ABSTRACT BOOK

XVI IMIBIC
YOUNG INVESTIGATORS MEETING

OCTOBER 1 2

ASSEMBLY HALL OF THE IMIBIC

IMIBIC
INSTITUTO MAIMÓNIDES DE INVESTIGACIÓN BIOMÉDICA DE CÓRDOBA

HURS

UNIVERSIDAD D CÓRDOBA

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We thank the External Reviewers and the members of the Scientific Committee for their kind collaboration. We greatly acknowledge the "Colegio Oficial de Médicos de Córdoba" for its support and commitment to promote research among residents. We are also deeply grateful to Biomol for generously sponsoring this event. Finally, we thank the students from the Escuela Politécnica Superior

de la Universidad de Córdoba for their selfless participation in the Special Session "Biomedicine & bioengineering: a practical case".

PROGRAMME

Day 1 (1st OCT)

08:00 – 08:30 – Registration and Poster display

08:30 – 09:00 – Opening ceremony (IMIBIC Assembly Hall)

09:00 – 10:30 – SESSION I. Cancer I (IMIBIC Assembly Hall)

Chairs: Dr. Juan Antonio Moreno Gutiérrez and Dr. Francisco Rojas Vega

Ia. 09:00 – 09:15	Dysregulation of a RNA exosome component: A driving force for prostate cancer progression and metastasis. **Francisco Porcel Pastrana.**
Ib. 09:15 – 09:30	DYRK2 orchestrates MAPK signaling and melanoma therapy resistance. **Miguel Torres Ramos.**
Ic. 09:30 – 09:45	Dysregulation of splicing machinery influences molecular heterogeneity and cellular metabolism of bladder cancer cells. **Ignacio Gil Duque.**
Id. 09:45 – 10:00	Role of alternative splicing in lung neuroendocrine tumors: exploring the OTP-CD44 axis. **Laura Gutiérrez Camacho.**
Ie. 10:00 – 10:15	Microbial profiles in pseudomyxoma peritonei reveal novel findings, including fungal detection. **Rafaela Rocha Pezzopane.**
If. 10:15 – 10:30	Exploring the molecular and immune profile of breast cancer from pregnancy to postpartum: shedding light on the tumor-immune microenvironment during lactation. **Regina Peña Enríquez.**

10:30 – 11:00 – Coffee Break

11:00 – 12:30 – SESSION II. Chronic and inflammatory diseases I (IMIBIC Assembly Hall)

Chairs: **Dr. Hatim Boughanem & Dr. André Sarmento Cabral**

IIa. 11:00 – 11:15	Integrative Multi-Omics stratification of rheumatoid arthritis reveals disease stage–specific profiles and predictors of treatment response. **Ismael Sánchez Pareja.**
IIb. 11:15 – 11:30	FGF23 neutralization leads to impaired vascular dysfunction through modulation of arterial stiffness and vascular remodeling. **Raquel María García Sáez.**

IIc. 11:30 – 11:45 Integrative lipidomic and inflammatory profiling in rheumatoid arthritis: links to disease activity, therapeutic response, and hepatic mechanisms. **Laura Muñoz Barrera.**

IId. 11:45 – 12:00 Clinical and ultrasonographic evaluation in patients with early-onset rheumatoid arthritis: treatment response and histological pathotypes in synovial biopsy. **Andrea Cid Chaves.**

IIe. 12:00 – 12:15 Multi-Omic characterization of systemic lupus erythematosus endotypes: advancing precision understanding of cardiovascular and renal involvement. **Lydia Formanti Alonso.**

IIf. 12:15 – 12:30 Ferroptosis is involved in renal damage associated to hemoglobin overload in a murine model of Sickle Cell Disease. **Mercedes Vallejo Mudarra.**

12.30 - 13.30 – Special Session & Awards - Fundación Biomol (IMIBIC Assembly Hall)

13.30 - 15.00 – Lunch

15:00 – 15:45 – Poster Session I (IMIBIC Meeting & Multipurpose Room)

Chairs: **Dr. Silvia Fernández Álvarez, Dr. Iván Arias de la Rosa & Dr. David García Galiano**

PSI.a. Assessment of the neuroendocrine landscape in metabolic liver disease and cancer through the somatostatin system. **Antonio García Estrada.**

PSI.b. Dissecting the roles of Kiss1AVPV neurons in the control of reproduction by functional genomics. **José Joaquín García Vera.**

