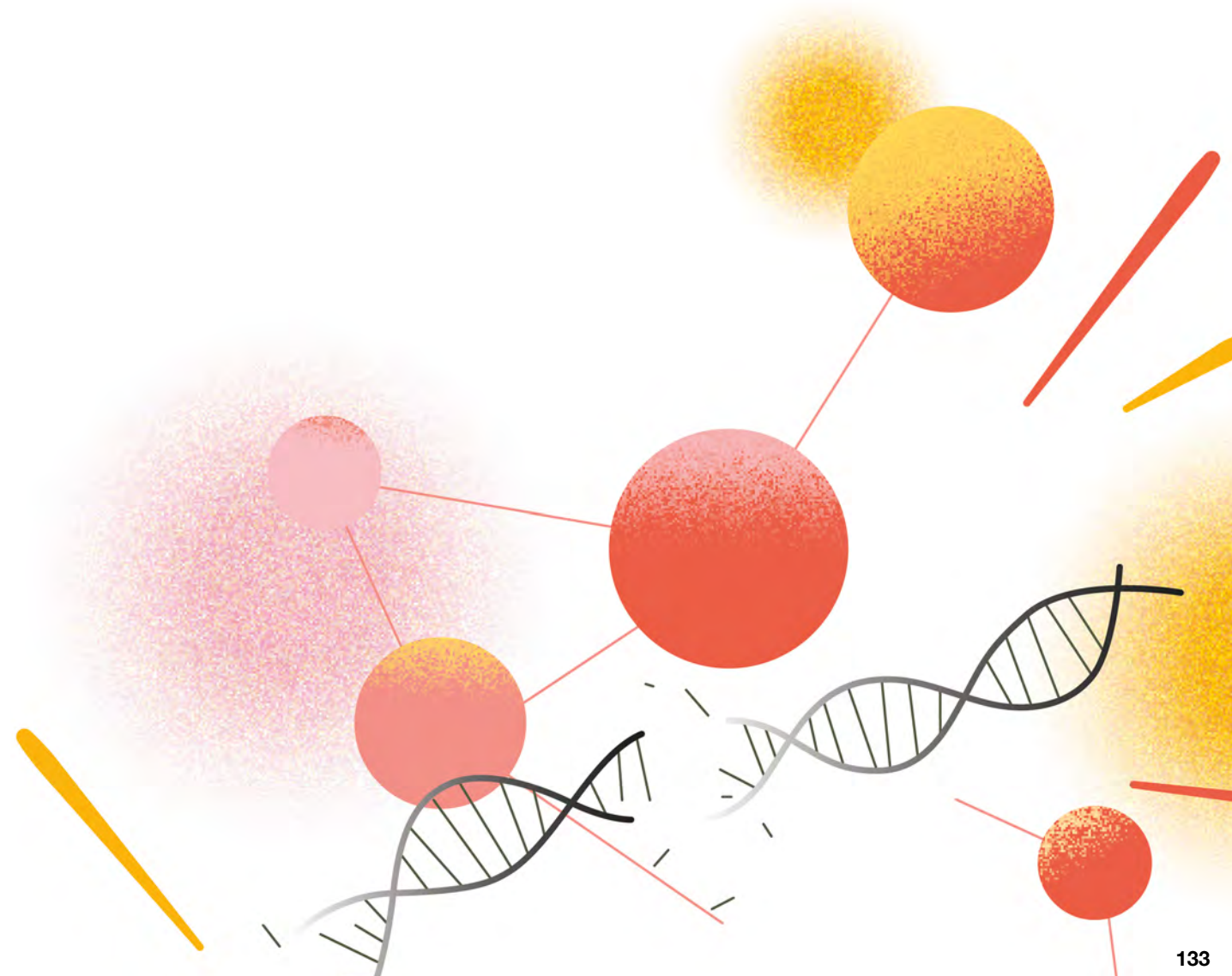
Metabolomics, NMR Spectroscopy, Glioblastoma, Small EVs, Biomarkers



GRUPOS CIENTÍFICOS DE LA SEBBM:

BASES MOLECULARES DE LA PATOLOGÍA

9 DE SEPTIEMBRE





O-066

Hepatic Metabolism: Mitochondrial Dynamics And The Liver–Uterus Axis

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Mitofusin 2 (Mfn2) has emerged as a key regulator of liver metabolism, with growing evidence linking its dysfunction to metabolic dysfunction-associated steatohepatitis (MASH). When Mfn2 is lost, the consequences extend well beyond mitochondrial morphology: impaired lipid and phospholipid handling, oxidative stress, and mitochondrial dysfunction collectively drive liver disease progression.

Our group has shown that male mice with liver-specific Mfn2 knockout (L-KO) display defective phospholipid transport between the endoplasmic reticulum and mitochondria. This defect is tied to reduced activity of key enzymes at mitochondria-associated membranes (MAMs) responsible for phosphatidylserine synthesis, ultimately disrupting lipid homeostasis and developing steatohepatitis.

Strikingly, Mfn2 deficiency does not affect both sexes equally. In female L-KO mice, hepatic loss of Mfn2 is associated with a dysregulated estrus cycle and marked morphological disruptions in reproductive organs, including the ovaries and uterus. This points to a complex interplay between Mfn2 function and hormonal regulation, one that may operate through lipid availability, given the central role of lipids in steroidogenesis and estrogen-related metabolic pathways.

Together, these findings reveal a sex-dependent dimension of Mfn2 biology in the liver, with implications for understanding MASH heterogeneity and the hormonal factors that shape its progression.

Keywords:

Liver, Mfn2, Mitochondria, MASH

O-067

Metabolic plasticity and therapy resistance in glioblastoma

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During last years, a great amount of effort has been dedicated to elucidate the crosstalk between cellular metabolic and bioenergetic flows with signaling processes, and how this interaction contributes to coordinate the growth and homeostasis of cells and tissues. Particularly, how these interaction mechanisms are deregulated in cancer at the molecular and cellular level is a matter of intense research, with the aim of using this knowledge to propose new therapeutic alternatives. Our research has established the processes of interaction between the metabolism of the amino acid glutamine, the most abundant in human blood and the most important from an energetic point of view for cells, with cell signaling via the mTOR pathway, a protein complex essential in the regulation of cell growth and metabolism, and autophagy. More recently, we focused our research on metabolic adaptation associated to therapy resistance in glioblastoma (GBM), one of the tumor types with the poorest survival outcomes. This work resulted in the identification of FGFR1 pathway as a major regulator of the signaling and metabolic rewiring associated with temozolomide (TMZ) resistance in GBM. Hence, we described a mechanism of resistance that operates at two major levels. First, a p53-mediated regulation of cell cycle inducing cell cycle arrest to allow DNA repair in response to TMZ. And second, a complete metabolic rewiring promoting lipid catabolism and preventing lipid peroxidation. Both the p53-mediated response and the metabolic adaptation are controlled by FGFR1, as inhibition of the FGFR1 pathway completely abolishes this signaling and metabolic reprogramming, restoring sensitivity to TMZ. Our results also indicated a correlation of FGFR1 activity with poor prognosis in GBM patients, and validated the treatment of TMZ in combination with FGFR1 inhibitors as an efficient strategy to induce tumor cell death in pre-clinical animal models. This data position the receptor FGFR1 as a very promising candidate for evaluation in future clinical approaches to limit the development of therapy resistance to TMZ in GBM patients.

Keywords:

Metabolic Plasticity, Therapy Resistance, Glioblastoma

O-068/P-091

Stage-Dependent Role Of The Succinate-SUCNR1 Axis In Metabolic Dysfunction-Associated Hepatocellular Carcinoma

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Succinate is considered an oncometabolite in several cancers, but its extracellular effects through its receptor SUCNR1 remain poorly explored. Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, with metabolic dysfunction-associated steatotic liver disease (MASLD) emerging as a major risk factor. Here, we studied the role of the succinate/SUCNR1 axis in MASLD-related HCC.

In humans, SUCNR1 expression was significantly lower in tumoral versus paired non-tumoral liver from HCC patients, while higher expression in adjacent non-tumoral liver correlated with poorer survival rate. Similarly, hepatic Sucnr1 expression was reduced in murine MASLD-HCC models,

particularly within tumoral areas.

In a Western diet + CCl₄ model, Sucnr1 expression showed dynamic regulation during disease progression, with early upregulation during liver injury followed by downregulation upon HCC development, supporting a stage-dependent role of Sucnr1.

To investigate the role of hepatocyte SUCNR1, we used hepatocyte-specific Sucnr1 KO mice subjected to DEN+CDAHFD-induced HCC. KO mice showed reduced expression of HCC-related genes, increased CD3+ T-cell infiltration, and reduced Ki-67 and PD-L1 expression. Proteomic analysis revealed alterations in steroid, retinol, and arachidonic acid metabolism pathways.

In vitro, stable SUCNR1 overexpression in HepG2 cells enhanced migration and clonogenicity, effects potentiated by succinate stimulation and reversed by SUCNR1 antagonism. Moreover, SUCNR1 overexpression increased HIF1A, PDK1, and LDHA expression and enhanced mitochondrial respiratory capacity.

These data support a model in which SUCNR1 exerts a stage-dependent role in liver disease and identify the succinate/SUCNR1 axis as a key regulator of MASLD-related HCC progression.

Keywords:

MASLD-Related HCC, Succinate, SUCNR1, Metabolic Reprogramming, Hepatocarcinogenesis, Immunomodulation

O-069/P-092

Adipose-Derived EVs From High-Risk Prostate Cancer Patients Remodel The Tumor Transcriptome And Microenvironment

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Background: The periprostatic adipose tissue (PPAT) is an active player in prostate cancer (PCa) progression, partly through the release of extracellular vesicles (EVs). However, it remains unclear whether the EVs derived from the PPAT of patients with different levels of PCa aggressiveness exert distinct tumorigenic effects.

Methods: EVs were isolated from the PPAT of low-risk (ISUP I-II, n=12) and high-risk (ISUP III-V, n=12) PCa patients and characterized by TEM, NTA, and WB. PCa cell lines (22Rv1, LNCaP), macrophages (THP-1), and endothelial cells (HUVECs) were stimulated with risk-stratified EVs to evaluate their effect on proliferation, migration, transcriptomic profiles, inflammatory cytokines, and endothelial tube formation.

Results: Low-risk EVs increased PCa cell proliferation and induced a pro-inflammatory macrophage phenotype, characterized by increased IL1B and TNF expression. Conversely, high-risk EVs promoted cell migration, attenuated macrophage inflammation, and enhanced angiogenesis in HUVECs, as evidenced by enhanced tube formation and VEGFA upregulation. Transcriptomic analysis revealed that high-risk EVs uniquely dysregulated 146 genes in LNCaP (FDR<0.05, |FC|>2), a signature absent following low-risk EV stimulation. This transcriptional signature was enriched in oncogenic pathways linked to cell cycle, myeloid immunity, and angiogenesis.

Conclusion: PPAT-EVs drive PCa progression in a risk-dependent manner. High-risk EVs reshape the tumor transcriptome toward aggressive pathways and create an immunosuppressive, pro-angiogenic niche, whereas low-risk EVs trigger proliferative and inflammatory programs. Targeting high-risk EV cargo may represent a therapeutic opportunity within the tumor microenvironment.

Funding:

AECC Project Ref: PRYES246650RODR.

Keywords:

Extracellular Vesicles (EVs), Periprostatic Adipose Tissue (PPAT), Prostate Cancer, Tumour Microenvironment.

O-070/P-093

Proteomic And Functional Analysis Of SLC8A1 In Colorectal Cancer Progression And Metastasis

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Colorectal cancer (CRC) is a major contributor to cancer mortality worldwide. The prognosis of CRC significantly depends on stage at diagnosis, emphasizing the urgent need for novel prognostic methods. Recent proteomics analyses have identified SLC8A1 (Solute Carrier family 8 member A1) as a novel and barely studied protein overexpressed in CRC. The aim of this work is to characterize the functional role of SLC8A1 in CRC progression and metastasis to get a better understanding of the CRC molecular biology, and to identify new potential diagnostic or prognostic biomarkers associated with CRC. The KM12 CRC cell model, composed of three isogenic cell lines with different metastatic capabilities, was used for stably silencing of SLC8A1 using shRNAs. *In vitro* cell-based assays (migration, adhesion, proliferation, and invasion) and *in vivo* experiments were performed to functionally elucidate the role of SLC8A1 in the disease. Furthermore, we performed DIA label-free quantitative proteomics to characterize the SLC8A1-associated proteome and its interactome via immunoprecipitation followed by mass spectrometry using an Orbitrap Astral. Functional *in vitro* and *in vivo* assays showed a decrease in the tumorigenic and metastatic properties of KM12 CRC cells upon SLC8A1 stable depletion. Proteomic analyses identified dysregulated proteins associated with SLC8A1 depletion and SLC8A1 interactors, which were involved in signaling pathways, focal adhesion formation, and mitochondrial activity. Collectively, this study demonstrates a key role for SLC8A1 in CRC progression and metastasis, and highlight its potential as novel biomarker and therapeutic target in CRC.

Keywords:

Colorectal Cancer, SLC8A1, Proteomics, Biomarker

O-071/P-094

METTL3-Mediated M6A Epitranscriptomic Remodeling In Human MASH

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing health concern due to its high prevalence and potential progression to steatohepatitis (MASH), fibrosis, and hepatocellular carcinoma. The methyltransferase METTL3, the primary enzyme catalyzing the epitranscriptomic N6-methyladenosine (m6A) modification, has emerged as a key regulator of lipid metabolism, inflammation, and hepatic fibrogenesis, leading to increased interest in its role in human MASLD.

Methods: We evaluated the expression of METTL3 by RT-qPCR and immunohistochemistry in liver biopsies from patients with different MASLD stages. Nanopore sequencing of mRNA was performed to assess transcriptome-wide m6A alterations. Human liver organoids (HLOs) derived from biopsies were exposed to palmitic acid (PA) to model MASLD-associated lipotoxicity. METTL3 was pharmacologically inhibited using STM2457 to evaluate its effects on

cell viability, hepatocyte injury, and expression of lipogenic genes.

Results: METTL3 expression was increased in patients with MASH at both mRNA and protein levels. Direct RNA nanopore sequencing revealed widespread epitranscriptomic remodeling in patients with MASH, characterized by an increased number of m6A-modified transcripts associated with metabolic pathways. In HLOs, PA treatment induced METTL3 expression, lipotoxic injury, and lipogenic gene expression, all of which were attenuated by pharmacological inhibition of METTL3.

Conclusions: Our findings demonstrate that MASH is associated with global m6A epitranscriptome remodelling and identify METTL3 as a key regulator linking epitranscriptomic alterations to lipotoxic liver injury.

Keywords:

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Metabolic Dysfunction-Associated Steatohepatitis (MASH), METTL3, M6A RNA Methylation, Epitranscriptomics, Lipotoxicity, Human Liver Organoids

O-072/P-095

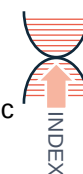
The Weakest Link: In Vivo And In Vitro Modeling Of TTN P.C3575S-Driven DCM

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Dilated cardiomyopathy (DCM) is a leading cause of heart transplantation, with less than 60% survival at 10 years. Although up to 35% of cases have a genetic origin, many remain unexplained due to the high number of variants of uncertain significance (VUS) in titin (TTN), the largest sarcomeric protein. Among the few TTN missense variants reclassified as pathogenic, p.C3575S is especially relevant. Located in the I21 domain, this mutation disrupts the hydrophobic core and strongly destabilizes the domain without altering its overall structure, suggesting a broader pathogenic mechanism for TTN VUS.

To investigate the causal role of p.C3575S in DCM, two complementary disease models have been developed. A CRISPR-Cas9 knock-in mouse carrying the equivalent mutation enables *in vivo* analysis of disease progression, while engineered heart tissues (EHTs) derived from homozygous hiPSC-cardiomyocytes provide a human platform to study





contractile function and sarcomeric organization *in vitro*. Preliminary data show that mutant EHTs undergo progressive thinning, tissue rupture under contraction, and weaker, faster, and more irregular beating than controls, indicating increased mechanical fragility caused by I21 destabilization.

Both models will also be used to evaluate therapeutic strategies aimed at restoring I21 stability, including pharmacological chaperones such as nanobodies and small molecules. Demonstrating a direct causal link between p.C3575S and DCM would support the reclassification of destabilizing TTN missense variants as pathogenic and could open new avenues for targeted therapies in a disease that currently lacks specific treatments.

Keywords:

Titin, DCM, EHT, In-Vivo, Missense, Destabilization, Nanobodies, Small Molecules

O-073/P-096

Hyperhomocysteinemia-Induced MiR-30d-5p Regulates TIMP3 And MMP9, Enhancing Atherosclerosis Progression

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Elevated homocysteine (Hcy) is a cardiovascular risk factor implicated in atherosclerosis, yet the contribution of microRNAs (miRNAs) to hyperhomocysteinemia (HHcy)-driven vascular damage remains poorly understood. miR-30d-5p is up-regulated in patients with HHcy and deep venous thrombosis (DVT), with TIMP3 identified as a potential target. Knowing that DVT shares common risk factors with atherosclerosis, in this study we aimed to determine whether

er HHcy-induced miR-30d-5p and regulates metalloproteinase inhibitor 3 (TIMP3) in atherosclerosis. Mouse and human macrophages exposed to Hcy showed increased miR-30d-5p and reduced TIMP3 expression. Luciferase assays confirmed TIMP3 as a direct target of miR-30d-5p. Moreover, miR-30d-5p overexpression enhanced MMP2 and MMP9 protein levels and activity, whereas its inhibition restored TIMP3. In ApoE^{-/-} mice supplemented with Hcy, atherosclerotic lesions were larger and displayed higher macrophage and miR-30d-5p content, reduced TIMP3, and increased metalloproteinase activity compared with controls. These findings indicate that miR-30d-5p downregulates TIMP3 and promotes MMP activation, uncovering a novel mechanism by which HHcy contributes to atherogenesis.

Keywords:

MicroRNA, MiR-30d-5p, Hyperhomocysteinemia, Atherosclerosis, Macrophages, Metalloproteinase Inhibitor 3 (TIMP3)

O-074/P-097

Mapping IGF Axis Gene Expression Across Human ARDS/COVID-19 Databases And Bleomycin-Induced Acute Lung Injury Mouse Models

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Background: Acute Respiratory Distress Syndrome (ARDS) and severe COVID-19 cause lethal respiratory failure with massive cellular and transcriptomic disruptions. The Insulin-like Growth Factor (IGF) system regulates tissue homeostasis, yet a comparative mapping of how components of the IGF axis are expressed across human autopsies and classic mouse models of acute lung injury (ALI) has been lacking.

Methods: We performed single-cell RNA-sequencing (scRNA-seq) data mining to map IGF genes in control vs. lethal COVID-19 human lungs, alongside bulk RNA-seq in healthy vs. bleomycin (BLM)-treated mouse lungs at day 3 post-injury. To determine how IGF1R influences the transcriptome after BLM challenge, bulk RNA-seq was performed on lungs of widespread *Igf1r*-deficient mice.

Results: scRNA-seq demonstrated that signaling receptors-*IGF1R*, *IGF2R*, and *INSR*-are ubiquitously expressed

across most pulmonary cell populations in both species. Conversely, *IGF1* is restricted to vascular smooth muscle cells, fibroblasts, and macrophages. *IGFBP* genes display distinct cellular niches, with *IGFBP4* present across stromal and endothelial cells and *PAPPA* predominating in fibroblasts. Following BLM injury in wild-type mice, bulk RNA-seq revealed strong alterations in IGF axis gene expression characterized by marked upregulation of *Igfbp3* and *Igfbp6*. Crucially, global *Igf1r* deficiency profoundly counter-regulated these transcriptomic shifts.

Conclusions: The IGF axis occupies specialized, cell-type-specific niches conserved between humans and mice. *Igf1r* depletion in BLM-challenged mice triggers a profound transcriptomic reversion of various aberrant IGF system genes, proving that the IGF axis actively coordinates the molecular landscape of acute lung injury.

Keywords:

IGF System, RNA Seq, Lung Transcriptomic, Bleomycin Mouse Model

O-075/P-098

GDF11-Associated SMAD2/3 Activation And Cell Cycle Arrest In Metabolic Dysfunction-Associated Steatotic Liver Disease

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum from simple steatosis (SS) to steatohepatitis (MASH), with incompletely understood progression mechanisms. GDF11 activates SMAD2/3 signaling and may regulate cell cycle arrest in hepatocytes, but its role in human MASLD remains unclear.

Objectives: To characterize hepatic transcriptomic and protein expression of cell cycle-related genes across MASLD stages, explore their expression in visceral adipose tissue (VAT), and evaluate circulating GDF11 as a non-invasive diagnostic biomarker.

Methods: Liver biopsies from 47 women with morbid obesity (NL n=8, SS n=22, MASH n=17) were analyzed by targeted RTqPCR of 13 cell cycle genes. VAT gene expression was assessed in a secondary cohort (n=22). p-Rb and SMAD2/3 protein levels were quantified by Western blot,

and circulating GDF11 by ELISA.

Results: All analyzed genes were significantly upregulated in MASH, with increasing transcriptomic heterogeneity across disease stages. Hepatic gene expression correlated positively with histological severity markers. At the protein level, p-Rb was significantly reduced in MASH, indicating G1/S checkpoint impairment, while total SMAD2/3 levels showed no significant variation. In VAT, most of genes were significantly upregulated in MASLD, and correlated with metabolic parameters and inflammatory markers. Circulating GDF11 showed no discriminatory capacity between histological groups.

Conclusions: MASLD progression involves transcriptomic dysregulation of the GDF11-SMAD2/3-cell cycle axis in both liver and VAT, with reduced Rb phosphorylation in MASH supporting impaired cell cycle control at advanced stages. Circulating GDF11 does not support its use as a non-invasive MASH biomarker.

Keywords:

MASLD, MASH, GDF11, Cell Cycle, P-Rb, SMAD2/3, Simple Steatosis, Obesity, Biomarker, Transcriptomics

O-076/P-099

Proteomic Identification Of Glaucoma Biomarkers In Eye-Derived Small Extracellular Vesicles

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Glaucoma is a major cause of visual impairment and blindness worldwide. Small extracellular vesicles (sEVs) can play an essential role in intercellular communication and molecular transport in eye. However, the proteomic profile of sEVs in glaucoma remains largely underexplored. This study aims to characterize the proteomic landscape of sEVs isolated from the aqueous humor of glaucoma patients, in comparison with cataract patients and healthy controls, as well as from retinal ganglion cells subjected to oxidative stress, a key factor in glaucoma pathogenesis.

sEVs were isolated using ultracentrifugation and characterized by nanoparticle tracking analysis and transmission electron microscopy. Proteomic profiling was performed by quantitative proteomics using an Orbitrap Exploris 480



mass spectrometer. Validation was performed using Western blot and ELISA. Functional assays were conducted using RNA interference and MTT assays.

Data analysis revealed 16 dysregulated proteins in aqueous humor sEVs from glaucoma patients, showing a ≥ 1.5 -fold change compared to those from cataract patients. In comparison with healthy controls, five proteins were identified as downregulated in glaucoma samples. Additionally, in retinal ganglion cells exposed to oxidative stress, 9 proteins were dysregulated. Validation of these dysregulated proteins using immunoassays confirmed the results obtained from mass spectrometry and the diagnostic potential of these proteins. Additionally, functional assays showed the contribution of these proteins to cell viability and response to oxidative stress.

Overall, this study provides new insights into the molecular mechanisms underlying glaucoma and may facilitate the identification of novel diagnostic biomarkers.

Keywords:

Small Extracellular Vesicles, Glaucoma, Proteomics, Oxidative Stress, Aqueous Humor, Biomarkers

O-077/P-100

The Synthetic Strigolactone Analog GR-24 Orchestrates Dual Vascular And Hepatic Protection: From Endothelial Anti-Inflammatory Response To Mitigation Of Pro-Steatosis Markers

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Background: Metabolic syndrome is characterized by the concurrent progression of vascular dysfunction and hepatic lipid dysregulation. Addressing both pathways simultaneously represents a significant clinical challenge. This study investigates the therapeutic potential of the synthetic strigolactone analog GR-24 in modulating these pathological landscapes.

Methods: We evaluated the effects of GR-24 in human endothelial cells under pro-inflammatory conditions and in hepatocyte models of lipid metabolism. Functional assays and molecular markers were analyzed to determine the compound's impact on inflammation and lipid homeostasis.

Results: Our results demonstrate that GR-24 exerts potent anti-inflammatory effects in human endothelial cells. Concurrently, in hepatic models, the compound significantly modulated key lipid metabolism enzymes, leading to a marked mitigation of pro-steatotic markers. Mechanistic insights reveal that these dual-protective effects are orchestrated through the crosstalk between NF- κ B and Nrf2 signaling pathways, shifting the cellular state toward vascular and metabolic homeostasis.

Conclusion: The synthetic strigolactone analog GR-24 displays a robust dual vascular-metabolic protective profile. By targeting both endothelial inflammation and hepatic lipid accumulation, GR-24 emerges as a promising therapeutic candidate for the management of metabolic syndrome-related pathologies.

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* These authors contributed to the work equally.

Keywords:

GR-24, Endothelium, Inflammation, Hepatocyte, Steatosis, Bioactivity

P-101

NLRP1 Activation As A Potential Strategy To Modulate Erythropoiesis In Polycythemia Vera

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Polycythemia Vera (PV) is a chronic myeloproliferative neoplasm characterized by excessive erythrocyte production, mainly driven by constitutive activation of the JAK2-STAT pathway. However, beyond JAK2 signaling, inflammatory and stress-related pathways may also contribute to the regulation of pathological erythropoiesis. The NLRP1 inflammasome is activated in response to ribotoxic stress induced by compounds such as anisomycin. Activation of NLRP1 has been linked to impairing erythropoiesis. Therefore, in this context, NLRP1 activation could act as a negative regulator of erythropoiesis production in diseases such as PV. Peripheral blood samples were obtained from 11 PV patients and 3 controls (Table 1).

PBMCs were isolated by Ficoll-Paque density gradient centrifugation and cultured using two complementary experimental approaches: methylcellulose-based colony-forming assays and liquid culture (Fig. 1). For colony-forming assays, 100,000 cells per condition were seeded in methylcellulose to assess erythroid colony formation and 1×10^6 cells in liquid medium for Wb, allowing evaluation of erythroid differentiation over time. Cells were collected at indicated days in figures.

Wb analysis in representative PV patients showed NLRP1 activation after anisomycin treatment (Fig. 2). Activation of NLRP1 reduced normalized erythroid colony formation across most sample groups, resulting in an overall mean reduction of approximately 62.1% compared with paired untreated controls (Fig. 3).

NLRP1 activation reduced erythroid colony formation in PV samples, suggesting that NLRP1-related cellular stress may reduce erythroid proliferation and differentiation. These preliminary findings support a potential role for NLRP1 as a modulator of pathological erythropoiesis in PV.

Keywords:

NLRP1, PV, Inflammatory, Activation

P-102

Decreased Serum Arginine-To-Ornithine Ratio As A Marker Of Advanced Fibrosis And Early Oncogenic Programming In Metabolic Dysfunction-Associated Steatotic Liver Disease-Related Hepatocellular Carcinoma (MASLD-Related HCC)

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading and rapidly growing cause of hepatocellular carcinoma (HCC). Resolving the underlying mechanisms linking advanced MASLD to HCC can pinpoint novel therapeutic targets and reliable markers for early detection.

Here, 3-month-old C57BL/6J male adult mice were given a Western diet (high-fat, high-cholesterol, and high-fructose diet) combined with low-dose 4-week interval intraperitoneal carbon tetrachloride (CCl₄) injections for 30 weeks, and compared to C57BL/6L control mice. A sub-group of animals was treated in the last 6 weeks of dietary intervention with an ammonia chelating agent: 0.81 mg/g body weight/ day of glycerol phenylbutyrate (GP) in the drinking water. At the end point, livers were collected for histopathological characterization, and serum amino acids were analyzed by LC-MS.



Western-diet-fed animals for 30 weeks exhibit histological features of metabolic dysfunction-associated steatohepatitis (MASH) (steatosis and inflammation) and marked bridging fibrosis. Likewise, this group of animals is characterized by increased hepatic transcriptional regulation of crucial oncogenic markers of HCC such as Cyclin B1 (*CCNB1*) and Cyclin D1 (*CCND1*). Treatment with GP significantly reduced liver fibrosis and decreased early oncogenic markers. Of relevance, our results highlight a highly significant negative correlation between these parameters and the serum arginine-to-ornithine ratio (AOr) ($r=-0.7169$ with fibrosis, $p=0.0003$; $r=-0.6174$ with hepatic *CCNB1*, $p=0.0029$; $r=-0.4697$ with hepatic *CCND1*, $p=0.0356$).

Taken together, our results suggest that serum AOr is a potential non-invasive biomarker of disease progression as well as response to treatment in experimental MASLD-related HCC.

Keywords:

Metabolic Dysfunction-Associated Steatotic Liver Disease, Arginine, Ornithine, Glycerol Phenylbutyrate, Liver Fibrosis, Hepatocellular Carcinoma

P-103

The AmyloGraph Amyloid-Antibody Database: Decoding Antibody-Mediated Modulation Of Amyloid Self-Assembly

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Notwithstanding the vast economic and time resources devoted over the last three decades in actively investigating treatments for neurodegenerative amyloidosis, their success remains scarce. Immunotherapies have shown substantial promise in reducing the pathologic and clinical signs of amyloidosis, a trend crystallised with the approval of the first disease-modifying treatments for Alzheimer's Disease (AD). Additionally, mAbs are in clinical trials for various amyloidoses with no current disease-modifying therapies, including Parkinson's Disease (PD), Huntington's disease or Amyloid light chain (AL) amyloidosis. Instead, multiple mAbs have shown insufficient results or are only

useful for certain disease stages, genotypes or phenotypes. Understanding the molecular mechanisms of why certain antibody therapeutics succeed and others do not could allow for increasing the success rate and decreasing economic burden for these incurable conditions. We have applied FAIR guidelines to develop two-step manual curation protocols, trained a machine-learning model for assistance in manuscript selection, introduced standardised guidelines for annotation and description of the data, and applied state-of-the-art large language model (LLM)-assisted curation to avoid data leakage to integrate previous knowledge into the first amyloid-antibody dedicated resource. We anticipate that the AmyloGraph Antibody Database will significantly advance the understanding of the mechanisms that underlie successful amyloid-targeting antibody therapeutics, thereby accelerating the development of more effective treatments for currently incurable amyloid diseases.

Keywords:

Antibody, Amyloids, Data Acquisition, Manual Curation, Machine Learning, Assisted Curation, Data Extraction, Amyloidosis, Monoclonal Antibodies, Protein Aggregation

P-104

Anti-Inflammatory Effects Of Wine Pomace Product In LPS-Stimulated Caco2 And TNF α -Induced HUVEC Models

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The intestinal epithelium is a selective and functional barrier that regulates nutrient absorption and provides protection. Its close interaction with the vascular endothelium promotes continuous barrier communication. The healthy properties of the polyphenols and other bioactive compounds in wine pomace are well known due to their antioxidant and anti-inflammatory effects. Therefore, this study aimed to evaluate the potential anti-inflammatory effects of a bioaccessible wine pomace product using a dual model of inflammation: Caco2 cells stimulated with LPS and HUVEC cells exposed to TNF α in a Transwell indirect co-culture system that allows communication only via secretory factors. To achieve this, Caco2 cells were seeded in the apical compartment above the Transwell inserts, while HUVEC cells were grown in the basolateral compartment above the well area. The bioaccessible fraction of wine pomace product was introduced to the apical compartment at a concentration of 2.5 μ g GAE/mL for 24 hours, after which the Caco2 cells were incubated with 5 μ g/mL of LPS and HUVEC with 1 ng/mL of TNF- α for 24 hours to induce inflammation. Antioxidant capacity (FC

and ABTS), cell viability (LDH leakage) and barrier integrity (immunofluorescence) were then evaluated. The wine pomace reduced LDH leakage and maintained actin cytoskeleton, thereby restoring cell viability and barrier integrity under inflammatory conditions. These were associated with increased levels of gallic acid, coumaric acid, catechin and epicatechin in the basolateral compartment, as well as increased total polyphenol and antioxidant capacities in both cell types. Overall, these findings highlight the potential of wine pomace products as functional ingredients in the prevention of inflammation-related disorders.

Keywords:

Bioactive Compounds; Antiinflammatory; Oxidative Stress

P-105

Improving The Effect Of Radiation-Induced DNA Damage On Cancer Cells Via Chronotherapy

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Cancer cells exhibit sensitivity to DNA-damaging agents such as ionizing radiation and various chemotherapeutic drugs. Recent research in our group revealed that the circadian protein CRY1 plays a crucial role in regulating the repair of DNA damage caused by these genotoxic agents. Remarkably, cancer cell lines lacking CRY1 exhibit reduced sensitivity to these treatments, which correlates with a poorer prognosis for the host according to analyses of patient databases. Additionally, our analysis of data from the University Hospital Virgen Macarena revealed differential responses to radiotherapy when administered at different times of the day in certain cancer types, including breast cancer. This variability may be attributed to circadian oscillation of CRY1 expression.

We are investigating the impact of CRY1 levels in various advanced breast cancer models, combining cellular models reflecting the differential status of cancer progression and organoids derived from those cellular models. Our preliminary results show that in coculture competition assays non-tumoral cells lacking CRY1 are more resistant to radiation, whereas premalignant cells are always more sensitive, regardless of CRY1 expression. Now, following these recent results in 2D culture, we are focusing on optimizing 3D assays. Through survival assays and analyses of DNA damage and repair, we aim to confirm CRY1 dependent differences in the response to radiation and reinforce its relevance in a more physiological context.

Keywords:

DNA Damage, Radiation Therapy, Homologous Recombination, Chronotherapy

P-106

Improving Radiotherapy By Using CRY1 As A Marker Of Time-Specific Irradiation

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Cancer cells exhibit sensitivity to DNA-damaging agents such as ionizing radiation and various chemotherapeutic drugs. Recent research in our group revealed that the circadian protein CRY1 plays a crucial role in regulating the repair of DNA damage caused by these genotoxic agents. Remarkably, cancer cell lines lacking CRY1 exhibit reduced sensitivity to these treatments, which correlates with a poorer prognosis for the host according to analyses of patient databases. Additionally, our analysis of data from the University Hospital Virgen Macarena revealed differential responses to radiotherapy when administered at different times of the day in certain cancer types, including breast cancer. This variability may be attributed to circadian oscillation of CRY1 expression.

We are investigating the impact of CRY1 levels in various advanced breast cancer models, combining cellular models reflecting the differential status of cancer progression and organoids derived from those cellular models. Our preliminary results show that in coculture competition assays non-tumoral cells are more resistant to irradiation when depleted for CRY1 contrary to the results obtained from premalignant cells. In non-tumorigenic and premalignant cocultures, we have observed that premalignant cells are more sensitive to irradiation regardless of the expression of CRY1 in either cell type.

Additionally, we are studying the role of CRY1 specifically in recombination-defective and treatment resistant cancer models. This way, we aim to elucidate if CRY1 expression can be exploited as a tool to further sensitize these cancers to first-line cancer treatments such as radiation therapy and PARP inhibitors.

Keywords:

DNA Damage, Radiation Therapy, Homologous Recombination, Chronotherapy



P-107

Are Klotho Proteins Useful Biomarkers For Mineral Metabolism Dysregulation In The Elderly?

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BACKGROUND Understanding how α and β -klotho relate to mineral metabolism may help identify individuals at risk of age-related decline and uncover potential therapeutic targets, as they have been linked to altered mineral metabolism, renal dysfunction and age-related metabolic disorders. This study aimed to evaluate klotho proteins association with mineral metabolism parameters in older adults. **METHODS** A prospective observational study was conducted in adults aged >65 years and approved by the Local Ethics Committee-Burgos Health Area (CEIC1446). α and β -klotho plasma concentrations were measured by ELISA (DY5334-05/DY5889-05, BioTechne, MN, USA). Statistical analyses were performed with SPSS Statistics 29.0. Significance was set at $p < 0.05$. **RESULTS** 283 old adults (150 women) were included (mean age 76 years). Mean plasma α and β -klotho concentrations were 513.13 ± 1464.28 and 956.52 ± 1095.01 pg/mL, respectively. A strong positive association between α and β -klotho was observed in women ($r = 0.665$, $p < 0.01$) and men ($r = 0.518$, $p < 0.01$). In women, α and β -klotho levels were inversely correlated with serum calcium ($r = -0.173$, $p = 0.043$; $r = -0.220$, $p < 0.01$, respectively). **CONCLUSIONS** The positive correlation between α and β -klotho in both sexes supports the existence of partially shared regulatory pathways. The inverse association

of both proteins with serum calcium in women suggests a sex-specific role of klotho in mineral metabolism during aging, consistent with evidence linking klotho pathways to FGF23-mediated calcium and vitamin D homeostasis. Further studies in hormonal and bone metabolism markers are needed to clarify mechanisms underlying these sex-specific associations and to assess the potential role of klotho proteins as biomarkers of age-related mineral metabolism dysregulation.

Keywords:

α -Klotho, β -Klotho, Mineral Metabolism, Calcium, Elderly, Aging

P-108

Sex-Dependent Effects Of Succinate-Modulated Adipose Tissue On Leptin Signaling And Cardiomyocyte Remodeling

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The adipo-vascular axis plays a central role in cardiometabolic disease by mediating communication between adipose tissue and the cardiovascular system. Metabolites such as succinate are emerging as important modulators of adipose endocrine activity, potentially influencing cardiovascular function through adipose derived signaling pathways. Here, we evaluated the effects of conditioned media (CM) from gonadal white adipose tissue (gWAT) explants of male and female rats treated with succinate or the SUCNR1 agonist cis-epoxysuccinic acid (cESA) on differentiated H9c2 cardiomyocytes. Rat gWAT explants were exposed to succinate (400 μ M) or cESA (100 μ M), and the resulting CM was used to stimulate H9c2 cells for 24 h. Leptin secretion and gene expression were assessed in CM and gWAT explants, respectively. Markers related to cardiac remodeling, oxidative stress, and mitochondrial dynamics were analyzed by RT-qPCR, while hypertrophic-like response was evaluated through the protein/DNA ratio. Male gWAT exhibited higher leptin expression and secretion than female tissue, with cESA further enhancing leptin production in males. CM from succinate-treated gWAT induced an early hypertroph-

ic-like response in cardiomyocytes from both sexes. Furthermore, treated H9c2 cells displayed altered expression of remodeling- and redox-related genes, together with increased Socs3 expression, suggesting activation of leptin signaling pathways. This response was accompanied by Endothelin-1 upregulation. Metabolic stimulation of adipose tissue enhances its endocrine activity, with male gWAT exhibiting a greater leptin secretory capacity. Adipose-derived factors released under succinate stimulation promote early pro-remodeling responses in cardiomyocytes.

Keywords:

Succinate, Adipose Tissue, Leptin, Cardiomyocyte Remodeling, SUCNR1, Cis-Epoxy succinic Acid (CESA), Endothelin-1

P-109

Differential Hepatic Metabolic Responses To Antiretroviral Treatment Under Palmitate-Induced Lipotoxic Conditions In A HepG2 Model Of MASLD

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People living with HIV present a higher prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), potentially influenced by antiretroviral treatment (ART). However, the mechanisms underlying ART-associated hepatic metabolic alterations remain incompletely understood. This study evaluated the effects of rilpivirine (RPV) and tenofovir alafenamide (TAF) on hepatocellular metabolic responses under basal and lipotoxic conditions.

HepG2 cells were exposed to increasing concentrations of RPV or TAF for 24 h and 48 h in the presence or absence of palmitate (0.5 mM). Markers related to lipid metabolism, mitochondrial function, oxidative stress, gluconeogenesis, and inflammation were analyzed by RT-qPCR and flow cytometry. Insulin pathway activation was assessed by Western blot following insulin stimulation (100 nM, 10 min).

ART induced drug- and context-dependent effects. TAF promoted a pro-dysmetabolic phenotype characterized by altered gluconeogenic signaling and impaired mitochondrial homeostasis, both under basal and lipotoxic conditions. RPV showed milder metabolic effects on mitochondrial biogenesis, oxidative stress, and lipid accumulation mainly under lipotoxic conditions. Additionally, TAF suppressed insulin-stimulated pathway activation under lipotoxic conditions, whereas RPV preserved the capacity to activate it.

RPV and TAF exert opposite effects on hepatic metabolic homeostasis in a MASLD *in vitro* model. RPV may support adaptive metabolic resilience and preserves insulin signaling, while TAF drives mitochondrial dysfunction and insulin resistance-like signaling. These findings reveal drug-specific metabolic liabilities of ART and support further investigation of their role in MASLD progression in people living with HIV.

Keywords:

Metabolic Dysfunction-Associated Steatotic Liver Disease, Antiretroviral Treatment, Hepatic Metabolism, Lipotoxicity, Mitochondrial Dysfunction, Insulin Resistance

P-110

Metabolic Adaptation Of Metastatic Breast Cancer Cells Is Governed By The GRK2-HDAC6 Axis

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Metastatic breast cancer (mBC) remains a major challenge. Despite favorable early-stage outcomes, metastatic recurrence is common and therapeutic options are limited. Understanding mechanisms underlying mBC progression is essential for improving treatments.

During metastasis, tumor cells encounter fluctuating nutrient availability, oxygen tension, and redox conditions, requiring metabolic rewiring and flexibility in fuel utilization and biosynthetic pathways. Protein phosphorylation and acetylation enable rapid cellular responses and support cancer survival. We demonstrated that GRK2 promotes breast cancer progression by modulating signaling pathways involved in cell proliferation, survival, and migration through direct phosphorylation of HDAC6, dependent on prior GRK2 phosphorylation at Ser670.

These findings led us to explore whether the GRK2-HDAC6 axis contributes to mBC progression. High GRK2 expression correlates with poor outcome, and both GRK2 levels



and Ser670 phosphorylation are enriched in metastatic lesions. Since metastasis is multistep, we investigated GRK2-HDAC6 in early survival of circulating metastatic cells. HDAC6-WT-expressing MDA-MB-231 cells display a more aggressive phenotype, while cells expressing the GRK2-phosphodeficient HDAC6-S3A mutant show enhanced survival, suggesting selective advantage from uncoupling GRK2-HDAC6 during circulation and/or early lung colonization. Metabolic analysis showed HDAC6-WT cells exhibit glycolytic, Warburg-like phenotype, whereas HDAC6-S3A cells rely more on mitochondrial oxidative metabolism, maintain redox homeostasis better, and display greater mitochondrial plasticity.

Our findings identify the GRK2-HDAC6 axis as a key regulator of metabolic reprogramming enhancing metastatic fitness in breast cancer.

Keywords:

Metastasis, Breast Cancer, Cancer Metabolism

notherapy target for Parkinson's disease previously unexplored, highlighting advances in structural biology and AI-driven protein design.