PSI.c. Early lifestyle intervention based on the Mediterranean diet and physical activity: a preventive strategy for childhood obesity in at-risk preschoolers. **Cristina Castro Collado.**

PSI.d. Cytokine-induced memory-like NK cells: a new strategy for cancer immunotherapy. **Isabel María Vallejo Bermúdez.**

PSI.e. Exploring the redox status in Pseudomyxoma Peritonei: insights from proteomic and functional analyses. **Javier López Jiménez.**

PSI.f. Type 2 diabetes and immune-related genetic variants modulate etanercept drug survival in psoriasis patients. **Juan de Luque Fernández.**

PSI.g. Integrating machine learning and proteomics to predict response to anti-TNFα therapy in psoriatic arthritis: insights into drug-modulated proteins. **Jesús Eduardo Martín Salazar.**

PSI.h. Impact on work capacity in post-covid sindrome patients: analisis of sociodemographic and clinical factors. **Laura Sierra Ferris.**

PSI.i. Influence of psychological variables on adherence to the Mediterranean diet and its impact on health: analysis of blood biomarkers in a pediatric endocrinology sample. **Sebastián Vivas Herrera.**

PSI.j. RNA exosome complex is impaired in oral squamous cell carcinomas and linked to key pathophysiological features. **José Ángel Montserrat Barbudo.**

PSI.k. Genomic evolution of colistin-resistance in Klebsiella pneumoniae ST512: impact on virulence and fitness cost. **Victor Gálvez Soto.**

PSI.l. Molecular and functional characterization of aminoacyl-tRNA synthetases in hepatocellular carcinoma. **María Serrano Jiménez.**

PSI.m A sarcoma with late diagnosis. **Raquel Gracia Rodríguez.**

PSI.n. Understanding adipose tissue fibrosis: LRG1 as a mediator in the crosstalk between adipocytes and macrophages. **Olga García Ruiz.**

PSI.o. Task engagement patterns in a CBT-based eHealth intervention for adolescents with type 1 diabetes: a usability analysis of the ERES app. **Sofía de la Villa García Roldán.**

PSI.p. Clinical potential and non-canonical roles of the cytosolic aspartyl-tRNA synthetase (DARS1) in hepatocellular carcinoma. **Natalia Hernán Sánchez.**

PSI.q. Deciphering the contribution of hyperandrogenism to metabolic dysfunction-associated steatotic liver disease (MASLD) development in the context of polycystic ovary syndrome. **Andrea Rodríguez Martín.**

PSI.r. Deciphering systemic sclerosis phenotypes: a novel approach using clustering algorithms and proteomic insights. Results from the PRECISESADS Study. **Santiago Dans Caballero.**

PSI.s. Differences in the clinical profile between ratHEV and HEV. **María Casares Jiménez.**

PSI.t. Innovation in the study of alopecia areata: tape strips as a noninvasive tool for transcriptional characterization. **Carmen Mochón Jiménez.**

PSI.u. Effectiveness of Nintendo Wii Fit© for physical therapy in patients with multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. **Álvaro Alba Rueda.**

PSI.v. Impacts of COVID-19 and antimicrobial stewardship on nosocomial and non-nosocomial KPC-producing Klebsiella pneumoniae Infections: a ten-year longitudinal cohort study with interrupted time series analysis. **Manuel Recio Rufián.**

PSI.w. Constructing enzymatic nanoparticles for in situ drug synthesis. **Irene Bruque Monge.**

PSI.x. Dietary modulation of advanced glycation end products metabolism and its influence on peripheral artery disease in coronary heart disease patients. **Alejandro López Moreno.**

PSI.y. Development of a 3D human hepatic spheroid model to investigate obesity-associated liver disease. **Beatriz Domingues Farinha.**

PSI.z. Tumour-intrinsic GSK-3β drives a fibrotic immunosuppressive microenvironment in colorectal cancer and emerges as a target to overcome immunotherapy resistance. **Aurora Rivas Crespo.**

PSI.aa. Regenerative medicine applications of sustainable hydrogel from cellulose nanofibers. **Guadalupe Estrella Guisado.**

PSI.bb. Workers' satisfaction with health surveillance: development and validation of a new scale. **Adrián Fernández del Peral.**

PSI.cc. Multicenter experimental study to evaluate the efficacy of targeted exercise in combination with cytisinicline in smoking cessation (MEDSEC-CTA). **Sofía Ruiz Salcedo.**

15:45 – 17:15 – SESSION III. Nutrition (IMIBIC Assembly Hall)

Chairs: **Dr. Cristian Rodelo Haad & Dr. Alejandro Ibáñez Costa**

IIIa. 15:45 – 16:00 Alterations of the hypothalamic Kiss1 neuronal activity in the arcuate nucleus in response to different diets. **Rodrigo Jiménez Ulloa.**

IIIb. 16:00 – 16:15 Preventing sepsis in preterm infants with bovine lactoferrin: a randomized trial exploring immune and antioxidant effects. **Virginia Plaza Astasio.**

IIIc. 16:15 – 16:30 Hypothalamic SIRT1-mediated regulation of the hormonal trigger of ovulation and its repression in energy deficit. **Silvia Daza Dueñas.**

IIId. 16:30 – 16:45 3D spheroid models as a novel strategies to analyze obesity-associated adipose tissue dysfunction and fibrosis. **Beatriz González Almécija.**

IIIe. 16:45 – 17:00 Analysis of the role of hepatic kisspeptin system in energy and metabolic homeostasis: Influence of sex and feeding status. **Esperanza Uceda Rodríguez.**

IIIf. 17:00 – 17:15 Nimacimab, a peripherally restricted CB1R inverse agonist, alleviates diet-induced obesity and improves metabolic function in humanized CB1R Mice. **Francisco José Ponce Díaz.**

17:15 – 17:45 **– Biomedicine & Bioengineering: a practical case (IMIBIC Assembly Hall)**

17:45 – 19:15 **– SESSION IV. Infectious and immunological diseases (IMIBIC Assembly Hall)**

Chairs: **Dr. Rafael González Manzanares & Dr. Henning Kirst**

IVa. 17:45 – 18:00 Mortality of bloodstream infections caused by ESBL-producing Enterobacterales in solid organ transplant recipients versus non-transplant patients: a multicentre, international, retrospective matched cohort study (INCREMENT vs INCREMENT-SOT). **Elisa Ruiz Arabí.**

IVb. 18:00 – 18:15 Decoding tissue-specific virulence mechanisms of Salmonella Typhimurium in porcine hosts. **Antonio Romero Guillén.**

IVc. 18:15 – 18:30 Gut microbiome diversity predicts mortality in carbapenemase-producing Klebsiella pneumoniae colonized patients. **Juan Antonio Marín Sánz.**

IVd. 18:30 – 18:45 Emergence of infections caused by carbapenemase-producing Proteus mirabilis: OXA-48: analysis of the PROTECOR cohort. **Juan Jesús Pineda Capitán.**

IVe. 18:45 – 19:00 Surveillance of rat Hepatitis E Virus in Nigeria: serological and molecular evidence and associated risk factors. **Lucía Ríos Muñoz.**

IVf. 19:00 – 19:15 Immunometabolic remodeling in the porcine ileum during Salmonella infection: insights from Single-Cell RNA sequencing. **José Manuel Suárez Cárdenas.**

Day 2 (2nd OCT)

08:00 – 08:30 – Registration and Poster display

08:30 – 10:00 – SESSION V. Cancer II (IMIBIC Assembly Hall)

Chairs: **Dr. Juan Luis Romero Cabrera & Dr. Elena Pérez Nadales**

Va. 08:30 – 08:45 The role of RNA methylation and splicing dysregulation in neuroendocrine neoplasms biology. **Daniel Ruiz Palacios**.

Vb. 08:45 – 09:00 A novel feedback loop between DYRK2 and USP28 regulates cancer homeostasis and DNA damage signaling. **Lucía Suanes Cobos.**

Vc. 09:00 – 09:15 Exploring MUC13 as potential therapeutic target in pseudomyxoma peritonei**. Melissa Granados Rodríguez.**

Vd. 09:15 – 09:30 Dysregulation of the matrisome in periprostatic adipose tissue drives prostate cancer progression: oncogenic role of LAMB1/RPSA-receptor axis. **Antonio Prats Escribano.**

Ve. 09:30 – 09:45 Relevance of mRNA metabolism dysregulation in glioblastoma. **Miguel Eduardo García García.**

Vf. 09:45 – 10:00 Differential gene expression analysis according to the CEBPA gene mutational status in Acute Myeloid Leukemia patients. **Esther Prados de la Torre.**