Keywords:

Parkinson'S Disease, Alpha-Synuclein, Antibodies, Artificial Intelligence, Therapies

P-112

Inducción Del Cotransportador Renal Na-K-2Cl (NKCC2) Y Modificación Del Patrón De Splicing En Una Línea Celular Epitelial De Origen Humano

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La función del cotransportador renal NKCC2 es crucial para el mantenimiento del balance hidroelectrolítico, siendo la diana de los fármacos antidiuréticos más empleados y estando involucrado en la fisiopatología renal y cardiovascular. Su regulación postransduccional es bien conocida. No tanto así su regulación transcripcional, debido en parte a la carencia de modelos *in vitro* que lo expresen de forma nativa. Aquí demostramos que la expresión de NKCC2, incluyendo el patrón de *splicing* alternativo, puede ser regulada farmacológicamente en una línea celular epitelial renal de origen humano (RPTEC). La expresión del mRNA para NKCC2 aumentó 3.6 veces respecto a células no tratadas. Más destacable fue el cambio en el patrón de *splicing* alternativo hacia variantes con una mayor afinidad por los iones, confirmando que es un mecanismo regulado por factores hormonales. El aumento en la transcripción se tradujo en un incremento similar de la proteína, observado por LC-MS, junto al de otras proteínas típicas del asa de Henle relevantes para su regulación (quinasas WNK). En Western blots la proteína inducida mostró un tamaño correspondiente al de la proteína madura glicosilada. A nivel de distribución subcelular, la proteína se observó exclusivamente en el compartimiento apical. Finalmente, se demostró un aumento en el transporte de rubidio inhibido por furosemida, confirmando que la proteína inducida es funcional. La inducción de NKCC2 nativa de forma controlada permitirá estudiar los mecanismos implicados en su regulación génica,

ca, en especial aquellos que controlan el patrón de *splicing* alternativo, y su relación con la regulación postransduccional, cerrando un vacío relevante para la investigación de la patología cardiorrenal.

Keywords:

NKCC2, Slc12A1, Asa De Henle, Diurético, Furosemida, Síndrome Cardiorrenal, Hipertensión, Síndrome Bartter

P-111

An Artificial Intelligence-Generated Monoclonal Antibody For Parkinson's Disease

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Parkinson's Disease (PD) is the second most common and fastest-growing neurodegenerative disorder, yet current therapies can only help manage early symptoms, but they do not slow or stop disease progression.

The characteristic loss of dopaminergic neurons in the substantia nigra of PD patients leads to motor symptoms like bradykinesia, tremors or rigidity. The principal pathological hallmark of PD is the accumulation of insoluble protein inclusions in the brain, named Lewy bodies, primarily composed of aggregated α -Synuclein (α Syn). During the amyloid aggregation process of α Syn a prefibrillar toxic intermediate is formed, the oligomer. α Syn oligomers are considered to be the most toxic species in PD accounting for in-brain propagation of the disease and homeostasis disruption. Our team has recently identified a structurally defined region only present in oligomeric species that mediates the oligomer-to-fibril conversion.

Using advanced artificial intelligence, we have developed a battery of antibodies that aim to specifically target this region and impair aggregate formation. So far, our results suggest that we have developed a first-in-class antibody able to selectively bind oligomeric forms as well as halt oligomer-to-fibril progression.

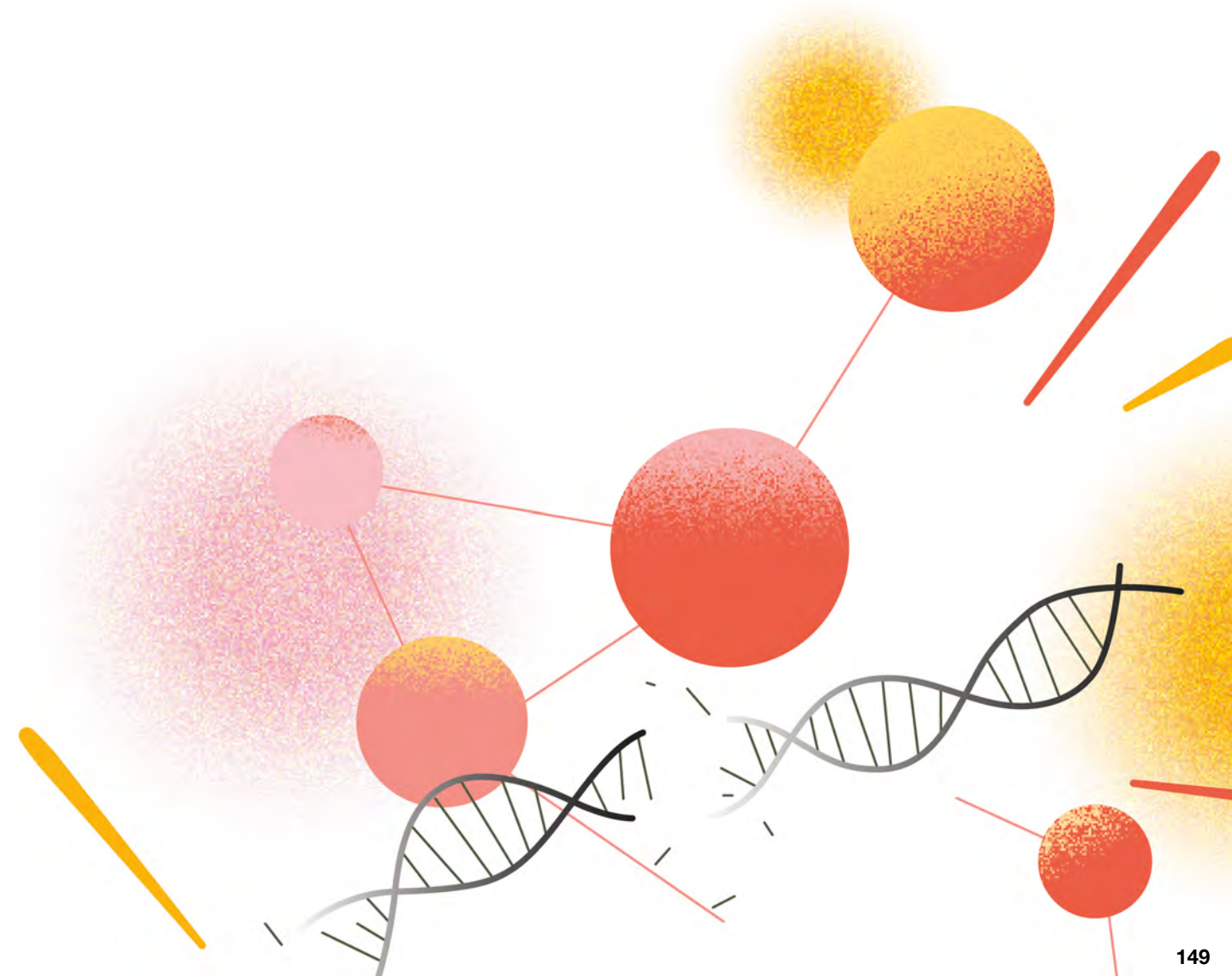
These results pave the way for a promising new immu-



GRUPOS CIENTÍFICOS DE LA SEBBM:

ESTRUCTURA Y FUNCIÓN DE PROTEÍNAS

9 DE SEPTIEMBRE





O-078

From Correlative Sub-Cellular Bioimaging At The Nano Scale To Serial Micro-Crystallography: The New Opportunities Of The ALBA Upgrade In Life Sciences

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ALBA is fully geared to its upgrade to a 4th generation synchrotron facility, ALBA-II, expected to deliver first light by 2031. Besides the photon source, ALBA-II includes the upgrade of the operating beamlines and the construction of new ones, which will altogether expand the user program and increase the scientific and societal impact with the provision of an integrative and multimodal platform at all relevant scales, from macromolecules to tissues.

We will review the two new beamlines, CALIMA and CORUS. CALIMA will be a highly automatized beamline enabling several bioSAXS techniques, including SEC, TR and 3D-scanning SAXS. CORUS, a 250-meter-long, flagship beamline, will feature two end-stations providing nanometric-sized beams for high-resolution imaging and elemental or chemical mapping. The first end-station (nanomag) will be dedicated to nano-tomography on tissues, while the second end-station (nanoFluoSpec) will focus on cryo-nano-fluorescence and spectroscopy on whole cells or lamella.

We will also review the significant upgrades of the operational beamlines. At the cellular and tissue levels, we will discuss the micron-beam of the phase-contrast hard X-ray tomography beamline FaXToR, the enhanced correlative studies using infrared spectro-microscopy beamline MIRAS, and new, dedicated full-field X-ray microscope of the soft X-ray microscopy beamline MISTRAL. At the macromolecular level, we will detail the instrumentation upgrades and the plans to implement serial methods and time-resolved studies in the macromolecular crystallography beamlines XALOC and XAIRA.

Last, not least, we will discuss the implementation of new services such as the crystallization and fragment-screening platforms, and the forecoming installation of a 300kV cryo-electron microscope.

Keywords:

Structural Biology, Synchrotron, Integrative Biology, X-Ray Microscopy, Correlative Techniques, Electron Microscopy, Infra-Red Spectromicroscopy, Neurobiology, Infectious Diseases

O-079

Integrated Structural, Computational, And Surface Biophysics Reveal The Mechanisms Of The P. Aeruginosa T6SS-Dependent Pore-Forming Toxin Tse5

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Background: Type VI secretion system (T6SS)-dependent Rhs polymorphic toxins encapsulate lethal payloads within a protective beta-barrel cocoon. How these massive effectors safely package and selectively deploy toxic cargo, avoiding premature deployment in the producer cell, remains a fundamental biological mystery.

Methods: We used an integrated structural, computational, and biophysical approach to study the *Pseudomonas aeruginosa* effector Tse5. This approach included 2.2 Å single-particle cryo-EM, planar lipid bilayer electrophysiology, QM/MM metadynamics simulations, Fast-Atomic Force Microscopy, and Neutron Reflectometry.

Results: Cryo-EM resolved a membrane-activated intermediate of Tse5 at 2.2 Å, revealing that target membrane docking serves as a thermodynamic trigger. This interaction forces the disordered C-terminal pore-forming toxin (Tse5-CT¹) to fold, initiating localized unzipping along a conserved lateral cleft in the cocoon. Electrophysiology showed that a conserved disulfide bond tethers the N-terminal PAAR-like fragment (Tse5-NT) to the payload. This bond acts as a “voltage-sensing leash,” restricting pore assembly to target membranes with a negative membrane potential and serving as an intra-bacterial fail-safe. QM/MM simulations elucidated the atomic-level chemical reactions driving autoproteolytic cleavage at the N- and C-termini. Real-time unzipping and membrane-leaflet remodeling were tracked using Fast-AFM and Neutron Reflectometry.

Conclusion: Our findings establish a self-contained paradigm for autonomous, voltage-regulated toxin deployment, providing a unifying structural and energetic framework for T6SS Rhs-family effectors.²

References:

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Keywords:

Type VI Secretion System (T6SS), Rhs Polymorphic Effectors, Cryo-EM, Pore-Forming Toxins, QM/MM, Surface Biophysics

O-080/P-113

Recognizing Tn And STn Epitopes In Protein Context

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Traditional antibody-based cancer therapies often struggle to precisely distinguish between healthy and cancerous cells, leading to significant side effects and reduced efficacy. Tumor-associated carbohydrate antigens (TACAs), such as Tn and STn, are cancer-specific markers with great therapeutic potential. However, designing monoclonal antibodies (mAbs) with high affinity and specificity for these antigens remains challenging, as most previous mAbs recognize glycans alone, rather than the combined glycan-protein epitopes (combotoxes) critical for cancer-specific targeting.

In this study, we solved the crystal structures of mAbs targeting Tn- and STn-modified glycoproteins. The analysis revealed a division of labor between VH and VL domains: VH primarily recognizes glycans, while VL binds to peptides. This synergy enables precise tumor targeting by recognizing both the glycan and its protein backbone. Additionally, we discovered that small mutations in VH CDR3 can switch binding preferences between bis-Tn and bis-STn O-glycans.

Leveraging these insights, we developed phage display libraries to selectively target Tn- and STn-modified MUC1 and CD43 glycoproteins. This approach enhances cancer-selective antibody therapies, providing a pathway to more precise and effective treatments with reduced off-target effects.

O-081/P-114

Structural Deciphering Of First Step Of Eukaryotic Arginine Synthesis: CryoEM Of Yeast N-Acetylglutamate Synthase(NAGS)/N-Acetylglutamate Kinase Metabolon Yields The First Structure Of An Eukaryotic NAGS, Shedding Light On Human NAGS And Its Defects

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NAGS, whose deficiency (NAGSD) causes clinical hyperammonemia, was the only human enzyme of unknown structure among those involved in arginine biosynthesis. In fact, no structure of any eukaryotic NAGS was known, possibly due to instability, well known for mammalian NAGS and yeast NAGS (yNAGS). In fact, yNAGS, even *in vivo*, only exists associated with its paralogous next-step enzyme, N-acetylglutamate kinase (yNAGK), forming with it a metabolon. Now we report cryoEM structures of this metabolon with and without its feed-back regulator arginine, at up to 2.7 Å resolution, revealing the first structure of an eukaryotic NAGS.

The *S. cerevisiae* metabolon, produced in *E. coli* from a duet plasmid and purified by Ni-affinity chromatography, was an octamer composed of 2:6 yNAGS:yNAGK chains, with yNAGS and yNAGK active and arginine-inhibited. Architecturally it was a closed dimer of tetramers, each resembling our reported (De Cima, 2012) structure of the yNAGK tetramer, except for substitution of one yNAGK subunit by a yNAGS subunit per tetramer. Both enzymes, presenting dual AAK-GNAT domain architecture (where AAK and GNAT domains are respectively catalytic in yNAGK and yNAGS) showed mutual structural differences, best exemplified by a large α-helix hairpin protruding from yNAGSs and linking both tetramers. Arginine, bound only to yNAGK, triggers changes on both enzymes. Our data rationalize NAGS stabilization, clarifies the integrated mechanism of metabolon regulation by arginine, and provides illuminating inferences on human NAGS structure and *in vivo* stabilization, and on NAGSD disease-causation by missense mutations.

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Keywords:

Urea Cycle, S. Cerevisiae, NAGS Deficiency, Bienzyme Complex, Arginine Synthesis, Aminoacid Kinase, GNAT Domain, Arginine Regulation

O-082/P-115

Structural Dynamics Driving The Precursor In NifEN Scaffold For Nitrogenase FeMo-Cofactor Assembly

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The **iron-molybdenum cofactor (FeMo-co)**, [MoFe₇S₉C-(R)-homocitrate], is the catalytic center of **molybdenum nitrogenases**, where dinitrogen reduction occurs. As one of the most complex metallocofactors found in nature, FeMo-co requires a dedicated biosynthetic pathway involving the coordinated action of multiple Nif proteins which can be summarized in three major steps. First, the precursor NifB-co [Fe₈S₉C], the core of FeMo-co, is synthesized by the radical S-adenosylmethionine (SAM) enzyme NifB through the coupling of two [Fe₄S₄] clusters and SAM-dependent carbide insertion. Subsequently, NifB-co is transferred by the carrier protein NifX to **NifEN, the central scaffold of FeMo-co biosynthesis**. At this key maturation stage, NifEN assisted by NifH, orchestrates a cofactor remodeling by the replacement of one iron atom by molybdenum and the incorporation of R-homocitrate, generating the mature FeMo-co. Finally, the cofactor is delivered by the

carrier protein NafY to apo-NifDK, containing P-clusters but no FeMo-co, enabling **nitrogenase activation**.

In this study, we investigated the FeMo-co biosynthetic pathway focusing on NifEN using **cryo-electron microscopy (cryo-EM)**. High-resolution structural analysis revealed a **dynamic maturation process** involving structural rearrangements, domain motions, and partial protein unfolding facilitating NifB-co transfer from the surface docking site into a specialized internal cavity for maturation. Furthermore, cryo-EM enabled the isolation of a NifEN subpopulation containing NifB-co in transit between both protein locations. These findings illuminate the dynamic mechanisms underlying FeMo-co assembly and emphasize the functional specialization of NifEN as the biosynthetic scaffold distinct from the catalytic NifDK component of nitrogenase.

Keywords:

Nitrogenase, Nitrogen Fixation, Metalloprotein, Metallic Cofactor, FeMo-Co, NifEN, Scaffold, Maturation, Cryo-EM.

O-083/P-116

Allosteric Control Of TIA-1 Phase Separation Via Phosphorylation-Induced β -Hairpin Formation

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In response to diverse harmful stimuli, eukaryotic cells generate cytoplasmic stress granules (SGs), mainly composed of mRNAs and RNA-binding proteins (RBPs). RBPs are fine-tuned by a diverse array of post-translational modifications (PTMs), with important consequences for the assembly, dynamics and clearance of SGs. One of the best characterized SG nucleators is the RBP T-cell intracellular antigen 1 (TIA-1), although knowledge about the structural and functional impact of its

identified PTMs is very limited. TIA-1 is organized into three RNA-recognition motifs (RRMs) and a C-terminal prion-related domain (PRD) that drives its phase separation from the cytosol. Here, we analyzed the effect of TIA-1 double phosphorylation in RRM3, at serines 198 and 199. Microscopic observations revealed an increased propensity of the phosphomimetic TIA-1 S198/199E to undergo liquid-liquid phase separation (LLPS) and self-assemble into SGs independently of stress stimuli. Our computational simulations, supported by NMR and SAXS data, have suggested that such phosphorylations promote the formation of a β -hairpin motif at the beginning of the PRD. Moreover, the ALS-associated mutation V283M in TIA-1 was predicted to lead to the formation of an aberrant structure in the β -hairpin region, highlighting the fine balance between physiological and pathogenic TIA-1 phase transition, and the importance of a better understanding of the molecular mechanisms underlying the liquid demixing of this RBP.

Keywords:

Amyotrophic Lateral Sclerosis, Liquid-Liquid Phase Separation, Post-Translational Modifications, Prion-Related Domain, RNA-Binding Proteins, Stress Granules

O-084/P-117

NLRP3 Acts As A Direct Sensor Of Cytosolic Potassium Ions

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The NLRP3 inflammasome is a sentinel of cellular homeostasis whose activation drives inflammation in infectious, cardiovascular, metabolic, and neurodegenerative diseases. Most NLRP3 activators induce potassium (K⁺) efflux, a key danger signal of compromised cellular integrity. However, how decreased intracellular K⁺ is translated into the conformational changes that promote inflammasome assembly, interleukin (IL)-1 release, and cell death has remained unclear. Here, we show that K⁺ levels directly regulate NLRP3 conformation. In cell-free lysates from cell lines

and primary blood immune cells, high K⁺ concentrations stabilized a compact, protease-resistant structure resembling inhibitor-bound NLRP3, whereas low K⁺ conditions or a K⁺ chelator promoted an open, flexible, and protease-accessible conformation. Human NLRP3 remained responsive to K⁺ when expressed in macrophage-like Drosophila cells or purified as recombinant protein, indicating that K⁺ sensing occurs independently of cellular cofactors and is consistent with direct ion coordination. Notably, the K⁺-independent NLRP3 agonist CL097 failed to reproduce the conformational transition induced by nigericin. In contrast, pathogenic gain-of-function NLRP3 variants constitutively adopted the open, protease-accessible conformation. Computational analyses suggested that K⁺ ions occupy the nucleotide-binding pocket of the FISNA–NACHT module and stabilize inactive oligomeric “cage” assemblies through interactions with the NACHT-adjacent acidic loop. Together, these findings support a model in which intracellular K⁺ directly restrains NLRP3 activation before efflux, identifying NLRP3 as a direct K⁺-sensing protein that responds to cellular danger through changes in intracellular K⁺ concentration.

Keywords:

NLRP3, Inflammasome, Potassium, Macrophage, Inflammation.

O-085/P-118

Structural And Functional Characterization Of Ligand Binding In The Rcs System From Salmonella

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Isolates of *Salmonella enterica* serovar Typhimurium are pathogenic enterobacteria that cause gastroenteritis. In *Enterobacteriaceae*, envelope stress is sensed by the conserved Rcs phosphorelay system inducing exopolysaccharide capsule production and repressing motility. Rcs system activation has been shown to occur mainly in non-host environments. The signal is transmitted from the inner membrane-associated receptors RcsC and RcsD to the cytosolic response regulator RcsB and is negatively regulated by in-



ner membrane protein IgaA and positively by the lipoprotein RcsF. The periplasmic regions of RcsC and RcsD contain double-CACHE domains, a large family of sensor domains known to respond to diverse ligands. However, the ligands recognized by the Rcs system remain unidentified.

We identified in RcsB and RcsD the binding of a divalent cation and characterized this interaction through structural and functional studies. Binding sites were identified by anomalous diffraction data collected from RcsB crystals and those corresponding to the periplasmic region of RcsD (RcsDP). Notably, the presence of the cation in RcsDP altered the oligomeric state, an effect that was also detected by size-exclusion chromatography. Dissociation constants for cation binding to each protein were determined, as well as for its effect on RcsD-RcsB complex formation.

Phenotypic assays were performed using a *S. Typhimurium* strain with partial loss of IgaA function and knockouts for endogenous *rcsB* or *rcsD* complemented with mutant variants in the corresponding binding sites. Mutants of RcsB impaired capsule production, while mutants of RcsD did not show differences from the wild type variant.

Overall, our results identified ligand binding in the Rcs system and suggest a role in capsule production.

Keywords:

Phosphorelay, Cation Binding, Crystal Structure, Double-CACHE, Rcs, Salmonella

O-086/P-119

Molecular Characterization Of A Mitochondrial Transmembrane Protein Involved In A Neurodegenerative Rare Disease

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Rare diseases affect a very low number of individuals (less than 5 in 10,000 in Europe), are difficult to diagnose, and the vast majority lack specific treatment. Shining light onto underlying molecular mechanisms can improve disorder identification and pave the way towards targeted orphan drug development. We are working with a supposedly hexameric and/or dimeric transmembrane protein, crucial for mitochondrial architecture, whose mutations lead to mitochondrial fragmentation, bioenergetic defects, and neurodegeneration at early stages in life. However, the precise molecular determinants that govern oligomerization, crucial for function, remain elusive.

In this project, we utilized crosslinking and crystallographic techniques to investigate the structural and oligomerization nature of a soluble fragment of the N-terminal domain, localized at the mitochondrial intermembrane space. It has been reported that a mutation could detrimentally affect oligomer formation, especially its dimeric form. Our findings reveal dimer formation and higher-order oligomers for both mutant and wild-type constructs, yet with distinct behaviour. Chemical crosslinking showed that, while the single-point mutation did not entirely abolish self-assembly, a shift in the dimer-to-oligomer ratio was observed, suggesting that mutant constructs allow for initial dimerization but prevent subsequent recruitment of monomers. Moreover, crystallization trials showed a high tendency to undergo liquid-liquid phase separation (LLPS), suggesting highly flexible interactions between these constructs. Ultimately, these insights demonstrate a novel structural mechanism at the basis of mitochondrial dysfunction characteristic of various orphan diseases, opening new paths for targeted orphan drug development.

Keywords:

Mitochondria, Neurodegenerative Disease, Protein Crosslinking, Macromolecular Crystallography

O-087/P-120

Enhanced Dual Inhibition Of PDE1 And PDE4 By Trimethylated Resveratrol: Combined Experimental HPLC And Molecular Docking Insights

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Phosphodiesterases (PDEs) regulate intracellular cyclic nucleotide signaling and represent key therapeutic targets in inflammation. Among them, PDE1 and PDE4 play critical roles in modulating cAMP levels. In this study, we evaluated the effect of structural modification of resveratrol (RSV) through trimethylation, yielding 3,4,5'-trimethoxy-trans-stilbene (TMS), on its inhibitory activity against PDE1 and PDE4.

An HPLC-based method was optimized to quantify cAMP hydrolysis and determine inhibitory parameters. Kinetic analyses confirmed different substrate affinities between isoenzymes, with PDE4 showing higher affinity. Inhibition assays revealed that RSV exhibits low potency, while TMS significantly improves activity, increasing potency ~4-fold for PDE1 and ~8-fold for PDE4. However, both compounds remain less potent than roflumilast, whose activity lies in the nanomolar range.

Molecular docking showed that RSV, TMS, and roflumilast bind to the same catalytic pocket, interacting with conserved residues such as glutamine. The improved activity of TMS is attributed to better adaptation to the hydrophobic active site, enhancing ligand-enzyme interactions.

Overall, trimethylation enhances the inhibitory capacity of resveratrol derivatives, supporting their potential as dual PDE modulators and highlighting the value of combining experimental and computational approaches.

Acknowledgement

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Keywords:

Resveratrol, Phosphodiesterases, PDE1, PDE4, Molecular Docking

O-088/P-121

Revising The Carboxysome Paradigm: A Self Remodeling Organelle With Exchangeable Shell Components

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Carboxysomes are proteinbased bacterial microcompartments that encapsulate RuBisCO and carbonic anhydrase and drive about 1/3rd of the global CO₂ fixation. They are generally depicted as rigid, architecturally stable shells. Here we show that carboxysomes are instead intrinsically dynamic assemblies. By independently labeling purified carboxysomes with distinct fluorophores and analyzing mixed populations by flow cytometry, we observe the rapid appearance of doublepositive particles, demonstrating interparticle exchange of shell components through continual partial disassembly-reassembly. This structural plasticity likely enables limited protein turnover and shell renewal, features that would be essential for maintaining permea-

bility, repairing damage, and sustaining high carbonfixation efficiency over the cell cycle. Our findings redefine carboxysomes as selfremodeling organelles rather than static containers, with direct implications for understanding the robustness of bacterial CO₂ fixation and for engineering nextgeneration BMCbased synthetic organelles.

Keywords:

Carboxysome, CO₂ Fixation, Cyanobacteria, Protein Exchange, Dynamic Systems

P-122

Altered Photochemical Pathway As A Molecular Mechanism Of Inherited Retinal Degeneration In M39R Rhodopsin

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Rhodopsin is a light-sensitive G protein-coupled receptor expressed in rod photoreceptor cells and responsible for scotopic vision at dim-light intensities. Its function is to initiate the phototransduction cascade upon light stimulation, converting light stimuli into neural signals in the complex process of vision.

Mutations in rhodopsin have been associated with retinitis pigmentosa (RP), a heterogeneous group of inherited retinal disorders that lead to photoreceptor degeneration. Sector RP is a clinical subtype of RP characterized by localized retinal degeneration. The M39R rhodopsin mutation, in transmembrane helix I of the receptor, has been clinically associated with sector RP but the molecular mechanism of this phenotype is elusive.

In this study, we investigated the biochemical and photochemical properties of the M39R variant in comparison with wild-type rhodopsin. To this aim, rhodopsin was immunopurified from retinas isolated from *Rho*^{WT} and *Rho*^{M39R} mice. UV-visible spectroscopy revealed that the M39R mutant displayed an altered response to light stimulation, associated with a modified photointermediate pathway. This photointermediate change was characterized by reduced stability and faster decay of the Meta III conformation. Moreover, fluorescence spectroscopy demonstrated an accelerated release of all-*trans*-retinal in the M39R mutant, consistent with the observed Meta III decay features.

These findings indicate that the M39R mutation alters the normal photointermediate pathway of rhodopsin upon photoactivation, promoting a premature release of all-*trans*-ret-



inal. The lack of proper recycling and accumulation of this retinal isomer -known to be toxic to rod cells- may contribute to the pathogenic mechanism associated with sector RP.

Keywords:

Rhodopsin, Retinitis Pigmentosa, Photointermediate, Protein Conformational Stability, Inherited Retinal Disease

tor selectivity and to guide the rational design of selective MLK3 inhibitors with therapeutic potential in ALS.

Keywords:

Amyotrophic Lateral Sclerosis, MLK3, TTBK1, X-Ray Crystallography, Kinase Inhibitors, Selectivity

P-124

Integrating And Validating Experimental And Computational Information In Cryo Electron Microscopy

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Cryo Electron Microscopy (cryo EM) is expanding its capacity to provide information on large structural ensembles, opening many interesting avenues but also posing complex issues: First, methods in this area are still largely evolving, implying that they remain inaccurate and difficult to compare. Second, cryo EM typically provides information in the form of “maps”, quasi-atomic resolution “volumes” that then have to be modelled in terms of atomistic features (structural models). This is different from the information provided by approaches such as Molecular Dynamics or structural predictions, which are directly expressed as atomic models. In much the same way, it is difficult to devise ways to co-project these two types of information. As a first step towards information integration, we present in this communication FlexConsensus (Herreros et al., Nat. Methods, 22:2118, 2025), which, through a combination of different deep learning steps, provides consensus capabilities across different methods and representation forms.

Keywords:

Cryo Electron Microscopy, 3DBioinformatics

P-123

Structural Characterisation Of Kinase–inhibitor Complexes To Guide The Design Of Selective MLK3 Inhibitors As Neuroprotective Agents For ALS

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterised by motor neuron degeneration and its limited therapeutic options. Mixed-lineage kinase 3 (MLK3) plays a key role in stress-induced MAPK signalling associated with neuroinflammation and neuronal cell death, making its inhibition a promising neuroprotective strategy. Compounds previously identified and synthesised to target Tau tubulin kinase 1 (TTBK1), while avoiding TTBK2 due to its role in ciliogenesis, also display activity toward MLK family members, suggesting shared structural determinants of ligand recognition and further validating MLK3 as a therapeutic target in ALS.

To characterise these interactions at a structural level, we generated purified kinase domains of TTBK1, TTBK2, MLK1 and MLK3. The TTBKs were expressed and purified from bacterial systems, and 8 crystal structures of TTBK1 in complex with inhibitors have been determined, 5 of which show clear ligand density at the hinge region. These structures reveal conserved binding modes within the ATP-binding pocket and provide a template for rationalising inhibitor binding across MLK family members. MLK1 and MLK3 were successfully expressed using Sf9 insect cells and HEK cells. Crystals were obtained and resulted in one resolved MLK1 structure, and current efforts are focused on improving crystal quality and diffraction.

Structural findings are being integrated with biochemical inhibition data to guide inhibitor optimisation, and complementary thermal shift assays have shown that selected compounds can stabilise the target proteins. Overall, this work aims to provide structural insights into kinase inhibi-

P-125

TIA-1 Linker Phosphorylation Between N-Terminal RRM Controls Nucleic Acid Binding And Phase Separation

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T-cell intracellular antigen 1 (TIA-1) is an RNA-binding protein involved in RNA translation, splicing, and stress granules (SGs) assembly during eukaryotic stress response.¹ SGs are dynamic RNA-protein condensates that protect untranslated mRNAs from degradation. Altered SG dynamics have been linked to neurodegenerative diseases, including amyotrophic lateral sclerosis, frontotemporal dementia, and tauopathies, where impaired SG disassembly may promote aggregation of SG-associated proteins and pathological inclusions.²

Mutations in the prion-like domain of TIA-1 alter liquid-liquid phase separation (LLPS) and promote aggregate accumulation that disrupts cellular homeostasis.³ TIA-1 LLPS is further enhanced by binding to multivalent nucleic acids and Zn²⁺ ions, which also protect against fibrillar aggregation.^{4,5} Moreover, phosphorylation at Ser198/199 allosterically modulates LLPS, highlighting post-translational modifications as regulators of TIA-1 condensation.⁶

Here, we combined cellular, biophysical, and molecular dynamics approaches to study the effect of Thr83 phosphorylation, located between RNA-Recognition Motifs 1 and 2, on TIA-1 LLPS and nucleic acid binding. Our results show that Thr83 phosphorylation induces LLPS both *in vitro* and *in vivo*, even in the absence of stress or nucleic acids, and reduces TIA-1 affinity for DNA, providing new insights into the regulation of TIA-1 LLPS and its potential role in disease mechanisms.

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Keywords:

Post Translational Modifications, Liquid Liquid Phase Separation, RNA Binding Proteins, Stress Granules

P-126

Deciphering The Structural Plasticity Of A Yeast Repressor: From Nuclear Co-Repression To Mitochondrial Stress Response

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Under basal conditions, a key *Saccharomyces cerevisiae* transcription factor resides in the nucleus, where it complexes with the Ssn6 co-repressor to inhibit target gene expression. However, upon mitochondrial protein import impairment, this factor undergoes a critical relocation to the mitochondria. In this work, we explore the structural conformation of this repressor using limited proteolysis and Small-Angle X-ray Scattering (SAXS), evaluating its flexible architecture, which contains a structured DNA-binding HMG-box domain and intrinsically disordered regions (IDRs). Furthermore, we examine its propensity to undergo liquid-liquid phase separation (LLPS) in both the presence and absence of DNA, providing new insights into its macro-molecular behavior.

Keywords:

Saccharomyces Cerevisiae, Transcription Factor, Mitochondrial Stress, Nuclear Co-Repression, Small-Angle X-Ray Scattering (SAXS), HMG-Box Domain, Intrinsically Disordered Regions (IDRs), Liquid-Liquid Phase Separation (LLPS), Structural Plasticity

P-127

Structural Insights Into A Conserved Mechanism Of Choline Translocation Through CHT

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Choline is an essential nutrient critical for cellular homeostasis across all domains of life. In humans, choline uptake in cholinergic neurons for its recycling into acetylcholine is mediated by the high-affinity Na⁺-dependent transporter SLC5A7 (CHT1). Prokaryotes also depend on choline as



an osmo-protectant and as metabolite, raising the possibility that bacteria also possess choline transporters akin to CHT1. Here, we identify and characterize a bacterial Na⁺-dependent choline transporter (sfCHT) with high sequence identity to CHT1. Cryo-EM structures of Na⁺- and choline-bound sfCHT reveal a LeuT-fold architecture with Na⁺ coordination geometry similar to CHT1. Captured in an inward-facing conformation, in sfCHT choline is found at a site near the cytoplasmic side. Computational analysis and transport assays of sfCHT and CHT1 variants reveal local conformational rearrangements in conserved residues along a defined pathway to the cytosolic site. These findings provide structural and mechanistic insights into intracellular choline transition suggesting an evolutionarily conserved mechanism between the bacterial and human choline transporters.

Keywords:

Choline Transporter (CHT), Cryo-EM, LeuT-Fold, Choline Translocation, Evolutionary Conservation, Inward-Facing Conformation, Cytoplasmic Binding Site, SLC5A7

P-128

Targeted Glycoproteomics Identifies A REG1 Glycopeptide Signature Associated With Pancreatic Cancer

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Pancreatic adenocarcinoma (PaC) has a poor prognosis due to late diagnosis and resistance to current therapies, making the identification of noninvasive biomarkers essential. Regenerative protein 1 (REG1) is a glycoprotein overexpressed in PaC and detectable in serum. Since altered glycosylation is a hallmark of malignancy, tumour-associated glycoforms of REG1 may improve diagnostic specificity.

Recombinant REG1 O-glycoforms were characterised by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry. Subsequently, a liquid chromatography-mass spectrometry method based on hydrophilic interaction liquid chromatography, electrospray ionization and triple quadrupole (HILIC-ESI-TQ) was devel-

oped to quantify REG1 glycopeptides from immunopurified serum. This method was applied to 94 serum samples from PaC patients and control groups.

MALDI-TOF analysis of REG1 glycoprotein and glycopeptides identified 16 O-glycan structures, including Tn, STn, sialylated core 1 and disialylT, alongside the non-glycosylated protein. However, as MALDI-TOF lacked sufficient sensitivity for serum samples analysis, quantification was performed by HILIC-ESI-TQ. PaC samples showed a significant increase in five REG1 glycopeptides, including Tn and disialyl-T structures, compared to controls. Their combination showed strong potential as a PaC biomarker, yielding an area under the curve (AUC) of 0.883. These glycan changes are consistent with the overexpression of sialyltransferases ST3GAL1 and ST6GALNAC1 in tumour cells.

In conclusion, this research points out that five REG1 glycopeptides are significantly increased in PaC serum samples. Their performance, particularly when combined, revealed their promising potential as non-invasive biomarkers for PaC diagnosis.

Keywords:

Biomarkers, Glycosylation, Mass Spectrometry, Pancreatic Cancer, REG1

P-129

The Co-Translational Step-By-Step Birth Of The SAGA Deubiquitinating Module

Estructura y función de proteínas / Regulación de la expresión génica y dinámica del genoma

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The mechanisms by which functional modules of large transcriptional coactivator complexes are assembled *in vivo*, and how these pathways influence their organization and activity, remain poorly understood. The SAGA coactivator complex offers a powerful framework to address this question due to its modular organization and detailed structural and functional characterization. However, the precise pathway governing the assembly of its 19 subunits in cells remains undefined.

Using ribosome-associated immunoprecipitation, genetic perturbations, and protein interaction analyses, we delineate the assembly mechanism of the yeast SAGA deubiquit-

inating (DUB) module. We demonstrate that its biogenesis relies on a defined series of directional, co-translational interactions. Additionally, our data show that co-translational engagement differentially contributes to subunit stability.

Finally, our data indicate that the DUB module itself constitutes an assembly intermediate prior to its incorporation into SAGA and that module capture by the SAGA core occurs post-translationally.

Keywords:

Co-Translational Assembly, SAGA Complex, Deubiquitination Module, Ribosome-Associated Interactions, Directional Assembly, Protein Stability, Transcription Regulation

P-130

Endocytic Vesicular Trafficking Promotes Tolerance To Salt And Heavy Metal Stress In Solanum Lycopersicum (Tomato)

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Under salinity or heavy metal stress conditions, endocytosis and pre-vacuolar vesicle trafficking can play very important role, since both the removal of transporters and ion channels from the plasma membrane and the compartmentalization of toxic ions require the formation of vesicles, which can be maintained as multivesicular bodies, or be fused to the central vacuole. In the regulation of this vesicular traffic system, two large protein superfamilies are key components: RabGTPases and SNAREs proteins. In previous work, we have shown that the individual expression of *SchRabGTPaseG3e*, *SchRabGDP1* (a GDP dissociation inhibitor associated with RabGTPases), and SNARE proteins such as *SISNAP33* and *SIVAM721* confers salt tolerance in *Arabidopsis thaliana* and *Solanum lycopersicum* var. Monemaker. Here, we show that co-expression of these genes, driven by the root-specific promoter in tomato, confers greater salinity tolerance and higher productivity under saline stress compared to wild-type (WT) and empty-vector transformed plants (EVTP). Triple and quadruple-transgenic genotypes accumulated approximately 40% and 50% less sodium in their leaves, respectively, compared to WT and EVTP plants grown at 250 mM NaCl. In addition, these transgenic plants show a high accumulation of sodium in their vacuoles and multivesicular bodies of the root cells. Furthermore, the overexpressing genotypes showed a greater number of fruits, which were heavier, larger in di-

ameter, and had a greater number of seeds compared to the WT and EVTP. On the other hand, when these same overexpressing genotypes are exposed to heavy metals, also greater tolerance is observed, confirming the key role of endocytic vesicular trafficking in abiotic stress tolerance.

Funding: ANID-FONDECYT No. 1241609 and 1211180

Keywords:

Tomato, Abiotic Stress, Salt, Heavy Metals

P-131

From Order To Disorder: Structural Insights Into The C-Terminal DNA-Binding Domain Of Nucleophosmin In Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is a genetically heterogeneous hematological malignancy responsible for a substantial portion of leukemic deaths worldwide. Among the recurrent genetic drivers, mutations in nucleophosmin (NPM1) highlights for being present in nearly one-third of adult patients. NPM1 is a key nucleolar protein that establishes a complex network of interaction with nucleic acids and protein partners. However, frameshift mutations affecting its C-terminal DNA binding domain disrupt this contact network and causes the unfolding of this domain, leading to NPM1 aberrant cytoplasmic localization. However, despite the advances in the development of targeted therapies, current strategies often fail to consider the defective folding of the DNA-binding domain which supports the need for drugs to selectively target it. In this work, we characterize the structural properties of the C-terminal DNA binding domain of NPM1 in the context of AML using both *in silico* and *in vitro* approaches and elucidate its functional impact on DNA binding and ability to undergo liquid-liquid phase separation (LLPS), thereby providing a structural framework for the rational design of targeted therapies for NPM1-mutated AML.

Keywords:

Acute Myeloid Leukemia, G-Quadruplex, Liquid-Liquid Phase Separation, Molecular Dynamics, Nucleophosmin



P-132

Towards Understanding The Assembly Of The Yeast Translation Initiation Multifactor Complex

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Protein synthesis begins with translation initiation, the most tightly regulated stage of the process. In eukaryotes, accurate recognition of the AUG start codon requires the coordinated action of several eukaryotic initiation factors (eIFs), including eIF1, eIF3, eIF5 and the eIF2 ternary complex (eIF2-GTP-Met-tRNAiMet). Prior to ribosome recruitment, these factors associate to form the multifactor complex (MFC), a key intermediate in translation initiation whose molecular organization remains incompletely understood.

Although interactions among initiation factors have been extensively studied within the ribosomal pre-initiation complex, the architecture and assembly pathway of the free MFC are still largely unresolved. To address this question, we combined complementary biophysical and biochemical approaches, including mass photometry and native mass spectrometry, with structural biology techniques such as electron microscopy.

Our analyses reveal an unexpected role for eIF5 in MFC organization and suggest that two copies of eIF5 participate in complex assembly. The data support a model in which one eIF5 molecule associates with eIF2β and eIF2γ, while a second eIF5 molecule interacts with eIF1 together with eIF3c. These findings provide new insights into the structural basis of MFC formation and advance our understanding of the early molecular events that govern translation initiation in eukaryotes.

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Keywords:

Multifactor Complex, Eukaryotic Initiation Factors, Translation Initiation, EIF5, 40S Ribosome, Electron Microscopy, Native Mass Spectrometry

P-133

A Distinct Domain Organization Of Cystathionine β-Synthase Underlies Cysteine And H2S Biosynthesis In *Pseudomonas Aeruginosa* And *Klebsiella Pneumoniae*

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Activation of the reverse transsulfuration pathway (RTP), the conserved metabolic route that allows the endogenous synthesis of cysteine (a precursor of glutathione) in most organisms from bacteria to humans, contributes to the survival and persistence of multidrug-resistant bacteria. The first step of this pathway, catalyzed by the enzyme cystathionine beta-synthase (CBS), plays a crucial role in maintaining redox balance and cysteine homeostasis, making it an attractive therapeutic target against multidrug-resistant infections. The specific inhibition of the RTP via CBS is not trivial, as this enzyme presents a wide variety of domain distributions, overall 3D architecture, and allosteric regulation along evolution, many of which remain poorly known so far. In this study, we demonstrate that both *Pseudomonas aeruginosa* CBS and *Klebsiella pneumoniae* CBS exhibit high responsiveness to the allosteric activator S-adenosylmethionine (SAM) and preferentially utilize O-acetylserine (OAS) as a substrate over serine (the main substrate in mammals). The crystal structure of PaCBS and the AlphaFold-2 model of KpCBS reveal for the first time a novel domain organization characterized by an inverted arrangement of the regulatory Bateman module relative to the catalytic core. These findings not only provide a structural and functional basis for the selective inhibition of CBS in multidrug-resistant pathogens, but confirms experimentally one novel and so far unknown three-dimensional fold of the CBS enzyme arising from a high-throughput AlphaFold analysis, that required experimental confirmation.

Keywords:

Cystathionine Beta-Synthase (CBS), Hydrogen Sulfide, MDR Bacteria, Transsulfuration Pathway, Oxidative Stress

P-134

Structural Characterization And Functional Reconstitution Of HLAT3

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LAT3 (SLC43A1) is a sodium-independent amino acid uniporter that mediates the facilitated diffusion of branched-chain amino acids and phenylalanine. It is overexpressed in prostate cancer, where it has been linked to mTORC1 signaling through leucine availability. However, as a facilitated diffusion system, LAT3 is predicted to operate bidirectionally, raising unresolved questions regarding its role in amino acid homeostasis and mTORC1 activation. Despite its biological relevance, no experimental structure is currently available.