10:00 - 10:30 – Coffee Break

10:30 – 11:15 – Poster session II (IMIBIC Meeting & Multipurpose Room)

Chairs: **Dr. Silvia Fernández Álvarez, Dr. Iván Arias de la Rosa & Dr. David García Galiano**

PSII.a. Systemic cytokine signatures associated with disease activity and IL-17A inhibitor response in spondylarthritis. **Adrián Llamas Urbano.**

PSII.b. Corneal incision contracture: literature review and report of a novel therapeutic strategy using intrastromal corneal ring segments. **Juan Prados Carmona.**

PSII.c. Cefiderocol resistance in clinical isolates of KPC-producing Klebsiella pneumoniae resistant to ceftazidime/avibactam: molecular insights. **Cristina Laura Riazzo Damas.**

PSII.d. Major cardiovascular events in patients with atrial fibrillation and active lung cancer: data from the CANAC-FA registry, a multicentre, retrospective, observational study. **Alberto Piserra López Fernández de Heredia.**

PSII.e. Inflammation in uremia: Can hemodialysis make a difference? **Raquel Ojeda López.**

PSII.f. Genetic markers for the evaluation of cardiovascular event recurrence risk. CORDIOPREV-HERITAGE. **María José Párraga Viúdez.**

PSII.g. Lung health predicts mortality in SMI. **Cristina Camacho Rodríguez.**

PSII.h. Peripubertal changes in the hypothalamic transcriptome of a Prader-Willi syndrome mouse model with altered metabolic and pubertal phenotype. **Álvaro Aranda Torrecillas.**

PSII.i. Transcriptomic characterization of primary lymphocytic cicatricial scarring alopecia: systematic review and meta-analysis. **Irene Rivera Ruiz.**

PSII.j. Defining the clinical value of MYD88, a component of the inflammasome machinery, as a diagnosis, prognosis and therapeutic tool in brain endocrine cancers. **Natalio Leiva Hidalgo.**

PSII.k. Optimizing QIIME2 workflows for 16S metagenomics of clinical samples from patients colonized by KPC-carbapenemase-producing Klebsiella pneumoniae. **Rafael Jiménez Sánchez.**

PSII.l. Hepatic artery atherosclerosis is a risk factor for biliary strictures after liver transplantation. **Paloma Elma Alañón Martínez.**

PSII.m. Regulatory T-cell response in young and older healthy adults vaccinated against influenza: impact of human cytomegalovirus infection. **Mónica Espinar García.**

PSII.n. Histopathological analysis of synovial biopsies in patients with early-onset rheumatoid arthritis. **Julio Osuna Soto.**

PSII.o. Establishment and validation of animal models and 3D-cell culture models of Pseudomyxoma Peritonei. **Ana Martínez López.**

PSII.p. Endothelial-to-mesenchymal transition in calcific aortic valve disease: a Single-Cell transcriptomics approach. **Álvaro Méndez Maguilla.**

PSII.q. Circulating miRNA profiling for improved molecular diagnosis of obesity-induced hypogonadism in men. **Yolanda Guerrero Ruiz.**

PSII.r. The role of the RNA-exosome machinery and the component EXOSC4 in hepatocellular carcinoma. **María Isabel Pozo Relaño.**

PSII.s. Sex-based differences in secondary prevention following acute coronary syndrome at one-year follow-up: are current strategies adequate? **Javier Herrera Flores.**

PSII.t. Induction with thymoglobulin or basiliximab versus no induction in kidney transplantation with low immune risk. **Casimiro Antonio Valle Domínguez.**

PSII.u. Measles immunity among users of HIV pre-exposure prophylaxis (PrEP). **Claudia Sofía Ferreira Tátá.**

PSII.v. Caloric restriction: a new approach to improve regenerative capacity. **Victoria Pulido Escribano.**

PSII.w. Identification of a translatable animal model for dry eye disease using comparative analysis of tear inflammatory-soluble factors across species. **Mayelín Pérez Perdomo.**

PSII.x. Virtual reality and digital twins as tools for intervention in child health: a preventive approach to childhood overweight. **María del Mar Uclés Torrente.**

PSII.y. Digital twin and virtual reality in eating disorders: a multifactorial investigation. **Gema Esperanza Ruiz Gamarra.**

PSII.z. MiR-191-5p represents a potential personalized diagnostic and therapeutic tool in prostate cancer. **Laura Arroyo Millán.**