We combined structural and functional approaches to characterize human LAT3. The transporter was heterologously expressed in HEK293 cells and purified to homogeneity. Single-particle cryo-EM analysis yielded a 3D reconstruction at 4 Å resolution, revealing a monomeric transporter architecture in an outward-facing conformation. An additional density is observed within the putative substrate-binding pocket, consistent with bound L-isoleucine. Ongoing efforts focus on improving grid preparation and image processing to obtain higher-resolution reconstructions and define substrate coordination in greater detail.

In parallel, purified LAT3 was reconstituted into proteoliposomes to establish transport assays under controlled conditions. Successful incorporation was confirmed biochemically by flotation assays. Functional measurements indicate that further optimization is required to address background signal, transporter orientation, and potential lipid-dependent effects.

Together, these studies provide the first structural insights into LAT3 and establish a framework for understanding its transport mechanism and contribution to cancer cell amino acid regulation, supporting its evaluation as a potential therapeutic target in prostate cancer.

Keywords:

LAT3, SLC43A1, Amino Acid Transporter, Structure, Prostatic Cancer, Substrate Specificity

P-135

Impacts Of Membrane Cholesterol On The Flexibility And Conformational Heterogeneity Of LAT1-CD98hc

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LAT1-CD98hc is a broadly expressed heterodimeric membrane protein involved in the transport of large neutral amino acids, including leucine, isoleucine, phenylalanine and tyrosine, across the cell membrane. Access to these essential amino acids is of critical importance for cell growth and proliferation, which naturally implicates LAT1-CD98hc in the development of various cancers. Indeed, overexpression of the heterodimer is observed in, amongst others, colorectal, prostate, ovarian, renal and thyroid cancers. The two monomers comprising the heterodimer serve different functions. LAT1, the light chain, is made of 12 transmembrane helices linked together by extracellular loops and is responsible for the amino acid transport function. The heavy chain, CD98hc, is a glycoprotein with a large extracellular domain anchored to the membrane by a transmembrane helix. It's function involves the trafficking of the light chain to the cell membrane. It also complexes with other amino acid transporters and integrin receptor proteins. The two monomers are linked together by an extracellular disulfide bond.

Recent computational work has suggested that membrane cholesterol occupies crucial binding sites on the LAT1 surface within the membrane, which may control not only the partition between inward and outward facing conformations of the transporter, but also in the coupling of movement between the CD98hc and LAT1 monomers. This work investigates the LAT1-CD98hc structure in nanodiscs without cholesterol to experimentally determine changes in conformation and heterodimer flexibility and therefore elucidate the importance of cholesterol for LAT1-CD98hc function.

Keywords:

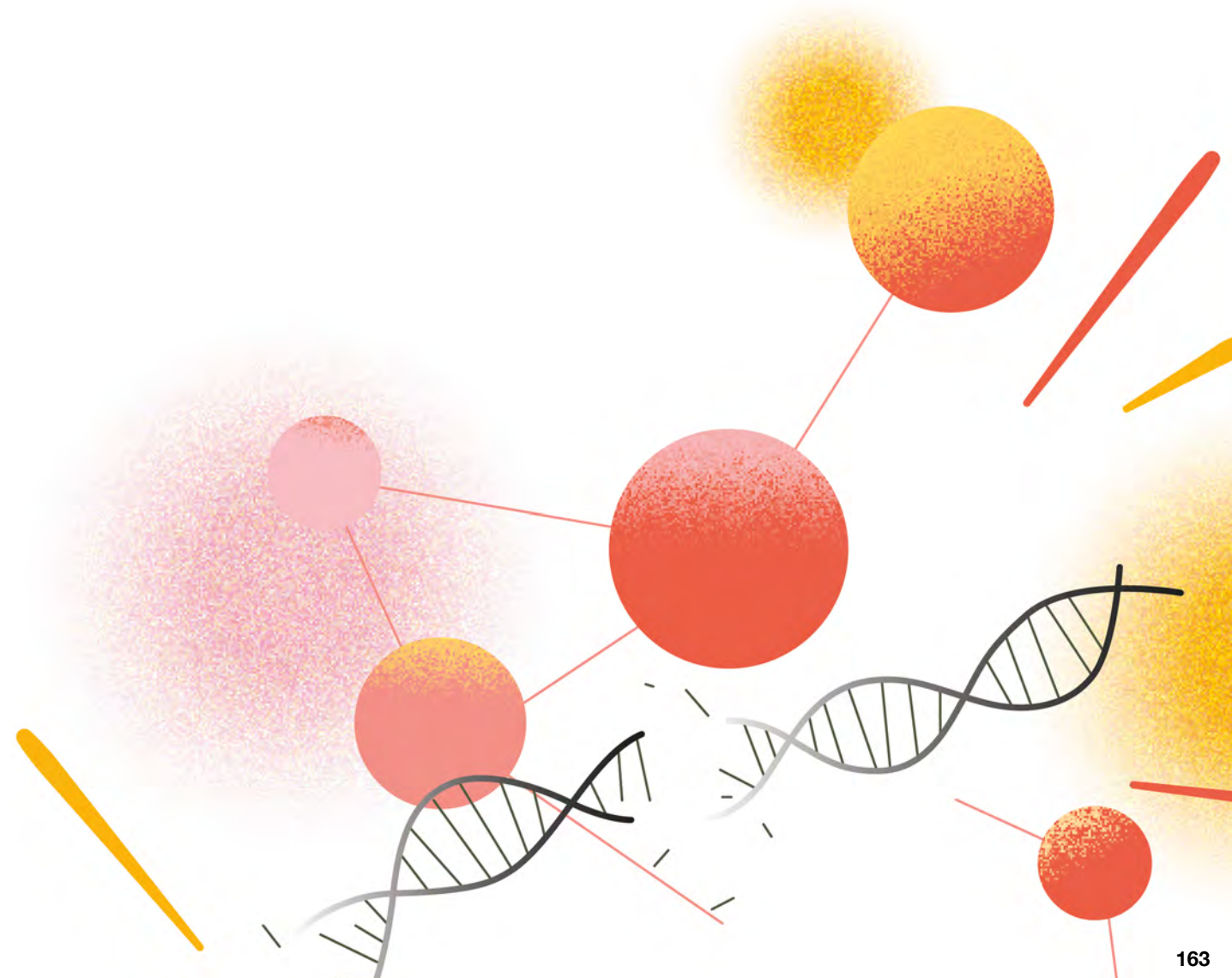
CryoEM, Membrane, Protein, Structure, Cholesterol, Transporter



GRUPOS CIENTÍFICOS DE LA SEBBM:

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9 DE SEPTIEMBRE





O-089

ERK5 Sustains High-Risk Neuroblastoma Proliferation By Regulating MYCN Proteostasis And Downstream Polyamine Metabolism

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Neuroblastoma is the most common extracranial solid tumour in childhood and a leading cause of cancer-related mortality in paediatric patients. The oncogene MYCN, a member of the MYC family of transcription factors, is amplified in approximately 50% of high-risk neuroblastomas. MYCN is a major driver of aggressive disease, promoting tumour cell proliferation, metabolic reprogramming, and metastasis. Here, we identify ERK5 as a regulator of MYCN proteostasis and MYCN-driven metabolic vulnerability in neuroblastoma. Using a panel of human neuroblastoma cell lines and murine xenograft models, we describe that ERK5 stabilizes the MYCN protein. Accordingly, genetic or pharmacological inhibition of the MEK5–ERK5 pathway repressed MYCN-dependent transcriptional programs, and impaired neuroblastoma cell proliferation and xenograft tumor growth in vivo. Of relevance, ERK5 inhibition also impaired MYCN-dependent polyamine metabolism, a key pathway sustaining the proliferation of high-risk neuroblastoma cells, and potentiated the antitumor activity of a clinically approved inhibitor of polyamine biosynthesis in neuroblastoma xenografts. Collectively, these findings identify ERK5 as a druggable regulator of MYCN proteostasis and of polyamine-dependent neuroblastoma growth.

Keywords:

Cancer, MAP Kinase, MYC Oncogen

O-090

Expanding The KRAS Signaling Network In Lung Cancer

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Mutations in *KRAS* are found in approximately 25% of lung adenocarcinomas. Although the recent development of *KRAS* inhibitors has offered new hope for patients with these tumors, most eventually develop resistance to these therapies. This underscores the need for a deeper understanding of *KRAS* signaling to inform combination strate-

gies that could delay or prevent the rapid emergence of resistance.

We have identified the transcriptional repressor Capicua (CIC) as a central effector of *KRAS*/MAPK signaling in lung adenocarcinoma. We demonstrate that loss of CIC function recapitulates the key phenotypic consequences of oncogenic *KRAS* activation, suppresses the dependency on *KRAS* allelic imbalance, and accelerates the transformation of bronchiolar Club cells. As loss of CIC also promotes resistance to *KRAS*/MAPK pathway inhibition, we explore different strategies to target resistant tumor cells including restoration of CIC activity. Moreover, we identify CIC target genes implicated in resistance to *KRAS*/MAPK pathway inhibitors and discern their mechanism of promoting resistance.

Together, these findings establish CIC as a critical regulator of lung tumorigenesis and suggest that selective pressure to abolish CIC function promotes the amplification of *KRAS*/MAPK signaling during tumor progression. At the same time, this mechanism exposes new vulnerabilities that can be exploited therapeutically.

Keywords:

KRAS, Lung Cancer, Capicua, Resistance

O-091/P-136

Impact Of Hepatocyte C3G On Hepatocellular Carcinoma Development

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Chronic liver damage induces fibrosis, which can progress to cirrhosis and eventually lead to hepatocarcinoma (HCC). C3G is a guanine nucleotide exchange factor (GEF) for

Rap1, which regulates several cellular functions through mechanisms dependent or independent of its GEF activity. C3G expression is high in hepatic progenitor cells and neonatal hepatocytes, but low in adult hepatocytes, being upregulated in HCC. Based on this, we have studied the role of C3G in the development of HCC using a hepatocyte C3G deficient mice (C3GKO^{Alb}) treated with either DEN (Diethylnitrosamine) or DEN+CCl₄ to induce HCC or HCC associated with fibrosis, respectively. In the DEN model, more tumors with a smaller size were generated in C3GKO^{Alb} compared to wt mice. In addition, C3G deletion resulted in an increased recruitment of platelets and macrophages and a higher expression of chemokines such as *Ccl2*, *Cx3cl1* and *Cxcl7*, and the glycolytic enzymes *Pkm2* and *Fbp1*. In the DEN+CCl₄ model, before tumors were developed, C3G-KO^{Alb} mice showed an enhanced fibrosis, increased recruitment of macrophages and platelets and a higher expression of chemokines than wt mice. A decreased expression of FAS and ACC upon C3G deletion was also observed. Once tumors were developed, fibrosis also seemed to be increased in C3GKO^{Alb} compared to wt mice, as well as *Fbp1* expression.

In summary, our data support a relevant role for hepatocyte C3G in the development of HCC, together with an impact on the metabolic rewiring that takes place in HCC.

Keywords:

C3G; Liver; Hepatocarcinoma; Metabolism

O-092/P-137

Greatwall Kinase Regulates Acute Myeloid Leukaemia Cell Division Through A Non-Canonical Mechanism

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Greatwall kinase regulates mitotic progression by phosphorylating ENSA and ARPP19, thereby inhibiting the PP2A-B55 complex. Moreover, Greatwall has been implicated in oncogenesis, particularly in solid tumours, but the mechanisms by which this kinase regulates the cell cycle in other malignancies remain unclear.

Here, we investigated the role of Greatwall in acute myeloid leukaemia (AML) cell lines and primary samples using functional, biochemical, and phosphoproteomic approaches. We show that, consistent with its role in cells of epithelial origin, AML cells require Greatwall activity to proliferate, as revealed by pharmacological and systematic genetic perturbation experiments. However, unlike in cells derived from solid tumors, we unexpectedly found that Greatwall regulates cytokinesis and cell cycle progression in AML cells through a pathway distinct from the canonical ENSA–PP2A-B55 axis.

Mechanistically, Greatwall inactivation – using a novel specific small molecule inhibitor or by genetic depletion – does not measurably affect the ENSA–PP2A-B55 pathway. Contrary to other models, pharmacological Greatwall kinase inhibition does not reduce ENSA phosphorylation and does not impair ENSA–PP2A-B55 interaction. Instead, loss of Greatwall function alters cytokinesis, and the phosphorylation of proteins involved in cytoskeletal organisation and cytokinesis, including MARK3, which we identify as a direct Greatwall substrate in AML cells. Altered cytokinesis leads to the generation of multinucleated cells and reduced proliferation in most of the AML cell lines tested.

Together, these findings reveal a novel mechanism of cell cycle regulation in cells of myeloid origin, by which Greatwall regulates cell cycle progression independently of the canonical ENSA-PP2A-B55 axis.

Keywords:

Cell Cycle, Mitosis, Greatwall Kinase, Cytokinesis, Phosphoproteomics, Signalling, AML

O-093/P-138

C3G Downregulation Promotes Invasion And Drives Metabolic Reprogramming And Stemness In Glioblastoma Through PKM2

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Glioblastoma (GBM), the most common and aggressive primary brain tumor, exhibits profound metabolic rewiring



that sustains progression, invasiveness and therapy resistance. We previously demonstrated that C3G expression is downregulated in GBM, promoting migration and invasion. Here, we show that C3G silencing or knockout in GBM cells reprograms glucose metabolism toward glycolysis and lactate production through increased PKM2 and LDHA expression, together with enhanced respiratory capacity revealed by Seahorse profiling. Mechanistically, C3G downregulation increases the levels of the splicing factors PTBP1 and SRSF3, promoting PKM splicing toward PKM2 expression. Moreover, C3G knockdown enhances sphere formation, stemness and tumor-initiating capacity, rescued by C3G re-expression. Importantly, transient PKM2 silencing or pharmacological inhibition suppresses stemness, and decreases viability in GBM spheres, supporting a specific role for the C3G/PKM2 axis in GBM stem cells.

To assess the effect of C3G downregulation in physiologically relevant models, human iPSC-derived cortical organoids were co-cultured with mCherry-labeled GBM neurospheres. GBM cells' invasive capacity was enhanced upon C3G silencing, leading to the formation of secondary invasive foci within the organoids. C3G-silenced cells were GFAP-positive and β III-tubulin-negative, supporting maintenance of a glial tumor phenotype during invasion. In addition, C3G silencing in murine SB-28 GBM cells increased tumor burden in an orthotopic syngeneic xenograft mouse model, determined by bioluminescence imaging four weeks after intracranial injection.

Altogether, our findings identify C3G as a central regulator of GBM metabolism, stemness and invasiveness, highlighting the relevance of C3G/PKM2 axis.

Keywords:

Glioblastoma, C3G, PKM2, Metabolism, Cancer Stem Cells, Brain Organoids

O-094/P-139

SEC22B R-SNARE Modulates CIC-5/TMEM9 Trafficking, Serving As A Renal Decline Indicator In Dent's Disease

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Dent's disease type 1 (DD1) is a renal tubulopathy characterized by hypercalciuria and low molecular weight proteinuria leading to kidney failure, with variable severity in between patients. DD1 is caused by loss of function mutations in the Cl⁻/H⁺ antiporter CIC-5, a key regulator of renal proximal tubule function by controlling endosomal acidification. To further understand the mechanism linking CIC-5 loss of function with DD1 phenotypic heterogeneity, we have used cellular models of the disease using renal proximal tubule epithelial cells (RPTEC) expressing three CIC-5 pathogenic variants (I524K, E527D and V523Δ). We have found distinct intracellular retention patterns of these CIC-5 mutants, all leading to altered endolysosomal pH and disrupted secretory pathway organization. Through an interactome analysis, we identified the R-SNARE protein SEC22B, which interacts with wildtype CIC-5, but not DD1 mutants. SEC22B deletion impaired CIC-5 trafficking, leading to its retention at the Golgi and endosomes. Moreover, this loss of SEC22B recapitulated key DD1 cellular hallmarks, including defective endocytosis, epithelial dedifferentiation, and altered secretory pathway. Surprisingly, SEC22B depletion evidenced enhanced endosomal acidification. We have here shown this effect being due to SEC22B also regulating TMEM9, a known CIC-5 inhibitor that associates with both wildtype and DD1 cell models. Thus, our findings suggest that SEC22B is essential for the sorting of the CIC-5/TMEM9 complex. Finally, we have observed elevated SEC22B levels in urinary extracellular vesicles from DD1 patients, also correlating with declining renal function. Altogether, our findings establish SEC22B as a critical modifier of DD1 pathophysiology and a potential biomarker for disease progression.

Keywords:

SEC22B, TMEM9, CIC-5, Dent's Disease, Proximal Tubule, Biomarker, Renal Fibrosis

O-095/P-140

Quantitative Live-Cell Analysis Of GPCR Signaling Dynamics Using Endogenous Bioluminescent Reporters: From Ligand Engagement To Downstream Effector Activation

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G protein-coupled receptors (GPCRs) mediate a vast array of signaling events and represent major therapeutic targets across metabolic, cardiovascular, and neurological diseases. Despite their pharmacological relevance, the temporal resolution of receptor-level events – ligand binding, β -arrestin recruitment, internalization, and second messenger generation– remains technically challenging at endogenous expression levels.

Here we present an integrated bioluminescence platform for the quantitative, real-time dissection of GPCR signaling dynamics in living cells, applied to incretin receptor pharmacology (GLP-1R, GIPR, GCGR). Using CRISPR/Cas9-mediated HiBiT endogenous tagging, we monitored agonist-induced receptor internalization at physiological expression levels without antibody-based detection, enabling selective quantification of cell-surface receptor density in kinetic and endpoint formats. Complementary NanoBRET target engagement assays allowed direct measurement of ligand binding affinity to HiBiT-GLP-1R in live cells, yielding apparent IC₅₀ values of 12.8, 3.0, and 1.6 nM for semaglutide, tirzepatide, and retatrutide.

GPCR: β -arrestin-1/2 interactions were resolved using NanoBiT-based recruitment assays, capturing interaction kinetics and reversibility in real time across a broad agonist concentration range. Downstream cAMP dynamics were continuously monitored with live-cell GloSensor technology, providing high-resolution readout of G α s-mediated signaling.

Together, these orthogonal assays resolve the full pharmacological cascade – from receptor occupancy to effector activation– and reveal differential signaling bias among structurally related agonists. This platform is broadly applicable to the mechanistic study of GPCR signaling in disease-relevant contexts.

Keywords:

GPCR Signaling Dynamics, Endogenous Protein Tagging,

Receptor Internalization, β -Arrestin Recruitment, Live-Cell Imaging, Receptor Trafficking, Signal Transduction

O-096/P-141

Metabolic Stress Uncovers ISR-Independent Mitochondrial Adaptations

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Mitochondrial diseases (MDs) are rare metabolic disorders affecting approximately 1 in 5000 adults and are caused by mutations in either mitochondrial DNA (mtDNA) or the nuclear genome. Because mtDNA is present in multiple copies per cell, mutant and wild-type molecules can coexist within the same cell in a state known as heteroplasmy. Changes in nutrient availability have been proposed to influence mutant load, but the molecular mechanisms underlying this effect remain poorly understood. As nutrient sensing pathways frequently activate the Integrated Stress Response (ISR), its downstream effector ATF4 has been proposed as a potential regulator of mitochondrial adaptations in these conditions.

Here, we examined how nutrient sensing and ISR signalling influence mitochondrial phenotypes in human cells harboring heteroplasmic mtDNA variants. By combining nutrient restriction with pharmacological and genetic modulation of the ISR, we explored the relationship between metabolic stress responses and mitochondrial adaptations. Nutrient restriction triggered pronounced changes in mitochondrial phenotypes and partially restored mitochondrial protein levels and functional features. Notably, these responses occurred largely independently of canonical ISR signalling. Together, these findings highlight an unexpected link between nutrient sensing and mitochondrial adaptation in mitochondrial disease and suggest the existence of regulatory mechanisms operating beyond canonical ISR pathways.

Keywords:

Mitochondrial Diseases, Nutrient Restriction, Metabolic Rewiring, MtDNA Heteroplasmy, Integrated Stress Response (ISR)



O-097/P-142

Asparaginyl Endopeptidase Stabilizes Epithelial Growth Factor Receptor (EGFR)-Mediated Downstream Signalling And Contributes To EGFR-Based Therapy Resistance In Triple Negative Breast Cancer (TNBC)

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Although it only represents 10-20% of total breast cancer (BRCA) cases, triple-negative breast cancer (TNBC) accounts for more than 40% of BRCA deaths, due to its high aggressiveness and the current lack of targeted therapies. In this context, lysosomal alterations are present in most human solid tumors, with lysosomal protease overexpression correlating with worse prognosis and reduced overall survival. Remarkably, our previous work and preliminary data demonstrate a dependency of certain cancer types on specific lysosomal proteases, thereby raising the possibility of exploiting these weaknesses for the development of novel therapeutic approaches. In this scenario, our previous work has revealed a striking dependency of TNBC on asparaginyl endopeptidase (AEP), revealing that a nuclear pool of AEP contributes to radio- and chemotherapy resistance through the regulation of ATR and PPP1R10 levels, thus allowing cancer cells to escape DNA-damage induced apoptosis while maintaining DNA repair and cell cycle checkpoint activation [1]. Interestingly, our recent work is allowing us to further rationalize TNBC dependency on AEP. Specifically, our work using TNBC cells, publicly available TNBC patient phosphoproteomic data and further validated in an independent cohort of TNBC patients, demonstrate that AEP contributes to the endolysosomal stabilization of EGFR, leading to sustained downstream activation, independently of EGFR levels. Importantly, our data explain why promising anti-EGFR therapies have failed to improve TNBC patient outcome despite EGFR overexpression. Furthermore, our data reveals AEP not only as a predictive bio-

marker, but also as a druggable target to sensitize TNBC to anti-EGFR therapies, allowing us to design novel, personalized strategies for TNBC treatment

Keywords:

TNBC, Lysosomes, Asparagine Endopeptidase, Cell Signalling, EGFR, Therapy Resistance, Personalised Medicine, Novel Biomarkers, Novel Therapeutic Approaches

O-098/P-143

TAS2R Signaling Diversity Controls Enteroendocrine GLP-1 Secretion Through Distinct G Protein Pathways

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Bitter taste receptors (TAS2Rs) are G protein-coupled receptors (GPCRs) classically linked to Ca²⁺-dependent signaling pathways. In the gastrointestinal tract, they regulate enteroendocrine hormone secretion, including GLP-1 release. However, subtype-specific signaling mechanisms and the contribution of additional second messenger pathways, such as cAMP, remain unclear.

Selected TAS2R subtypes were functionally investigated using receptor-specific silencing in HUTU80-cells. TAS2R1 and -4 knockdowns avoid GLP-1 release, whereas TAS2R14 silencing increased secretion, indicating differential regulation of enteroendocrine signaling.

To dissect the underlying signaling mechanisms, Gα protein coupling profiles were first analyzed. TAS2R1, -4 and -14 activated Gα-gustducin, with TAS2R4 showing preferential coupling to Gαq, whereas TAS2R14 additionally engaged Gαi. No activation of Gαs was observed.

Downstream intracellular signaling was then assessed by measuring IP3 accumulation. TAS2R4 exhibited strong constitutive-like IP3 signaling, whereas TAS2R1 and -14 displayed a concentration-dependent response. Finally, cAMP signaling was evaluated using BRET-based assay following forskolin stimulation. TAS2R1 and -14 induced a reduction in cAMP levels. Remarkably, co-expression of TAS2R4 with -14 or -1 resulted in a stronger and more stable decrease in cAMP signaling together with enhanced IP3 accumulation, suggesting functional receptor interactions and cooperative

modulation of intracellular pathways.

Overall, our results identify specific TAS2Rs involved in enterohormone secretion and reveal receptor-specific signaling profiles. These findings suggest that a balance between enhanced IP3 signaling and a restricted cAMP accumulation may contribute to GLP-1 secretion.

Keywords:

TAS2Rs, GLP-1 Secretion, IP3, CAMP, Gα Protein Coupling, Enteroendocrine Signaling

O-099/P-144

Exploring Succinate As An Autocrine/Paracrine Signal In Breast Cancer

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Breast cancer (BC) is the most frequently diagnosed malignancy among women worldwide and, despite major therapeutic advances, remains a leading cause of cancer-related mortality. Increasing evidence suggests that succinate, an immunometabolic intermediate closely linked to inflammation and immune regulation, contributes to tumour progression. Although intracellular succinate signalling has been extensively studied in cancer biology, the contribution of its cognate receptor, succinate receptor 1 (SUCNR1/GPR91), to BC pathogenesis remains poorly understood. We hypothesize that succinate, through SUCNR1 activation, acts as an autocrine/paracrine metabolic-immune signal that promotes BC aggressiveness by reshaping tumour metabolism and the immune microenvironment. *In silico* analyses of publicly available transcriptomic datasets revealed that elevated SUCNR1 expression correlates with reduced overall survival and is enriched in aggressive BC subtypes. Consistently, immunohistochemical analyses demonstrated increased SUCNR1 expression in aggressive BC specimens associated with elevated circulating succinate levels. Functionally, genetic ablation of *Sucnr1* in a syngeneic triple-negative BC mouse model attenuated tumour growth, M2-like macrophage infiltration, peritumoral adipose tissue

inflammation, and immunosuppressive gene signatures. Furthermore, SUCNR1 inhibition modulates metabolic activity and mitochondrial respiration, promoted AMPK signalling activation, and reduced proliferative, invasive, migratory, and clonogenic capacities in an aggressive BC cell line model. Collectively, these findings identify the succinate/SUCNR1 axis as a potential driver of BC progression and highlight SUCNR1 as a promising therapeutic target.

Keywords:

Breast Cancer, SUCNR1, Succinate, Inflammation

O-100/P-145

Gαq Regulates Organelle Contacts

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Lysosomes and mitochondria are highly dynamic organelles essential for cellular homeostasis, and their dysfunction is implicated in numerous diseases. The contacts between these organelles are critical for proper cellular function. These contacts are finely regulated by a tethering untethering protein machinery that includes Rab7, the RabGAP protein TBC1D15, and the mitochondrial protein Fis1. Our proteome analysis, in vitro immunoprecipitation, and pull-down studies have identified Fis1 and TBC1D15 as interacting partners of Gαq in mitochondria. Furthermore, we demonstrated that both TBC1D15/Gαq and Fis1/Gαq are found in close proximity within the cell. Notably, in the absence of Gαq: there is a decrease in the TBC1D15 protein levels; an increase in the Rab7 activity; an increase in

the mitochondrial-lysosome contacts; lysosomes increase in size and present a more clustered pattern; and mitochondria exhibit more fragmentation indicating an increase of fission. These phenotypes can be reversed by expressing Gαq, but not when expressing a mutant of Gαq lacking the interaction with TBC1D15 and Fis1, GαqE234/E245-AA (GqEEAA). Interestingly, the mechanism of regulation of mitochondria-lysosome contact by Gαq is dependent of Fis1, since cells lacking both Gαq and Fis1 recover the wild type phenotype. These findings further support the role of the G protein cycle as a key regulator of mitochondria-lysosome contacts. Given that dysfunction in both organelles is linked to various diseases, targeting GPCR signaling pathways could provide novel therapeutic strategies for modulating these processes in disease contexts.

Keywords:

Signak Transduction, Lysosomes, Mitochondria, TBC1D15, Rab7



P-146

The Succinate/SUCNR1 Axis In Macrophages Drives Lipid Accumulation And Atherosclerosis

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Background and Objective: Succinate, a Krebs cycle metabolite, acts as a signaling molecule via the SUCNR1 receptor. Although this axis regulates inflammatory and metabolic processes, its role in atherosclerosis remains unclear. This study investigated the succinate/SUCNR1 axis in foam cell formation and atherosclerosis progression.

Methods: The role of SUCNR1 in macrophages was evaluated *in vivo* using myeloid-specific *Sucnr1*-deficient mice (*LysM-CreSucnr1*^{fl/fl}). Atherosclerosis was induced via a *Pcsk9*-encoding adeno-associated virus and a high-fat, high-cholesterol (HFHC) diet. *In vitro* impacts on foam cell function were analyzed using J774A.1 cells and bone marrow-derived macrophages (BMDMs) isolated from *Sucnr1*-deficient mice.

Results: After 4 weeks of HFHC diet, *LysM-CreSucnr1*^{fl/fl} mice showed reduced circulating cholesterol and triglycerides. After 12 weeks, *Sucnr1*-deficient mice exhibited significantly reduced aortic plaques. *In vitro*, acetylated LDL increased *Sucnr1* expression and succinate release. SUCNR1 activation promoted lipid accumulation, cholesterol efflux, and migration in J774A.1 cells without affecting proliferation. Validation in *Sucnr1*-deficient BMDMs confirmed that succinate-induced lipid accumulation is strictly SUCNR1-dependent.

Conclusions: Macrophage SUCNR1 activation promotes foam cell formation and atherosclerosis progression. Conversely, *Sucnr1* deficiency reduces plaque development and improves metabolic profiles. These findings highlight SUCNR1 as a potential therapeutic target for the prevention and treatment of atherosclerosis.

Keywords:

SUCNR1, Succinate, Atherosclerosis, Macrophages, Foam Cells, Lipid Accumulation, Cholesterol, Plaque, Metabolism, Inflammation

P-147

The Transcriptional Control Of LXR-Alpha In The Temporal Activation Of Macrophage Inflammation

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Macrophages regulate essential aspects of innate immunity against pathogens. In response to microbial components, macrophages activate primary and secondary inflammatory gene programs crucial for host defense. The liver X receptors (LXRα, LXRβ), are ligand-dependent nuclear receptors that direct gene expression important for cholesterol metabolism and also modulate inflammation. While anti-inflammatory actions have been described for dual LXRα/LXRβ synthetic agonists, comparatively little is known about the individual roles of LXRα and LXRβ in microbial responses. Here we demonstrate that the induction of LXRα transcription by lipopolysaccharide (LPS) supports inflammatory gene expression at later phases of the innate immune response in macrophages. LXRα transcription is induced by NF-κB and type-I interferon signaling pathways downstream of TLR4 activation. Moreover, LPS triggers a reprogramming of the LXRα cisome that promotes cytokine and chemokine gene expression through direct LXRα binding to consensus sequences within cis-regulatory regions. LXRα-deficient mice showed impaired responses to bacterial endotoxin in a peritonitis model, with reduced immune cell recruitment and activation at sites of inflammation. Together, these results define a previously unrecognized function for LXRα-dependent transcriptional cis-activation of macrophage inflammatory gene expression and the host response to microbial ligands.

Keywords:

Macrophage, Inflammation, LXR, Liver X Receptor, Innate Immunity

P-148

Insights From A CRISPR Knock-In Cell Line: ERK5 Kinase Activity Promotes Proliferation, Migration And Survival Of Endometrioid Cancer Cells

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The MAP kinase ERK5 regulates cancer cell proliferation, and ERK5 inhibitors have shown anticancer activity in murine preclinical models of several solid tumors. Unlike other MAPKs, ERK5 has a unique C-terminal tail with a transcriptional activating domain (TAD) that allows ERK5 to act as a transcriptional co-activator independently of its kinase activity. Thus, ERK5 has both kinase activity-dependent and -independent functions.

We previously found that ERK5 pharmacologic or genetic inhibition impairs EC cell proliferation and the growth of tumor xenografts implanted in mice. However, whether this effect is mediated by ERK5 kinase or by the TAD activity remains to be elucidated. To address this, using CRISPR/Cas9 knock-in technology, we generated an EC cell line deficient for ERK5 kinase activity. Here, we have characterized an EC Ishikawa cell line encoding a ERK5 kinase catalytically inactive.

Compared to the parental EC cells, ERK5 kinase-inactive cells did not show ERK5 activation in response to growth factors or osmotic stress, while the activation of other relevant signaling pathways (ERK1/2, JNKs and the Akt-mTORC1 axis) was not affected. Notably, ERK5 kinase-inactive cells showed impaired basal proliferation and migration, thus supporting that EC cell proliferation is mediated by ERK5 kinase activity rather than its TAD activity. Furthermore, flow cytometry apoptosis analysis revealed that ERK5 kinase-inactive EC cells were more sensitive to serum deprivation, compared to the parental EC cells. Hence, our results provide evidence that EC cells require ERK5 kinase activity for basal cancer cell proliferation and migration as well as for survival in serum-deprivation conditions.

Keywords:

ERK5, Endometrial Cancer

P-149

MNK1-Targeting Aptamer Impairs Cytoskeletal Dynamics And Glycolysis Through Post-Translational Regulation Of Cofilin (CFL1) And PGAM1

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Targeting oncogenic signaling pathways can induce profound changes in tumor cell behavior through post-translational regulation of proteins involved in migration and metabolism. In this study, we investigated the molecular effects of the MNK1-targeting aptamer apMNKQ2 in triple-negative breast cancer cells. Proteomic analysis by 2D-DIGE coupled to MALDI-TOF mass spectrometry identified cofilin (CFL1) and phosphoglycerate mutase 1 (PGAM1) as proteins displaying changes in isoelectric point consistent with post-translational modification after apMNKQ2 treatment.

Functional analyses revealed that apMNKQ2 increased phosphorylation of cofilin at Ser3, a modification associated with inhibition of actin filament turnover and reduced cytoskeletal dynamics. Expression of a non-phosphorylatable cofilin mutant partially attenuated the anti-migratory effect of apMNKQ2, supporting the involvement of cofilin regulation in the inhibition of tumor cell migration.

In parallel, apMNKQ2 induced a shift in PGAM1 proteoforms accompanied by decreased PGAM enzymatic activity and inhibition of both basal and compensatory glycolysis. Stable overexpression of PGAM1 partially rescued glycolytic activity and reduced sensitivity to the antiproliferative effects of the aptamer, indicating a functional role for PGAM1 regulation in the antitumoral response. Biochemical analyses further suggested that altered acetylation might contribute to PGAM1 inhibition downstream of MNK1 targeting.

Together, these findings demonstrate that MNK1 aptamer targeting impairs cytoskeletal dynamics and glycolytic metabolism through post-translational regulation of cofilin and PGAM1, highlighting these pathways as relevant mediators of the antitumoral effects of apMNKQ2.

Keywords:

Aptamers, MNK1, Post-Translational Regulation, Cancer



P-150

Pitpnm3 As A Novel Downstream Effector Of HGF/Met Signaling In Intrahepatic Cholangiocarcinoma

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Background and Aims: Intrahepatic cholangiocarcinoma (iCCA) is a primary liver tumor associated with poor prognosis, due to late diagnosis and limited curative therapies available. The hepatocyte growth factor receptor (Met) is one of the iCCA molecular drivers, overexpressed in 7-21% of cases. A transcriptomic study using MACE (Massive Analysis of cDNA ends = 3'mRNASeq) technology identified Pitpnm3, a membrane-associated phosphatidylinositol transfer protein, as a target of the HGF/Met pathway in hepatic progenitor cells (HPC), bipotential cells that play a key role in chronic liver disease. Our work has linked Pitpnm3 with HGF-mediated functions in HPC and, according to public cancer databases, Pitpnm3 is overexpressed in iCCA patients. Therefore, we investigated the role of Pitpnm3 in the HGF/Met signaling pathway in iCCA cells.

Methods: Two iCCA cell lines were employed: a murine (SB1) and a human cell line (KKU213A). In SB1 cells, Pitpnm3 was silenced using siRNA and CRISPR-Cas9 strategies, while in KKU213A cells, a Pitpnm3 specific inhibitor was evaluated. HGF-mediated cellular functions (proliferation, invasion, etc) were assessed.

Results: HGF-driven proliferative and invasive activities were abolished in SB1 cells upon Pitpnm3 silencing. Pitpnm3 silencing also interfered with HGF-triggered signaling

pathways in these cells, specifically the STAT3 pathway. Pitpnm3 inhibitor was validated in KKU213A cells, and its inhibition blocks the HGF-mediated invasion.

Conclusion: Pitpnm3 silencing disrupts HGF-mediated cellular functions and associated signaling pathways in murine iCCA cells. Ongoing studies are assessing the effects of pharmacological Pitpnm3 inhibition in human iCCA cells. Potential therapeutic interest of Pitpnm3 for iCCA will be discussed.

Keywords:

Liver, HGF, Signaling, Cholangiocarcinoma.

P-151

New NLRP1 Interactors In Congenital Anemias

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The NLRP1 inflammasome has emerged as a key regulator of the inflammatory response; however, its role in erythropoiesis and erythroid homeostasis remains poorly characterized. In this study, we developed a novel NLRP1 knockout (KO) model in erythroid cells, observing a marked accumulation of hemoglobin and alterations associated with the erythroid differentiation program.

To identify the molecular mechanisms involved, we performed mass spectrometry analyses comparing WT and CRISPR-Cas9-generated KO cells, through which we identified novel NLRP1 interactors potentially involved in erythropoietic processes. A couple of the identified interactions, involving proteins known to interact with one another, were subsequently validated experimentally through confocal imaging and protein-protein interaction assays. Furthermore, we generated a recombinant NLRP1 protein for functional

phosphorylation assays, enabling the exploration of new post-translational regulatory pathways associated with its activity.

Overall, our findings identify novel biomarkers and interactors associated with NLRP1 and provide innovative tools for the study of this inflammasome in hematopoietic disorders, including congenital anemias and other erythroid pathologies.

Keywords:

NLRP1, Inflammasome, Congenital Anemias, Erythropoiesis, NLRP1 Interactors

P-152

Gαq Regulates Organelle Contacts

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Lysosomes and mitochondria are highly dynamic organelles essential for cellular homeostasis, and their dysfunction is implicated in numerous diseases. The contacts between these organelles are critical for proper cellular function. These contacts are finely regulated by a tethering/untethering protein machinery that includes Rab7, the RabGAP protein TBC1D15, and the mitochondrial protein Fis1. Our proteome analysis, in vitro immunoprecipitation, and pull-down studies have identified Fis1 and TBC1D15 as interacting partners of Gα_q in mitochondria. Furthermore, we demonstrated that both TBC1D15/Gα_q and Fis1/Gα_q are found in close proximity within the cell. Notably, in the absence of Gα_q, there is a decrease in the TBC1D15 protein levels; an increase in the Rab7 activity; an increase in the mitochondrial-lysosome contacts; lysosomes increase in size and present a more clustered pattern; and mitochondria exhibit more fragmentation indicating an increase of fission. These phenotypes can be reversed by expressing Gα_q, but not when expressing a mutant of Gα_q lacking the interaction with TBC1D15 and Fis1, Gα_qE234/E245-AA (GqEEAA). Interestingly, the mechanism of regulation of mitochondria-lysosome contact by Gα_q is dependent of Fis1, since cells lacking both Gα_q and Fis1 recover the wild type phenotype. These findings further support the role of the G protein cycle as a key regulator of mitochondria-lysosome contacts. Given that dysfunction in both organelles is linked to various diseases, targeting GPCR signaling pathways could provide novel therapeutic strategies for modulating these processes in disease contexts.

Keywords:

Gαq, Mitochondria, Lysosome, Membrane Contact Sites, Mitochondrial Fission

P-153

Identification Of PRMT3 As An Epigenetic Regulator Of The Oncogenic Signaling Network

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Cancer remains a major therapeutic challenge due to, among other factors, its intrinsic heterogeneity and the activation of compensatory signaling mechanisms that limit the efficacy of anticancer drugs. Epigenetic alterations can reprogram cellular signaling pathways that drive tumor growth, thus promoting resistance to anticancer therapies. Therefore, epigenetic enzymes represent promising targets to overcome resistance to kinase inhibitors. To identify additional epigenetic regulators of oncogenic kinase signaling in a pan-cancer context, we used a bioinformatic approach named Functional Pathway Inference Analysis (FPIA). Using PIK3CA and MAP2K1 as bait genes, PRMT3 was identified as one of the most differentially associated epigenetic genes between PI3K and MEK/MAPK signaling pathways, suggesting a potential regulatory role. To validate this finding, HCC cell lines were treated with a PRMT3 inhibitor (SCG707) followed by either a MEK inhibitor (trametinib) or a PI3K inhibitor (pictilisib). No synergistic effect was observed with pictilisib; however, pretreatment with SCG707 sensitized a subset of HCC models to trametinib. Phosphoproteomic analysis showed that PRMT3 inhibition by itself increased cell viability and the phosphorylation of MEK1 and its downstream targets ERK1/2, while also altering the phosphorylation status of proteins in the PI3K/AKT/mTOR pathway, as well as translation and transcription-related factors. These preliminary data support a role for PRMT3 in the regulation of PI3K and MEK/MAPK signaling pathways and their downstream effectors. Our findings open new avenues to study how PRMT3 controls cancer cell proliferation and highlight the potential of this protein – in combination with kinase-targeted agents – as a target for anticancer therapy.

Keywords:

Cancer, Signaling, Epigenetic Inhibitors, Phosphoproteomics, PRMT3



P-154

Proteomic Background Determines The Extent By Which LSD1 Inhibitors Sensitize AML Cells To Kinase Inhibitors

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Epigenetic and kinase signalling pathways are often dysregulated in AML, but most targeted therapies show limited efficacy. LSD1 inhibition can overcome kinase inhibitor resistance, although responses vary depending on molecular background.

Here, we systematically evaluated the combinatorial effects of the LSD1 inhibitor iadademstat with kinase-targeting agents—gilteritinib (FLT3), trametinib (MEK1/2), pictilisib (PI3K α/δ)—and the pan-RAS inhibitor RMC-7977 across 18 AML cell lines. In parallel, we integrated drug response data with proteomic and phosphoproteomic profiling in MV4-11 (FLT3-mutant), KMOE-2 (NRAS-mutant), and HEL (JAK2-mutant) cells following sequential treatment with iadademstat and kinase inhibitors.

Iadademstat consistently sensitised AML cells to all kinase inhibitors tested, irrespective of FLT3 or RAS mutational status, but the nature of the kinase inhibitor was context-dependent. Reverse treatment showed no synergy, suggesting LSD1 inhibition primes cells for kinase inhibitor sensitivity. All three models were sensitised to gilteritinib, while trametinib sensitivity was limited to MV4-11 and KMOE-2 cells. Proteomic analyses revealed proteins associated with response to treatments, while phosphoproteomic identified highly heterogeneous signalling adaptations upon LSD1 inhibition, indicating context-dependent rewiring of kinase networks.

Our data show that LSD1 inhibition broadly increases AML sensitivity to kinase-targeted therapies, independent of mutational background. We instead identified proteins associated to responses that could inform personalised treatment strategies. These findings underscore the importance of understanding molecular context beyond genomics for the rational design of effective epigenetic–kinase combination therapies in AML.