PSII.aa. Relationship between knowledge of menopause and quality of life in women aged 40-60: a cross-sectional study. **Isabel Dolores Ruiz Gutiérrez.**

PSII.bb. Identifying musculoskeletal risk profiles in athletes with patellar tendinopathy: a cross-sectional study. **Ángel Carnero Díaz.**

PSII.cc. Aerobic exercise prescription for the management of pain in fibromyalgia patients. **David Casanova Rodríguez.**

PSII.dd. Risk scores for predicting incident heart failure admission in patients with chronic coronary syndromes: validation in a prospective, monocentric, long-term, cohort study. **Josué López Baizán.**

PSII.ee. Rewiring tumor vulnerability: targeting SAMHD1 to boost VACV oncolysis and chemotherapy. **Gloria Llamas Jiménez.**

PSII.ff. Exploring the protective role of miR-191-5p in the development of early obesity and metabolic comorbidities. **Carmen Torres Granados.**

PSII.nn. Non-hospital onset infection due to KPC-producing Klebsiella pneumoniae: an emerging problem. **Manuel Recio Rufián.**

PSI.ññ. Loss of peroxiredoxin 6 impairs mitochondrial function and biogenesis in the human colon cancer cell line HCT116. **Alberto Ortiz Olivencia.**

11:15 – 12:45 **– Session VI. Chronic and inflammatory diseases II (IMIBIC Assembly Hall)**

Chairs: **Dr. Pedro Gómez Arias & Dr. Antonio Carlos Fuentes Fayos**

VIa. 11:15 – 11:30 Safety and tolerability of diuretics withdrawal in patients with heart failure with reduced ejection fraction. REDICAE trial. **Jesús Alberto Torres Zamudio.**

VIb. 11:30 – 11:45 Distinct ex vivo immune signatures modulated by JAK and TNF inhibitors predict treatment response in biologic and targeted synthetic DMARDs-naïve rheumatoid arthritis Patients. **Sagrario Corrales Díaz-Flores.**

VIc. 11:45 – 12:00 Percutaneous revascularization of chronic total coronary artery occlusions reduce pro-inflammatory and hypoxic status in cardiac microenvironment. **Luis Carlos Maestre Luque.**

VId. 12:00 – 12:15 FGF23 as a bridge between energy metabolism and hypertension in chronic kidney disease. **Antonio Rivas Domínguez.**

VIe. 12:15 – 12:30 Therapeutic modulation of NAD+ metabolism in inflammatory rheumatic disorders by TNFi and NAD+ precursors. **Beatriz Vellón García.**

VIf. 12:30 – 12:45 Design of 3D scaffolds for hypoximetic drugs-controlled release and their application in wound healing. **Isabel Lastres Cubillo.**

12:45 – 13:45 – **Plenary Lecture: *"Harnessing CCR7⁺ Dendritic Cells for Enhanced Cancer Immunotherapy".* Dr. Mauro Di Pilato (MD Anderson Cancer Center). (IMIBIC Assembly Hall)**

13:45 – 14:15 – **Awards and Closing ceremony (IMIBIC Assembly Hall)**

Description of the review process for selecting oral/poster presentations

Authors submitted their works through the Young Investigators abstract submission website from June 4th to June 25th. During the submission process, each author selected a specific scientific category (among the five IMIBIC Scientific Programs) and a preferred type of presentation (oral or poster). At the deadline, a total of 100 abstracts were received. The Organizing Committee distributed all abstracts received amongst 39 external reviewers in a completely anonymized manner. All reviewers were selected based on their expertise in the scientific areas aligned with the abstracts submitted. The full list of the external reviewers can be found at the beginning of this book. Abstracts were peer-reviewed by the external reviewers, scoring the communications between 1 (very poor) and 10 (very good). It should be noted that the Organizing Committee has not evaluated or scored any of the submitted abstracts.

On September 9th, 2024, the Organizing Committee held a meeting to distribute all abstracts evaluated into oral communications or poster presentations based on the scores provided by the external reviewers and the participants preferred presentation choice (oral vs. poster). Thus, oral communications were divided in 6 sessions, while poster presentations were distributed in 2 sessions. Considering the number and scores of oral presentations submitted for each category, the Organizing Committee decided to establish two sessions for Cancer and Chronic and Inflammatory Diseases, and one session for Nutrition and Infectious and Immunological diseases.

Description of the review process for award selection

In order to motivate and boost high-quality presentations, IMIBIC establishes awards to the best oral communication within each of the 6 sessions. These awards will be selected based on the scores derived from the Scientific Committee, which includes 1 translational researcher and coordinator and 5 researchers (1 clinical and 4 translational), and all the chairs of the sessions (12 researchers). The full list of members of the Scientific Committee and chairs can be found at the beginning of this book. The Scientific Committee and chairs will score every presentation from 1 to 10, taking into consideration the following criteria: (i) scientific quality of the work, (ii) presentation skills of the presenter, and (iii) capacity to answer the questions raised by both the audience and chairs. The final score for each presentation will consist of the average of the score obtained by the Scientific Committee and chairs. The score of the external reviewers will only be used in the event of a tie. The six highest scored oral communications will compete for the Best Presentation Award of the Meeting. The best oral communication presented by a Resident Medical Intern will be also awarded by the "Colegio Oficial de Médicos de Córdoba". To assess the poster presentations, two chairs will visit the highest scored abstracts according to the external reviewers, distributed into two sessions. They will be scored following the same criteria applied for oral presentations. The highest scored poster per session will be awarded.

Presenters who were awarded in the two previous editions will be excluded from the process.

ORAL COMUNICATIONS

Abstracts

SESSION I.

CANCER I

Ia. Dysregulation of a RNA exosome component: A driving force for prostate cancer progression and metastasis.

Authors: Francisco Porcel-Pastrana[1,2,3], Prudencio Sáez-Martínez[1,2,3,4*#], Rafael Sanchez-Sanchez[1,3,8], María M Malagón[1,2,3,11], Marco A Calzado1,2,3, Enrique Gómez-Gómez[1,3,12], Manuel D Gahete[1,2,3,11], David Tollervey6, Raúl M Luque[1,2,3,11#].
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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: RNA-Exosome, REC-C, prostate cancer, biomarkers, therapeutic targets, metastasis.

Abstract:

Despite significant advances in the treatment of prostate cancer (PCa), this disease remains highly lethal, emphasizing the urgent need for effective, novel molecular/therapeutic tools. Emerging evidence indicates that the dysregulation of the RNA metabolism is a relevant characteristic frequently found during the progression of different cancer types, but the role of certain components of the RNA-Exosome complex (REC), a poorly explored RNA-controlling cellular machinery, remains unknown in PCa. Herein, comprehensive analyses of REC-C alterations (at mRNA/protein levels and cellular localization) were conducted using six well-characterized PCa cohorts and the TRAMP transgenic model. REC-C was up-regulated in advanced PCa samples, correlating with adverse clinical parameters (including shorter Disease-Free Survival, and presence of significant-PCa, advanced T-stage, recurrence and metastasis). Functional assays, in vitro (cell-proliferation, migration, colony/tumorsphere-formation) and in vivo (tumor progression and volume in xenograft tumors), demonstrated the impact of REC-C-silencing on critical cancer hallmarks. Mechanistic analyses, including RNA-sequencing, UV cross-linking (CRAC), and confocal-microscopy revealed that REC-C regulates the expression of multiple RNAs (>2500), especially inflammatory-related RNAs (e.g. IFN-γ/IFN-α responses), and the activity of key oncogenic signalling-pathways in PCa cells (JAK-STAT/MAPK/AKT/NF-κB/TGF-β/MYC). Finally, we discovered links between the REC-C subcellular distribution and its oncogenic role in prostate cells, being nucleoplasmic REC-C accumulation correlated with PCa progression/metastatic features. These findings reveal that interaction of relevant RNAs with REC-C in the nucleoplasm facilitates their roles in suppressing immune responses and enhance oncogenic signalling, promoting PCa progression to advanced disease. Therefore, REC-C may represent a promising prognostic biomarker and an innovative exploitable therapeutic target for PCa/advanced-stage PCa

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*Identity of RNA-Exosome Complex Component (REC-C) is not revealed in an agreement with "Innovation and Transference Service" to avoid conflicts in a patent recently presented.

Ib. DYRK2 orchestrates MAPK signaling and melanoma therapy resistance.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: DYRK2, MAPK/ERK pathway, melanoma, therapy resistance, plasticity.