Keywords:

LSD-1, AML, Phosphoproteomics, Kinase Inhibitors, Signalling, Epigenetics

P-155

Protective Effects Of Aspalathus Linearis And Polypodium Leucotomos Extracts Against Blue Light-Induced Oxidative Stress And Hyperpigmentation

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The skin acts as a physical barrier against environmental stressors, including solar radiation. Although ultraviolet radiation is considered the most harmful portion of the spectrum, visible light, particularly high-energy visible light (HEVL) such as blue light, also contributes to skin damage by inducing oxidative stress, photoaging and hyperpigmentation. These effects are especially relevant in darker skin phototypes and pigmentary disorders such as melasma and post-inflammatory hyperpigmentation. Since conventional sunscreens mainly target ultraviolet radiation, novel strategies against HEVL-induced pigmentation are needed. This study investigated the effects of a botanical antioxidant combination containing *Aspalathus linearis* and *Polypodium leucotomos* extracts on the molecular pathways activated by blue light exposure. Human melanocytes exposed to prolonged blue light irradiation were evaluated for cellular viability, reactive oxygen species (ROS) production, and melanin synthesis. Autophagy- and pigmentation-related pathways were explored through markers including p38, ERK, Tyrosinase, Clusterin, LC3B, ATG7 and Opsin-3. The botanical combination reduced ROS production and melanin levels induced by blue light, showing significant improvements across several parameters. In addition, the study explored the role of fibroblast-derived SFRP1 in blue light-induced melanogenesis. SFRP1 acts as an inhibitor of melanogenic signaling, and blue light exposure reduced its expression, potentially enhancing melanogenesis through fibroblast–melanocyte communication. These findings improve the understanding of the molecular mechanisms involved in blue light-induced pigmentation and support the potential use of this botanical combination in photoprotective strategies.

Keywords:

Blue Light, Hyperpigmentation, Oxidative Stress, Botanical Extracts

P-156

Modelling Rare Renal Pathologies: From CIC-5 Dysfunction To Therapeutics In Dent's Disease

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Dent's Disease type 1 (DD1) is a rare proximal tubule (PT) pathology caused by mutations in the H⁺/Cl⁻ antiporter CIC-5. The disease is characterized by PT dysfunction, with low-molecular-weight proteinuria serving as its clinical hallmark. DD1 inevitably progresses to chronic kidney disease, renal fibrosis and kidney failure, significantly reducing patients' life expectancy and increasing cardiovascular risk. However, there are no current specific treatments or reliable biomarkers for DD1.

In our laboratory, we use human cell-based disease models to investigate how impaired endosomal acidification disrupts critical cellular processes, including glycosylation, protein trafficking and cell differentiation. Our work demonstrates how these defects drive PT dysfunction and trigger the fibrotic cascade. Through these in vitro platforms, we have identified several candidate biomarkers that are currently being validated in DD1 patient samples. Furthermore, by employing in silico disease modeling, we have identified novel therapeutic targets and repurposed drugs with the potential to halt disease progression.

Collectively, our multi-modal approach has advanced the understanding of DD1 pathophysiology while providing a pipeline for biomarker and therapy discovery. These findings offer a broader framework for studying other PT-related disorders, such as those presenting with Fanconi's syndrome, whether triggered by inherited conditions like cystinosis or acquired through pharmacologic toxicity and immunologic injury.

Keywords:

Renal Organoid, Dent Disease, CIC-5, MUC1, Renal Fibrosis, Protein Trafficking

P-157

Elucidating The Role Of PKC In The DNA Integrity Checkpoint

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The Protein Kinase C (PKC) superfamily has numerous key roles in different cellular processes. In *Saccharomyces cerevisiae*, where there is only a single PKC, Pkc1, its main function is cell wall integrity maintenance. However, we discovered the implication of Pkc1 in the regulation of the DNA integrity checkpoint, and established mammalian PKC δ as the main PKC isoform involved in this process, showing that this regulation is conserved from yeast to mammals. Pkc1 and its kinase activity are required for the optimal phosphorylation and recruitment to the site of damage of different proteins of the DNA integrity checkpoint cascade. We have analysed Pkc1 kinase activity observing that there are no significant changes on its activity when the DNA integrity is compromised. To test whether spatial regulation of PKC may be important for its function, we used *S. cerevisiae* to determine the localization of different minimal functional versions of PKC and mouse Embryonic Stem Cells (mESCs) to study PKC δ localization. PKC nuclear accumulation was observed under DNA damage conditions. Moreover, when the Nuclear Localization Signal (NLS) in PKC δ was mutated, the checkpoint activation was deficient. These results suggest that the role of PKC in the DNA integrity checkpoint may take place in the nucleus. Finally, we demonstrated that PKC function affects the kinase activity of the checkpoint sensor kinase Mec1, as *pkc1* mutant cells showed an impaired activation of Mec1 under DNA damage conditions. Importantly, activation of mammalian checkpoint kinase ATR is also impaired in PKC δ ^{-/-} mutants mESCs. All our results provide a better understanding for the role of PKC in the DNA integrity checkpoint.

Keywords:

Pkc1, PKC δ , DNA Integrity Checkpoint, Mec1, ATR



P-158

FGF23 Is Associated With Systemic Inflammation, Reduced Muscle Function, And Impaired Pulmonary Capacity In Children And Adolescents With Cystic Fibrosis Receiving CFTR Modulators (FIQMODE Study)

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Introduction: Physical fitness, particularly peak oxygen uptake (VO₂peak), is a strong prognostic marker in cystic fibrosis (CF), inversely associated with mortality and disease progression(1). Fibroblast growth factor 23 (FGF23) regulates mineral metabolism and contributes to systemic inflammation(2). In CF, FGF23 levels are elevated and may enhance TGF- β -mediated IL-8 secretion, promoting a pro-inflammatory environment(3). However, its role appears context-dependent. Despite CFTR modulators reducing inflammation, some patients retain residual inflammatory activity, making the study of FGF23 in pediatric CF relevant(4). **Objective:** To explore associations between FGF23, inflammatory biomarkers, muscle performance, and pulmonary function in children and adolescents with CF receiving elxacaftor/tezacaftor/ivacaftor. **Methods:** Partial Pearson correlations were performed in 46 participants. FGF23 levels were correlated with inflammatory markers, body composition, muscle strength, respiratory muscle function, aerobic capacity, and pulmonary function. **Results:** FGF23 positively correlated with TNF α (p=0.017) and sTNFR1 (p=0.031). Negative correlations were observed with lean mass (p=0.023), handgrip (p=0.018), knee flexion (p=0.018), knee extension (p=0.034), maximal inspiratory (p=0.049) and expiratory pressures (p=0.012). It was also inversely correlated with FEV1 (p=0.005) and FVC (p=0.002). **Conclusion:** FGF23 was associated with systemic inflammation, reduced muscle and respiratory function, and impaired pulmonary capacity in pediatric CF on ETI. It may serve as an integrated biomarker of inflammation and functional deterioration despite modulator therapy.

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1 PMID:30206131; 2 PMID:31461904; 3 PMID:29085059;

4 PMID: 40967763

Keywords:

Fibrosis Quística, ETI, FGF23, Physical Fitness

P-159

Establishing In Vitro Models Of IGF1R Deficiency Across Diverse Lung Cell Types To Study Respiratory Pathologies

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Background: The Insulin-like Growth Factor 1 Receptor (IGF1R) signaling pathway is a critical regulator of respiratory homeostasis; its dysregulation is heavily implicated in pulmonary pathologies, including asthma, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Deciphering cell-specific IGF1R contributions remains challenging due to the cellular complexity of the lung microenvironment.

Methods: We established a multifaceted *in vitro* modeling platform combining primary mouse tissue isolation with CRISPR-Cas9 genome editing in human lung epithelial cell lines (A549 and BEAS-2B) as tools to mechanistically investigate IGF1R-mediated signaling and cellular cross-talk in monocultures and organoids. Primary mouse embryonic fibroblasts (MEFs) from *Igf1r*^{-/-} embryos and adult mouse lung fibroblasts (AMLFs) from conditionally deficient mice were isolated to evaluate baseline knockout phenotypes.

Results: Profiling revealed distinct, cell-specific baseline IGF-system gene expression patterns in human fibroblasts and A549 cells following pro-fibrotic TGF- β stimulation. Under baseline conditions, primary *Igf1r*^{-/-} MEFs and AMLFs exhibited no significant alterations in growth kinetics, morphology, or inflammatory cytokine/chemokine secretion. Notably, following a bleomycin (BLM) challenge, IGF1R deficiency normalized both cellular and mitochondrial ultrastructural morphology, though it did not alter the induced pro-inflammatory profile.

Conclusion: Together, these CRISPR-engineered human cell lines and primary murine models provide a robust, targeted framework to decipher cell-specific IGF1R downstream signaling mechanisms and evaluate its viability as a therapeutic target in respiratory pathology.

Keywords:

IGF1R, Cell Signaling, CRISPR-Cas9, Pulmonary Fibrosis, Lung Fibroblasts, Respiratory Diseases

P-160

A Novel Tumor-Endothelial Crosstalk Linked To Aggressiveness In Colorectal Cancer

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Colorectal cancer (CRC) is among the most prevalent cancers worldwide. Currently, important challenges remain in identifying patients at high risk of recurrence and effectively treating metastatic CRC disease. This highlights the urgent need to uncover novel mediators of CRC progression that can help cover these gaps. While tumor angiogenesis is known to drive CRC growth and metastasis, relevant tumor-endothelial interactions remain poorly understood. Previous work from our group showed that melanoma and breast cancer cells reduce the expression of the protein kinase GRK2 in tumor-associated endothelial cells, leading to aberrant angiogenesis and enhanced tumor growth. However, the specific tumor-secreted factors responsible for endothelial GRK2 downregulation and its potential contribution to CRC progression have not yet been evaluated. In this study, we demonstrate that CRC cells secrete the pro-angiogenic factor PDGF-BB in correlation with both tumor grade and intrinsic GRK2 expression. Notably, we also showed that purified and CRC-secreted PDGF-BB reduce the levels of GRK2 and endoglin (ENG), a TGF- β co-receptor essential for angiogenesis, in endothelial cells. Functionally, this concurrent downregulation impairs GRK2-mediated phosphorylation of ENG, disrupting its interaction with focal adhesion-modulating proteins and increasing endothelial cell proliferation, changes that drive pathological angiogenesis. Altogether, our findings reveal a novel GRK2-dependent tumor-endothelial crosstalk in CRC and provide new insights into mechanisms driving this communication axis, with potential implications for diagnosis and therapy of these tumors.

Keywords:

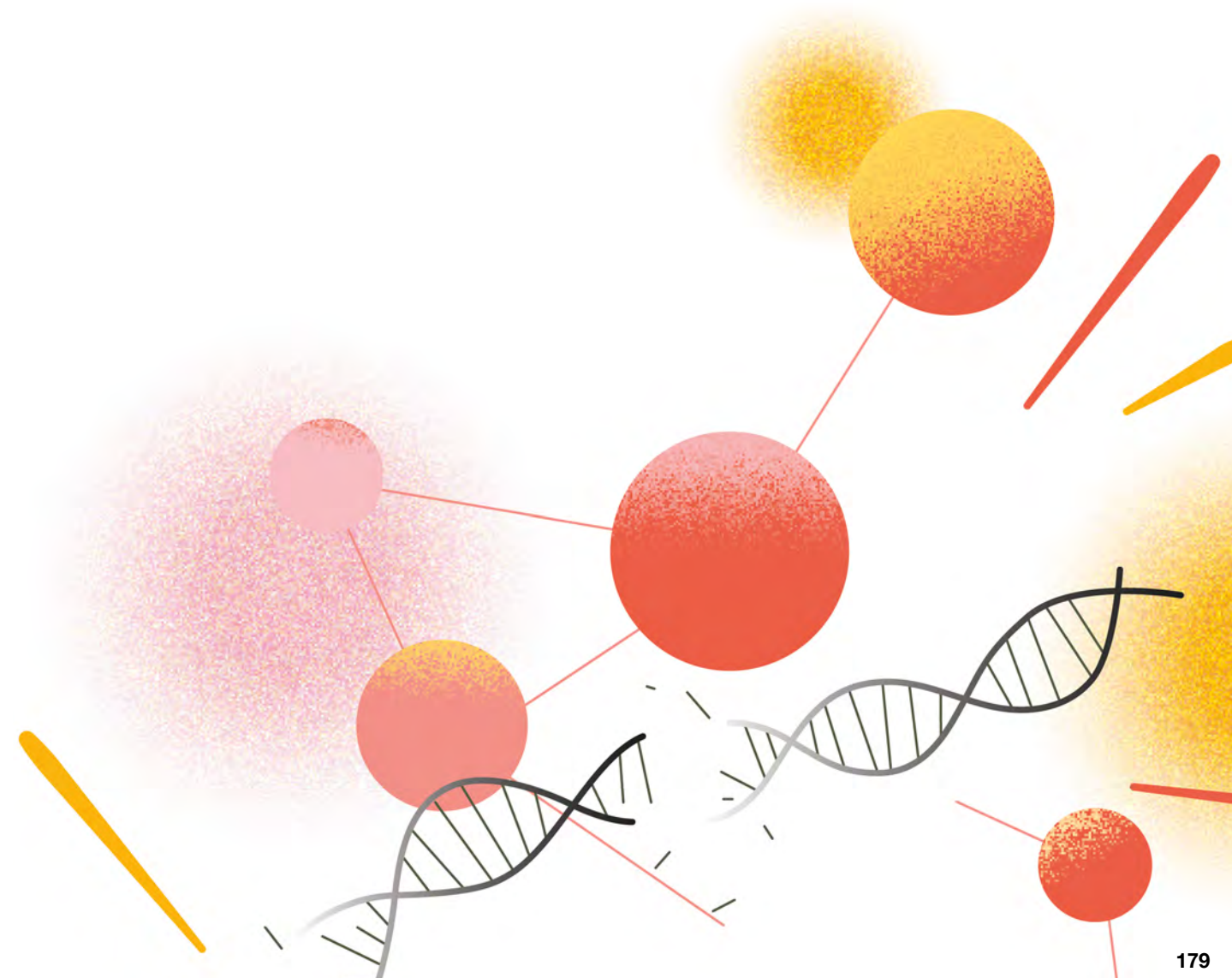
Colorectal Cancer, Angiogenesis, GRK2, PDGF-BB, ENG.



GRUPOS CIENTÍFICOS DE LA SEBBM:

MATRIZ EXTRACELULAR, FIBROSIS Y MICROENTORNO TUMORAL

9 DE SEPTIEMBRE





O-101

Uncovering The Role Of CTHRC1 In Fibrosis Across Organ Systems

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Fibrosis is a conserved response to tissue injury and a major contributor to organ dysfunction and mortality. Although fibroblasts drive extracellular matrix (ECM) deposition and scar formation, increasing evidence suggests that fibroblast heterogeneity critically determines fibrosis progression. Here, we investigated fibroblast heterogeneity across multiple fibrotic organs during the healing-scar phase to identify conserved activation states and shared profibrotic populations.

We performed an integrative analysis of published single-cell transcriptomic datasets from murine models of heart, lung, liver, and kidney fibrosis, complemented by spatial validation approaches and characterization of fibroblast activation dynamics after myocardial infarction.

Cross-organ integration identified 13 fibroblast clusters shared across all the datasets. Among them, one population of activated fibroblasts displayed the highest ECM-related and fibrotic transcriptional signatures and was consistently characterized by expression of Collagen Triple Helix Repeat Containing 1 (Cthrc1). These Cthrc1⁺ fibroblasts were detected across all organs analysed, independently of tissue origin, suggesting that Cthrc1 defines a conserved activated fibroblast state associated with pathological ECM deposition and scar formation. Additional analyses in myocardial infarction revealed activation trajectories involving Postn and Aspn, supporting a transition from early activated fibroblasts toward sustained profibrotic states.

Together, our findings reveal conserved patterns of fibroblast heterogeneity across organs and identify Cthrc1⁺ fibroblasts as a potential universal marker of activated profibrotic

ic fibroblasts, providing a framework for broadly applicable antifibrotic therapies.

Keywords:

Fibrosis, Fibroblasts, ScRNASeq, CTHRC1

O-102

Fibrosis In Lung Cancer: Translational Opportunities

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The desmoplastic/fibrotic tumor microenvironment rich in cancer-associated myofibroblasts (myCAFs) is a hallmark of non-small cell lung cancer (NSCLC). We have found that standard fibrosis and myCAF markers are associated with poor prognosis beyond TNM staging in the two major histologic NSCLC subtypes: lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC), supporting their use for adjuvant treatment decisions. However, the fibrosis regulation is complex and strongly dependent on the histologic subtype. Using functional assays and genetic loss- and gain-of-function approaches, we have observed that LUAD-myCAFs activate the profibrotic TGF- β 1/SMAD3 pathway, which drives excessive production of fibrosis markers and the collagenase inhibitor TIMP-1. Intriguingly, TIMP-1 acts as a cytokine in LUAD-myCAFs, driving CD63-dependent growth and invasion in cancer cells, and angiogenesis by amplifying VEGF-A signaling in endothelial cells. In contrast, the TGF- β 1/SMAD3 pathway is dysfunctional in LUSC-myCAFs, owing to a marked epigenetic repression of SMAD3, which is largely driven by a greater exposure to cigarette smoke particles. The epigenetic reprogramming in LUSC-myCAFs elicits a compensatory SMAD2 activation, resulting in reduced fibrosis, diminished angiogenesis, aberrant hypoxic/VEGF signaling, and intrinsic resistance to antifibrotic and antiangiogenic drugs such as nintedanib. Consistently, nintedanib has demonstrated clinical benefit in LUAD but not in LUSC in the LUME-1 clinical trial. Collectively, these findings identify the stromal SMAD3/TIMP-1 axis as a promising therapeutic vulnerability for precision medicine in LUAD-myCAFs, and highlight the need to identify alternative fibrosis regulators and stromal-targeted strategies in LUSC.

Keywords:

Fibrosis, Cáncer De Pulmón, Fibroblastos, TGF- β , SMAD3, TIMP1

O-103/P-161

HDAC11 Deficiency Restricts Fibrosis and Improves Muscle Function

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Duchenne muscular dystrophy (DMD) is a devastating genetic disorder caused by mutations in the dystrophin gene, which encodes for an essential protein to maintain muscle integrity. Loss of dystrophin leads to progressive muscle degeneration, chronic inflammation and replacement of muscle by fibro/adipose tissue. To date there is no cure for DMD and the identification of novel molecular targets is needed to design new therapies to slow DMD progression and prolong survival. Our group has recently identified HDAC11 as a new potential target to increase muscle regeneration, enhance mitochondrial function and improve muscle performance in young and old mice. To evaluate the therapeutic potential of HDAC11 targeting in muscular dystrophies, we have generated dystrophic mice lacking HDAC11. Our results show a positive impact of HDAC11 deficiency slowing down DMD pathology by reducing inflammation, muscle fibrosis and intramuscular fat deposition and improving muscle force and function. Importantly, a partial reduction in HDAC11 levels also improved the dystrophic phenotype and this therapeutic impact was also observed in old dystrophic mice. Fibro/adipogenic progenitors (FAPs) are considered the major contributors of muscular fibro/fat deposition, and both murine and human dystrophic FAPs lacking HDAC11 exhibit a reduced fibro/adipogenic potential. DMD muscles display profound metabolic alterations and preliminary results show that HDAC11 deficiency induces a muscle metabolic reprogramming toward a more oxidative phenotype, enhancing fatty acid oxidation. Collectively, our results demonstrate that the absence of HDAC11 attenuates the dystrophic phenotype and enhances muscle function, highlighting HDAC11 as a novel and promising therapeutic target for muscular dystrophies.

Keywords:

Muscle Dystrophies, Fibrosis, Metabolism, HDAC11, Therapy

O-104/P-162

A Lysyl Oxidase (LOX)/Bone Morphogenetic Protein-1 (BMP1) Complex To Facilitate Collagen Remodeling

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Proper extracellular matrix (ECM) formation is essential for tissue integrity and intercellular communication. When this balance is disrupted, fibrosis may develop, a process characterized by tissue stiffening due to excessive ECM deposition, mainly collagens, which replace functional tissue and impair organ function. Fibrosis is a clinical challenge and contributes to an estimated 45% of deaths in the developed world. Although multiple pathways involved in fibrotic progression have been identified, current treatments remain limited, noting the need for new therapeutic strategies and a deeper understanding of fibrotic mechanisms to uncover novel druggable targets. Collagen fibrillogenesis depends on C-terminal propeptide cleavage by bone morphogenetic protein-1 (BMP1), followed by lysyl oxidase (LOX) mediated oxidative deamination of lysine residues, enabling covalent cross-linking between fibrils. While BMP1 activates LOX through extracellular proteolytic processing, the regulatory mechanisms controlling BMP1/LOX axis remain unclear. Here, we examined the molecular dynamics of the LOX/BMP1 interaction and its relevance for ECM assembly. Confocal microscopy revealed colocalization of both proteins throughout the cell, with a punctate pattern consistent with ER/Golgi trafficking. To assess functional interaction, we used NanoBIT technology, detecting strong NanoLuc activity upon LOX-LgBIT/BMP1-SmBIT complementation. Domain mapping showed that BMP1 CUB2–CUB3 domains are required for binding, while in LOX, the catalytic domain contains a basic residue-rich segment that supports the interaction. These findings identify the LOX/BMP1 interface as a key regulatory axis in collagen deposition and matrix remodeling, representing a potential therapeutic target for fibrosis.

Keywords:

Extracellular Matrix, Collagen, Lysyl Oxidase, BMP1, Protein-Protein Interaction, Proteolysis.



O-105/P-163

Lung Fibroblasts Regulate Disseminated Tumor Cells Survival, Dormancy And Progression To Metastasis Through FGFR2 Pathway

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Metastasis is the main cause of death in patients with solid tumors. Disseminated tumor cells (DTCs) can remain dormant for extended periods before forming metastases. The microenvironment of secondary organs plays a key role in regulating this dormancy-proliferation switch. We previously identified lung fibroblast-derived TGFβ1 as a critical mediator of DTC proliferation. We now explore the role of the lung stroma and fibroblast growth factor receptor 2 (FGFR2), a receptor tyrosine kinase often altered in head and neck cancer, in regulating DTCs fate.

We use healthy lung fibroblasts and head and neck cancer cell lines as an *in vitro* dormancy model, including a lung DTCs-derived cell line (LU-HEp3) and a dormant cell line (D-HEp3).

Our results show that FGFR2 is overexpressed in LU-HEp3 cells while D-HEp3 cells upregulate FGFR1. Pharmacological and genetic inhibition of FGFR2 in proliferative cells reprograms them into a dormant phenotype, as it induces cell cycle arrest, upregulates dormancy markers and reduces proliferation *in vitro* and *in ovo*. Transcriptomic analysis showed that LU-HEp3 FGFR2 knockout cells upregulate extracellular matrix composition pathways and downregulate immune chemotaxis, migration and RNA processing pathways. Notably, FGFR1 pharmacological inhibition in dormant cells induces apoptosis and inhibits tumor growth *in ovo*. Additionally, conditioned media from healthy lung fi-

broblasts increases proliferation of LU-HEp3 cells, inducing cell cycle progression and activating ERK signaling *in vitro* and *in ovo*.

Our findings suggest that there is a crosstalk between fibroblasts and DTCs at metastatic organs that influence lung DTCs biology. Besides, FGFRs regulate DTCs fate. FGFR2 promotes DTCs proliferation while FGFR1 regulates dormant DTCs survival.

Keywords:

FGFR2, Fibroblasts, Dormancy, Head And Neck Cancer, Metastasis

O-106/P-164

Antineoplastic Targeted Therapy: Identifying And Manipulating Cancer-Associated Fibroblasts (CAFs) With Aberrant Mechanotransduction

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The tumor microenvironment (TME), composed of resident and infiltrating stromal cells, plays a central role in tumor progression, metastasis, and therapeutic resistance. Among stromal populations, mechanically activated cancer-associated fibroblasts (myCAFs) are key modulators of extracellular matrix (ECM) remodeling and tumor aggressiveness. These CAFs exhibit aberrant activation of Yes-associated protein (YAP), a transcriptional co-activator of the Hippo pathway that promotes ECM stiffening, angiogenesis, and cancer invasion. However, the absence of specific markers for aggressive CAF subsets limits the development of targeted therapies.

We hypothesize that aggressive YAP-high CAFs display unique membrane epitopes resulting from YAP-dependent transcriptional or post-translational regulation, which could serve as selective biomarkers. To identify these epitopes, we use cell-based SELEX (Systematic Evolution of Ligands by Exponential Enrichment) to generate aptamers with selective affinity for aggressive CAFs.

To distinguish YAP-high CAFs from less aggressive counterparts, we engineered a murine CAF line with inducible YAP degradation through a degron-tag system. Functional validation by Western blot, qPCR, luciferase assays, RNA-

seq, ECM remodeling, 2D coculture, and cell-derived matrix assays confirmed effective YAP inhibition and reduced mechanotransduction activity. This model provides a robust platform to evaluate the therapeutic impact of YAP targeting in CAFs and to perform comparative cell-SELEX screening. Selected aptamers will subsequently be used to isolate and identify membrane targets.

Overall, this strategy may enable the selective targeting and reprogramming of aggressive CAFs, reducing off-target toxicity and improving therapeutic outcomes.

Keywords:

Tumor Microenvironment, Cancer-Associated Fibroblasts, YAP, Targeted Therapies

O-107/P-165

Identification Of Fibroblast Cell State Markers In Cardiac Fibrosis Using Human Engineered Cardiac Connective Tissues (HECCTs)

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Cardiovascular diseases are the leading cause of death worldwide, and most share cardiac fibrosis as a common pathological feature. Cardiac fibrosis involves extracellular matrix (ECM) remodeling, leading to impaired cardiac structure and function. Cardiac fibroblasts (CFs), the primary ECM-producing cells, are highly heterogeneous and dynamically respond to stress or injury. Recent evidence supports the existence of distinct CF functional subtypes; the lack of specific biomarkers makes their identification challenging. Advances in RNA-Seq have revealed transcriptionally distinct fibroblast populations associated to localization and function. In heart failure, multiple CF subpopulations have been identified.

We developed human engineered cardiac connective tissues (hECCT) using three CF sources. hECCTs mimic fibrotic mechanical forces, and activation with transforming growth factor β1, allows fibroblasts activation. We performed bulk RNA-Seq for activated-hECCTs separated into two subtypes, superficial and core fibroblasts. Data was analyzed using differential gene expression and functional analysis to define common genes in each fibroblasts subtype corresponding to the different hECCT under study. Results indicated that the superficial fibroblasts are more metabolically active. Meanwhile, the core fibroblasts, appears to overexpress genes important for response to cellular stress. qPCR analysis shows a trend toward genes such as ACTA2, PFAS, PCK2, URHF2, to be used as markers for each layer.

Overall, these results support the existence of spatially distinct fibroblast states within profibrotic hECCTs, characterized by differential metabolic and inflammatory transcriptional programs.

Keywords:

Human Cardiac Fibrosis, Fibroblast, Bioinformatics, Cardiovascular Diseases, RNA-Sequencing

O-108/P-166

Establishment Of Human Engineered Cardiac Connective Tissue (HECCT) And A Murine Model To Investigate Radiation-Induced Cardiac Pro-Fibrotic Side-Effects In Breast Cancer Radiotherapy

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Radiotherapy is an essential component of breast cancer treatment, significantly reducing the risk of tumor recurrence. However, incidental radiation exposure in the thoracic area may affect healthy organs, such as the heart, contributing to the late onset of radiation-induced cardiac fibrosis. In this study, we investigate early radiation-induced pro-fibrotic responses in human and murine experimental cardiac models.

Human induced pluripotent stem cell-derived cardiac fibroblast (iPSC-CFs) were exposed to clinically approved FAST-FORWARD radiation regimen. Radiation-induced DNA damage was evaluated by confocal microscopy through the assessment of phosphorylated H2AX (γH2AX) nuclear foci accumulation. Increased γH2AX foci formation confirmed activation of DNA damage response and nuclear stress signaling in irradiated fibroblasts.

iPSC-CFs were used to generate three-dimensional human cardiac connective tissue (hECCT). Biomechanical characterization, including pole deflection and perimeter measurements, showed no significant differences between irradiated and control groups. Similarly, transcriptional analysis revealed no significant alterations in pro-fibrotic gene expression after radiation and 7 days of recovery.

These findings suggest that hypo-fractionated FAST-FORWARD radiation-induced DNA damage response in fibroblasts detectable at the protein level, that after a relapse of



7 days was not reflected into biomechanical parameters of 3D hECCT.

Overall, this work establishes a 3D platform including extracellular matrix and cardiac fibroblasts for studying radiation-associated cardiac toxicity and highlights the importance of multi-level readouts to detect early pro-fibrotic changes in human cardiac models.

Keywords:

Cardiac Fibrosis, Radiotherapy, Breast Cancer

O-109/P-167

When Tumours Bend Time: Daily Host-Microbiota Crosstalk In Colorectal Cancer

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Disturbed circadian rhythmicity and colorectal cancer development are tightly linked. On the one hand, disrupted daily environmental rhythms have been associated with an increased risk for developing colorectal cancer in shift workers. On the other hand, daily rhythmicity is altered on the molecular level in tumours, and disruption of circadian clock function in colorectal cancer cells has been shown to promote tumour growth. Thus, disturbed circadian rhythmicity both within the tumour and on the organismal level can promote tumour growth. However, not only the host tissue but also the microbiota is forming part of the colorectal tumour niche. Intriguingly, the circadian clock network is a central regulator of host-microbiota crosstalk. Nevertheless, up to now it is neither known how colorectal cancer might impact on daily microbiome dynamics, nor whether disturbed daily communication between the host and the microbiome might promote disease progression. Applying a multi-omics approach combining metagenomics, metabolomics, and transcriptomics, we find that colorectal cancer alters daily microbiome composition, with potentially far-reaching implications for the tumour and its environment. How disturbed crosstalk between the tumour and the microbiome around the clock might impact on colorectal cancer progression will be discussed.

Keywords:

Circadian Rhythm, Colorectal Cancer, Host-Microbiota Crosstalk

O-111/P-169

CD98hc Drives Fibroblast Plasticity And Matrix Invasion: Implications For The Tumor Microenvironment

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CD98hc is a transmembrane protein that functions as an ancillary subunit forming heterodimers with members of the LAT family of amino acid transporters. Beyond its essential role in amino acid transport, CD98hc also interacts with galectins and integrins, modulating cellular processes including adhesion, spreading, migration, and proliferation. To investigate the impact of CD98hc on cell plasticity, we used genetically modified mouse dermal fibroblasts (MDF) in which the Slc3a2 gene encoding CD98hc is either flanked by loxP sites (WT) or excised upon Cre recombination (KO). We saw that CD98hc is critical for fibroblast motility and wound repair, as its ablation severely impairs proliferation, migration, spheroid formation, and matrix invasion. To explore the molecular mechanisms underlying these differences, we performed mRNA sequencing of MDF WT and KO cells. Transcriptomic analysis revealed the overexpression of genes associated with cell-cell adhesion, extracellular matrix organization, and epithelial-to-mesenchymal transition (EMT)-related pathways in the presence of CD98hc, suggesting an altered cell-cell contact. In parallel, we used BioID as a proximity-labelling approach to identify CD98hc-interacting proteins that could explain the observed phenotypes. Using biotin ligase-tagged CD98hc, we detected 245 proteins significantly enriched compared to controls. Among them, Gene Ontology (GO) analysis revealed association with several biological processes such as cell migration, junction organization, and polarity establishment. Together, these results point to a role of CD98hc in modulating actin dynamics and epithelial-to-mesenchymal transition, providing new insights into its contribution to cell plasticity.

Keywords:

Migration, Invasion, Actin, Plasticity, EMT

P-170/O-112

Dysregulation Of The Matrisome In Periprostatic Adipose Tissue Drives Prostate Cancer Progression Involving The Oncogenic LAMB1/ RPSA-Receptor Axis

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Despite advances in understanding the molecular mechanisms of prostate cancer (PCa) development/progression (a leading cause of cancer-related mortality), the contribution of periprostatic adipose tissue (PPAT) remains poorly understood. We explored the influence of dysregulated PPAT-matrisome components in PCa development/progression by an integrative multiomic approach (transcriptomic/proteomic...) across multiple patient cohorts and cell-culture/preclinical models. A significant dysregulation in PCa patients vs. control subjects (with benign prostate-hyperplasia) was observed. LAMB1/RPSA (laminin-receptor) system emerged as a key oncogenic player, being its expression levels significantly elevated in the PPAT/prostate tissue of PCa patients and correlated with key aggressiveness features. LAN411 (laminin-containing LAMB1) is a major contributor in mediating the pathophysiological interaction between PPAT-PCa through RPSA. Functional assays, both *in vitro* (RPSA silencing and overexpression) and *in vivo* (preclinical models with RPSA silencing or with LAN411 integrated in basement membrane extract), demonstrated the impact of LAMB1/RPSA-axis modulation on critical cancer hallmarks (proliferation/migration/invasion/adhesion/colony-tumorspheres formation and tumor-growth). Mechanistically, RPSA dysregulation was associated with alteration in different critical oncogenic pathways (including c-MYC, energy-homeostasis, mitotic-spindle), occurring in parallel to changes in RPSA cellular distribution after RPSA silencing. These findings underscore the role of PPAT-derived LAMB1/RPSA-axis in promoting PCa development and progression, offering a unique opportunity for novel therapeutic research targeting PPAT matrisome-components in PCa.

Keywords:

Matrisome, Periprostatic Adipose Tissue, Prostate Cancer, Laminin B1, RPSA.

P-171

Tumor Microenvironment Innervation Co-Option As A Key Driver In Bile Duct Cancer Dissemination

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The innervation of the tumor microenvironment is a powerful driver of tumor growth and malignancy. Consequently, targeting tumor innervation has recently emerged as a promising strategy to enhance treatment efficacy across various cancer types. In this study, we developed a sophisticated 3D neuron-cancer assembloid model to investigate interactions between neuronal cells and intrahepatic cholangiocarcinoma (iCCA), an extremely aggressive bile duct cancer. Our molecular and functional analyses of iCCA-neuron assembloids reveal a highly intricate cancer-neuron interactome and identify a distinctive transcriptional signature linking cancer invasion to neuronal mimicry. Notably, this signature is enriched for neurodevelopmental and synaptic communication pathways, also overrepresented in subsets of patient bile cancer cells associated with poor prognosis, as demonstrated through single-cell RNA sequencing. By prioritizing neuronal mimicry genes based on patient survival data and *in vitro* validation, we have pinpointed several actionable genes and signaling pathways, paving the way for testing new therapeutic options in preclinical models of cholangiocarcinoma. Overall, our innovative assembloid platform provides critical insights into how neuronal interactions orchestrate aggressive cancer behavior and unveils novel therapeutic targets with high clinical potential.

Keywords:

Cholangiocarcinoma, TME, Innervation, Cancer Dissemination



P-172

Exosomal PSMD7 Deubiquitinase Stabilizes PI3K/AKT Oncogenic Signaling By Targeting PTEN For Proteasomal Degradation: A Novel Mechanism Of Chemoresistance Transmission In Pancreatic Ductal Adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) displays acquired resistance to the standard-of-care regimens. Tumor-derived exosomes transfer oncogenic molecular cargo between cells, yet the biochemical mechanisms of exosome-mediated chemoresistance remain uncharacterized.

Methods: Exosomes were isolated by sequential ultracentrifugation and characterized by NTA, TEM, and Western blot. Tumor tropism was quantified by flow cytometry and confocal microscopy. Drug encapsulation efficiency was determined by HPLC. Quantitative proteomics identified differentially expressed exosomal proteins. PSMD7 was functionally evaluated via shRNA and functional experiments, proteasome activity assays, co-immunoprecipitation, and xenograft models.

Results: PDAC-derived exosomes exhibited tropism for tumor cells, enabling delivery of treatments at 10-fold reduced concentrations while preserving antitumor efficacy and minimizing toxicity in non-malignant cells. Quantitative proteomics of exosomes identified 31 commonly upregulated proteins, with pathway enrichment analysis converging on proteasomal deubiquitination and PTEN stability regulation. PSMD7, a regulatory particle deubiquitinase of the proteasome, was the top candidate: its upregulation correlated with poor survival of patients. Mechanistically, PSMD7 interacts with PTEN, promoting its proteasomal degradation; thereby, constitutively activating PI3K/AKT signaling. PSMD7 silencing restored PTEN protein stability, suppressed p-AKT, and re-sensitized resistant PDAC cells to treatments both *in vitro* and *in vivo*.

Conclusions: Exosomal PSMD7 is a novel post-translational regulator of the PTEN/PI3K/AKT axis involved in chemoresistance transmission in PDAC, positioning it as a dual prognostic biomarker and druggable target.

Keywords:

Exosomes, Proteasome, PSMD7, PTEN, Chemoresistance, Pancreatic Cancer, Chemocarrier

P-173

Exploring The Therapeutic Potential Of MUC13 In Pseudomyxoma Peritonei

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Pseudomyxoma peritonei (PMP) is a rare malignant disease characterized by the accumulation of mucin within the peritoneal cavity. The current treatment involves an aggressive surgery; however, recurrence remains frequent, highlighting the need for novel biomarkers and therapeutic approaches. Recently, our group published the first mucin proteomic profile in PMP, identifying a unique mucin isoform profile and proposing MUC13 as a potential tumour biomarker.

This study investigates the role of MUC13 in PMP using cellular and animal models. First, MUC13 expression was evaluated in 2D and 3D cultures using different approaches. To further explore its function, MUC13 expression was silenced using specific siRNAs in PMP cell lines. We also generated a monoclonal anti-MUC13 antibody and tested its efficacy in cell cultures. Furthermore, a toxicity experiment was conducted using a PMP xenograft mouse model (PMP-PDX) to assess the impact of anti-MUC13.

Our results showed that MUC13 was highly expressed in PMP cells, and its membrane localization was confirmed. Silencing MUC13 significantly reduced the viability of PMP cell lines. Treatment with anti-MUC13 also decreased cell viability and MUC2 secretion. Long-term treatment produced a clear reduction in cell viability and organoid size when treatment was administered on day 0. However, this effect was attenuated when treatment was administered on day 6. These results suggest that MUC13 may play a role in the initial stages of tumour development. Finally, toxicity studies revealed no adverse effects at the tested doses in the PMP-PDX model.

Overall, these findings support the potential of MUC13 as a promising therapeutic target for PMP and suggest that

targeting this protein could help reduce postoperative recurrence rates.

Keywords:

Cancer; Pseudomyxoma Peritonei; Mucin; MUC13; Antibody

P-174

GLUT12 Expression And Activity In Breast Cancer May Be Affected By Cancer-Associated Adipocytes In The Tumor Microenvironment

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Obesity predisposes postmenopausal women to a higher risk of developing breast cancer and a lower survival rate due to increased estrogen levels, chronic low-grade inflammation, and dysregulation of glucose metabolism, which promote tumor development. Insulin resistance, common in individuals with obesity, can lead to hyperglycemia and hyperinsulinemia, which increase Warburg effect, contributing to tumor development. GLUT12 is an insulin responsive glucose transporter expressed in breast tumors, whose expression is increased by estrogens and high extracellular glucose in MCF-7 cells. GLUT12 has also been associated with breast cancer development and progression for its implication in the Warburg effect. Our hypothesis is that GLUT12 expression and activity is increased in breast tumors of overweight/obese postmenopausal patients com-

pared to lean patients, and that this increase is influenced by cancer-associated adipocytes (CAA) in the tumor microenvironment. We first show that the rise in extracellular glucose increases sugar uptake selectively by GLUT12 in MCF-7 cells. Immunohistochemical studies in luminal breast tumors from postmenopausal patients show that GLUT12 and GLUT1 expression does not correlate with the BMI. However, in both lean and overweight/obese patients, in the tumor cells in contact with the CAAs GLUT12 is highly expressed; while this is not observed for GLUT1. Preliminary studies in co-cultures of MCF-7 cells with adipocytes from peritumoral breast tissue from overweight/obese patients show an increase in sugar uptake by GLUT12 compared to non-cocultured MCF-7 cells. These results open up the way for future research to elucidate whether GLUT12 could be a potential therapeutic target in breast cancer tumor microenvironment.

Keywords:

Breast Cancer, Cancer-Associated Adipocytes, GLUT12

P-175

Optimization And Application Of Primary Fibroblast In Vitro Models To Characterize Responses To Antifibrotic Therapies In Idiopathic Pulmonary Fibrosis (IPF)

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown origin, characterized by abnormal remodeling of the pulmonary stroma, leading to excessive extracellular matrix deposition and progressive loss of tissue architecture and respiratory function. Although current antifibrotic therapies, such as pirfenidone and nintedanib, have been shown to slow disease progression, their precise mechanisms of action remain incompletely understood. Moreover, the heterogeneous clinical response observed among patients suggests the existence of intrinsic differences in the cellular populations involved in fibrotic processes.

In this context, lung fibroblasts play a central role in IPF pathogenesis due to their ability to differentiate into an activated myofibroblastic phenotype, characterized by increased extracellular matrix production and stromal contraction, ultimately contributing to tissue stiffening.

In the present study, we used 23 primary fibroblast cultures



derived from IPF patients to characterize their functional behavior following treatment with pirfenidone and nintedanib. Proliferation, analysis of protein expression fibrosis markers, and evaluation of contractile capacity in collagen, was assessed to determine their functional response to treatment. In addition, RNAseq and differential gene expression analysis comparing fibroblast with differential response to treatment, to elucidate potential mechanisms of treatment resistance.

Our preliminary data suggest the presence of heterogeneity in the response of IPF fibroblasts to antifibrotic treatments. This observation supports the possibility of stratifying samples into sensitivity and resistance profiles and to extend these findings to identify biomarkers for patient selection.

Keywords:

Idiopathic Pulmonary Fibrosis (IPF), Primary Lung Fibroblasts, Antifibrotic Therapies, Treatment Response Heterogeneity, Biomarker Discovery

P-176

Study Of MiRNA-Driven Modulation Of Cardiac Fibrosis By CAR-FAP Extracellular Vesicles In 3D Organoids

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Cardiac fibrosis is characterized by sustained fibroblast activation and extracellular matrix remodeling, leading to progressive tissue dysfunction and heart failure. Extracellular vesicles (EVs) mediate intercellular communication by transferring bioactive cargo and are emerging as modulators of fibrotic processes, with therapeutic potential largely attributed to their miRNA content.

Here, we used a hollow-fiber bioreactor (HFBR) system to produce EVs under conditions that more closely mimic the physiological microenvironment. These EVs were derived from HaCaT cells expressing a fibroblast activation protein (FAP)-targeting construct (FAP-CAR EVs), promoting the target to fibroblasts and incorporating CD63 domains to enhance vesicular loading and stability under dynamic conditions. Western blot analysis confirmed enrichment of CD63-positive vesicles and the presence of the CAR construct compared to wild-type EVs.

Fibrotic human cardiac organoids were generated using collagen scaffolds and iPSC-derived fibroblasts, followed by TGF- β 1 activation. Treatment with CAR-FAP EVs reduced pro-fibrotic gene expression compared to untreated controls, with effects comparable to wild-type EVs. These effects were accompanied by improved biomechanical parameters, including control-like behavior in pole deflection, perimeter, and organoid area.

Small RNA sequencing of FAP-CAR EVs content showed enrichment of miRNA let-7 family known for their anti-fibrotic actions, suggesting their role in regulating fibrotic responses in a 3D human cardiac model.

Overall, this work establishes an HFBR-based platform for CAR-FAP EV production and studies the contribution of EV-associated miRNAs to the modulation of cardiac fibrosis in 3D organoid models.

Keywords:

Extracellular Vesicles, Organoids, MiRNAs, Cardiac Fibrosis, Hollow-Fiber Bioreactor

P-177

Macrophages And Cardiomyocytes Modulate Pro-Fibrotic Responses In TGF- β -Induced Cardiac Organoids

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Cardiac fibrosis is a major contributor to heart failure progression and is characterized by excessive extracellular matrix deposition and impaired cardiac function. This process is driven by complex interactions among fibroblasts, immune cells, and cardiomyocytes that regulate tissue remodeling. Multicellular cardiac organoid models were developed to investigate the contribution of immune and contractile cells to fibrotic remodeling.

3D organoids were generated using primary mouse cardiac fibroblasts alone (Fi), fibroblasts with macrophages (MaFi), or fibroblasts, macrophages, and spontaneously beating murine cardiomyocytes (CaMaFi). TGF- β 1 stimulation induced fibrosis, resulting in biomechanical alterations compared with non-fibrotic controls. Pole deflection increased significantly in Fi and MaFi organoids (****p<0.0001), whereas CaMaFi organoids exhibited lower pole deflection (**p<0.01).

Fibrotic stimulation also reduced organoid volume in Fi (6.3 mm³ vs. 3.3 mm³), MaFi (5.1 mm³ vs. 2.6 mm³), and CaMaFi (5.6 mm³ vs. 2.5 mm³), suggesting that cardiomyocytes influence tissue biomechanics during remodeling.

qPCR analysis revealed increased expression of COL1 (***p<0.001) and FGF2 (**p<0.01) in Fi organoids following TGF- β 1 stimulation. MaFi organoids displayed an attenuated fibrotic response, with a smaller increase in COL1 than Fi organoids (*p<0.05). In CaMaFi organoids, TGF- β 1 significantly increased Tnnt2 expression (*p<0.05), indicating cardiomyocyte adaptation to fibrotic remodeling.

These findings highlight the importance of multicellular crosstalk in regulating fibroblast-driven fibrosis and establish integrated murine cardiac organoids as a physiologically relevant platform for studying the biomechanical and molecular mechanisms of cardiac fibrotic remodeling.

Keywords:

Cardiac Fibrosis, Organoids, Tissue Remodeling

P-178

The Natural Compound C3 Reduces Tumor Progression And Metastasis In Triple-Negative Breast Cancer Models With Potential Antiangiogenic Activity

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The urgent need for new therapeutic options for triple-negative breast cancer (TNBC) is driven by its aggressiveness, high metastatic potential, and limited treatment options. C3, a natural compound derived from the olive tree among other plant sources, exhibits antioxidant activity and the ability to modulate autophagy. Given the relevance of oxidative stress and autophagy in tumor progression, C3 was evaluated as a potential antitumor and antiangiogenic agent.

In vitro cytotoxicity assays were performed in human MDA-

MB-231 and murine 4T1 breast cancer cells to determine viability and IC50 values. In addition, human endothelial HMEC-1 cells were used to evaluate proliferation, migration, and tube formation. A wound-healing assay was also conducted in MDA-MB-231 cells to assess effects on cell migration. C3 reduced cell viability in cancer cell lines and partially inhibited migration in both tumor and endothelial models, suggesting effects on cell proliferation and motility.

Based on these results, BALB/c mice inoculated with 4T1 cells were used as an in vivo TNBC model. Tumor volume, growth rate, proliferation (Ki-67), metastatic burden, and systemic toxicity were evaluated over time. In vivo, C3 treatment led to a slight reduction in tumor growth and a significant decrease in Ki-67 expression and metastasis, without observable toxicity in major organs.

Overall, these findings indicate that C3 exerts antiproliferative and antimetastatic effects in TNBC models, suggesting potential effects on tumor progression and preliminary antiangiogenic activity, supporting its further preclinical evaluation in aggressive breast cancer.

Keywords:

Triple-Negative Breast Cancer, Tumor, Metastasis, Cancer, Angiogenesis, Antiangiogenic, Antitumoral, In Vivo, Tumor Microenvironment, Natural Compound

P-179

Stromal Gq α Deficiency Triggers A Hypoxia-Like Response That Drives Aberrant Tumor Vascularization And Metastasis In Oral Cancer

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Head and Neck Squamous Cell Carcinoma (HNSCC) is an aggressive malignancy whose progression is critically shaped by the tumor microenvironment (TME), particularly by Cancer-Associated Fibroblasts (CAFs). We previously showed that Gq α loss reprograms fibroblasts toward a CAF-like phenotype through ceramide accumulation and altered intracellular trafficking, promoting tumor cell growth and invasion via exosome-mediated signaling.

Here, we demonstrate that Gq α -deficient fibroblasts also drive aberrant tumor vascularization, a key cancer hallmark required to sustain tumor growth and metastatic dissemination. Accordingly, Gq α -KO MEFs secretome is shifted toward a pro-vascular phenotype, characterized by increased



pro-angiogenic and reduced anti-angiogenic factors. These changes are accompanied by increased secretion and deposition of versican, a proteoglycan that promotes angiogenesis and hypoxic niche formation, in a process dependent on the HIF-1 α transcriptional response and mimicked by exposing WT MEFs to hypoxia.

Functionally, conditioned medium from G α q-KO MEFs enhances sprouting of Human Umbilical Vein Endothelial Cell (HUVEC) spheroids and modestly reduces permeability, an effect reproduced in G α q-silenced human oral fibroblasts (hOMFs). Interestingly, *in vivo*, co-injection of G α q-deficient fibroblasts with Cal27 cancer cells generated highly vascularized tumors with increased metastatic dissemination.

Overall, these findings identify G α q-deficient fibroblasts as key stromal contributors to the establishment of a pro-angiogenic tumor microenvironment, thereby contributing to HNSCC progression. These results highlight the tumor stroma as an active driver of disease progression and a potential therapeutic target.

Keywords:

G α q, Stroma, Oral Cancer, Tumor Vasculature, Cancer Associated Fibroblasts (CAF)

ganic gold nanomaterials, specifically **gold nanoprisms (AuNPrs)**, $\lambda_{\text{max}} = 1100 \text{ nm}$), with tailored optothermal properties for next-generation opto-thermal POC biosensors. Here, we present a series of rapid **lateral flow diagnostic platforms** that exploit the photothermal properties of AuNPrs to enable calorimetric signal amplification. In one representative approach, a CLFIA was developed for the detection of some specific miRNA, using a sandwich configuration combining AuNPrs functionalized with complementary DNA probes enabled the detection of PDAC-associated miRNAs contained within EVs, reaching a detection limit of **0.1 fmol miRNA μL^{-1}** through NIR-induced photothermal signal amplification. Validation against qRT-PCR on EVs from pancreatic cell lines shows strong concordance, with advantages in cost, speed, and simplicity. These results demonstrate the potential of optothermal lateral flow biosensors to exploit the molecular cargo of EVs for highly sensitive liquid biopsy applications, although further large-scale clinical validation is required.

Keywords:

MiRNAs, Opto-Thermal Sensing, Gold Nanotriangles, LFIA, Extracellular Vesicles (EVs), Pancreatic Ductal Adenocarcinoma (PDAC), Liquid Biopsies.

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Detection Of Tumour-Related MicroRNAs (MiRNA) From Extracellular Vesicles (EVs) Using Calorimetric Lateral Flow Immunoassays (CLFIA) Based On Gold Nanoprisms (AuNPrs)

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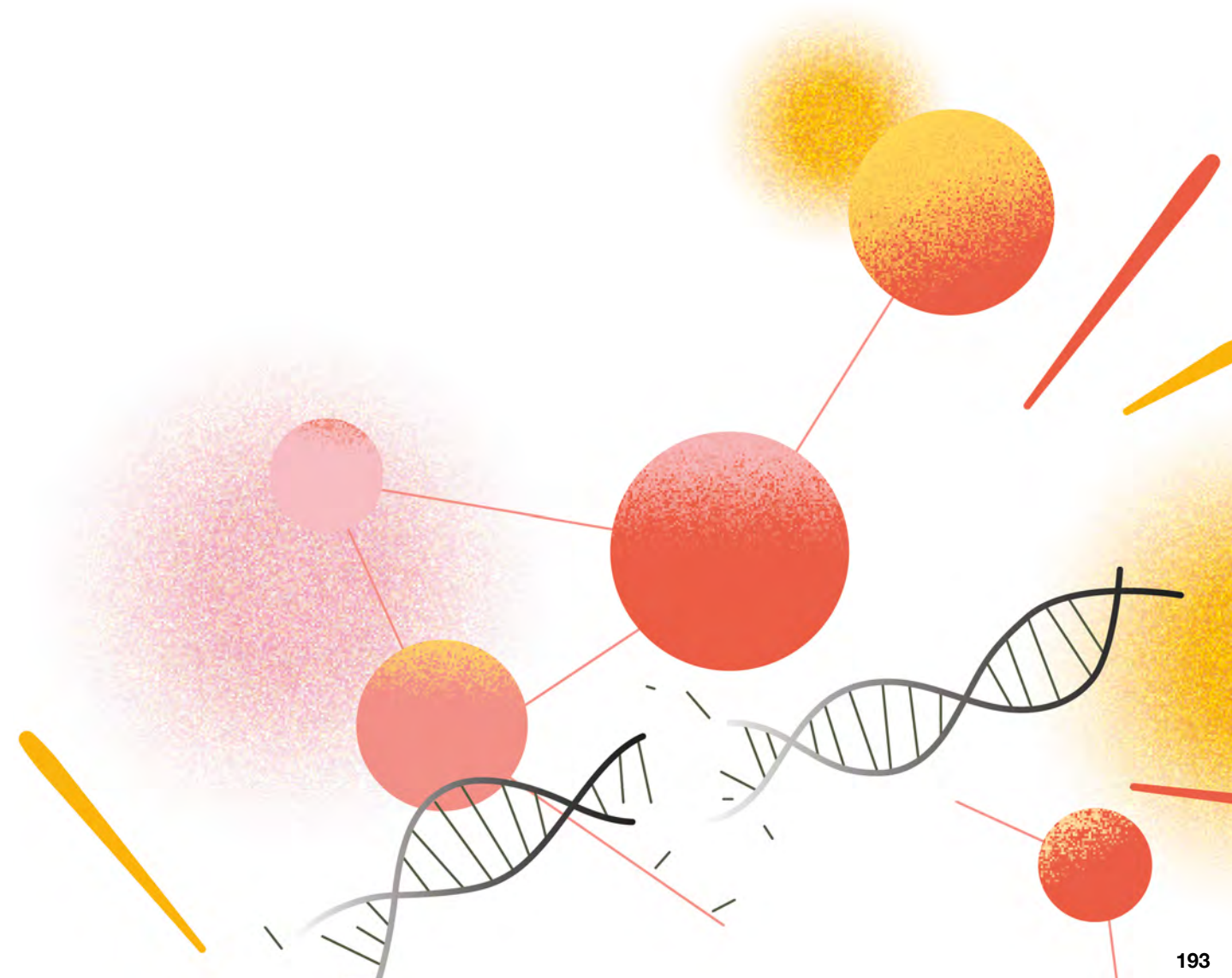
Pancreatic ductal adenocarcinoma (PDAC) remains one of the leading causes of cancer-related deaths, driven by late diagnosis, limited treatments, and poor therapeutic responses. **Extracellular vesicles (EVs)** have emerged as promising liquid biopsy biomarkers, as they carry a wide range of tumor-associated molecules, including surface membrane proteins and intravesicular nucleic acids such as disease-specific miRNAs, that reflect the molecular landscape of their parental tumor cells. As mediators of cellular communication, EVs provide valuable information on tumor progression, metastasis, chemoresistance, and inflammation, while offering unique opportunities for early diagnosis and therapy monitoring in PDAC. Our team exploits inor-



GRUPOS CIENTÍFICOS DE LA SEBBM:

REGULACIÓN DE LA EXPRESIÓN GÉNICA Y DINÁMICA DEL GENOMA

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Cyclin B1-CDK1 Regulates Mitotic Spindle Dynamics: Implications For Epithelial Morphogenesis And Cancer

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Cyclin B1-CDK1 is the master kinase complex driving mitosis. To extend our understanding of this complex, we generated a CRISPR/Cas9 Cyclin B1 cell line and combined live-cell imaging, advanced microscopy, quantitative proteomics, biochemistry, and functional assays. We demonstrated that Cyclin B1-CDK1 localizes to unattached kinetochores, where it functions as both an integral component and upstream regulator of the Spindle Assembly Checkpoint. In addition, we identified a second pool of Cyclin B1-CDK1 at spindle poles, although its functional role remains to be fully elucidated. Mass spectrometry analysis identified Nuclear Mitotic Apparatus protein (NuMA), a key regulator of spindle assembly, spindle orientation, and chromosome segregation, as a major interactor of Cyclin B1 in mitosis. Cyclin B1 and NuMA colocalize at spindle poles, interact in close proximity, and display a dynamic association at these structures. Furthermore, we identified a region within NuMA required for Cyclin B1 binding, while preliminary depletion experiments suggest that NuMA contributes to Cyclin B1 recruitment at spindle poles. These findings identify a previously unrecognized Cyclin B1-CDK1-NuMA assembly at spindle poles and suggest that Cyclin B1-CDK1 regulates spindle dynamics through its interaction with NuMA, extending its functions beyond mitotic entry and checkpoint signaling. Given the essential role of the mitotic spindle in accurate chromosome segregation and oriented cell division, this assembly may contribute to genome stability, tissue homeostasis, and epithelial morphogenesis. Ongoing studies aim to define the contribution of the Cyclin B1-CDK1-NuMA assembly to epithelial morphogenesis and tumorigenesis.

Keywords:

Mitosis, Cyclin B1-CDK1, Spindle Assembly Checkpoint, Kinetochores, Spindle Poles, NuMA, Spindle Dynamics, Epithelial Morphogenesis, Tumorigenesis

O-114

Host chromatin architecture remodeling via transcription machinery hijacking in viral infection

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Herpes simplex virus type 1 (HSV-1) induces extensive remodeling of host chromatin and a host-to-virus transcriptional switch during lytic infection. By combining super-resolution imaging (STORM, DNA-PAINT, and OligoSTORM) with chromosome-capture technologies, we quantitatively dissect the nanoscale mechanism of this remodeling. Super-resolution microscopy enables, for the first time, direct quantification of host chromatin condensation and visualization of how this compaction arises through the hijacking of RNA polymerase II (RNAP II) and topoisomerase I (TOP1). We map the positions of viral genomes and their nanometric associations with RNAP II and cohesin, revealing distinct spatial patterns of host-virus genome interactions. These data, integrated with Hi-C analysis, uncover how HSV-1 reconfigures chromatin topology while maintaining A/B compartments. Finally, TOP1 inhibition fully blocks infection, suggesting an exploitable vulnerability in this virus-driven chromatin rewiring process.

Keywords:

Chromatin Architecture, HSV-1, Transcription, Host-Virus Genome Interactions

O-115

Super-Resolution Microscopy Reveals Chromatin Remodeling Under Mechanical Stimuli

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Single Molecule Localization Microscopy (SMLM) has emerged as a powerful super-resolution fluorescence imaging strategy, bypassing the optical diffraction limit to achieve a spatial resolution of approximately 20 nm. In recent years, SMLM has expanded our knowledge of chromatin architec-

ture by enabling the direct visualization of higher-order DNA folding and epigenetic domains at the nanoscale. Here, we leverage this high-resolution capability to address a fundamental question in nuclear mechanotransduction: **how cells respond to physical stimuli from their microenvironment**. While mechanical forces are known to drastically alter cell behavior, mapping the resulting structural rearrangements of chromatin has been hindered by a lack of precise perturbation tools. By combining SMLM with localized mechanical stimuli provided by nanopillar arrays, we systematically characterize the architectural modifications of chromatin under targeted physical stress.

Keywords:

SMLM, Mecanostrucción, Super Resolution Microscopy, Chromatin Architecture

O-116/P-181

Rpb4, An RNA Pol II Subunit, Cooperates With The 5'-3' Exoribonuclease Xrn1 To Modulate mRNA Synthesis And Stability In *Saccharomyces Cerevisiae*

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Gene expression involves the coordination of the mRNA degradation/gene transcription crosstalk. Some elements are involved in this regulation, such as the 5'-3' exoribonuclease Xrn1 in parallel to Ccr4, another mRNA degradation factors that also contributes to RNA pol II elongation. In addition, the RNA pol II subunit Rpb4, dissociable from the rest of the complex, also participates in transcription elongation, mRNA imprinting, and mRNA stability. Our data and those of other authors suggest that this may be a central element in the connection between the transcriptional machinery (RNA pol II) and that of mRNAs degradation and, therefore, a crucial point in the mechanism of mRNA cross-talk. Our recent data show that Rpb4 interacts with other RNA binding proteins (RBPs), modulating the imprinting and stability of RBP-dependent mRNA groups. The data suggest that this mechanism may operate with degradosome proteins such as Xrn1, Ccr4, Dhh1 or others. We will present data of the coordination of Rpb4 and Xrn1 on the mRNA crosstalk.

Keywords:

RNA Pol II, RPB, XRN1, MRNA, Transcription, Imprinting

O-117/P-182

Unraveling The Role Of The Prefoldin-Like Protein Bud27 In Ribosomal DNA Transcription And Ribosome Biogenesis

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Cells require precise coordination of protein synthesis enabling cell proliferation and growth, but also response to environmental changes. The TOR pathway, controlled by the TOR complex, is the main link between external nutrient availability and protein production by regulating gene expression and ribosome synthesis. The prefoldin-like protein Bud27 acts as a TOR pathway effector participating in transcriptional regulation of RNA polymerases I, II, and III. While Bud27 role in RNA polymerases II and III involves association with the RSC chromatin remodeling complex and the RNA polymerase common subunit Rpb5, its impact on RNA polymerase I transcription remains unclear. This work focuses on Bud27 role in RNA polymerase I driven transcription and ribosomal RNA synthesis in *Saccharomyces cerevisiae*. Our data suggest that Bud27 acts on correct RNA polymerase I conformation and optimal ribosomal RNA processing, providing new insights into the coordination of ribosome biogenesis, cellular growth, and environment adaption.

Keywords:

Bud27, Ribosome Biogenesis, RNA Polymerase I, Transcription, TOR Pathway, Cell Signaling, Yeast

O-118/P-183

Functional Study Of Histone Post-Translational Modifications - Molecular Characterization Of H3K64

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Histone post-translational modifications (PTMs) regulate chromatin functions such as DNA transcription, replication or repair. Far from working in isolation, PTMs interact with



each other creating decision-making circuits, hypothesized as the Histone Code. Thanks to two decades of research targeting isolated histone residues, there is functional and mechanistic knowledge for a few histone PTM crosstalk examples. However, from the hundreds of histone PTM sites identified, the function of many of them, their interactions and regulation remains vastly unknown.

To address this knowledge gap, we combined reverse genetics and chemical genomics in *Saccharomyces cerevisiae* across 152 unique stress conditions. We are analysing the similarities between the resulting phenotypic fingerprints and identifying functional associations between histone PTM mutants and their potential regulators in specific conditions. We are currently exploring potentially new functions and interactions for histone PTMs arising from our data.

Keywords:

Histone, Post-Translational Modifications, Crosstalk, Chromatin Regulation, Chemical Genomics, H3 K64

O-119/P-184

Dysregulation Of GLP-1 Signalling Is Associated With Inflammatory, Epithelial And Metabolic Alterations In Crohn's Disease Ileal Mucosa

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Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by intestinal barrier disruption, immune dysregulation, and altered mucosal homeostasis. Recent evidence suggests that GLP-1 receptor agonists (GLP-1RAs) may exert beneficial effects in IBD, although the underlying molecular mechanisms remain unclear. This study aimed to characterize alterations in GLP-1 signalling pathways in CD ileal mucosa and evaluate the ex vivo effects of GLP-1RAs.

Transcriptomic analyses were performed in ileal mucosal samples from CD patients (n=20) and IBD-free controls (n=10). Inflamed and non-inflamed CD mucosa were analysed for genes related with GLP-1 signalling, inflammation, barrier integrity, goblet cell function and metabolism. In addition, CD mucosal explants were treated ex vivo with Exendin-4 or Li-raglutide and gene expression was evaluated by RT-qPCR.

CD ileal mucosa showed significant downregulation of GLP-1 axis-related genes, including GCG, GLP1R and DPP4, particularly in inflamed tissue. These alterations were associated with increased inflammatory mediators oxidative stress and reduced epithelial and goblet cell-associated markers. Metabolic alterations included reduced PPARG-C1A and CPT1A expression. Functional analyses revealed strong connectivity among GLP-1 signalling, inflammation, epithelial homeostasis, and metabolic regulation. Ex vivo GLP-1RA treatment induced transcriptional modulation of inflammatory and metabolic markers.

Overall, these findings identify significant dysregulation of GLP-1-associated pathways in CD ileal mucosa and support a potential immunometabolic role of GLP-1 signalling in intestinal inflammation. GLP-1R agonists may represent promising therapeutic modulators in Crohn's disease.

Keywords:

Inflammatory Bowel Disease, Incretin, Intestine, GLP-1RA, Transcriptomics

O-120/P-185

Sex-Dependent Modulation Of Intestinal Inflammatory And Barrier-Related Markers Following Lupinus Luteus Protein Isolate And Beef Protein Supplementation In Rats

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Lupin-derived proteins are promising sustainable alternatives to animal proteins, although their effects on intestinal inflammation and barrier-related responses remain poorly characterised. This study evaluated the intestinal and systemic responses induced by *Lupinus luteus* protein isolate (LPI) compared with beef protein supplementation.

Forty-eight Wistar rats (24 females and 24 males) received daily oral supplementation with beef protein, LPI or water (control) at 300 mg/kg body weight for four weeks (22 administrations). Expression of inflammatory and barrier-related genes was analysed in the duodenum, jejunum and ileum by RT-qPCR. Circulating CCL2, IL-1β, TNF-α and IgE were quantified by ELISA. Multivariate analyses were performed to integrate intestinal, systemic and metabolic variables.

Intestinal responses were modest and depended on sex and intestinal segment. Females displayed a generally stable transcriptional profile with limited treatment-related changes. In contrast, males showed localised alterations in inflammatory and barrier-related markers, including increased duodenal *Il1b* and *Tnf* expression and reduced ileal *Tjp1* expression following LPI supplementation. Despite these local effects, no evidence of systemic inflammatory activation was detected. Integrative analyses revealed substantial overlap among dietary groups, whereas sex emerged as the main source of variability. Intestinal inflammatory and barrier-related genes were the principal contributors to group discrimination.

In conclusion, LPI induced intestinal and systemic responses comparable to those elicited by beef protein. These findings identify biological sex as a major determinant of immune variability and support the inclusion of sex as a key factor in studies evaluating dietary proteins.

Keywords:

Lupinus Luteus, Protein Isolate, Intestinal Inflammation, Intestinal Barrier, Sex Differences, Dietary Proteins

O-121/P-186

A Direct Metabolic Role For Histone Lysine Methyltransferases In Fatty Acid Oxidation

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Epigenetic modifications are deeply entangled with cellular metabolism—and this relationship is not unidirectional. Beyond their epigenetic role in directing gene regulation, histone (lysine) methyltransferases (HMTs) are the sole known enzymes capable of generating trimethyllysine (TML), the obligate precursor for carnitine biosynthesis. Since carnitine is essential for mitochondrial fatty acid oxidation, we hypothesize that HMTs contribute directly to energy metabolism through this biosynthetic link—a role entirely independent of their transcriptional function.

Using *C. elegans* as a model, we established that the carnitine pathway is functionally required for survival under metabolic stress. Knockdown of *gbh-2* and *gbh-1*, encoding the first and last enzymes of carnitine synthesis, significantly reduced survival during starvation, while disruption of CPT-1 (carnitine palmitoyl transferase I), both with RNAi and pharmacological inhibition, produced similar phenotypes. Additionally, both conditions led to increased lipid staining relative to control during starvation, suggesting that endogenous carnitine synthesis is necessary to appropriately utilize fat reserves under nutrient stress. Experiments in *gbh-2/1* knockdown animals are currently underway to determine whether exogenous carnitine supplementation can rescue these phenotypes.

To identify which proteins serve as the primary TML source, we performed multiplexed Western blot analysis using pan-Kme3 and H3 antibodies—and found that only ~1.4% of total lysine trimethylation in *C. elegans* resides on histone H3, with ~97% concentrated on two as-yet unidentified proteins. Mass spectrometry of immunoprecipitated Kme3-containing proteins is ongoing to identify these candidates and the HMTs responsible for their modification

Keywords:

Epigenetics, Mitochondria, Histones, C. Elegans, Metabolism, Fatty Acid Oxidation, Chromatin, Histone Methylation, DNA



O-122/P-187

Grape Supplementation Modulates Sex-Specific Circadian Responses To Short Photoperiod Change In Healthy Rats

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Recent studies have demonstrated a sex-specific response to circadian modulation by external cues, such as changes in light (L)–dark (D) cycles or (poly)phenol-rich fruit intake, in both central and peripheral tissues. Thus, the aim of this study was to assess whether chronic grape intake, a seasonal autumn-winter (poly)phenol-rich fruit, could facilitate adaptation to a short photoperiod in rats. For this purpose, 96 male and female rats were supplemented for 4 weeks with grapes or water under a 12 h L/12 h D cycle. Then, animals were switched to a 6 h L/18 h D cycle for 1 week and fruit supplementation was discontinued. After this, animals were sacrificed every 6 h to evaluate diurnal oscillations of biochemical parameters and hypothalamic and inguinal white adipose tissue (iWAT) clock gene expression. The results showed that females exhibited a greater capacity to adapt to the photoperiod shift than males, showing better preservation of rhythmicity in biochemical parameters, whereas male rats displayed a greater loss of rhythmicity in parameters related to glucose and lipid metabolism. Additionally, enhanced rhythmicity of hypothalamic clock genes, including *Bmal1*, *Per1*, *Cry1*, and *Rev-erba*, was observed in female rats. Regarding iWAT, both sexes showed disrupted rhythmicity in several clock genes, with sex differences observed for *Per1*. Moreover, grape intake was associated with improvements in plasma cholesterol, HDL and phospholipid levels in female rats. In conclusion, the photoperiod shift induced a sex-specific circadian response, and grape intake modulated this response, promoting adaptation to the new photoperiod.

Keywords:

Biological Rhythms, Grape Consumption, Winter Season, Cosinor, Nutrition, Sex-Specific Responses

O-123/P-188

MODULACIÓN DE LA EXPRESIÓN DE PPARγ POR PTHrP EN PODOCITOS DE RATÓN, IMPLICACIONES DE RBP4

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Introducción: Los podocitos son células altamente especializadas que forman parte de la barrera de filtración glomerular, cuya disfunción se asocia a la enfermedad renal. El receptor activado por proliferadores de peroxisomas (PPARγ), conocido por su papel central en el metabolismo lipídico y glucídico, está implicado en el mantenimiento de la integridad podocitaria. Recientemente, se ha identificado una relación funcional entre PPARγ y la proteína relacionada con la parathormona (PTHrP), así como con la proteína de unión al retinol 4 (RBP4). **Objetivo:** estudiar la regulación de la expresión de PPARγ por PTHrP en los podocitos. **Material y Métodos:** se utilizó el riñón completo de ratones *wild type* y de ratones con sobreexpresión de PTHrP. También se utilizaron líneas de podocitos de ratón control y *knockout* para PPARγ, que se trataron con un análogo de PTHrP (Abaloparatide). Se analizaron los cambios en la expresión de genes diana de PPARγ. **Resultados:** El tratamiento con Abaloparatide moduló significativamente la expresión de genes relacionados con la regulación transcripcional de PPARγ el metabolismo celular (incrementando NCoR1 y disminuyendo PGC1α, y ZFP407) y otros genes diana de PPARγ. Además, se observó que el tratamiento con Abaloparatide favorece la liberación extracelular de RBP4 en podocitos control, mientras que este efecto disminuyó en ausencia de PPARγ. Por otra parte, se observó un incremento significativo del represor de PPARγ NCoR1 en riñón completo de ratones que sobreexpresan PTHrP. **Conclusión:** existe una relación funcional entre PTHrP, PPARγ y RBP4 en podocitos. El tratamiento con Abaloparatide o PTHrP provoca una respuesta transcripcional selectiva capaz de modular reguladores nucleares de PPARγ implicados la homeostasis metabólica del podocito.

Keywords:

PTHrP, PPAR?, RBP4, Podocitos Y Riñón

O-124/P-189

Anti-TNF-Driven Reprogramming Of Adipose-Derived Mesenchymal Stem Cells Enhances The Immunometabolic Activity Of Their Extracellular Vesicles

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Background and Aims: Creeping fat (CrF) is a metabolically active adipose niche contributing to Crohn's disease immunopathology. Adipose-derived mesenchymal stem cells (AdMSCs) regulate this environment via extracellular vesicles (EVs), mediators of intercellular communication. We previously showed AdMSC-derived EVs exert anti-inflammatory and regenerative effects in ex vivo CrF explants and therapeutic activity in a TNBS model. Anti-tumour necrosis factor (anti-TNF) signalling promotes adipose browning, linked to mitochondrial activation and anti-inflammatory signalling. We hypothesised that anti-TNF reprograms AdMSCs enhancing EV therapeutic function.

Methods: CrF samples from anti-TNF-treated (n=10) and naïve CD patients (n=14) were analysed. Adipocytes and AdMSCs were isolated and gene expression assessed by RT-qPCR. Secretome was profiled by LC-MS/MS. Healthy donor AdMSCs (n=4) were treated with infliximab (0.1 mg/mL, 24 h). EVs from AdMSCs anti-TNF-primed and non-primed were isolated by size-exclusion chromatography and characterised by nanoparticle tracking analysis and flow cytometry. Functional effects were tested in inflamed CrF explants.

Results: Anti-TNF increased UCP1 and activated mitochondrial and anti-inflammatory pathways with reduced pro-inflammatory mediators. Proteomics showed enrichment of adipocyte and metabolic regulators (ADIPOQ, PPARG). *In vitro*, infliximab induced a beige program with higher UCP1, IL4, and IL10. EVs from primed AdMSCs showed higher particle yield and enhanced immunomodulatory activity, reducing TNF, IL1B, CCL2 and increasing UCP1 and IL10.

Conclusion: Anti-TNF signalling induces metabolic reprogramming of AdMSCs, reshaping their secretome and enhancing EV immunometabolic activity.

Keywords:

Inflammatory Bowel Disease, Extracellular Vesicles, Adipose-Derived Mesenchymal Stem Cells, Immunometabolism, Browning, Cell Reprogramming

O-125/P-190

Bitter Taste Receptor Expression Dynamics In Caco-2 And THP-1 Differentiation And Their Targeting To Modulate Intestinal Barrier Function And Inflammation

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Bitter taste receptors (TAS2Rs) are increasingly recognised as extraoral chemosensory receptors involved in the maintenance of intestinal homeostasis through enteroendocrine, immunological, and barrier functions. However, their specific role in regulating epithelial integrity and inflammation remains unclear.

This study characterised TAS2R expression patterns across differentiation stages in two human in vitro cell models: enterocytic Caco-2 cells, used to assess epithelial permeability, and monocytic THP-1 cells, used to model lipopolysaccharide (LPS)-induced inflammatory responses. Amarogentin, costunolide and KDT-501, as specific agonists, were employed at 50 uM for 3-6 h to investigate the mechanisms underlying extraoral TAS2R activation, and selected microRNAs (miRNAs) were analysed as potential downstream mediators.



In Caco-2 cells, epithelial maturation dynamically regulated TAS2R expression. Apical treatment with amarogentin, costunolide, or KDT-501 maintained TEER values against epithelial barrier disruption, without significant changes in tight junction gene expression. In THP-1 cells, macrophage differentiation and LPS exposure at 100 and 1000 ng/mL increased TAS2R expression in a time- and dose-dependent manner. Costunolide exerted robust anti-inflammatory effects, significantly reducing TNF- α secretion and expression in the LPS-challenged group. Expression analysis and subsequent functional validation of miRNAs in THP-1 did not reveal any significant effects, indicating that costunolide-mediated effects are independent of the miRNAs evaluated.

Collectively, these findings identify TAS2Rs as modulators of barrier function and macrophage inflammation and highlight bitter agonists, particularly costunolide, as potential regulators of intestinal homeostasis.

Keywords:

Bitter Taste Receptors (TAS2R), Inflammation, Epithelial Barrier Function, Costunolide, Amarogentin, KDT-501, Caco-2 Cells, THP-1 Cells

tionally, young mother cells exhibit longer S-G2-M phases and overexpress Whi5 before cytokinesis. We propose that the proliferative structure of a cell population is cumulatively shaped in every mitotic cycle from the very first division, when a mother cell has the opportunity to increase Whi5 expression levels and develop a slow-proliferating lineage. The role of Whi5 in the G1/S transition seems insufficient to explain the close correlation between Whi5 levels and proliferation rates. Therefore, we explored additional targets of Whi5 and found that it binds to the transcribed regions of numerous moderately and highly transcribed genes. We propose that Whi5 may act as a general negative regulator of gene expression, being its cellular levels a clue to explain growth rate diversity within cell populations.

Keywords:

Proliferative Heterogeneity, Yeast Mother Cell, Asymmetric Division, Cell Microencapsulation, Whi5

P-191

Whi5-Mediated Growth Rate: How Young Mother Cells Shape Clonal Lineages

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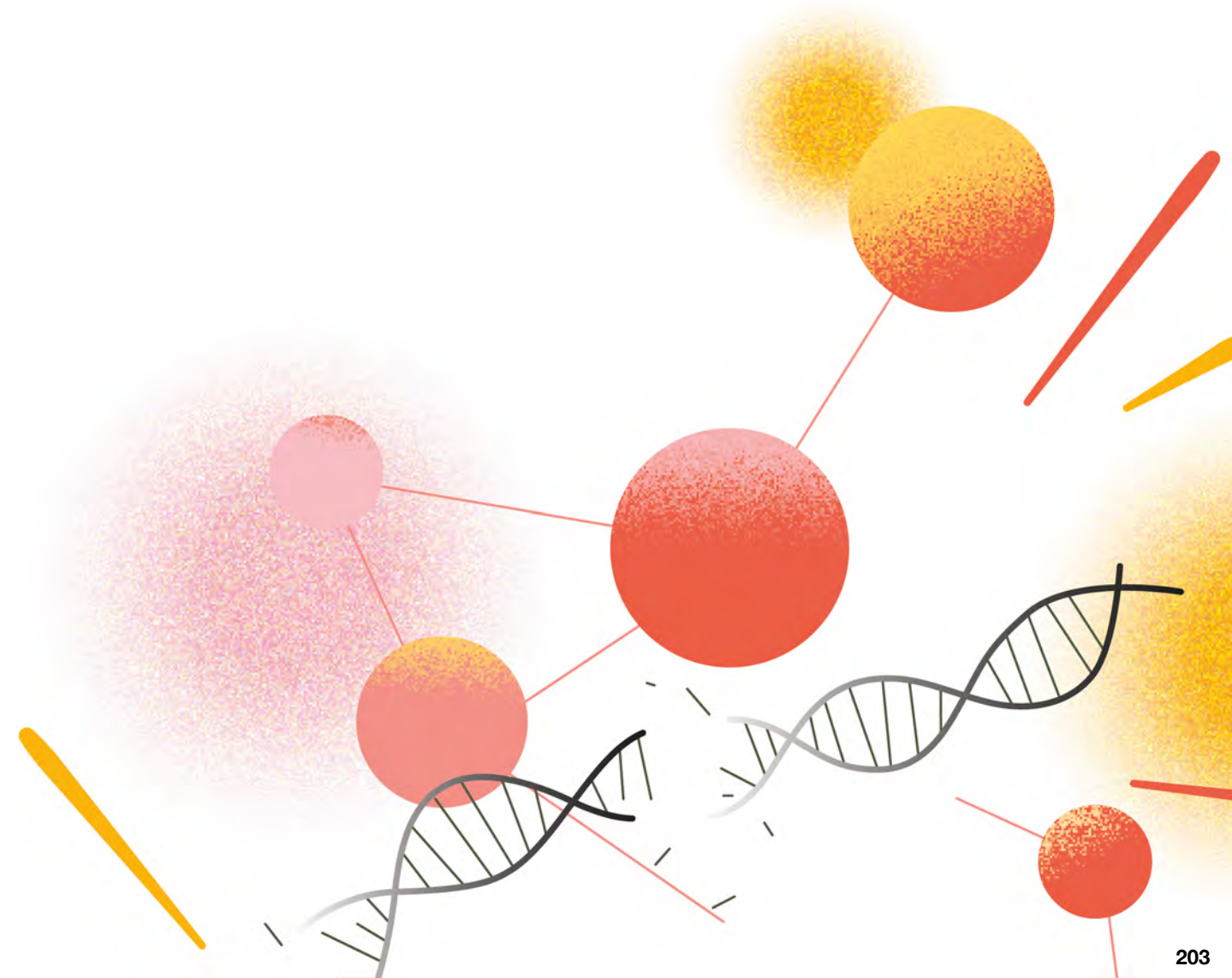
Microcolonies of *Saccharomyces cerevisiae* exhibit size variability due to heterogeneity in their proliferative capacity. To elucidate the underlying mechanisms of proliferative heterogeneity within clonal populations, our study focuses on comparing large (fast-growing) and small (slow-growing) microcolonies. By combining microencapsulation with confocal microscopy, we have developed a powerful technique to analyze cell lineages and determine the age of each cell within the microcolony. We found that slow-growing (small) microcolonies are mostly founded by young mother cells with a low number of cell division cycles, between 1 and 5 divisions. Notably, small microcolonies show elevated expression of Whi5, a negative regulator of the cell cycle at the G1/S transition. Whi5 has a functional homolog in metazoans, the Retinoblastoma (Rb) protein, which controls cell division and also plays a role in cellular senescence. Addi-



GRUPOS CIENTÍFICOS DE LA SEBBM:

REGULACIÓN METABÓLICA Y NUTRICIÓN

10 DE SEPTIEMBRE





O-126

Decoding Adipose Tissue Metabolism In Childhood Obesity

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Childhood obesity is a complex and rapidly growing global health challenge, associated with early-onset metabolic disturbances and increased risk of cardiometabolic and endocrine disorders in later life. Its development reflects the interplay of genetic predisposition, early-life environmental exposures, dietary and physical activity patterns, and psychosocial influences. White adipose tissue plays a pivotal role in energy storage, metabolism, reproduction, and has relevant endocrine and inflammatory functions. It suffers significant physical and metabolic alterations in obesity. Although it has been widely studied in adult mice and humans, a significant knowledge gap exists regarding the impact of obesity on children's adipose tissue biology. I will present our ongoing results related to adipose tissue from both mice and children with and without obesity aiming at identifying the molecular signatures underlying obesity at the early stages of life. Differences between subcutaneous and visceral depots as well as sexual dimorphism will be shown.

Keywords:

Obesidad Infantil, Tejido Adiposo, Ratones, Humanos

O-127

Ferroptosis In Pancreatic Disease: Redox Signalling, Inflammation And Mitochondrial Fitness

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Ferroptosis is a programmed form of cell death characterized by the iron-dependent accumulation of lipid hydroperoxides. Beyond lipid peroxidation, ferroptosis also triggers stress-responsive transcriptional programs, including induction of cytokines and metabolic regulators. However, the identification of redox regulatory nodes that integrate inflammation, antioxidant defence, and mitochondrial fitness during pancreatic injury remain challenging. We investigated the role of ACOD1-dependent itaconate metabolism in the regulation of redox homeostasis and ferroptosis in acute pancreatitis, and its modulation by obesity. Pancrea-

titis is an inflammatory pancreatic disorder associated with oxidative stress and disrupted cysteine redox metabolism. Obesity is a well-established risk factor for increased severity and mortality in acute pancreatitis. We demonstrate that infiltrating myeloid cells are a major source of itaconate in the inflamed pancreas and that myeloid-derived itaconate activates NRF2-dependent antioxidant programs, thereby limiting lipid peroxidation and ferroptotic cell death. Obesity disrupts this protective axis through metabolic reprogramming of infiltrating neutrophils, leading to reduced ACOD1 levels. Remarkably, the protective effects of itaconate also involve the maintenance of mitochondrial fitness. Pharmacological restoration of itaconate signaling with 4-octyl itaconate enhances NRF2 activity and increases expression of the mitochondrial fusion protein MFN2. Consistent with an NRF2-MFN2 regulatory axis, NRF2-deficient mice exhibit markedly reduced MFN2 levels. Furthermore, genetic deletion of MFN2 exacerbates pancreatic fibrosis following injury, highlighting the importance of mitochondrial dynamics in determining the outcome of pancreatic injury.

Keywords:

Acute Pancreatitis, Immunometabolism, Itaconate, Mitochondrial Dynamics

O-128/P-192

Time-Restricted Feeding Improves Metabolic Health And Modulates Immune Responses In Obese Mice During Lipopolysaccharide-Induced Sepsis

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Obesity is associated with chronic low-grade inflammation and impaired immunity, which increase susceptibility to infectious diseases and worsen clinical outcomes. Calorie restriction (CR) is known to improve metabolic health, immune function and revert meta-inflammation. However, adherence to this intervention is often poor, limiting its success. In this context, time-restricted feeding (TRF), a dietary intervention restricting food intake to a daily time window, has emerged as a promising strategy to improve metabolic homeostasis. However, the effects of TRF on immune competence in obese individuals remain poorly understood.

Here, we aimed to evaluate the impact that TRF has on metabolic homeostasis and host immune responses in an obese mouse model of lipopolysaccharide (LPS)-induced sepsis. For this, male and female mice were fed a high-

fat diet for two months and subsequently subjected to TRF (from ZT13 to ZT21) for two additional months. TRF reduced body weight and improved glucose homeostasis, with a more pronounced effect in males. At the end of the intervention, mice were challenged with an intraperitoneal injection of LPS (2 mg/kg) to mimic sepsis. LPS dramatically induced the expression of inflammatory cytokines in adipose tissue (AT) concomitantly with an activation of the inflammasome pathway. Remarkably, TRF enhanced cytokine expression in response to LPS in AT and increase circulating levels of neutrophils and monocytes. Also, TRF boosted phagocytic and microbicidal activities of AT resident macrophages.

These findings may provide new insights into the interaction between feeding behavior, metabolism and immune function, supporting TRF as a non-pharmacological strategy to improve metabolic and immune health in obese subjects.

Keywords:

Obesity, Metabolism, Adipose Tissue, Inflammation, Time-Restricted Feeding

O-129/P-193

Tissue Nanotransfection During Pregnancy Programs Maternal Physiology And Improves Offspring Cardiometabolic Health

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Background. Maternal exercise during pregnancy promotes long-term cardiometabolic health in offspring, but many pregnancies limit the capacity for sustained physical activity. Here, we report a minimally invasive engineering approach to augment an exercise-responsive lipokine (*exerkine*) during gestation using tissue nanotransfection (TNT), a skin-targeted plasmid delivery platform.

Methods. Among *exerkines*, 12,13-diHOME was selected due to its effects on cardiovascular physiology and skeletal muscle metabolism. Plasmid delivery consisted of genes encoding the rate-limiting enzymes for 12,13-diHOME synthesis, soluble epoxide hydrolases 1 and 2 (*Ephx1/2*). Female C57BL/6 mice were fed a high-fat diet (HFD, 60%) to mimic maternal obesity and received weekly sessions of TNT-*Ephx1/2* or TNT-Sham for 3 weeks before and during pregnancy, until delivery. Male and female offspring were chow-fed and studied throughout 44 weeks of age.

Results. In pregnant dams, TNT-*Ephx1/2* increased circulating 12,13-diHOME and placental blood flow while lowering blood pressure and hepatic triglycerides compared to those receiving TNT-Sham. Male and female offspring of TNT-*Ephx1/2* dams showed improved glucose tolerance (GTT) throughout 44 weeks of age. However, maternal TNT-*Ephx1/2* induced sex-specific effects to improve male offspring' body weight, body composition, endurance performance (VO₂ max. treadmill test), hepatocyte glucose uptake and OCR (Seahorse), and cardiovascular physiology *in vivo* (echocardiography, PV loops) and *ex vivo* (cardiomyocyte kinetics).