Abstract:

The MAPK/ERK pathway is among the most dysregulated cell signaling pathways in cancer, with hyperactivation observed in 85 % of all human cancers. In this sense, melanoma is one of the cancer types in which the MAPK/ERK pathway is frequently hyperactivated, being mutated in 70 % of all cases. Current melanoma therapies, including targeted therapies (MAPK/ERK 1/2 inhibitors) and Immune Checkpoint Blockade (ICB), are limited due to the emergence of resistance mechanisms after several months of treatment. These resistance mechanisms are mainly related to melanoma intra-tumour heterogeneity and the ability of tumour cells to switch phenotypes, from melanocytic (MEL) to mesenchymal (MES) phenotype. However, the molecular mechanisms and dynamics underlying this phenotype-switching remain poorly understood. In this work, we describe for the first time the DYRK2 kinase as a new modulator of MAPK/ERK pathway which contributes to plasticity and therapy resistance in melanoma. First, DYRK2 promotes the activation of MAPK/ERK pathway by regulating two of its components, BRAF and MEK1. On the other hand, DYRK2 and its downstream MAPK targets levels were increased in several human melanoma cell lines exhibiting MES phenotype or drug resistance. Furthermore, scRNA-seq data from spontaneous melanoma mouse models and patient samples showed that DYRK2 gene expression was increased in MES cells but reduced in MEL cells. Moreover, DYRK2 levels were significantly increased in matched patient samples from non-responders in comparison with responders. In this line, high DYRK2 expression is associated with worse overall survival and lower therapeutic response in melanoma patients. Finally, DYRK2 inhibition decreased the viability of melanoma cells derived from spontaneous melanoma mouse models and patient samples with diverse phenotypes. In conclusion, these findings identify DYRK2 as a novel driver of phenotype-switching and therapy resistance in melanoma, paving the way for new therapeutic approaches for treatment-resistant melanoma patients.

Ic. Dysregulation of splicing machinery influences molecular heterogeneity and cellular metabolism of bladder cancer cells.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Bladder cancer; alternative splicing; cell metabolism; apoptosis; mitochondrial respiration; polyamine metabolism.

Abstract:

Bladder cancer (BlCa) stands as the most common tumor pathology of the urinary tract. This malignancy generally progresses from a non-muscle invasive to an aggressive muscle-invasive stage, and the high inter and intra-patient heterogeneity critically hampers its clinical management. Despite being considered as a cornerstone of molecular diversity, alternative splicing has been underexplored in BlCa. Thus, we aimed to characterize the expression profile and role of a representative set of splicing machinery elements in BlCa as a potential strategy for cancer diagnosis, prognosis, and/or treatment. We found a drastic dysregulation in the expression levels of multiple components of the splicing machinery in BlCa which was associated with tumor aggressiveness parameters. Indeed, unsupervised clustering based on the expression of the splicing machinery elements identified four groups of patients associated with BlCa molecular heterogeneity. Specifically, C1 and C3 clusters included aggressive BlCa subtypes with poorer prognosis and specific molecular features (differentially enriched pathways and transcriptional factor activities). Notably, pharmacological inhibition of the spliceosome reduced aggressiveness parameters in BlCa cell-models, showing a higher vulnerability in C3-like models. A deeper characterization of C3 patients and C3-like models revealed an enrichment on MYC and mTOR pathways as well as oxidative metabolism. In this regard, the modulation of a C3-enriched splicing factor profile altered relevant metabolic pathways such as polyamine and branched-chain amino acid metabolism which likely potentiate oxidative phosphorylation. Indeed, splicing inhibition significantly affected mitochondrial respiration in both C3- and non-C3-like models, while only the latter partly rescued these effects through enhancing glycolytic rate. Altogether, our results suggest that the splicing machinery dysregulation influences BlCa molecular heterogeneity and aggressiveness by fueling cellular metabolism. These data invite to consider splicing inhibition as an exploitable patient's tailored therapeutic strategy for improving the clinical management of BlCa patients.

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Id. Role of alternative splicing in lung neuroendocrine tumors: exploring the OTP-CD44 axis.

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Keywords: RNA splicing, neuroendocrine tumors, CD44, typical carcinoids, atypical carcinoids.