Conclusion. These findings establish TNT as a platform for therapeutic programming of maternal physiology during pregnancy, and identify augmentation of 12,13-diHOME as a potential strategy to improve offspring cardiometabolic health.

Keywords:

Exerkines, Lipid Mediators, Maternal Programming, Lifestyle-Based Interventions

O-130/P-194

Targeting Cystine Addiction To Treat Breast Cancer Lung Metastasis

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Secondary metastatic disease remains the major cause of triple negative breast cancer. The dissemination to other organs comes with metabolic changes that allow cancer cells to adapt to new microenvironments along the process. A deeper knowledge about these specific metabolic features and associated vulnerabilities could lead to the development of more effective therapies against metastasis. We used *in*



vivo and ex vivo models of MYC-driven breast cancer to explore the key metabolic pathways that change when mammary gland tumour cells metastasise to the lung. We used stable isotope-resolved metabolomics, mass spectrometry imaging and single-cell RNA sequencing to demonstrate that mammary gland tumour-derived lung metastatic cells increase glutathione synthesis fuelled by increased cystine uptake. Consistently, we have uncovered that metastatic cells heavily rely on the availability of extracellular cystine, possibly due to downregulated intracellular cystine synthesis. Based on this cystine addiction of metastatic cells, we combined the amino acid degrader, cyst(e)inase, with radiotherapy to effectively reduce metastatic burden in the lungs. This novel combinatorial approach exploits a metabolic dependency that is unique to the metastatic cells, and acts as a sensitizer to radiotherapy-induced oxidative stress, offering a promising targeted strategy.

Keywords:

Cancer, Metabolism, Metastasis

O-131/P-195

Modulation Of The Hepatocyte Desmosterol Influences The Development Of Colorectal Liver Metastasis

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Colorectal liver metastasis (CRLM) is the second leading cause of cancer-related death. Cholesterol (CL) metabolism is altered in CRLM. CL synthesis intermediate desmosterol is high in many cancers but inhibiting Δ (24)-sterol reductase (DHCR24), which converts desmosterol to CL, benefits HCC. This study aimed to: (1) investigate desmosterol and CL synthesis remodeling in CRLM; (2) determine if desmosterol accumulation by hepatocyte *Dhcr24* inhibition affects CRLM proliferation.

Serum, tumor (T), and surrounding tissue (ST) from CRLM patients (n=20) were analyzed. CRLM was induced in mice fed chow Western diets. Hepatocytespecific *Pcsk9* overexpression and *Dhcr24* inhibition were achieved by ApoE-hAAT1AAV8 and GalNAcconjugated ASO. Lipid and protein levels were quantified. CRC proliferation was analyzed with isolated hepatocyteconditioned media *in vitro*.

Human CRLM T showed downregulation of CL synthesis enzymes (including DHCR24) vs ST. This remodeling was associated with increased desmosterol and CL in T, suggesting enhanced circulating CL uptake and decreased flux with accumulation of *de novo* synthesis intermediates. Human samples and preclinical models exhibited reduced serum LDLCL and increased hepatic LDLR levels. Hepatocytespecific *Pcsk9* overexpression reduced CRLM, promoting *de novo* CL synthesis and reducing desmosterol in ST. Conversely, hepatocytespecific *Dhcr24* inhibition increased desmosterol and promoted CRLM progression, accompanied by elevated LDLCL. *Pcsk9*overexpressing hepatocyte secretome decreased CRC proliferation *in vitro*, whereas direct desmosterol treatment enhanced it.

Dysregulation of CL synthesis/uptake in CRLM alters desmosterol in hepatocytes and tumor cells. Targeting hepatocyte desmosterol metabolism is a promising strategy for CRLM.

Keywords:

CRLM, Cholesterol, DHCR24, Desmosterol

O-132/P-196

Fasting-To-Refeeding Transitions Reprogram Circulating Host- And Microbiota-Derived Extracellular Vesicles To Regulate Systemic Metabolism

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Metabolic homeostasis depends on efficient transitions between fasting and refeeding states, coordinated in part by inter-organ signalling via extracellular vesicles (EVs). Disruption of these pathways contributes to metabolic disease, and postprandial dysfunction is linked to obesity. However, how host-derived EVs (hEVs) and microbiota-derived EVs (mEVs) are regulated by nutritional status and how they impact metabolic adaptation remain unclear. Here, we investigated whether hEVs and mEVs from fasted or refed lean and obese mice differentially modulate metabolic function *in vivo*. EVs were isolated from plasma by size-exclusion chromatography followed by iodixanol density gradient ultracentrifugation. EV concentration was then assessed by nanoparticle tracking analysis, and proteomic cargo was analysed by label-free SWATH-MS. Finally, EVs were administered to lean recipient mice for metabolic and phenotypic studies. Refed conditions increased circulating EV abundance in lean but not obese mice. hEVs from refed lean donors improved glucose disposal, consistent with physiological postprandial metabolic adaptation. This adaptive effect was lost in obesity, as hEVs from refed obese donors elicited the most deleterious phenotype, worsening glucose tolerance and promoting adipose tissue accumulation, consistent with dysregulated anabolic signalling. Similarly, mEVs from refed obese mice decreased insulin sensitivity. Overall, hEVs are dynamically regulated by nutritional status and promote metabolic adaptation in lean conditions, whereas this response is impaired and becomes maladaptive in obesity.

Keywords:

Extracellular Vesicles, Microbiota, Metabolism, Postprandial State, Inter-Organ Communication, Obesity

O-133/P-197

Metabolic And Pancreatic Characterization Of A Model Of Central Leptin Resistance. Potential Protective Effect Of Elafibranor

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Leptin, an adipocyte-derived hormone, acts mainly in the central nervous system, where it integrates peripheral metabolic signals to regulate food intake, energy expenditure, and endocrine function. Impaired leptin signaling is linked to obesity, insulin resistance, and pancreatic dysfunction.

This study aims to characterize a male Wistar rat model deficient in central leptin signaling induced by chronic intracerebroventricular administration of a superactive leptin receptor antagonist (SLA), which develops a phenotype resembling metabolic syndrome. In addition, we hypothesized that treatment with Elafibranor (ELA), a dual PPAR agonist involved in lipid and glucose metabolism, could improve insulin sensitivity and partially restore metabolic flexibility.

To characterize the model, physiological parameters, peripheral tissue weight, and thermogenesis (by infrared thermography) were monitored. Systemic glucose homeostasis was evaluated through intraperitoneal glucose tolerance tests (ipGTTs), measuring plasma glucose, insulin, and glucagon levels to assess hypothalamic-pancreatic axis function. Pancreatic endocrine function was analyzed *ex vivo* using isolated islets to quantify insulin and glucagon secretion by ELISA after Glucose-Stimulated Insulin Secretion (GSIS) test. Combining *in vivo* and *in vitro* approaches, this study comprehensively evaluates how central leptin signaling blockade affects pancreatic endocrine function.

Preliminary findings indicate that proper hypothalamic leptin signaling is essential for maintaining pancreatic endocrine function and metabolic homeostasis. Ongoing studies focus on determining ELA's capacity to reverse SLA-induced metabolic dysfunction and elucidating molecular and functional mechanisms underlying this neuroendocrine communication.

Keywords:

Leptin Resistance, Endocrine Pancreas, Metabolic Syndrome, Elafibranor, Glycemic Homeostasis, Pancreatic



Islets, Neuroendocrine Communication, Leptin Receptor Antagonist, PPAR Receptors, Metabolic Flexibility.

O-134/P-198

Characterization Of A Mouse Model Of Childhood Obesity

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Background: Childhood obesity is associated with early metabolic dysfunction, highlighting the need for translational models reproducing systemic and tissue-specific alterations. Post-weaning diet-induced murine models are useful, but their biochemical and adipose tissue transcriptional profiles remain incompletely characterized.

Aim: To characterize a post-weaning childhood obesity murine model induced by high-fat and high-sucrose diets, assessing systemic metabolic and white adipose tissue transcriptional profiles.

Methods: Post-weaning female and male C57BL/6 mice at week 3 of age were fed with control, 60% high-fat (HFD), or 45% high-fat sucrose (HFSD) diets for 4 weeks. Body weight and food intake were monitored, and body composition was analyzed by EchoMRI. Metabolic parameters were analyzed in serum samples and white adipose tissue (WAT) was used to assess relative gene expression.

Results: HFSD and HFD increased male body weight and expanded fat mass in both sexes, consistent with obesity-related adiposity gain. Males were more sensitive to HFD, showing reduced serum glycerol and NEFA levels across diets, plus diet-specific changes in insulin and triglycerides. Females showed a more preserved phenotype, with serum cholesterol elevated in both interventions and increased glycerol and glucose under HFD. HFD increased HOMA-IR in both sexes. WAT transcriptional profiling showed HFD-induced adiponectin downregulation and increased inflammatory markers in males.

Conclusion: Our post-weaning childhood obesity murine model demonstrates increased body weight and fat mass,

more pronounced in the HFD group, accompanied by sex-dimorphic metabolic and transcriptional responses.

Keywords:

Childhood Obesity, Diet-Induced Obesity, Mouse Model, White Adipose Tissue, Metabolic Alterations, Gene Expression

O-135/P-199

The Plasmalogen PE(P-16:0/20:4) Plays A Role In The Metabolic Dysfunction Of Obese-Related MASH Patients

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Metabolic Dysfunction-Associated Steatohepatitis (MASH) is characterized by excessive lipid accumulation; however, the role of phospholipid metabolism remains unclear. Aims: 1) to analyze fluctuations in phosphatidylcholine (PC) and phosphatidylethanolamine (PE) species in MASH, and 2) to identify the metabolic pathways involved.

The proteome and lipidome of patients (BioBizkaia cohort) were analyzed. MASH patients were defined histologically, requiring a score of ≥ 1 for steatosis, ≥ 1 for hepatocellular ballooning, and ≥ 1 for lobular inflammation.

Patients with MASH exhibited a proteome enriched not only in pathways involved in lipid metabolism, but more specifically in those related to glycerophospholipid synthesis, including proteins involved in the conversion of PC to PE and in their *de novo* synthesis. However, no changes were observed in total liver PC or PE levels. A deeper analysis of liver PC and PE species revealed a selective increase in certain PE species in MASH patients, particularly in all identified plasmalogen species (PE plasmalogens), compared to non-MASH patients. Among these, only PE plasmalogens containing 20:4 chains increased in parallel with steatosis and inflammation grade. Consistently, an enrichment of proteins related to plasmalogen metabolism was

observed, including those involved in peroxisomal biogenesis and catabolism in MASH versus non-MASH patients. Additionally, MASH patients with levels of PE(P-16:0/20:4) above the median showed higher insulin resistance and worse metabolic profile.

In conclusion, metabolic reprogramming of PC and PE in MASH primarily affects lipid species remodeling. MASH progression is associated with the selective accumulation of plasmalogen species, some of which may play a role in disease progression.

Keywords:

MASH, Glycerophospholipid Metabolism, Plasmalogens, Plasmalogen, Phospholipid Metabolism, Proteomics, Lipidomics, Metabolic Dysfunction

O-136/P-200

Plant-Derived Protein Hydrolysate Ameliorates Hypertension And Induces Sex-Dependent Metabolic Benefits In A Dietary Model Of Metabolic Syndrome

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Metabolic syndrome (MetS) is a major public health challenge, driving the search for multitarget preventive compounds. Bioactive peptides have attracted attention due to their beneficial effects on several MetS-related alterations. In a previous study, we developed a protein hydrolysate from a plant-based agro-food by-product that showed antihypertensive activity after acute administration in spontaneously hypertensive rats.

This study evaluated its long-term antihypertensive efficacy in a diet-induced animal model of MetS, as well as its metabolic effects and the influence of sex on treatment response. Male and female Wistar rats were fed either a standard or cafeteria (CAF) diet for 12 weeks. During the final 4 weeks, animals received vehicle (water) or protein hydrolysate (55 mg/kg/day). Food intake, body weight and systolic blood pressure (SBP) were monitored weekly. Oral lipid and glucose tolerance tests were performed during weeks 2 and 3 of supplementation, respectively. Plasma biochemical parameters and adiposity index were assessed at study end.

The CAF diet increased SBP to hypertensive levels in both sexes. Protein hydrolysate supplementation significantly reduced SBP in CAF-fed rats, restoring normotensive values. Treatment also induced sex-dependent metabolic benefits.

Females showed lower adiposity index and plasma leptin concentrations and a tendency toward reduced postprandial triglyceride response (OLTT, AUC). In contrast, males showed improved glucose tolerance (OGTT, 15 min).

These findings support the potential of this plant-derived protein hydrolysate for MetS prevention. Its antihypertensive and metabolic effects highlight a multitarget mode of action and emphasize the importance of including both sexes in preclinical nutrition studies.

Keywords:

Metabolic Syndrome, Protein Hydrolysate, Hypertension, Bioactive Peptides, Sex Differences.

O-137/P-201

Chronotype As A Determinant Of Metabolic Vulnerability To Night Shift-induced Circadian Disruption

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Circadian rhythms coordinate metabolic homeostasis by synchronizing physiological processes with environmental cycles. Rotating night shift work disrupts this temporal organization and increases the risk of metabolic disorders. However, marked interindividual differences in adaptation to chronodisruption suggest that chronotype may influence metabolic vulnerability. Therefore, this study evaluated whether chronotype modulates metabolic, nutritional and sleep-related parameters in rotating night shift workers.

A cross-sectional analysis was performed using 35 baseline observations from 18 participants enrolled in a crossover clinical trial. Chronotype was assessed using the Morningness-Eveningness Questionnaire and classified as intermediate or extreme. Anthropometric, biochemical, hormonal, dietary and actigraphic variables were analyzed.

No differences were observed in body composition or blood pressure between groups. However, extreme chronotypes showed higher fasting glucose, lower HDL-cholesterol and reduced active ghrelin levels. They also reported higher energy intake, with greater consumption of carbohydrates, sugars, proteins and fats. Actigraphy-derived sleep duration and fragmentation were comparable between groups, suggesting a homogenizing effect of occupational chrono-





disruption on sleep quality. Principal component analysis revealed a clear separation between chronotypes based on biochemical variables, whereas sleep-related variables largely overlapped.

Extreme chronotypes exhibited a less favorable metabolic phenotype despite similar anthropometric and sleep characteristics. These findings suggest that chronotype modulates metabolic vulnerability to job-induced chronodisruption and should be considered in preventive strategies for shift workers.

Keywords:

Chronodisruption, Circadian Rhythms, Molecular Biology, Shift-Workers, Chronotype

P-202

Identifying Key Metabolic Pathways That Contribute To Metastasis Of Breast Cancer To The Lung

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Secondary metastatic disease is still a major cause of cancer-related deaths. Recent research suggests that cancer cells that successfully metastasize often undergo significant changes in their metabolism, allowing them to adapt to the new microenvironment. Exploring these specific metabolic features may contribute to the development of more effective therapies against the spread of tumour cells. We used a mouse model of MYC-induced breast cancer together with a panel of cell lines, derived from this model, with gradually enriched metastatic capacities to explore the key metabolic pathways that change when mammary gland tumour cells metastasize into the lung. We used stable-isotope resolved metabolomics to determine differences in metabolite abundances and fluxes between primary tumours and lung metastases. Furthermore, cutting-edge technologies such as mass spectrometry imaging and single-cell RNA sequencing were also used to better understand the metabolic interactions between the tumour and its microenvironment. We uncovered that one-carbon metabolism and antioxidant pathways are upregulated in the lung metastatic cells compared to the primary mammary gland tumours. Specifically, metastases have higher levels of methionine cycle intermediates and glutathione. Consistently with the latter, we have

determined that metastatic cells heavily rely on the availability of the glutathione precursor amino acid cysteine. We thus explored the effect of different strategies decreasing cysteine availability in vivo, including a cysteine-free diet and the use of the amino acid degrader cyst(e)inase, on the ability of mammary gland tumours to metastasize into the lung.

Keywords:

Cancer, Metabolism, Metastasis

P-203

Bitter Taste Receptor (Tas2r) Agonists Modulate Gut Hormones And Metabolic Markers In Aged Rats

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Ageing is associated with impaired metabolic homeostasis and alterations in intestinal endocrine function. Bitter taste receptors (Tas2r), originally identified in the oral cavity as sensors of potentially toxic compounds, are also expressed in the gastrointestinal tract, where their role in enteroendocrine regulation remains poorly understood.

In this study, we investigated whether exposure to bitter compounds acting as selected Tas2r ligands modulates metabolic markers in aged female rats. Animals were assigned to two treatment groups: a chronic treatment with Costunolide for three months, and a MIX treatment (Costunolide + KDT501) administered during the final two weeks of the experimental period.

Ageing was associated with reduced energy expenditure and respiratory quotient (RQ), lower body weight gain, and increased circulating active GLP-1 and total cholesterol levels. Costunolide treatment attenuated age-related alterations in energy expenditure, RQ, and active GLP-1 levels. In contrast, the MIX treatment mitigated the reduction in body weight gain and prevented the increase in total cholesterol.

Overall, these findings provide in vivo evidence that modulation of Tas2r influences enteroendocrine signaling and metabolic outcomes during ageing, highlighting these receptors as a potentially relevant and underexplored pathway linking intestinal sensing to metabolic regulation.

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Rovira i Virgili. Additional funding was provided by an FPU fellowship (FPU24/01630) from the Spanish Ministry of Science, Innovation and Universities.

Keywords:

Ageing, Tas2r, Enterohormones, Metabolic Markers, Homeostasis

P-204

The Succinate/SUCNR1 Axis Is Involved In Adrenal Stress Responses In A Sex-Dependent Manner

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Stress responses are essential physiological processes mainly coordinated by the hypothalamic-pituitary-adrenal axis through the secretion of glucocorticoids and catecholamines. Dysregulation of stress hormone signalling is closely associated with metabolic disorders such as obesity and type 2 diabetes. Succinate, a central intermediate of the tricarboxylic acid cycle, accumulates under conditions of metabolic stress and has emerged as a biomarker of cellular metabolic dysfunction. Beyond its metabolic role, succinate can also act as an extracellular signalling molecule through its receptor SUCNR1. Given that succinate levels increase during metabolic stress, we hypothesise that the succinate/SUCNR1 axis contributes to the regulation of stress responses. To address this, we investigated the role of SUCNR1 in stress hormone regulation, focusing on its functional relevance in the adrenal gland.

We assessed SUCNR1 expression and localisation in adrenal tissue. In parallel, we compared wild-type and *Sucnr1* knockout mice to evaluate the effects of SUCNR1 deletion on circulating glucocorticoid levels and stress-related behavioural responses, including potential sex-dependent differences.

Our results show that SUCNR1 is expressed in the adrenal gland and is mainly localised in the adrenal cortex. *Sucnr1* deletion altered circulating glucocorticoid levels and disrupted their normal rhythmicity under both physiological and

stimulated conditions in a sex-dependent manner. Similarly, at the behavioural level, *Sucnr1* knockout mice exhibited a different phenotype compared with wild-type littermates depending on the sex.

Overall, our findings identify SUCNR1 as a potential contributor to adrenal stress hormone dynamics and behavioural stress responses.

Keywords:

Succinate, SUCNR1, Stress Response, Adrenal Gland, Behaviour

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Impact Of Functionalized Lupinus Luteus Protein On The Human Colonic Enteroendocrine System

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To satisfy demands for sustainable plant proteins, lupin has emerged as a strategic alternative to imported soy. *Lupinus* species, such as *Lupinus luteus*, represent an exceptional high-protein source for human nutrition. Recent advances in processing and functionalization successfully reduce anti-nutritional factors and improve nutritional value. Beyond these improvements, lupin exhibits potent gastrointestinal bioactivity; its digestion-derived peptides and γ -conglutinin modulate enteroendocrine signaling by stimulating GLP-1 secretion and inhibiting DPP-4, while exerting secondary anti-inflammatory benefits. However, the impact of structural pre-processing on optimizing these metabolic pathways



remains unexplored.

The present study aimed to evaluate the effects of *Lupinus luteus* protein isolates and their functionalized products on enteroendocrine secretion (GLP-1 and PYY) in human intestinal tissue. For this purpose, four distinct samples were analyzed: lupin protein isolates (LPI) as a control, enzymatically hydrolyzed LPI (HLPI), enzymatically cross-linked and high-pressure processed LPI (GLPI), and extruded LPI (ELPI). Following *in vitro* digestion, secretion assays were performed using human colon segments obtained from 15 donor patients of both sexes.

This work demonstrates that structural functionalization alters the susceptibility of lupin proteins to digestion, resulting in distinct partial proteolysis profiles. These variations directly influence enterohormone release in a sex-dependent manner, creating differential secretion profiles in human colonic enteroendocrine cells. Ultimately, these findings suggest that increased protein fragmentation in lupin favors the generation of specific bioactive peptides or amino acids crucial for GLP-1 and PYY stimulation.

Keywords:

Lupinus Luteus, Protein-Functionalized, Human Colon, Bioactive Peptides, Enterohormones

To characterize the model, physiological parameters, peripheral tissue weight, and thermogenesis (by infrared thermography) were monitored. Systemic glucose homeostasis was evaluated through intraperitoneal glucose tolerance tests (ipGTTs), measuring plasma glucose, insulin, and glucagon levels to assess hypothalamic–pancreatic axis function. Pancreatic endocrine function was analyzed *ex vivo* using isolated islets to quantify insulin and glucagon secretion by ELISA after Glucose-Stimulated Insulin Secretion (GSIS) test. Combining *in vivo* and *in vitro* approaches, this study comprehensively evaluates how central leptin signaling blockade affects pancreatic endocrine function. Preliminary findings indicate that proper hypothalamic leptin signaling is essential for maintaining pancreatic endocrine function and metabolic homeostasis. Ongoing studies focus on determining ELA's capacity to reverse SLA-induced metabolic dysfunction and elucidating molecular and functional mechanisms underlying this neuroendocrine communication.

Keywords:

Leptin Resistance, Endocrine Pancreas, Metabolic Syndrome, Elafibranor, Glycemic Homeostasis, Pancreatic Islets, Neuroendocrine Communication, Leptin Receptor Antagonist, PPAR Receptors, Metabolic Flexibility.

P-206

Metabolic And Pancreatic Characterization Of A Rat Model With Central Leptin Resistance. Possible Protective Effect Of Elafibranor

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Leptin, an adipocyte-derived hormone, acts mainly in the central nervous system, where it integrates peripheral metabolic signals to regulate food intake, energy expenditure, and endocrine function. Impaired leptin signaling is linked to obesity, insulin resistance, and pancreatic dysfunction.

This study aims to characterize a male Wistar rat model deficient in central leptin signaling induced by chronic intracerebroventricular administration of a superactive leptin receptor antagonist (SLA), which develops a phenotype resembling metabolic syndrome. In addition, we hypothesized that treatment with Elafibranor (ELA), a dual PPAR agonist involved in lipid and glucose metabolism, could improve insulin sensitivity and partially restore metabolic flexibility.

P-207

Hydroxytyrosol Restores Insulin Signaling And Glucose Homeostasis In The Hippocampus Of Aβ25–35-Treated Rats

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The term type 3 diabetes has been proposed to describe the cerebral insulin resistance (IR) observed in Alzheimer's disease (AD), which disrupts brain metabolism and cogni-

tive functions. It has been widely reported that the Mediterranean diet, rich in polyphenols mainly derived from extra virgin olive oil (EVOO), is associated with a lower incidence of AD.

We hypothesized that hydroxytyrosol (HT), the main polyphenol in EVOO, improves hippocampal IR and glucose levels in an animal model of AD. Twenty male rats were treated with Aβ25–35 (intracerebroventricular infusion, i.c.v., 300 pmol/day) for 2 weeks; Aβ25–35 followed by HT (intragastric, i.g., 10 mg/kg/day) for 4 weeks; HT alone; or saline (i.c.v. plus i.g.). Phosphorylated levels of IRS1 (Ser636), Akt (Ser473), mTOR (Ser2448), and S6K1 (Thr421–Ser424) were measured using multiplexed bead immunoassays, and serum and hippocampal glucose levels were determined using enzymatic methods.

Treatment with Aβ25–35 induced hippocampal insulin resistance by increasing IRS1 (Ser 636) phosphorylation, partly mediated by S6K1 hyperphosphorylation, and decreased glucose content in this brain region. However, HT treatment reversed the Aβ25–35-induced inhibition of insulin signaling and restored hippocampal glucose levels. Serum glucose levels were not affected by any treatment.

Therefore, these findings suggest that HT treatment may restore hippocampal energy status, enhance insulin sensitivity, and ultimately contribute to improved cognitive function.

Keywords:

Hydroxytyrosol, Alzheimer Disease, Hippocampus, Insulin, Amyloid β Peptide.

P-208

Hepatic Metabolic Disorder Associated With Ovarian-Uterine Dysfunction

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Recent findings highlight the significant role of the mitochondrial fusion protein Mfn2 in liver metabolism, particularly its involvement in metabolic dysfunction-associated steatohepatitis (MASH).

Loss of Mfn2 function disrupts this transfer, leading to impaired liver metabolism, oxidative stress, and mitochondrial dysfunction, all of which contribute to the progression of liver diseases. Our group has demonstrated that male Mfn2 liver knockout (L-KO) mice exhibit defective phospholipid transport between the ER and mitochondria, which is linked to a reduction in key enzymes involved in PS synthesis in mitochondria-associated membranes (MAMs). This deficiency results in altered lipid metabolism, ultimately leading to steatohepatitis.

There is a sexual dimorphism according to Mfn2 action in liver. We observed that ablation of Mfn2 in the liver of female mice is related to dysregulated estrus cycle, which can affect the proper development of various tissues, including the ovaries and uterus, where significant morphological disruptions are observed.

These findings suggest that Mfn2 deficiency in females interacts in a complex manner with hormonal regulation. Impaired Mfn2 function may impact lipid availability, thereby affecting hormonal synthesis and potentially influencing estrogen-related metabolic pathways.

Keywords:

Mfn2, MAMs, Sexual Dimorphism, Estrogen, MASH



P-209

Exploring The Role Of Mfn1 Ablation In Modulating Lipid Droplet Metablism

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Mitochondrial bioenergetics and morphology are dynamically regulated by fusion and fission processes. Mitofusin 1 (MFN1) is a key protein involved in outer membrane fusion; However, its broad functions in cellular metabolism are not well understood. The aim of this study is to investigate the metabolic and mitochondrial roles of MFN1 in vitro using MFN1 knockout and wild-type mouse embryonic fibroblasts (KO1) and in vivo using liver-specific MFN1 knockout mice. Microscopic analysis of liver tissues and MEF cells revealed that the lack of MFN1 increased the volume of lipid droplet. Consistently, triglyceride levels were increased in MFN1-deficient conditions. Under basal conditions, increased [¹⁴C]-palmitate incorporation was observed in KO1 MEFs and KO1 primary hepatocytes, although mitochondrial fatty acid beta-oxidation remained unchanged. Under fasted conditions, MFN1-deficient cells showed a greater increase in lipid droplet number and volume, displayed a twofold rise in triglyceride levels compared with basal condition. Despite reduced Dgat2 expression, the incorporation of radiolabeled palmitate was increased in MFN1-deficient MEFs and hepatocytes. Notably, beta-oxidation was reduced in MFN1 deficient cells under fasting conditions. High-resolution Orbitrap revealed improved mitochondrial activity in the fed state, but under fasted conditions, a significant functional decline was observed in MFN1-deficient mice. Furthermore, DNP-MRSI revealed an increased lactate to alanine ratio in the liver of KO mice during fasting, consistent with impaired mitochondrial pyruvate utilization. This ratio remained unchanged in the fed state. These data

indicate that MFN1 plays essential role in regulating lipid metabolism and mitochondrial activity in a nutrient-dependent manner.

Keywords:

Mfn1 ,Lipid Accumulation ,Metabolic Flexibility

P-210

Hypothalamic Astrocyte-Derived Extracellular Vesicles Regulate The Hypothalamus–brown Adipose Tissue Axis In Mice According To Sex During Acute High-Fat Feeding

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The hypothalamus integrates nutrient-derived signals to regulate energy balance and peripheral metabolism, including thermogenesis in brown adipose tissue (BAT). Hypothalamic astrocytes participate in nutrient sensing by releasing different metabolites to regulate neuronal activity. Previously, we demonstrated that the content of the extracellular vesicles (EVs) released by hypothalamic astrocytes is dependent on nutritional environment and sex. Here, we investigated whether these EVs influence the response to a high-fat diet (HFD) and whether this effect varies between the sexes. Primary hypothalamic astrocyte cultures from male and female mice were treated with oleic acid (OA, 0.5 mM) or vehicle for 24 h, after which the EVs were isolated. These EVs were then injected into the third ventricle of sex-matched adult mice 2 h before they were exposed to either a control diet (CD) or HFD. Metabolic parameters were assessed 24 h later. In male mice, EVs derived from OA-treated astrocytes increased POMC expression in the hypothalamus under HFD conditions, while decreasing the expression of BAT lipid oxidation and thermogenic markers including carnitine palmitoyltransferase 1A (CPT1A) and uncoupling protein 1 (UCP1). In contrast, EV-OA administration reduced body weight in female mice on a CD with no significant changes in POMC and UCP1 expression. Nevertheless, male EV-OA administration reduced CPT1A under both dietary conditions, whereas in females it did not modify the diet-induced response. These findings indicate that astrocytic EVs can acutely modulate the hypothalamic and peripheral response

to high-fat intake in a sex-dependent manner and suggesting a reprogramming of lipid metabolism.

Keywords:

Astrocytes, Hypothalamus, BAT, Sex, Extracellular Vesicles

P-211

Higher Cord Blood DLK1 Levels In Infants Born Small For Gestational Age

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Background: Delta-like protein 1 (DLK1) is a transmembrane and soluble protein containing epidermal growth factor (EGF)-like repeats that participates in cell differentiation and developmental processes. Increasing evidence supports a role for DLK1 in the regulation of human fetal growth.

Objective: To analyze circulating DLK1 levels in cord blood from newborns classified as appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA), and to explore their association with neonatal and parental anthropometric variables and neonatal biochemical variables.

Methods: Cord blood DLK1 concentrations were measured at birth in 101 newborns classified as SGA (n = 30), AGA (n = 44), or LGA (n = 27) infants according to sex-specific gestational age reference charts. DLK1 levels were compared among groups, and associations between DLK1 levels and neonatal anthropometric and biochemical variables and parental anthropometric variables were analyzed.

Results: Cord blood DLK1 concentrations were significantly higher in SGA infants than in AGA (p < 0.05) and LGA (p < 0.01) infants, whereas no significant differences were observed between the AGA and LGA groups. DLK1 was not associated with maternal anthropometric variables; however, an inverse correlation (p < 0.010) with paternal height was observed.

Conclusions: Elevated cord blood DLK1 levels in SGA infants support the involvement of this protein in fetal growth regulation. The lack of association with maternal

anthropometric parameters suggests that DLK1 may act independently of maternal nutritional status. These findings highlight DLK1 as a potential biomarker for altered fetal growth and birth weight-related health outcomes.

Keywords:

Cord Blood Biomarkers, DLK1, Fetal Growth

P-212

Hypusination Of EIF5A Controls Protein Synthesis During Erythroid Progenitor Development In A Sex Dependent Manner In Mice

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Erythropoiesis is a tightly regulated process with strong sex dependence, mainly driven by hormonal regulation. Given it is still unknown which are the molecular pathways differently regulated between sexes, this study aims to investigate the impact of sex on the regulation of erythropoiesis. To address this objective, first we confirmed C57BL/6 females present a higher percentage of erythroblasts in late terminal differentiation in the bone marrow. Then, a quantitative proteomic analysis in bone marrow cells was performed, revealing a sex-dependent regulation of translation. Global protein synthesis rate in erythroblasts validated the proteomics results, with higher levels found in females. To confirm the relevance of translation in the erythroid lineage, the treatment with homoharringtonine, a protein synthesis inhibitor, dramatically reduced erythroid progenitors. In particular, the eukaryotic translation initiation factor 5A (eIF5A), a translational regulator activated by hypusination, was previously shown is essential for human erythropoiesis. In vivo treatment with the inhibitor of hypusination GC7 reduced protein synthesis. Moreover, colony-forming unit assay showed a reduction in burst-forming unit-erythroid colonies, while FACS phenotyping revealed an accumulation of early erythroblasts in both sexes. Proteomics confirmed a different impact of GC7 on translation and stress-related pathways between sexes. In addition, metabolomic analysis revealed metabolic remodeling in GC7-treated males, supported by a loss of glucose dependence. Together, these results demonstrate that hypusination coordinates translational and metabolic programs in erythropoiesis in a sex-dependent manner, driving metabolic rewiring in males and distinct adaptive responses in females.

Keywords:

Haematopoiesis, Erythropoiesis, Metabolism, EIF5A



P-213

High-Fat Diet Consumption For 16 Weeks Induced NLRP3 Inflammasome Upregulation And Apoptosis In The Cochlea Of C57BL/6J Mice

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Obesity affects the auditory system, altering its functionality and auditory processing, but the subjacent molecular mechanisms are unclear. The NLRP3 inflammasome molecular platform has been associated to age-related hearing loss and may play a role in the development of sensorineural hearing loss in the context of obesity, contributing to apoptosis of cochlear sensory hair cells, and thus, impairing auditory function. We aimed to evaluate the effect of obesity induced by high-fat diet (HFD) consumption on NLRP3 inflammasome expression and survival of cochlear hair cells. For that, 6-7 weeks old male C57BL/6J mice (n=24) were fed a control diet (CD, 10% fat, 20% protein, and 70% carbohydrates) or a HFD (60% fat, 20% protein, and 20% carbohydrates), for 16 weeks. General parameters (body and adipose tissue weight), hearing function (distortion product otoacoustic emissions (DPOAEs)), NLRP3 inflammasome components expression (NLRP3, ASC, Caspase-1, IL-1 β and IL-18, IF/qPCR) and apoptosis (TUNEL, caspase-3, Bax and Bcl-2, IF/qPCR) were measured. As expected, HFD fed animals presented higher body (83%) and adipose tissue weight, and higher auditory thresholds (evaluated by DPOAEs). Moreover, the HFD group presented a lower number of cochlear hair cells compared to CD, along with higher apoptosis markers (TUNEL (by 47%, p=0.028) and caspase-3 staining). Interestingly, cochlear levels of NLRP3, ASC, IL-1 β , IL18 and were also increased. This data suggests a role for NLRP3 inflammasome and oxidative stress in hearing impairment induced by metabolic dysfunction, after the chronic consumption of a high-fat diet in C57BL/6J mice.

Keywords:

NLRP3 Inflammasome, Obesity, Hearing Loss

P-214

A 16-Week Exercise Intervention Maintains Stable Bilirubin Levels In Children With Cystic Fibrosis On CFTR Modulators: Insights Into A Context-Dependent Hepatic Adaptation (FIQMODE Study)

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Introduction: Liver involvement is a relevant comorbidity in cystic fibrosis (CF). Bilirubin is not only a marker of hepatic function but also of oxidative stress and metabolic regulation. In patients treated with ellexacaftor/tezacaftor/ivacaftor (ETI), mild bilirubin increases have been reported, even without significant liver disease. Exercise may increase bilirubin as an adaptive antioxidant response while simultaneously improving hepatic clearance and reducing oxidative stress.

Objective: To evaluate the effects of a 16-week exercise intervention on bilirubin and liver enzymes in children and adolescents with CF treated with ETI.

Methods: 48 participants were randomized to exercise group (n=21) or control group (n=27). Total bilirubin, AST, and ALT were measured at baseline and after 16 weeks. Data is presented as median (Q1–Q3). Group $\times$ time interactions were analyzed using repeated-measures models.

Results: Baseline bilirubin was within normal ranges in both groups. Significant group $\times$ time interaction was observed for bilirubin (p=0.047). The exercise group remained stable [0.61 (0.56–0.84) to 0.63 (0.41–0.81) mg/dL], whereas the control group increased [0.69 (0.57–0.93) to 0.80 (0.60–0.99) mg/dL]. No significant interactions were found

for AST (p=0.557) or ALT (p=0.531). **Conclusion:** A 16-week exercise program maintained stable bilirubin levels without altering transaminases in children and adolescents with CF receiving ETI. These findings suggest that exercise may help counteract treatment-related increases in bilirubin, potentially reflecting improved hepatic clearance and reduced oxidative stress, supporting a context-dependent hepatoprotective role.

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Keywords:

Cystic Fibrosis, Liver, Oxidative Stress, Exercise

P-215

Effects Of Sustained Changes In Physical Activity On Inflammatory Biomarkers And Myokines In Adults With Metabolic Syndrome

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Metabolic syndrome (MetS) is associated with metabolic disturbances, chronic low-grade inflammation, and muscle dysfunction, leading to an increased cardiometabolic risk. Although physical activity is a key therapeutic strategy, its effects on inflammatory biomarkers and myokines remain poorly understood. The aim of this study was to evaluate the impact of sustained improvements in physical activity on inflammatory parameters and myokines in adults with MetS.

Fifty participants from the FLIPAN study (Mallorca, Spain) with available baseline and 12-month follow-up data were analysed. Participants were classified according to changes in physical activity (Δ METs/day) into two groups: High PA (above the median) and Low PA (below the median). Inflammatory biomarkers (IL-6, TNF- α , MPO, and resolvin D1) and myokines (irisin, FGF21, and myostatin) were an-

alysed. Comparisons were performed using parametric or non-parametric tests and ANCOVA models adjusted for age, sex, and baseline values.

After 12 months, the High PA group showed a significant increase in physical activity, whereas the Low PA group exhibited a reduction. Compared with the Low PA group, the High PA group displayed lower concentrations of IL-6 and TNF- α , as well as reduced levels of resolvin D1 and myostatin. Additionally, irisin levels increased in the High PA group, while FGF21 levels increased in both groups. No relevant differences were observed in MPO levels.

In conclusion, sustained improvement in physical activity among adults with MetS is associated with a more favourable inflammatory profile and changes in biomarkers related to muscle function, reinforcing the role of physical activity as a therapeutic tool in the management of metabolic syndrome.

Keywords:

Metabolic Syndrome, Physical Activity, Inflammation, Myokines

P-216

Anti-Obesity Effects Of An NAD+ Precursor Are Independent Of SIRT1 And SIRT3 Signaling In Adipose Tissue

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Background: Sirtuins SIRT1 and SIRT3 are key regulators of metabolic homeostasis and mitochondrial function, implicated in obesity and adipose tissue biology. NAD⁺ precursors, as coenzymes of sirtuins, have shown anti-obesity effects; however, the specific role of adipose tissue SIRT1/SIRT3 signaling in these effects remains unclear.

Objective: This study aimed to investigate whether adipose tissue-specific signaling through SIRT1 and SIRT3 mediates the anti-obesity effects of an NAD⁺ precursor in a diet-induced obesity mouse model.

Methods: Genetically modified C57BL/6Ola mice with adipose tissue-specific deletion of SIRT1 and SIRT3 were generated using AdipoCre recombinase. Mice were fed a high-fat diet for 12 weeks to induce obesity and treated with niacin as appropriate. Gross variables, including body weight, fat mass, as well as key molecular targets of SIRT signaling, were analyzed by real-time qPCR.



Results: The administration of the NAD⁺ precursor prevented weight gain even in the absence of gene expression of SIRT1 or SIRT3 in adipose tissue. SIRT1/3 deficiency was confirmed by real-time qPCR analysis. Modulation of SIRT1 and SIRT3 signaling specifically in adipose tissue did not significantly influence fat accumulation, progression of diet-induced obesity, or feed efficiency. Real-time qPCR analysis revealed no major differences between knockout and control mice in the expression of genes involved in energy metabolism or inflammation.

Conclusions: These results challenge the proposed role of adipose tissue SIRT1 and SIRT3 in mediating the anti-obesity effects of NAD⁺ precursors in mice, suggesting that these beneficial effects may be mediated by other tissues or systemic pathways rather than direct adipose-specific mechanisms.

Keywords:

Obesity, Experimental, Vitamin B3, Niacin, Adiposity

antioxidants were frequently associated with reduced disease risk and improved symptom control. In contrast, high consumption of red meat, trans fats, and pro-inflammatory diets was associated with increased risk and symptom severity. Among nutritional interventions, low-FODMAP diets showed the most consistent clinical benefits, including reductions in gastrointestinal symptoms and pelvic pain. Mediterranean and antioxidant-rich diets also demonstrated beneficial effects, particularly regarding oxidative stress and pain-related outcomes. **Conclusions:** Dietary interventions may represent a promising complementary strategy in endometriosis management by modulating inflammatory and oxidative pathways. However, current evidence remains limited by study heterogeneity and variability in study design. Further randomized controlled trials are needed to establish evidence-based nutritional recommendations.

Keywords:

Endometriosis, Diet, Metabolism, Inflammation, Nutrition.

P-218

Sex-Dependent Hepatic Transcriptomic And Epigenetic Adaptation To Acute Circadian Disruption In F344 Rats

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Circadian rhythms regulate metabolic processes, and their disruption can influence hepatic metabolism. This project assessed the effects of an acute photoperiod disruption in male and female F344 rats. Twelve-week-old rats (n = 16 per sex) were maintained under a 12:12 light-dark cycle for 4 weeks. Half of the animals were then transferred to a 6:18 light-dark photoperiod for one week. Males and females showed distinct transcriptomic shifts revealed by RNA-seq. While males displayed minimal alterations, females exhibited broader transcriptomic changes, with a notable shift in lipid metabolism and mitochondrial pathways. Conversely, miRNA-seq analysis in females revealed a putative regulatory network targeting insulin signaling and PI3K-Akt/Foxo pathways, with Igf1r as a central node. The integrated interpretation of transcriptomic and miRNA-seq data supports a sex-dependent adaptive response to circadian disruption and suggests a potential post-transcriptional contribution of miRNAs to hepatic metabolic homeostasis. These results highlight sex-dependent responses to circadian disruption and provide new insights into the interplay between epigenetic post-transcriptional regulation and hepatic metabolism.

Keywords:

MiRNA-Seq; RNA-Seq; Photoperiod; Hepatic Metabolism; Sexual Dimorphism

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Sex-Dependent Hepatic Responses To Grape Supplementation Under Circadian Disruption In F344 Rats

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Circadian rhythms play a fundamental role in regulating metabolic functions, and their disruption to these rhythms can affect hepatic metabolism. This study investigated the impact of grape consumption on hepatic antioxidant status and molecular clock regulation in male and female F344 rats exposed to a photoperiod shift. Twelve-week-old animals (n = 32 per sex) were assigned to either control or grape-supplemented group (1 g/kg body weight) and maintained under a 12:12 h light-dark cycle for four weeks. Subsequently, half of the rats were subjected to a 6:18 h light-dark photoperiod shift for an additional week, inducing circadian disruption. Grape supplementation modulated hepatic antioxidant defences and circadian regulatory mechanisms in a sex-dependent manner under conditions of circadian disruption. While males displayed greater alterations in antioxidant gene and protein expression, as well as in clock-related responses, females exhibited greater oxidative and circadian resilience, suggesting higher adaptive capacity. Overall, these findings highlight sex-specific differences in the response to dietary antioxidants under altered circadian conditions and provide further insight into the interplay among redox homeostasis, circadian regulation, and nutritional modulation of metabolic health.

Keywords:

Circadian Disruption; Grape Supplementation; Hepatic Metabolism; Molecular Clock; Redox Homeostasis; Sexual Dimorphism; Transcriptomics.

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From Gastrointestinal Digestion To Hepatic Response: Implications Of Microplastic Transformations For The Gut-liver Axis

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Human exposure to microplastics (MPs), particularly through ingestion, is an increasing concern. Although many *in vitro* studies have investigated the biological effects of MPs, the impact of gastrointestinal digestion on particle properties and the resulting cellular responses remains poorly understood. Since ingested compounds reach the liver through the gut-liver axis and the liver plays a central role in lipid metabolism, understanding how digestion alters MP interactions with hepatic cells is important.

This study aimed to evaluate whether simulated gastrointestinal digestion modifies the physical properties of MPs and whether these transformations influence hepatic lipid accumulation.

Polystyrene MPs of four sizes were subjected to an *in vitro* digestion model including salivary, gastric and intestinal phases. Particle size, aggregation and morphology were characterised using dynamic light scattering, flow cytometry and electron microscopy. In parallel, HepG2 cells were exposed to pristine and digested MPs under lipid-loading conditions induced by oleic and palmitic acid, and lipid accumulation was assessed using Oil Red O staining.

Digestion increased MP size and aggregation, mainly due to ionic interactions and swelling effects, while no major surface alterations were detected. In HepG2 cells, exposure to digested MPs increased lipid accumulation compared with lipid-loaded control cells, whereas pristine MPs did not induce significant changes.

These findings suggest that gastrointestinal digestion alters MP behaviour and may modify their metabolic effects in hepatic cells, highlighting the importance of incorporating digestion pre-treatment to improve the physiological rele-

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Background: Endometriosis is a chronic estrogen-dependent inflammatory disease characterized by pelvic pain and impaired quality of life. Increasing evidence suggests that diet may act as a modifiable factor influencing disease risk and symptom severity through inflammatory and oxidative stress-related pathways. **Materials and Methods:** A structured literature review was performed following PRISMA guidelines. Searches were conducted in PubMed and Web of Science, focusing on studies published during the last decade. A total of 22 studies, including observational studies, prospective cohorts, and clinical trials, were analyzed to evaluate dietary patterns, nutrient intake, and nutritional interventions in endometriosis. **Results:** Anti-inflammatory dietary patterns rich in fruits, vegetables, legumes, fish, and



vance of microplastic toxicity studies.

Keywords:

Gastrointestinal Digestion, Gut-Liver Axis, Hepatic Cells, Microplastics, Particle Aggregation, Steatosis

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Chicken Protein Hydrolysate Rescues Metabolic Flexibility And Suppresses Hepatic De Novo Lipogenesis In Cafeteria Diet-Fed Rats

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Cafeteria (CAF) diets induce metabolic syndrome, characterized by hepatic lipid accumulation, insulin resistance, and chronic low-grade inflammation. This study evaluated the effects of an animal protein hydrolysate (APH) obtained from chicken by-products in sixteen female Wistar rats fed a CAF diet and randomized to vehicle (VH) or APH treatment. Polar serum metabolites were profiled using untargeted ¹H-NMR metabolomics, and hepatic gene expression was assessed by qPCR. PCA and cross-validated PLS-DA ($R^2 = 0.88$, $Q^2 = 0.028$) suggested that APH induces homeostatic adjustments rather than metabolic disruption. CAF-VH rats displayed a tightly coupled network of branched-chain amino acids (BCAAs) and related catabolites, alongside a central lactate hub, signaling impaired BCAA catabolism, anaerobic metabolism, and disrupted glucose handling. APH treatment appeared to attenuate this pattern, significantly reducing formate levels ($p=0.024$), while lysine and leucine showed lower concentrations. Network topology identified alterations in gut microbiota-derived co-metabolites (trimethylamine, acetate) and metabolites associated with insulin resistance (valine, glucose). Furthermore, APH shifted metabolism toward oxidative phosphorylation and increased ketogenesis (elevated acetone and β -hydroxybutyrate), suggesting improved metabolic flexibility. These systemic adjustments were accompanied by significant hepatic downregulation of sterol regulatory element-binding protein 1c (Srebp-1c), glucokinase (Gk), and glucose transporter 2 (Glut2), suppressing de novo lipogenesis. In conclusion, APH partially mitigates CAF diet-induced metabolic alterations by modulating pathways related to gut microbio-

ta, BCAA utilization, and mitochondrial energy metabolism, and hepatic nutrient handling.

Keywords:

Protein Hydrolysate, Gut Microbiota, Lipogenesis, Metabolomics

P-222

Untargeted Metabolomics Reveals Distinct Cecal Chemical Signatures Induced By Buttermilk-Based Beverages In Obese Mice

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High-fat diet (HFD) consumption destabilizes intestinal homeostasis, shifting the gut metabolomic profile. Dietary interventions with dairy co-products, such as buttermilk, probiotics and polyphenols represent promising strategies to mitigate these metabolic disorders. This study investigated the effects of functional beverages based on buttermilk, *Lactobacillus gasseri* LG08 and curcumin on the cecal metabolome of HFD-induced mice. Forty C57BL/6J mice fed an HFD for 12 weeks. Subsequently, they were divided into 5 groups and subjected to diet normalization combined with the gavage of different beverages for another 12 weeks: buttermilk (BM); buttermilk fermented by *Lactobacillus gasseri* LG08 (FBM); buttermilk with curcumin (CUR); curcumin-fermented buttermilk (FCUR); or water (CT). Cecal feces were subjected to LC-MS untargeted metabolomics. XCMS Online was used for peak picking and alignment, while MetaboAnalyst allowed data normalization and multivariate statistical analysis. In the negative ionization mode, pairwise PERMANOVA confirmed that the nutritional interventions promoted significant shifts in the overall metabolomic profile ($p_{\text{adj}} < 0.05$). The greatest metabolic divergence occurred between BM and FBM groups ($R^2 = 0.70$; $p_{\text{adj}} = 0.002$), highlighting the strong chemical remodeling driven by probiotic fermentation. Conversely, CUR and FCUR profiles showed no significant difference in negative polarity ($R^2 = 0.15$; $p_{\text{adj}} = 0.162$), indicating high similarity in the anionic metabolite signatures between the beverages with curcumin. In contrast, positive polarity successfully discriminated all five groups, suggesting that matrix fermentation alterations predominantly impact cationic features, while curcumin-derived organic acids remain stable across formulations.

Keywords:

Metabolomics, Nutrition, Probiotics, Fermentation, Polyphenols, Curcumin, Lactobacillus, Obesity, Dairy, Gut Metabolome

P-223

Grape Consumption Effect On Microbial Biodiversity And Its Role In Seasonal Photoperiod Adaptation

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Polyphenols are bioactive compounds generated as a stress response in plants. According to the Xenohormesis theory, animals may have developed mechanisms to detect these signals, triggering adaptive anticipatory responses to seasonal changes. The gut microbiota may play a key role in this process, as it is one of the main agents involved in (poly)phenol metabolism and a potential mediator between these compounds and host seasonal rhythms. Thus, the aim of this study was to evaluate the impact of polyphenol-rich fruit consumption on gut microbiota in response to a photoperiod change in male and female rats.

For this, 96 male and female Fischer 344 rats were treated with vehicle (water, control group) and two differently-harvested grapes (at an optimal time and a later date) for 4 weeks under a standard photoperiod (12h of light, L12). After this period, 48 animals, representative of each group, were sacrificed, while the rest of the group were transferred to a short photoperiod (6h of light, L6) for a week without treatment. Finally, caecum content samples were obtained for 16S rRNA sequencing.

The results showed similar α -diversity between the control and treatment groups in L12 females, but this changed in L6 females. In males, L12 rats showed changes in α -diversity in response to the treatment, but these changes did not persist after the photoperiod change. The differential abundance analysis showed changes between treatments and the added effect of sex and photoperiod, such as an increase in abundance of the Bacillota phylum in males compared to females. In conclusion, grape supplementation modulated gut microbiota composition in a sex- and photoperiod-dependent manner. Further studies are needed to elucidate the possible role of microbiota in photoperiod adaptation.

Keywords:

Nutrigenomics, Microbiota, Metagenomics, Bioinformatics, Polyphenols, Photoperiod, Circadian Rhythms, Xenohormesis

P-224

Liver Damage Caused By A High-Fat Diet: Sex Differences And Partial Reversibility Of Lipid Changes

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Obesity induced by a high-fat diet (HFD) is a key factor in the development of hepatic steatosis, with significant sex-dependent differences whose extent and reversibility are not yet fully understood. In this study, we analysed the differential response between males and females and the reversibility of hepatic alterations following a switch to a standard diet. Three-month-old wild-type (WT) male and female mice were fed a standard diet (STD) or HFD for 6 months. An additional group received HFD for 3 months, followed by 3 months on the STD to assess dietary reversibility. Male mice showed a greater increase in body weight and hepatomegaly in response to the HFD compared with females, along with greater hepatic lipid accumulation. Histological analysis revealed more severe steatosis in males, with greater hepatocellular ballooning and a predominance of microvesicular accumulation, whilst females mainly exhibited macrovesicular steatosis. In animals subjected to dietary reversal, body weight and hepatic lipid load decreased in both sexes. Lipid studies revealed a clear sexual dimorphism in response to the HFD, with male animals showing a greater accumulation of different lipid species than female animals. In addition, an overall normalisation of most lipid species following the dietary change was observed. These findings were consistent with the study of gene expression related to lipid synthesis (*Acc*, *Fas*, *Acl*), and degradation (*Ppara*, *ApoC2*, *Cpt1a*, *Acox1*). These results demonstrate greater susceptibility of males to HFD-induced liver damage and show that, although most lipid alterations are reversible, triacylglycerides show incomplete reversal, suggesting a persistence of diet-induced metabolic alteration.

Keywords:

Obesity, Fatty Liver Disease, Sexual Dimorphism, Dietary Reversal



P-225

Sex-Dependent Hepatic Lipid Overload And Stress Responses In Cafeteria Diet-Fed Rats Exposed To Different Photoperiods

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Circadian misalignment and obesogenic diets are associated with hepatic metabolic dysfunction, although their sex-specific impact remains poorly explored. This study evaluated the effects of photoperiod (short and long), sex and their interaction on hepatic lipid accumulation, endoplasmic reticulum (ER) stress, apoptosis, autophagy and lipid droplet remodeling in Fischer 344 rats fed a cafeteria diet. Males displayed a more severe metabolic phenotype, with higher body weight, liver weight and hepatic total lipids, cholesterol and triglycerides. This lipid overload was accompanied by a stronger stress-related hepatic profile, with increased cleaved caspase-3 and Chop expression, particularly under long photoperiod. Additionally, Atf6 and Grp78 expression were also modulated by photoperiod, suggesting activation of the unfolded protein response. Males under long photoperiod also showed increased Lc3 and Ulk1 expression, indicating possible compensatory activation of autophagy/lipophagy mechanisms in response to lipid overload and ER stress. Increased Plin5 expression may further reflect lipid droplet remodeling.

In contrast, females showed a less aggravated metabolic profile and distinct cellular response, with increased GRP78 protein abundance, LC3II/LC3I ratio, p-mTOR, PLIN2, FASN and p-AMPK. This suggests a female-specific hepatic adaptation involving nutrient sensing, lipid droplet organization and metabolic remodeling rather than progression toward ER stress and apoptosis. Overall, males were more susceptible to cafeteria diet-induced hepatic lipid overload, particularly under long photoperiod. In females, coordinated modulation of lipid metabolism and cellular stress markers may contribute to a more adaptive hepatic response to obesogenic and circadian challenges.

Keywords:

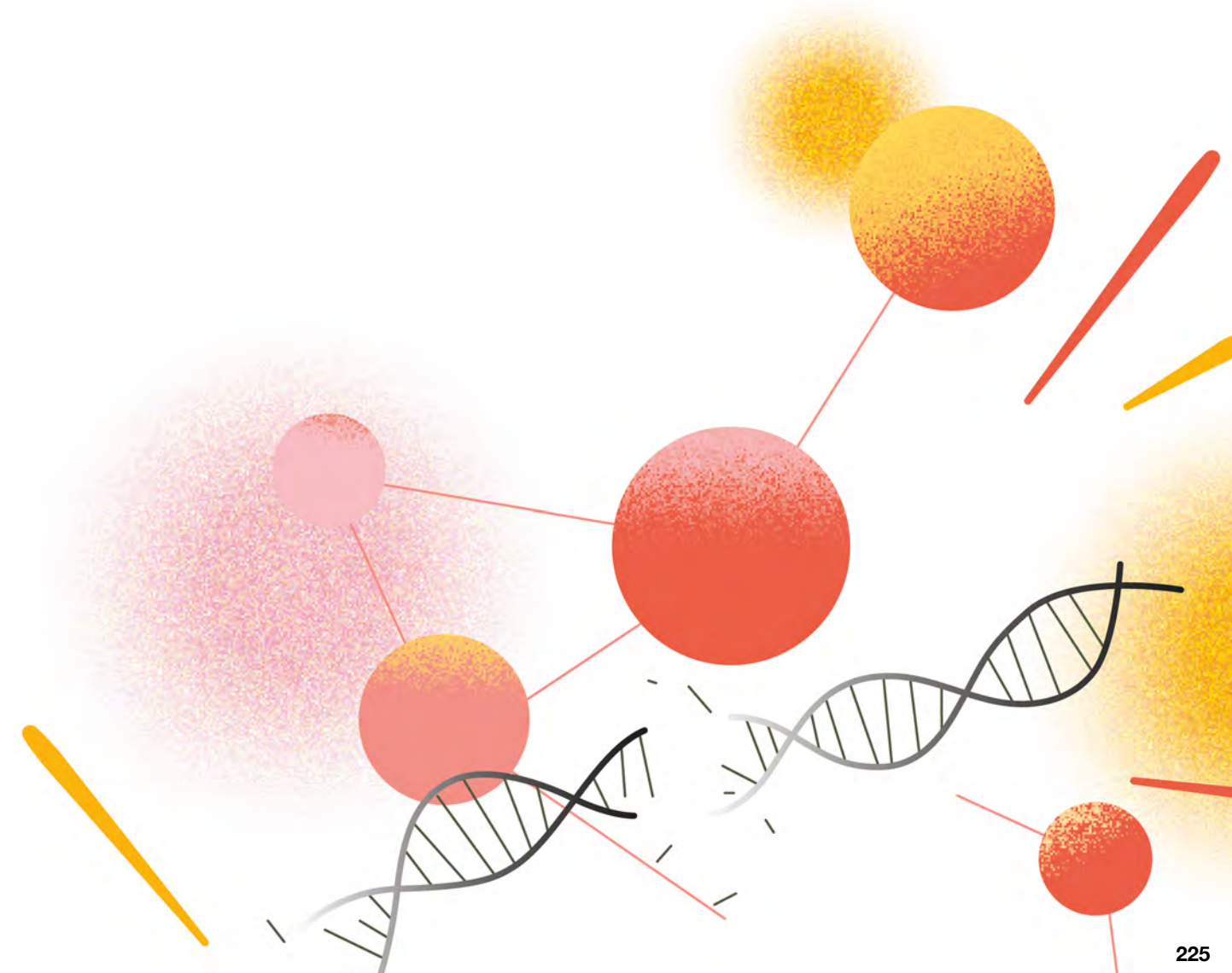
Cafeteria Diet, Obesity, Photoperiod, Sex Differences, Hepatic Lipid Accumulation, Endoplasmic Reticulum Stress, Autophagy, Lipid Droplet Remodeling



GRUPOS CIENTÍFICOS DE LA SEBBM:

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UNRAVELING BRAIN GLYCOGEN: CELL-TYPE–SPECIFIC ROLES IN PHYSIOLOGY AND PATHOLOGY

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Glycogen is a highly branched polymer of glucose and the only carbohydrate storage form in mammals. Although abundant in liver and skeletal muscle, it is present at much lower levels in the brain. Its function in the central nervous system was therefore long considered marginal and mainly restricted to emergency support. However, this view has changed substantially in recent years: our work and that of others have shown that brain glycogen plays important roles in normal brain function. Furthermore, brain glycogen was traditionally believed to be confined to astrocytes, but we demonstrated that neurons also contain an active glycogen metabolism that contributes to neuronal function. Thus, glycogen fulfils cell-type–specific functions in the brain and its metabolism must be tightly regulated.

This regulation becomes especially relevant in pathological conditions in which glycogen accumulates abnormally and becomes toxic. The clearest example is Lafora disease, a fatal adolescent-onset neurodegenerative condition characterized by the accumulation of poorly branched glycogen aggregates in the brain. Using mouse models, we have dissected the toxic contribution of glycogen accumulation in different brain cell types. Indeed, astrocytic glycogen accumulation drives neuroinflammation, metabolic alterations and autophagy-related defects, whereas epilepsy is mainly driven by neuronal glycogen accumulation, particularly in inhibitory interneurons. Importantly, beyond Lafora disease, glycogen-driven neurotoxicity may also contribute to prevalent neurodegenerative disorders, including Alzheimer's disease.

Overall, these findings establish brain glycogen as a key player in physiology and disease, pointing to glycogen metabolism as a potential target in neurological disease.

Keywords:

Brain Glycogen, Metabolism, Lafora Disease, Neurotoxicity, Epilepsy, Neuroinflammation, Neurodegeneration, Alzheimer's Disease

O-139

Synaptic Remodeling Of The Prefrontal Cortex In Parkinson's Disease: Serotonergic Implications For The Pathophysiology Of Non-Motor Symptoms

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Anxiety and depression are common in Parkinson's disease (PD) and significantly impact patients' quality of life. In the early stages of the disease, aggregates of the α -synuclein (α -Syn) protein are found within serotonergic (5-HT) neurons of the raphe nuclei; however, their exact relationship to broader brain alterations remains unclear. Here, I present a pathogenic model in which the accumulation and aggregation of human α -Syn in the mouse 5-HT system triggers a cascade of events, beginning with synaptic pathology. This initial stage is characterized by synaptic stress, impaired axonal transport, and structural remodeling of the medial prefrontal cortex, accompanied by glial activation. This synaptic failure progressively leads to large-scale network dysfunction, manifesting as reduced functional connectivity and impaired metabolism within the cortico-limbic circuits responsible for mood regulation. Validated in both a preclinical mouse model and postmortem human brain samples, our study identifies a critical early disease phase originating from alterations in the 5-HT system. These findings provide a direct mechanistic basis for the depressive phenotype, establishing it as a fundamental component of PD pathophysiology.

Keywords:

α -Synuclein, Depression, Parkinson's Disease, Brain Functional Connectivity, Serotonergic System, Synaptic Pathology

O-140/P-227

Characterization Of A Novel UROC1 Knockout Mouse Model

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Urocanic acid (UCA) is an intermediate of histidine catabolism degraded by urocanase (UROC1) in the liver. UROC1 deficiency is an ultra-rare inborn error of metabolism, with few patients and heterogeneous clinical presentations, including evidence of neurodevelopmental involvement. The absence of experimental models has limited understanding of its pathophysiology and biomarkers.

We generated and validated the first UROC1 knockout (KO) mouse model and we tested a specific antibody that detects urocanase in wild-type but not KO tissues. Expression analyses showed high levels in periportal hepatocytes and renal proximal tubules, with other tissues under study. Biochemical profiling revealed a clear phenotype: KO mice displayed markedly elevated UCA in plasma and strong urinary hyperexcretion, faithfully reproducing the biochemical hallmarks of the human condition. In contrast, amino acid plasma profiling showed no major changes in other metabolites, and preliminary histology revealed no major tissue abnormalities.

Beyond its role as a metabolic intermediate, UCA is increasingly recognized as a bioactive molecule with tissue-specific effects. In the skin, UV-activated UCA functions as a photoimmunosuppressor and contributes to immune regulation after sunlight exposure. In the brain, experimental evidence points to a role of UCA in modulating learning and memory, suggesting that alterations in its levels may influence neurodevelopmental trajectories. Furthermore, UROC1 overexpression in hepatocellular carcinoma has been associated with a protective effect.

This new model provides the first mammalian platform to

study urocanase deficiency and a unique tool to investigate systemic consequences of altered histidine metabolism across tissues and disease contexts.

Keywords:

Urocanase Deficiency, Urocanic Acid, Histidine Metabolism, Rare Diseases, Neurodevelopment, Knockout Mouse Model, Amino Acid Metabolism, Metabolic Disorders, Hyperurocanemia, Translational Research

O-141/P-228

Role Of Nr4a2 In Hippocampal Dendritogenesis And Synaptogenesis In A Cellular Model Of Alzheimer's Disease

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Alzheimer's disease (AD), the major cause of dementia in the elderly, affects 47 million people worldwide and represents nowadays a large health, social and economic burden. Disruption of neuronal communication in brain areas that are essential for learning and memory, such as the hippocampus, is a key pathological event underlying early memory loss in AD. Indeed, multiple studies have suggested that early oligomeric amyloid-beta ($\text{oA}\beta$) on hippocampal synaptic plasticity could contribute to cognitive dysfunction in AD.

In this context, transcription factors play a pivotal role, and it has been reported that the Nr4a family of transcription factors might be closely linked to processes associated with the modulation of hippocampal synaptic plasticity and cognitive functions. Since the underlying molecular and cellular mechanisms remain unknown, we are interested in studying the potential role of Nr4a2 in the development process of dendrites and synapses in hippocampal-cultured neurons.

In the present work we are analyzing the dendritic arborization and number of synapses in $\text{oA}\beta$ -treated neurons. Hippocampal cultures are treated with 0.5 μM $\text{oA}\beta$ every 2-3 days-in-vitro (DIV) until reaching maturity (17-21 DIV), when morphology and synapses are monitored by immunocytochemistry. We also determine whether Nr4a2 overexpression (via lentiviral vectors) can reverse the decrease of dendritic branching and synapses observed in hippocampal



cultures treated with oA β , as its regulatory functions suggest it could represent a promising therapeutic target for Alzheimer's disease.

Keywords:

Alzheimer'S, Nr4a2, Hippocampus, A β , Synapsis

O-142/P-229

Beneficial Effects Of Omaveloxolone On Oxidative And Iron Dysregulation In Friedreich Ataxia

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Introduction: Friedreich Ataxia (FA) is a rare inherited neurodegenerative disease characterized by gait and limb ataxia, dysarthria, and loss of lower limb reflexes. Most patients are homozygous for the GAA triplet expansion in the frataxin gene (FXN), resulting in reduced levels of frataxin, a mitochondrial protein. FA is considered a multisystem disorder affecting several organs, particularly the nervous system and heart.

Objectives: On one hand, to test the effectiveness of omaveloxolone (an NRF2 activator) in reversing some altered biomarkers of FA. On the other hand, to assess whether combining omaveloxolone and honokiol allows achieving similar beneficial effects with lower doses of each compound.

Methods: Dorsal root ganglia (DRG) neurons and cerebellar granule neurons (CGN) from neonatal rats were cultured and frataxin levels were reduced by shRNA lentivirus transduction. Cells were treated with omaveloxolone (alone or in combination with honokiol) and compared with vehicle-treated controls.

Results and Discussion: Omaveloxolone improved most of the analyzed parameters, including mitochondrial respiratory activity, iron homeostasis, and oxidative stress. Moreover, increased lipid peroxidation, a key marker of ferroptosis, was almost completely rescued by the treatment. Interestingly, the combination of omaveloxolone and honokiol was able to rescue both cell survival and mitochondrial function using reduced doses of each compound.

Conclusion: Combination therapy with omaveloxolone and honokiol may represent a promising strategy for FA patients, potentially reducing side effects through dose minimization.

Keywords:

Friedreich Ataxia, Omaveloxolone, Oxidative Stress, Dorsal Root Ganglia, Mitochondria

O-143/P-230

Methylene Blue Promotes Cell Survival Through Multiple Pathway-Dependent Mechanisms

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Purpose: Methylene Blue (MB) is a synthetic dye that has been used in medicine for decades. Previous studies have demonstrated a protective effect of MB in animal models of retinal degenerative diseases and neurodegenerative disorders. MB acts as a nitric oxide synthase inhibitor and has been proposed as a pleiotropic agent with bioenergetic, redox, and anti-inflammatory properties, making it a promising neuroprotective compound. Cuprizone (CPZ) is a copper chelator that disrupts cellular metabolism, is widely used as an inducer of central nervous system damage in experimental models. In this study, we aimed to evaluate the effects of MB treatment and the molecular pathways involved in the prevention of CPZ-induced cellular damage.

Methods: Cell viability and metabolic assays, videomicroscopy studies, and genome-wide transcriptomic analysis were performed in the human oligodendroglia cell line HOG, which was exposed to MB for 24 h prior to CPZ injury. Integrative functional enrichment analysis of transcriptomic data was conducted to gain insight into the cellular protective mechanisms induced by MB.

Results: Under basal conditions, MB promoted cell proliferation without significant metabolic alterations. CPZ exposure caused a reduced cell viability, mitochondrial dysfunction and cellular morphological abnormalities in HOG cells, whereas MB pre-treatment prevented the cytotoxic effects. Transcriptomic analysis revealed that MB modulated the expression of key genes associated with cell survival, metabolism, and stress response pathways.

Conclusion: MB administration promotes cell survival and modulates key pathways associated with cellular protection against injury. These findings support the potential therapeutic value of MB in neurodegenerative diseases.

Keywords:

Methylene Blue, Molecular Pathways, Cellular Damage, Prevention

O-144/P-231

A D-Galactose-Based Human Cerebral Organoid Model Of Neurosenescence And Neurodegeneration

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Human cerebral organoids represent a promising *in vitro* platform to model complex brain processes and disorders, offering a 3D context that recapitulates aspects of neurodevelopment and cell-type diversity. However, a key limitation is their developmental immaturity, which poses challenges in recapitulating long-term aging and modeling late-onset or age-related pathologies *in vitro*. In this study, we investigated whether exposure to D-galactose, a reducing sugar widely used to induce aging-like phenotypes in animal models and neural cell cultures, could induce a neurosenescent and a pro-inflammatory state in unguided human brain organoids derived from healthy iPSCs. After seven days of treatment (day 40 to 47), mRNA expression analyses and immunoassays revealed widespread molecular changes indicating neurosenescence and neuroinflammation. Genes related to neuronal development and mature neuronal identity (e.g., *TUBB3*, *SYP*, *CTIP2*) were downregulated, as well glial (*GFAP*) and oxidative stress-response markers (e.g., *HSP90AB1*, *CAT*). Conversely, the expression of *CASP9*,

a key apoptotic gene, was strongly upregulated. These transcriptional and protein-level alterations suggest the emergence of dysfunctional neural identity and activation of apoptotic and inflammatory pathways. Overall, D-galactose treatment during a critical phase of maturation induces a senescence-like phenotype in human cerebral organoids. This model offers a physiologically relevant platform for screening neuroprotective drugs and bioactive compounds targeting age-related neurodegeneration.

O-146/P-233

Role Of T Cells And Non-Coding RNAs In Post-Stroke Cognitive Decline

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Stroke is followed by extensive immune activation characterised by a number of cell populations infiltrating the brain parenchyma. Different T cell subsets affect the ischaemic lesion depending on their functional characteristics. Inhibition of mmu-miR-721, primarily secreted by Th17 cells, correlates with a decrease in inflammation and an increase in neuroprotection in healthy aged mice. As such, we aim to explore the impact of miR-721 on post-stroke inflammation and cognitive decline.

We induce a permanent middle cerebral artery occlusion via ferric chloride in miR-721 full knock-out mice and wild-type littermates (approximate age: 8 weeks). TTC, Nissl staining and MRI have been used to determine the volume of the ischaemic region at different time points. We have found that the absence of miR-721 does not affect lesion size nor oedema index in the acute phase (p>0.05, n=8-9). However, there may be a contribution to more extensive tissue damage at longer timepoints, suggesting a possible role in lesion resolution.

Preliminary results via qPCR suggest an increase in miR-721 expression in plasma 24 hours after stroke, but the implication of this has yet to be elucidated. Other ongoing experiments consist of the study of immune response kinetics via flow cytometry, infiltration of immune populations within the brain parenchyma via immunofluorescence, and behavior.





journal testing to assess different domains of cognition.

Future objectives include full characterisation of conditional miR-721 KO models (CD4 flox/flox, VE-cadherin flox/flox, Nes flox/flox), evaluation of the therapeutic potential of miRNA inhibition using miRNA sponges, and the study of the presence of miR-721 in human patient samples (plasma, CSF).

Keywords:

T Cell, MiRNA, Stroke, Cognitive Decline, Non-Coding RNA

O-147/P-234

Characterization Of GlyT2 Variants Associated To Hyperekplexia

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Hyperekplexia is a neuromotor syndrome characterized by hypertonia and exaggerated startle response to minor stimuli, which can be fatal in neonates due to cardiorespiratory complications. Although symptom severity typically diminishes during the first year of life, affected individuals continue to exhibit disabling motor dysfunction and frequent unprotected falls throughout adulthood. Hyperekplexia is caused by defective inhibitory glycinergic neurotransmission. The neuronal glycine transporter GlyT2 plays a crucial role in glycinergic synapses by reuptaking glycine from the synaptic cleft and supplying it to the presynaptic terminal, thereby maintaining the quantal glycine content within synaptic vesicles. Mutations in the human gene encoding GlyT2 (SLC6A5) cause hyperekplexia type III (OMIM 614618) and represent the second most common genetic cause of hyperekplexia. In this study, we investigate the properties of several previously uncharacterized SLC6A5 variants identified in patients with hyperekplexia. Specifically, we analyze the functional activity and intracellular trafficking of GlyT2 point mutants. Variant transporter cDNAs were generated by site-directed mutagenesis and expressed in cultured cells. Our results indicate that the mutant transporters retain partial activity. Using tritiated glycine uptake assays, quantitative analysis of surface expression, and immunocytochemistry with organelle markers, we demonstrate that these variants differ in plasma membrane expression and maximal transport rate, suggesting alterations in intracellular trafficking. Ongoing studies aim to determine their intracellular retention sites, assess their ubiquitination capacity,

and evaluate the potential for functional rescue using chemical chaperones.

Keywords:

Hyperekplexia, GlyT2 (Glycine Transporter 2), SLC6A5 Mutations, Glycinergic Neurotransmission, Intracellular Trafficking, Transport Activity, Surface Expression, Functional Rescue

O-148/P-235

Endothelial MT4 MMP Restrains VEGFA-NRP1 Signaling To Maintain Vascular Patterning During Development And Wound Repair

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Angiogenic remodeling requires precise spatiotemporal control of endothelial dynamics, yet the molecular mechanisms that fine-tune vessel expansion during development and tissue repair remain incompletely defined. Here, we identify the GPIanchored metalloprotease MT4MMP as a contextdependent regulator of endothelial morphogenesis. Global MT4MMP deficiency induces a transient delay in vascular network assembly in the embryonic hindbrain, whereas endothelialrestricted deletion results in a hyperangiogenic phenotype characterized by increased microvascular density, excessive branching, and disruption of hierarchical vascular patterning. MT4MMP expression is dynamically modulated during cutaneous wound healing, and its loss enhances vascularization and accelerates tissue closure, indicating a role in postnatal vascular homeostasis. At the cellular level, MT4MMP-null endothelial cells display defective front-rear polarization and exhibit sustained VEGFAdependent ERK activation. We identify NRP1 as a new MT4MMP substrate and demonstrate that MT4MMPmediated NRP1 ectodomain cleavage limits NRP1 surface abundance, thereby modulating VEGFA signaling. Pharmacological disruption of the VEGFA-NRP1 interaction partially normalizes the vascular abnormalities observed in MT4MMP-deficient endothelium *in vivo*.

These findings establish the MT4MMP/NRP1 axis as a critical regulatory node that prevents pathological vessel ex-

pansion and highlight membraneanchored proteolysis as a central mechanism governing angiogenic responses in both developmental and reparative contexts.

Keywords:

Neurovascular Development, Angiogenesis, MT4-MMP (MMP17), Neuropilin-1 (NRP1), VEGFA Signaling, Wound Healing, Vascular Remodeling

O-149/P-236

Impaired NOX4-Dependent Signalling Promotes Cochlear Degeneration And Hearing Loss

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Reactive oxygen species are widely implicated in cochlear injury, with the superoxide anion generated by NADPH oxidase 3 (NOX3) representing a major pathogenic source, especially in noise- and drug-induced damage. In contrast, NOX4 primarily produces hydrogen peroxide (H₂O₂), which is more closely associated with redox signaling and tissue homeostasis. However, the specific role of NOX4 in the inner ear remains poorly defined. Here, we characterize the auditory phenotype in the Nox4tm1.2Hwsc knockout (KO) mouse.

Nox4 KO mice exhibit premature, progressive age-related hearing loss, as assessed by auditory brainstem responses.

Histopathological analysis reveals a distinctive phenotype characterized by severe degeneration of the spiral ligament, including a marked loss of type II and IV fibrocytes and extensive disruption of the extracellular matrix. With time, further alterations become evident in the organ of Corti and the spiral ganglion.

Notably, these structural defects occur without a clear inflammatory or by a canonical oxidative stress gene expression profile and suggest impaired connective tissue homeostasis, likely due to altered extracellular matrix regulation through NOX4dependent pathways, including TGFβ signaling..

Although Nox4 deletion has been reported to exert protective effects in other tissues, our data indicate that NOX4 is necessary for preserving cochlear structural integrity. Overall, this study identifies NOX4 as a key factor in maintaining cochlear redox homeostasis and highlights the importance of physiological redox signalling in preserving inner ear function during aging.

Acknowledgments. The project was supported by MCIN PID2023-147347OB-I00 (SMC and IVN). SMC is senior CIBER researcher and MTM holds a MCIN PREP2023-001160 contract.

Keywords:

NOX4, Inner Ear, Cochlea, Hearing Loss, Spiral Ligament

P-237

Methylene Blue As A Neuroprotective Therapy For Glaucoma And Traumatic Optic Neuropathy

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Background and Aims: Optic neuropathies such as traumatic optic neuropathy (TON) and glaucoma cause progressive retinal ganglion cell (RGC) death and irreversible vision loss. Methylene blue (MB), a nitric oxide synthase inhibitor and free radical scavenger, has shown neuroprotective potential. This study evaluated MB effects in acute and chronic models of visual pathway injury.

Methods: Adult Wistar rats underwent intraorbital optic nerve compression (IONC) or episcleral vein cauterization (EVC). MB (2.0 mg/kg, i.p., every 12 h) or vehicle was administered for 7 days after IONC or 14 days after EVC. In the EVC model, treatment began after 1 week of untreated ocular hypertension and documented ERG decline. Visual pathway function was assessed using scotopic and photopic electroretinography (scERG/phERG), oscillatory potentials (OPs), and visual evoked potentials (VEPs). RGC survival was quantified by flat-mount immunohistochemistry.



Results: MB significantly reduced neuronal dysfunction. In IONC, MB preserved retinal function, improving scERG, phERG, and OPs. In EVC, longitudinal analysis showed that MB slowed progressive declines in VEPs and retinal electrophysiological responses. Functional preservation in EVC correlated with higher RGC survival quantified by immunohistochemistry in retinal flat mounts.

Discussion: Prolonged MB treatment produced neuroprotective effects in acute trauma and chronic ocular hypertension. Electrophysiological analyses demonstrated preservation of the visual pathway from retina to cortex, correlating with RGC survival. Given its low cost, availability, clinical approval, and favorable safety profile, MB shows strong translational potential for preventing vision loss in acute and progressive optic neuropathies.

Keywords:

Methylene Blue, Neuroprotective, Glaucoma, TON

P-238

Repurposing Of Doxepin Hydrochloride For Glioblastoma Cancer Stem-Like Cells

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Glioblastoma (GBM) is the most prevalent and lethal primary brain tumor. Despite current treatments, patient prognosis remains poor. This limited therapeutic efficacy is partly attributed to Glioblastoma Stem-like Cells (GSCs), a small population of cells with neural stem cell characteristics and high transcriptional activity. This activity increases the formation of DNA:RNA hybrids called R-loops. When R-loops are not properly regulated, they interfere with DNA replication, causing replicative stress, DNA double-strand breaks, and genomic instability.

Targeting GSCs remains challenging due to the overlap of key survival pathways with normal neural stem cells. To identify compounds capable of overcoming tumor resistance, a prior drug screening was performed using a library of FDA approved drugs capable of crossing the blood–brain barrier of the central nervous system. The accumulation of R-loops after treatment was used to identify compounds capable of increasing genomic instability in GSCs. Persistent DNA damage can stop the cell cycle and induce apoptosis. From this screening, doxepin, a tricyclic antidepressant pre-

viously associated with anti-inflammatory effects in glioma cells, was selected for further investigation.

This work evaluated the repositioning of doxepin as a possible therapy against GSCs by studying its ability to induce genomic instability, reduce cell viability, and cause mitochondrial damage, alone or combined with radiotherapy. The results showed high DNA repair capacity and radioresistance in GBM cells after irradiation, as well as a selective effect of doxepin on GSCs associated with R-loop accumulation and mitochondrial alterations. However, no radiosensitizing effect was observed with radiotherapy.

Keywords:

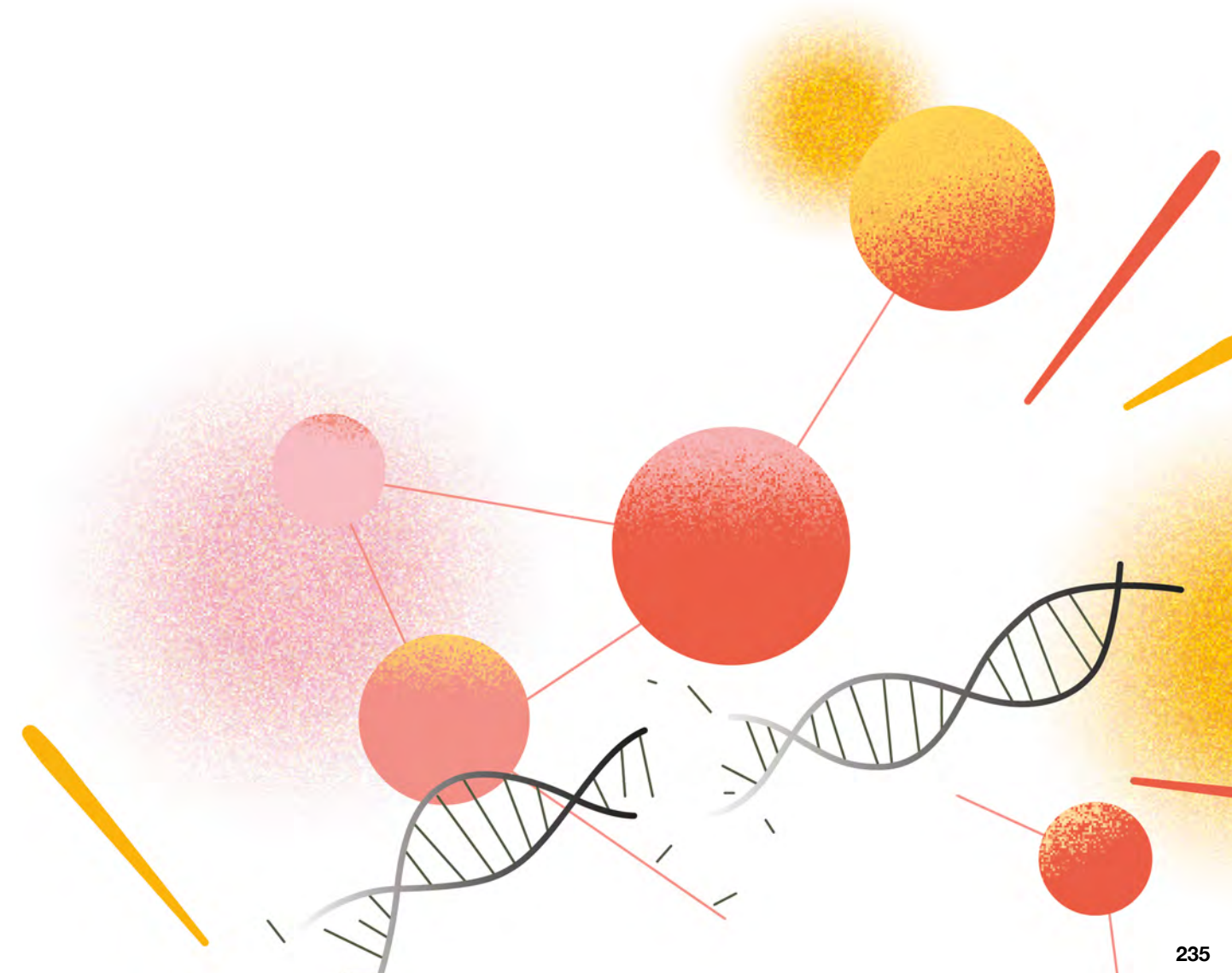
Glioblastoma, Glioblastoma Stem-Like Cells, Doxepin, R-Loops, DNA Repair



GRUPOS CIENTÍFICOS DE LA SEBBM:

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O-150

Dismantling BCL-2-driven Apoptotic Resistance By Targeted Protein Degradation In Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype in which chemotherapy remains the main systemic treatment. However, resistance frequently drives relapse and metastatic progression. Since resistant cells often rely on anti-apoptotic BCL-2 family proteins to evade cell death, we investigated whether disrupting this survival network could overcome therapeutic resistance.

Analysis of TNBC patient datasets (KM Plotter and ROC Plotter) revealed that high expression of anti-apoptotic BCL-2 family members is associated with poor prognosis and reduced chemotherapy response. Consistently, cisplatin- and taxane-resistant TNBC models (MDA-MB-231R and BT-549R) displayed an anti-apoptotic phenotype characterized by increased dependence on the BCL-2 network. Pharmacological targeting of this pathway using a pan-BH3 mimetic or a dual-targeting PROTAC reduced the abundance of anti-apoptotic BCL-2 proteins, inhibited proliferation, and impaired clonogenic, migratory, and invasive capacities. These effects were accompanied by robust activation of apoptosis, including increased cleavage of caspase-3 and PARP, together with elevated p2AX levels. Importantly, disruption of the BCL-2 survival network translated into significant antitumor activity in taxane-refractory patient-derived xenografts (PDXs) and syngeneic MMTV-PyMT breast cancer models, leading to marked reductions in tumor growth.

Collectively, our findings demonstrate that chemotherapy-resistant TNBC develops a critical dependency on the anti-apoptotic BCL-2 network. Targeted protein degradation effectively dismantles this adaptive survival mechanism, restores apoptotic competence, and identifies BCL-2-driven resistance as an actionable therapeutic vulnerability in refractory TNBC.

Keywords:

Chemoresistance, Patient-Derived Xenografts, Apoptosis, Therapeutic Vulnerability

O-151

The Exploitation Of Cell Death In Cancer Immunotherapy

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The relationship between cell death and inflammation is a key determinant of effective antitumor immunity. In the context of cancer, cytotoxic lymphocyte-mediated tumor cell death can be immunogenic, promoting the exposure and release of danger signals such as calreticulin and HMGB1, which facilitate antigen uptake by dendritic cells, cross-presentation, and the amplification of adaptive antitumor responses. At the same time, inflammatory pathways also shape the efficacy and toxicity of immune checkpoint blockade, as combined PD-1 and CTLA-4 inhibition enhances antitumor immunity but may induce severe immune-related adverse events such as colitis and hepatitis. Remarkably, blockade of TNF can reduce these toxicities while preserving therapeutic efficacy, underscoring the need to finely tune inflammation during immunotherapy. Beyond adaptive immunity, trained immunity provides an additional layer of antitumor defense. MV130, a mucosal immunotherapy composed of heat-killed bacteria, induces long-lasting trained immunity in innate immune cells, particularly alveolar macrophages, leading to a proinflammatory lung microenvironment and improved control of lung tumors and metastasis. Similarly, HKMTb supports the concept that heat-killed bacteria are sufficient to trigger trained immunity, indicating that live BCG is not strictly required to engage this mechanism. Together, these findings suggest that regulated forms of cell death and inflammation, whether induced by dying tumor cells or heat-killed bacteria, can converge to promote durable innate and adaptive antitumor responses and open new avenues for cancer immunotherapy.

Keywords:

Cell Death, Immunotherapy, Trained Immunity

O-152/P-239

Bispecific Anti-EGFR/MET CAR-M Cell Therapy For Lung Cancer: Functional Characterization In 2D And 3D In Vitro Models

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Lung cancer remains one of the leading causes of cancer-related mortality worldwide, with current therapies limited by toxicity and acquired resistance. Although CAR-T therapies have shown remarkable efficacy in hematological malignancies, their application in solid tumors remains challenging due to poor immune infiltration, antigen heterogeneity, and the immunosuppressive tumor microenvironment. In this context, macrophages represent a promising therapeutic platform because of their intrinsic tumor infiltration capacity, phagocytic activity, antigen presentation, and functional plasticity. Here, we are developing and evaluating anti-EGFR and bispecific anti-EGFR/MET chimeric antigen receptor macrophages (CAR-M) for the treatment of lung cancer.

THP-1 cells were differentiated into macrophages using PMA and polarized towards a pro-inflammatory M1 phenotype using the TLR agonists Poly(I:C) and R848. CAR constructs were introduced by retroviral transduction, achieving stable and efficient expression. Functional characterization against A549 and H1975 lung cancer cell lines demonstrated enhanced phagocytosis, particularly with the bispecific CAR. While cytotoxicity in 2D co-culture systems was partially CAR-independent, 3D tumor spheroid models revealed a clear CAR-dependent increase in apoptosis. The anti-EGFR/MET CAR exhibited the strongest and most sustained antitumor activity. Poly(I:C) and R848 stimulation enhanced CAR-M antitumor responses. Cytokine profiling by Bioplex confirmed a pro-inflammatory phenotype.

Overall, these findings support the therapeutic potential of

CAR-M cells for solid tumors, highlighting the importance of 3D models for functional evaluation, and demonstrate the advantages of bispecific targeting strategies in complex tumor environments.

Keywords:

CAR-M Therapy; Lung Cancer; EGFR/MET Targeting; Tumor Microenvironment; Macrophages; 3D Tumor Spheroids; Antitumoral Immunotherapy

O-153/P-240

Unraveling The Role Of MYD88 In The Pathophysiology Of Glioblastoma

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Glioblastoma (GBM) stands as the most prevalent and lethal brain tumor due to the late-stage diagnosis and resistance to gold-standard therapy, which results in a low survival rate after diagnosis (10-12 months). This study was focused on the study of the inflammasome, a cellular machinery activated by stress and damage which modulates the tumor microenvironment (TME) and cell death. A profound dysregulation of the expression pattern of the inflammasome machinery was observed in different internal and external cohorts of GBM vs. non-tumor brain (NTB) samples (transcriptomic and proteomic levels). Remarkably, the alteration of MYD88 expression (overexpression) was associated with several clinical parameters of aggressiveness/poor-prognosis (e.g. survival rate, recurrence, EGFR amplification and MGMT methylation status), as well as to key pathways related to GBM pathophysiology (e.g. epithelial to mesenchymal transition, hypoxia, or NFkB-signaling) and to temozolomide resistance *in vitro*. Moreover, the modulation of MYD88 (silencing by siRNA or pharmacological inhibition) significantly reduced several key functional parameters in different GBM cell models *in vitro*, as well as tumor growth *in vivo*. Additionally, MYD88 silencing reduced the expression of key mediators of proneural to mesenchymal transition and components of crucial oncogenic pathways. Altogether, our study demonstrates: i) the critical role of inflammasome machinery in GBM pathophysiology, highlighting the importance of MYD88 as a potential driver of GBM aggressiveness; and ii) a potential clinical utility of MYD88 as a novel diagnostic/prognostic biomarker



and therapeutic target in GBM patients.

Keywords:

Glioblastoma, Inflammasome, MYD88, Temozolomide Resistance, Proneural To Mesenchymal Transition.

O-154/P-241

Therapeutically Targetable Th17-Derived MiR-721 Drives Autoimmune Myocarditis Through PPARγ Repression

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Myocarditis is an inflammatory cardiac disease in which Th17-driven immune responses contribute to progression toward dilated cardiomyopathy and heart failure. Current therapies mainly rely on corticosteroids but lack specificity, while the role of miR-721, synthesized by Th17 cells, remains largely unexplored in disease pathogenesis.

Both mmu-miR-721 and human homolog hsa-RNA-Chr8:96 were found encapsulated in EVs and secreted by Th17 cells of mice and patients with myocarditis. Furthermore, using the murine model of experimental autoimmune myocarditis (EAM) model, we demonstrate that overexpression of

mmu-miR-721 in draining-lymph node cells from EAM mice inhibited *Pparg* transcription, leading to increased RORγt and IL-17 expression and promoting Th17 differentiation. In contrast, in the absence of *Pparg*, a target of miR-721, no differences in RORγt expression were observed, indicating that miR-721 promotes Th17 responses through repression of *Pparg*. Human *PPARG* was validated as a target gene of hsa-RNA-Chr8:96 and its overexpression in peripheral blood leukocytes downregulated *PPARG* mRNA levels, suggesting similar pathways involved in human pathology. Finally, we proved that *in vivo* blockade of mmu-miR-721 with an anti-miRNA sponge strategy increased *Pparg* expression, reducing RORγt and IL-17 activation in T cells and hence leading to decreased leukocyte infiltration in the heart and improved cardiac function.

Overall, the key role of mmu-miR-721 is validated in the context of exacerbating Th17 responses in autoimmune myocarditis. Moreover, this work presents miR-721 as both a mechanistic driver of disease and a potential therapeutic target to inhibit Th17 damaging responses and disease progress.

Keywords:

Autoimmune Myocarditis, Th17 Cells, MiR-721, PPARγ, Therapy

O-155/P-242

CD69 Expression On Regulatory T Cells As Potential Predictor Of Cardiovascular Events Risk Before Immunotherapy

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Immunotherapies enhance antitumor immune responses through inhibition of regulatory T cells but often leading to adverse events towards the heart. CD69 is a regulator of immune tolerance that promotes Treg function. Reduced CD69 expression on Tregs has been associated with worse outcomes in cardiovascular diseases. The Spanish Immunotherapy Registry of CardioVascular Toxicity (SIR-CVT) registry aims to characterize the immune profile of cancer patients to identify baseline biomarkers that allow stratification of patients according to their susceptibility to develop cardiotoxicities. Patient blood samples were collected at baseline and 1,3, 6, and 12 months after immunotherapy. Flow cytometry was performed on PBMCs from 500 patients. Patients showed, in the first month of treatment, a very significant drop in CD69+ regulatory T cells. Using bioinformatic analyses, patients were stratified into two groups based on baseline CD69 expression on Tregs: low and high CD69. Further analyses showed that low CD69 group exhibited the utmost loss of CD69 expression one month after immunotherapy. In fact, preliminary data suggest that patients with low CD69 expression at baseline present a twofold higher incidence of cardiovascular events compared with high CD69 patients. This study presents a new understanding of circulating lymphocytes dynamics during immunotherapy. Results suggest that the decrease in activated Tregs plays a key role in maintaining immune homeostasis. Preliminary findings indicate that baseline CD69 expression on Tregs may serve as a biomarker to stratify patients according to their risk of developing cardiotoxicities. Combined with clinical data, CD69 expression on Tregs at baseline could predict patient susceptibility to develop cardiotoxicities.

Keywords:

Immunotherapy, Biomarker, T Cells, Treg, Autoimmunity, Cardiovascular Toxicity

O-156/P-243

Functional And Inflammatory Characterization Of Menstrual-Derived Mesenchymal Stem Cells And Macrophages In Endometriosis

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Background: Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity, affecting approximately 10% of women of reproductive age and commonly associated with pelvic pain and infertility. Increasing evidence suggests that altered immune responses and dysfunctional endometrial cell populations contribute to disease pathophysiology. This study aims to characterize functional, molecular, and immunological alterations in menstrual blood-derived mesenchymal stem cells (MenSCs) and menstrual macrophages from women with endometriosis compared to healthy controls.

Materials and Methods: A cross-sectional analytical study was designed including 40 women (20 diagnosed with endometriosis and 20 healthy controls) recruited at a tertiary hospital. MenSCs and macrophages isolated from menstrual blood and peripheral blood are being analyzed regarding proliferative capacity, inflammatory profile, and immunomodulatory properties. Intra-menstrual variability (days 1–5) in MenSC immunomodulatory capacity is also being assessed in a selected subcohort. Molecular findings will be further validated in endometrial and endometrioma tissues and correlated with clinical parameters.

Results: The study is currently in the recruitment phase. Preliminary observations suggest differences in proliferation rates and inflammatory profiles between MenSCs from endometriosis patients and controls. In addition, intra-group variability associated with the day of menstrual collection has been observed.

Conclusions: This study may contribute to a better understanding of the cellular and immunological mechanisms involved in endometriosis and support the identification of novel cellular phenotypes and potential therapeutic targets.

Keywords:

Endometriosis, Menstrual Blood, MenSCs



O-158/P-245

Translational Profiling Of P38 MAPK Isoforms And Pharmacological Targeting In Non-Small Cell Lung Cancer

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Non-small cell lung cancer (NSCLC) is a major cause of cancer mortality, and new biomarkers and targets are needed. p38 MAPKs regulate stress and inflammatory responses and have context-dependent roles in cancer, but the isoform-specific contribution of p38 α , p38 β , p38 γ and p38 δ to NSCLC remains unclear. We profiled p38 MAPK isoforms in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) using human cancer datasets, integrating mRNA expression, survival, tumor stage, NSCLC-related genes, immune infiltration and immune-checkpoint genes. Protein expression and tissue distribution were assessed by immunohistochemistry in lung tumor specimens, and therapeutic relevance was tested in H1299 xenografts treated with the p38 α/β inhibitor PH-797804 or vehicle. All four p38 isoforms showed increased mRNA expression in LUAD and LUSC, paralleled by increased protein staining in tumor tissue. p38 expression was detected in alveolar type II cells, macrophages, lymphocytes, neutrophils and bronchial cells. High expression of all isoforms was associated with poorer overall survival in LUAD, whereas no survival association was observed in LUSC. Isoform expression showed tumor-stage-related patterns and distinct correlations with NSCLC genes, inflammatory infiltrates and immune-checkpoint genes, supporting non-redundant isoform-specific roles. *In vivo*, PH-797804 reduced phospho-p38 staining and H1299 xenograft growth. Treated tumors showed reduced Ki67 (proliferation) and CD34 (vascularization), in-

creased p21 (cell-cycle arrest), γ H2AX (DNA damage) and caspase-3 (apoptosis), and higher CD8⁺ lymphocytes. In conclusion, p38 isoform profiling identifies p38 signalling as a relevant biomarker axis in NSCLC and supports further evaluation of p38 α/β -targeted strategies.

Keywords:

P38, Non-Small Cell Lung Cancer (NSCLC), NSCLC Patients, Xenografts, P38 Inhibition

O-159/P-246

Dissecting Epithelial And Microenvironment-Associated Inflammasome Signatures In Colorectal Cancer Using Patient-Derived Organoids

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Introduction: Colorectal cancer (CRC) comprises conventional and serrated subtypes with distinct molecular features. Inflammasomes regulate inflammation through caspase-1 activation, IL-1 family cytokine processing and pyroptosis, but their role in CRC remains unclear. Patient-derived organoids (PDOs) provide a model to study epithelial-specific inflammatory programs. We compared inflammasome-related gene expression in healthy colonic mucosa, CRC tissues and matched PDOs.

Methods: PDOs were generated from CRC and healthy surgical specimens. Phenotype preservation was confirmed histologically. Transcriptomic profiling was performed by MACE-seq.

Results: Immunohistochemistry of healthy colonic mucosa revealed strong NLRP3 expression in immune cells and moderate staining in glandular epithelium. Transcriptomic analysis showed significantly reduced NLRP3 expression in both conventional and serrated CRC. Tumors also displayed increased CASP4 and IL33 expression, while IL6, TNF and IL10 remained unchanged, highlighting a predominant in-

volvement of the IL-1 family. In PDOs, NLRP3 expression was completely lost and CASP1 and IL1 β were markedly reduced compared with tissues. In contrast, CASP4, IL18, IL33 and GSDMD expression were preserved.

Conclusions: CRC is associated with extensive remodeling of inflammasome-related genes. Comparison of tissues and matched PDOs indicates that the canonical NLRP3–CASP1–IL1 β axis largely depends on the tumor microenvironment, whereas CASP4-, IL18-, IL33- and GSDMD-associated pathways are retained within colorectal epithelial cells

Keywords:

Inflammasomes, Colorectal Cancer, Organoids

O-160/P-247

Baseline IL-12 And MIP-1 α Levels Predict Immunological Non-Response Under Antiretroviral Therapy In People Living With HIV

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Background: Immunological non-response (INR) during antiretroviral therapy (ART) affects 15–30% of people living with HIV (PLHIV) who fail to recover CD4⁺ T cell counts despite viral suppression. The mechanisms underlying impaired immune reconstitution remain poorly defined. Pre-treatment immune dysregulation, reflected in cytokine signaling, may influence subsequent immune recovery independently of virological control.

Methods:

The study included ART-naïve PLHIV with baseline CD4⁺ T cell counts $\leq$ 200 cells/ μ L, defined as the case group, and a control group with CD4⁺ counts $>$ 200 cells/ μ L. After 48 weeks of ART, cases were classified as immunological responders (IR; CD4⁺ $>$ 250 cells/ μ L) or immunological non-responders (INR; CD4⁺ $\leq$ 250 cells/ μ L). Baseline plasma levels of 17 cytokines were measured using a multiplex immunoassay, followed by statistical analyses.

Results: At baseline, cases showed increased IP-10, MCP-1, TNF- α and IL-17A, and reduced IFN- γ compared with

controls, indicating a pro-inflammatory profile. Within case individuals, INR exhibited higher baseline levels of MIP-1 α and IL-12 than IR (p=0.0357 and p=0.0446, respectively). IL-12 showed the best individual predictive performance for INR (AUC=0.764), followed by MIP-1 α (AUC=0.728). Multivariable models adjusting for age and sex improved discrimination, with AUCs of 0.898 for IL-12, 0.877 for MIP-1 α and 0.907 for the combined model.

Conclusions: Baseline cytokine dysregulation is associated with impaired ART immune recovery. IL-12 and MIP-1 α may serve as early predictive biomarkers of immunological non-response, supporting the potential utility of cytokine profiling for risk stratification in PLHIV.

Keywords:

HIV, Antiretroviral Therapy, Immunological Non-Response, Cytokines, Biomarkers, IL-12, MIP-1a, Inflammation, Immune Recovery, Predictive Models

O-161/P-248

Influence Of GRK2 In The Early Inflammatory And Functional Landscape Of Myeloid Cells In Response To A Short-Term Western Diet Feeding

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Obesogenic diets, such as high-fat (HFD) and Western (WD) diets, promote the infiltration and activation of myeloid cells in white adipose tissue (WAT), contributing to systemic inflammation and metabolic dysfunction. While most studies have focused on long-term HFD exposure, the early pathogenic events that precede the development of obesity remain poorly understood. Moreover, G protein-coupled receptor kinase 2 (GRK2), highly expressed in myeloid cells, is involved in the regulation of both metabolism and inflammatory responses. Our previous work demonstrated that lowering myeloid GRK2 levels can prevent and even reverse HFD-induced pathological effects in different mice models. To investigate the early impact of short-term over-



nutrition, and the potential role of GRK2 in this process, we used LysM-Cre GRK2-deficient mice (WT and KO) fed a WD for 7 days. We quantified neutrophil (NΦ), monocyte, and macrophage infiltration in eWAT and evaluated changes in circulating and bone marrow (BM) myeloid populations, with special focus on NΦ trafficking. In addition, diet- and GRK2-dependent alterations in myeloid cell phenotypes across eWAT, BM, and blood were characterized using spectral flow cytometry and Omiq® analysis. Our results reveal that myeloid GRK2 regulates the early myeloid cell dynamics between BM, blood and eWAT. Myeloid GRK2 levels control the WD-induced changes in myeloid cell markers related to egression from the BM and infiltration into eWAT. Upon WD feeding, KO mice exhibit distinct patterns of myeloid subpopulation heterogeneity in eWAT and BM compared with WT mice. In summary, our findings show that GRK2 modulates inflammatory patterns that are triggered by this short-term WD feeding, in a moment when metabolic alterations are not yet established.

Keywords:

GRK2, Myeloid Cells, Metainflammation, Short-Term Western Diet, Adipose Tissue, Neutrophils

As previously reported, we observed that M1 cells were more resistant to RSL3 than M0. By using regression, we found that *Tnfa* and *Il1b* expression explained the decrease in sensitivity to RSL3 in M1 cells when compared with M0. As expected, we also found a positive relationship between *Tfrc* expression and sensitivity to RSL3 in M0 cells. In contrast, we found a negative relationship between *Tfrc* expression and sensitivity to RSL3 in M1 cells.

Overall, our results suggest that a shift in iron metabolism by macrophage polarization reprograms cell death induced by RSL3. Exploring how the expression of *Tfrc* correlates with lower RSL3-induced cell death in M1 macrophages warrants further research.

Keywords:

Ferroptosis, Macrophages, RSL3, Polarization, Fatty Acids, Oxidative Stress

P-250

Peroxiredoxin 6 Released By Astrocytes Contribute To Neuronal Loss In Cellular Models Of Parkinson's Disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons, although the underlying mechanism of this loss is unknown. Peroxiredoxin 6 (PRDX6), the only mammalian 1-Cys member of the peroxiredoxins family, is a multifunctional protein with glutathione peroxidase, calcium-independent phospholipase A2, and lysophosphatidylcholine acyl transferase activities. High levels of this protein have been related to the development of several neurodegenerative diseases, including PD. PRDX6 has been described to be present in astrocytes, but at very low levels in neurons and undetectable in other glial cells.

Several studies have shown that under pathological conditions, astrocytes can become activated and release PRDX6 into the extracellular environment, thereby contributing to neurodegeneration. Therefore, we hypothesize that, at the onset of PD, the release of PRDX6 by astrocytes and its interaction with neuronal receptors may trigger signaling

pathways related to inflammation and neuronal death.

In this study, we used primary cultures to investigate the role of PRDX6 in neuronal loss associated with PD. We detected extracellular PRDX6 in the culture medium of primary astrocytes maintained under basal growth conditions, and the protein levels were consistent with GFAP expression. We also observed a reduction in the number of primary neurons when treated with recombinant PRDX6, indicating that high levels of PRDX6 may be neurotoxic depending on its enzymatic activity. Neurotoxicity was further confirmed in co-cultures of neurons and reactive astrocytes overexpressing PRDX6, with neuronal death related to differences in the activation levels of signaling pathways involved in proliferation and inflammation, such as GSK-3β and STAT3.

Keywords:

Oxidative Stress, Redoxins, Peroxiredoxin 6, Neurodegeneration, Parkinson's Disease

P-251

The Cul1 Neddylation Inhibitor MLN4924 Sensitizes Bladder Cancer Cells To Cisplatin: The Role Of βTrCP

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Cisplatin therapy is used to treat many types of solid tumors, but its use can be limited by toxicity and acquired resistance. Analyzing resistance mechanisms could lead to more precise chemotherapy. The MRN protein complex (Mre11, Rad50, and Nbs1) is involved in homologous DNA repair and disrupting this complex could make cancer cells more susceptible to cisplatin treatment. SCF ubiquitin ligases regulate the stability and localization of the MRN complex and βTrCP is one of the F-box proteins of the SCF ubiquitin ligase. We observed that βTrCP may play a role in the degradation of FOXM1. This transcription factor is involved in suppressing senescence, raising the question of wheth-

er βTrCP could mediate senescence by controlling FOXM1 degradation. MLN4924, a Cul1 neddylation inhibitor, could alter the stability of βTrCP and the MRN complex, which could reverse cisplatin resistance. Using bladder cancer cells HT1197 and HT1376, we analyzed the behavior of MRN complex proteins in response to treatment with a combination of MLN4924 and cisplatin. We found that MLN4924 sensitizes HT1376 cells to cisplatin, whereas HT1197 cells are resistant to this treatment. Combined treatment increased the levels of p21 and β-galactosidase (markers of senescence), p27 (a cell cycle regulator associated with senescence), and βTrCP while reducing FOXM1. In HT1376 cells, MLN-induced senescence progresses to apoptosis when combined with cisplatin. However, the combined treatment does not induce cell death in HT1197 cells. We analyzed the role of senescence in response to MLN4924 and cisplatin therapy and how βTrCP mediates senescence by regulating FOXM1. We hypothesize that regulating βTrCP over FOXM1 may influence the induction of senescence and the response to this combination therapy.

Keywords:

Bladder Cancer, BTrCP, MRN Complex, Senescence

P-252

Translational Profiling Of Telomerase And Shelterin Proteins In Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality, and novel biomarkers and therapeutic targets are urgently needed due to late diagnosis, tumor heterogeneity and the limited long-term efficacy of current therapies. Telomere maintenance is a hallmark of malignant transformation, driven by telomerase reverse transcriptase (TERT) reactivation and regulated by the shelterin complex, but the translational relevance of TERT- and shelterin-associated proteins in HCC remains incompletely defined. We profiled TERT and the shelterin proteins TERF1 (TRF1), TERF2 (TRF2), ACD (TPP1), TIN2 (TIN2), POT1 and TERF2IP (RAP1) using human cancer datasets, integrating mRNA expression and survival analyses. Pro-



tein expression and tissue distribution were assessed by immunofluorescence in paired tumor and adjacent non-tumor liver specimens from HCC patients, quantifying fluorescence intensity and positive area. TERT and shelterin proteins showed a generalized increase in HCC tissue compared with adjacent non-tumor liver, with enhanced intensity and expanded positive areas in tumor regions. In agreement, human cancer datasets revealed increased mRNA expression of TERT- and shelterin-related genes in HCC tumors versus normal liver. Survival analyses showed that high TERT, ACD and POT1 expression was associated with poorer overall survival in HCC patients. Conversely, increased TERF2IP expression was associated with improved survival, whereas TERF1, TERF2 and TIN2 showed no significant impact on survival. In conclusion, this study identifies upregulation of the TERT-shelterin axis in HCC and distinct prognostic associations among telomere-regulatory proteins, supporting their value as biomarkers and targets.

Keywords:

Hepatocellular Carcinoma, Telomerase, Shelterin Proteins

P-253

Overcoming Cisplatin Resistance In 3D Oral Squamous Cell Carcinoma Models Via Nanoparticle-Mediated Pt(IV) Drug Delivery

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Advanced oral squamous cell carcinoma (OSCC) patients with cisplatin-refractory tumors face a poor prognosis and limited therapeutic options. Cisplatin-based system-

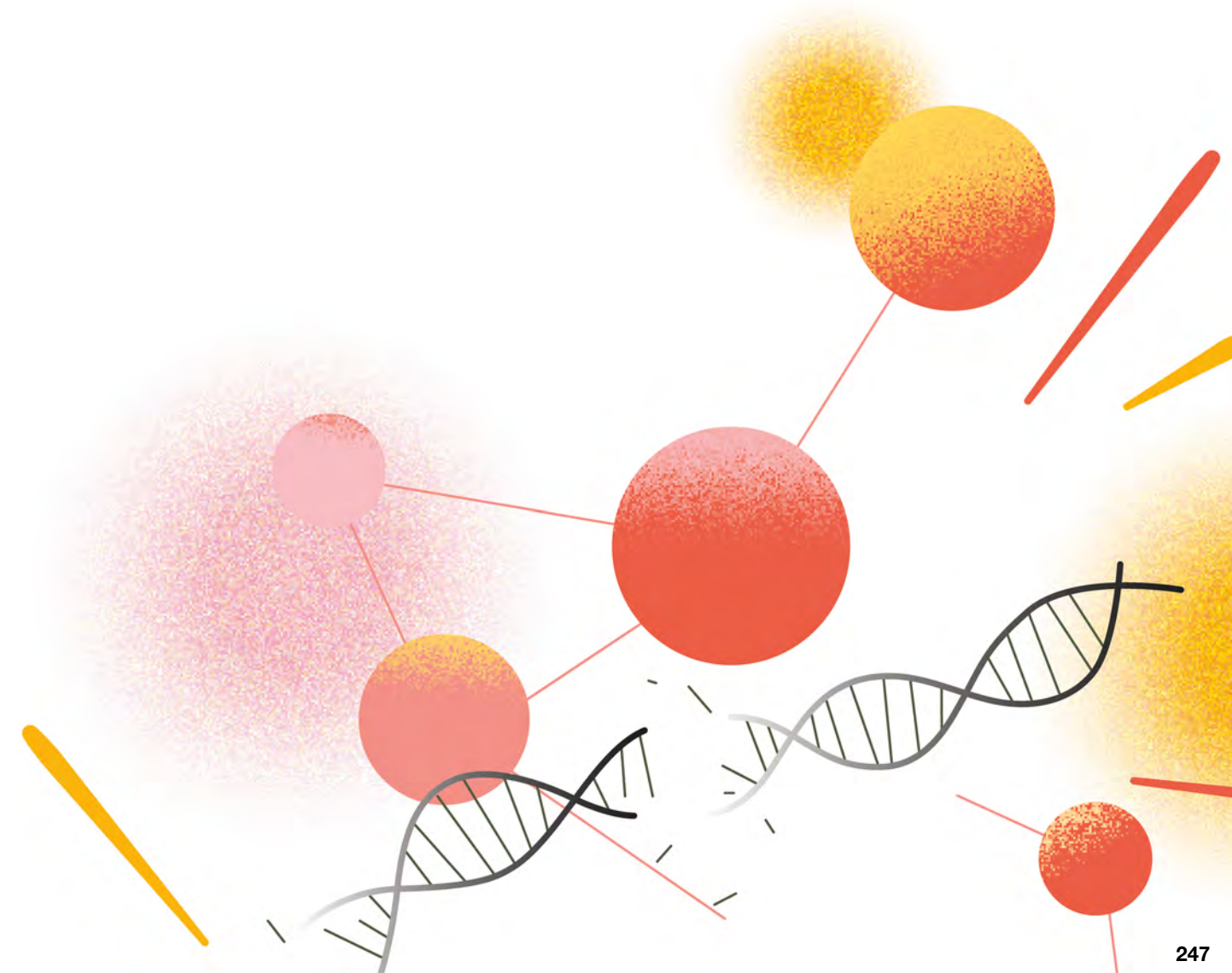
ic chemotherapy has long been the gold standard despite producing unmanageable adverse side effects and toxicity. Compared to Pt(II)-based analogs, octahedral Pt(IV)-based compounds have demonstrated remarkable potential as antitumor prodrugs. Pt(VI) derivatives are chemically inert, remaining intact until internalized within cells, demonstrating higher tolerability and selectivity towards cancer cells. In this study we compare antitumoral response implementing primary patient-derived 2D and 3D OSCC in vitro models treated with both cisplatin and a novel Pt(IV) compound. We also test the delivery and efficacy of these anticancer drugs via novel encapsulation of this Pt(IV) prodrug in the framework of mesoporous silica nanoparticles (Pt(IV)-cov@MSN). Our results show a significant improvement of delivery and cytotoxicity of Pt(IV)-cov@MSN in both cisplatin-responsive and cisplatin-resistant primary patient-derived in vitro models. We also show how Pt(IV)-cov@MSN elicits p53-dependent apoptotic cell death superior to that obtained with cisplatin treatment in OSCCs. These findings highlight 3D-primary models as key tools for drug and nanocarrier testing, as well as potential targeted and selective delivery strategies for novel chemotherapeutic agents.

Keywords:

Oral Squamous Cell Carcinoma (OSCC), Organoids, Chemoresistance, Novel Pt(IV) Compounds, Mesoporous Silica Nanoparticles (MSNs).



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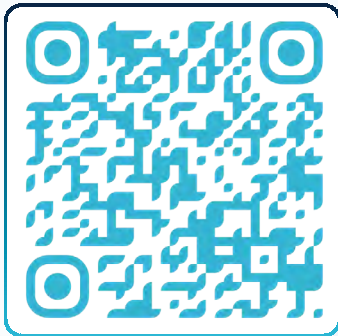
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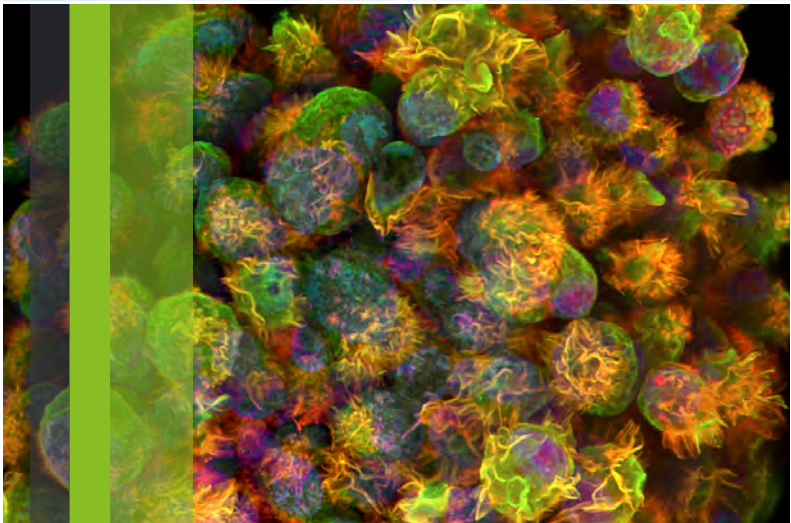
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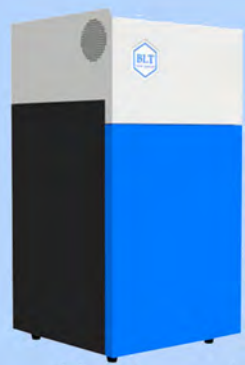
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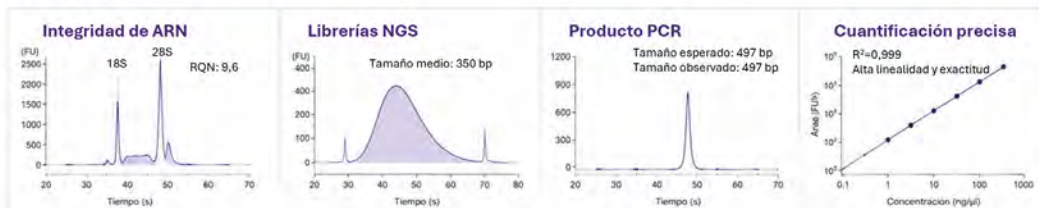
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Do more with every sample. The QX700 Droplet Digital PCR (ddPCR) Systems bring everything you need into one streamlined platform with advanced multiplexing and minimal hands-on time, so you can move from droplets to data faster.

One Platform. Three Ways to Scale Your ddPCR Workflow.



QX700 E System*

A modern entry point into ddPCR technology with 48-sample throughput



QX700 S System*

Scalable ddPCR performance with 192-sample throughput



QX700 HT System*

High-throughput ddPCR performance for up to 384 samples



RDG16 Cartridges: Precision Built In

Ready-to-use cartridges simplify droplet generation and deliver consistent, sensitive results with less complexity.

- 16 chambers/chip
- 5 µL/chamber†
- ~17,000–136,000 droplets/chamber
- Compatible with automated liquid handlers
- Built-in barcodes enable clear tracking and end-to-end traceability

† Load up to 40 µL by pooling chambers.



Visit bio-rad.com/QX700family for more information.

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MedChemExpress Exhibition!

How Can We Accelerate Your Research?

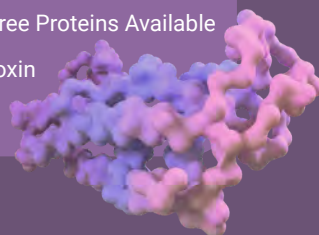
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EPIGENETIC AGING SERVICES

Human Epigenetic Age Analysis

Precisely Quantify Epigenetic Age with Human DNAge Services



Compatible with Blood & Urine Samples

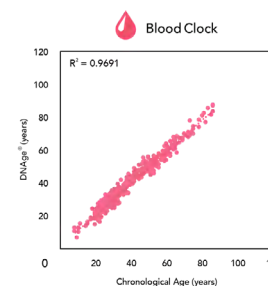


Accommodates Limited, Precious Inputs



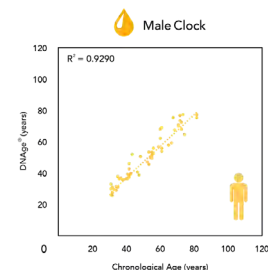
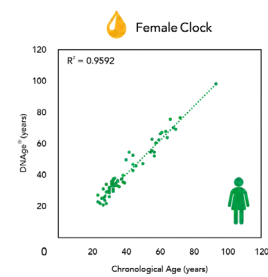
Highly Reproducible

Performance with Blood Samples



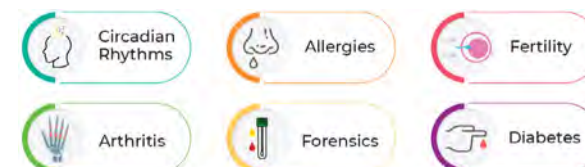
- ✓ **Age-Related**
DNAge is highly correlated with chronological age in a general population. Therefore, DNAge can accurately predict biological age.
- ✓ **Accommodates Low Inputs**
Reliable epigenetic age prediction using as little as 250 ng DNA human dnage reports.
- ✓ **Highly Reproducible**
Blood DNAge is highly reproducible with a median SD <1 year in technical replicates.

Performance with Urine Samples



- ✓ **The Only Urine DNAge Service**
Urine dnage is a non-invasive assay reflecting urinary tract health human dnage gender.
- ✓ **Gender-Specific**
A gender-specific algorithm is used to enhance the accuracy of Urine DNAge platform.
- ✓ **Highly Reproducible**
Urine DNAge is highly reproducible with a median SD of 2 years in technical replicates.

Potential Applications



Mouse Epigenetic Age Analysis

Precisely Quantify Biological Age Across Various Mouse Tissue Types



Multi-Tissue Panel



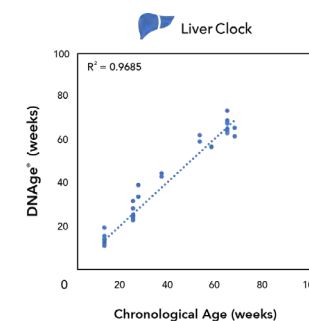
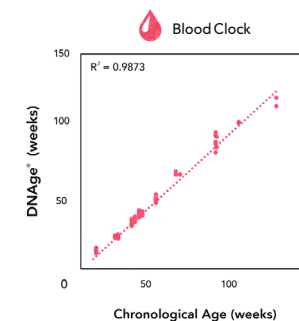
Over 2,000 Loci



High-Throughput

Mouse DNAge Performance

DNAge is highly correlated with chronological age.



Have Confidence In Your Data

The Mouse DNAge platform utilizes "Simplified Whole-panel Amplification Reaction Method" (SWARM®), a robust targeted bisulfite sequencing approach which helps deliver reproducible high-throughput methylation data.

- ✓ **Low Input:** as little as 250 ng DNA
- ✓ **High Throughput:** up to 640 samples per sequencing run
- ✓ **Deep Sequencing:** >1,000 sequencing depth

Potential Applications



More info: www.ecogen.com | ngs@ecogen.com





Soluciones de **AUTOMATIZACIÓN DE LABORATORIOS**

- Optimización de procesos, tiempos y costes
- Reducción de errores humanos
- Mejora de la productividad



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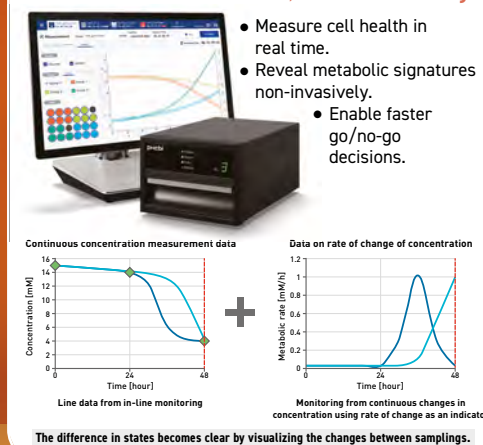
www.phchd.com/eu/biomedical

A complementary Workflow for Dynamic Characterization of Cellular Function

MEASURE

LiCellMo™

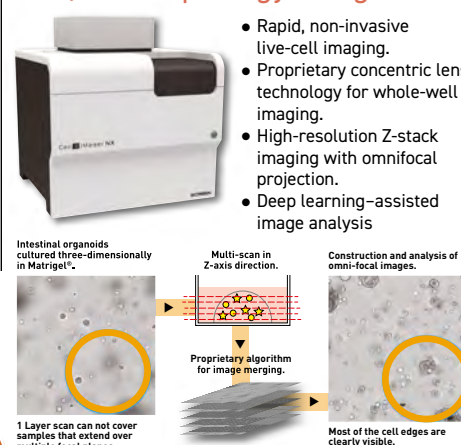
Glucose and lactate, continuously.



IMAGE

Cell3Imager NX

2D/3D morphology and growth.



CORRELATE

Connects multiple biological dimensions.

- Brings together:
- Metabolism
 - Cell number/growth
 - Morphology
 - Phenotyping/plasticity

Integrating continuous Metabolic Monitoring with Advanced Live-cell Imaging

A practical workflow to connect real-time metabolic activity (glucose and lactate levels) profile with cell morphology, growth, and phenotyping.

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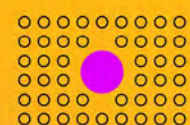
4.950€*

*Until 31st Dec 2026 & before taxes

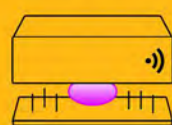


One Device. Two Workflows.

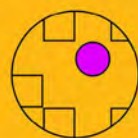
1. ADD



2. READ



3. RAW DATA



DOWNLOAD

Download raw data files for manual calculations in your preferred software

ANALYZE

Use the guided workflow for setup, reading, and cloud-based analysis in seconds

30s

15s

Life Sciences

Todo para tu laboratorio.

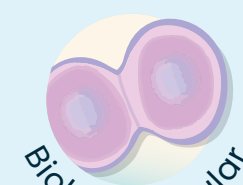
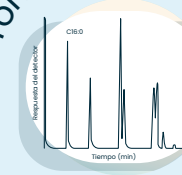
Siempre cerca de tu investigación.

Inmunología



Biología Molecular

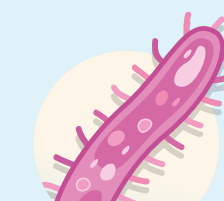
Cromatografía



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Proteómica



Microbiología

Con primeras marcas:

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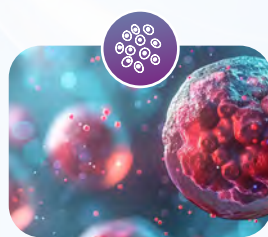
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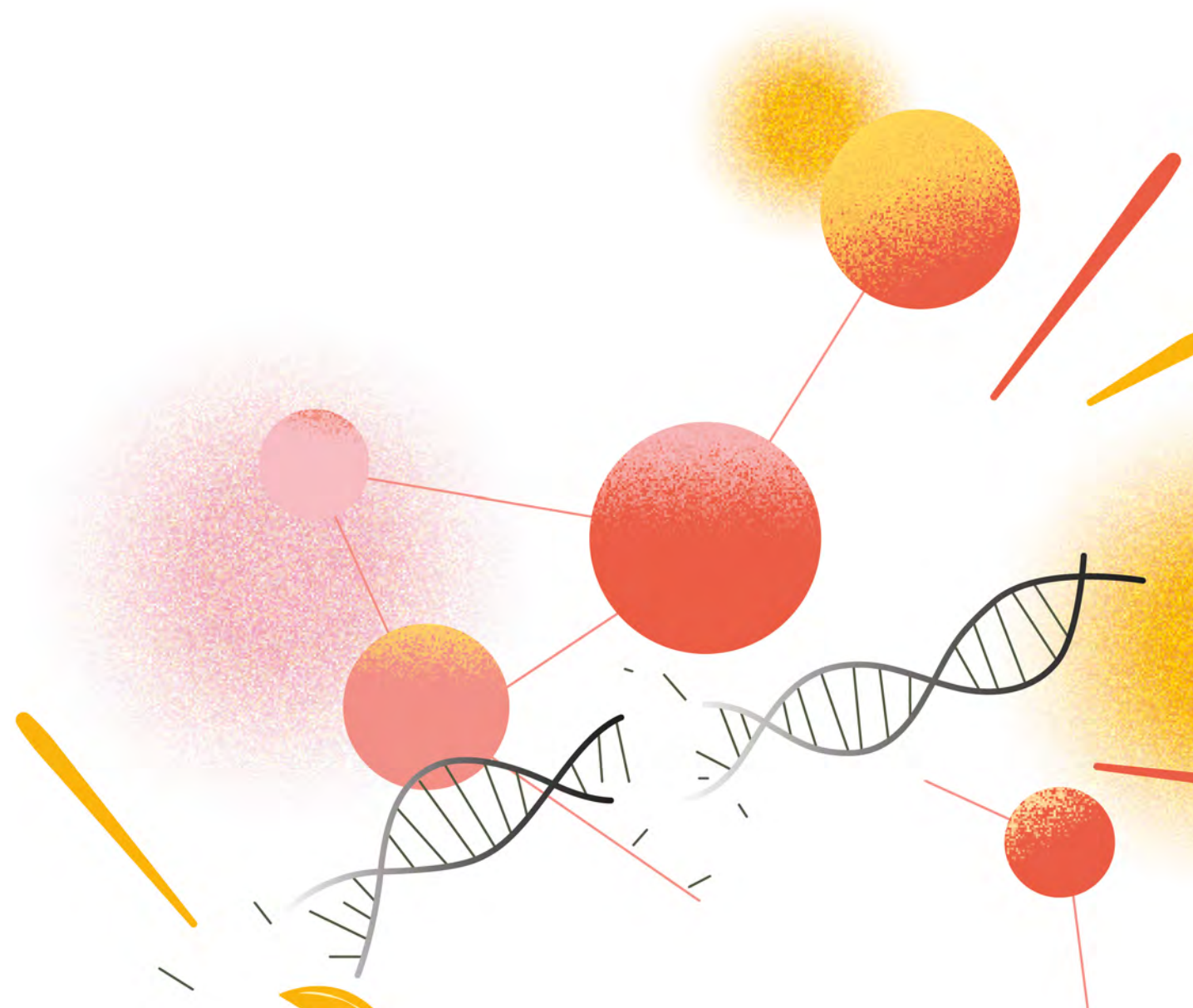
In vitro modeling



Biomarker mapping

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