Abstract:

Neuroendocrine tumors (NETs) are a heterogeneous group of low-grade neoplasms that arise from neuroendocrine cells. Among them, lung NETs (LungNETs) represent one of the most frequent subtypes and are histologically classified into typical (G1) and atypical (G2) carcinoids. G1 tumors are well-differentiated, slow-growing with lower risk of metastasis; whereas G2 carcinoids exhibit increased dedifferentiation and a higher metastatic potential. The molecular features of LungNETs remain insufficiently defined. Altered alternative splicing has emerged as a key post-transcriptional mechanism in cancer, but its precise role in LungNETs is still unclear. We hypothesize that G1 and G2 LungNETs are transcriptionally distinct due to differences in RNA splicing, which may serve as an active regulatory mechanism in tumor development and could reveal novel translational opportunities. To test this hypothesis, we performed differential gene expression and alternative splicing analyses on RNAseq from 76 G1 and 85 G2 LungNETs. Additionally, to functionally characterize our findings, we used two LungNET cell models. Our analysis revealed that the differentially expressed genes reflect a loss of neuroendocrine identity in G2, potentially contributing to higher aggressiveness. This included a decrease in *OTP* that has been associated with LungNET malignancy. Splicing analysis identified over 3000 differentially spliced genes between grades, including *CD44*, a gene implicated in cell adhesion and tumor progression. Interestingly, *OTP* and *CD44* expression levels were positively correlated. We observed that two *CD44* variants were differentially spliced between grades. Furthermore, the *in vitro* overexpression of *OTP* induced alterations in proliferation and apoptosis. Ongoing functional experiments aim to explore whether this association is mediated by specific splicing events or isoform dynamics. Altogether, our findings uncover splicing alterations in LungNETs and underscore the relevance of splicing (dys) regulation in tumor progression. The *OTP-CD44* axis emerges as a promising molecular target for further investigation with potential translational impact in the management of LungNETs.

Ie. Microbial profiles in pseudomyxoma peritonei reveal novel findings, including fungal detection.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Cancer, Microbiology, Bioinformatic, Fungi, Microbiome.

Abstract:

Pseudomyxoma peritonei (PMP) is a rare disease characterized by the accumulation of mucus-secreting cells within the peritoneal cavity, typically of appendiceal origin. The only available treatment involves complete cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. Therefore, finding ways to improve treatment and better understand how the disease develops is required. Microorganisms have previously been detected in PMP using genomic approaches and, because of this, antibacterial treatments have been suggested. However, all these previous studies are centered on the bacteriome without considering any other microorganisms. This work investigates the bacteriome and the mycobiome of PMP using different approaches such as: metagenomics, microbial culture, and staining techniques. In addition, we investigated the potential functional implications of these microorganisms using specific analytical approaches. Experiments with a PMP animal model using antibiotics and antifungals were also conducted to explore their pathophysiological effects on the disease. For the first time, the presence of fungi in PMP has been demonstrated. We have identified hundreds of bacterial families and dozens of fungal families. Bacterial diversity was significantly higher in tumors compared to controls, particularly across different tumor grades, a trend not observed for fungal diversity. Notably, significant shifts in microbial composition and predicted metabolic pathways were associated with tumor grade, including alterations in immune signaling pathways. Viable microorganisms were also successfully isolated. Our results provide valuable insights and indicate future research directions to elucidate the genesis and development of PMP.

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If. Exploring the molecular and immune profile of breast cancer from pregnancy to postpartum: shedding light on the tumor-immune microenvironment during lactation.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pregnancy-associated breast cancer; molecular profile; tumor signatures; breastfeeding; immune system; tumor microenvironment.

Abstract:

Pregnancy-associated breast cancer (PABC) is an aggressive disease affecting young women, associated with poorer prognosis and increased metastasis risk. While immune changes, such as immunosuppression during pregnancy and postpartum inflammation, may influence the tumor microenvironment, their impact remains unclear. This study aims to analyse the molecular and immunological patterns of PABC tumours to provide insights into their tumour landscape and potential therapeutic opportunities. We analysed the gene expression of FFPE tumour samples from 106 breast cancer patients using the nCounter BC360 panel (NanoString), to compare the tumour profile of PABC patients across three different stages: diagnosed during gestation (PABC-GS; n=21), breastfeeding (PABC-BF; n=21), or the first-year postpartum outside lactation (PABC-FY; n=15), against non-PABC patients (n=49). The immune cell composition of tumours was estimated using the CIBERSORTx platform with the LM22 matrix and a 5% significance threshold. Among the molecular subtypes, a significantly higher proportion of basal-like tumours (~40%) was observed in all PABC subgroups. Compared to non-PABC patients, our analysis revealed across all PABC subgroups significant enrichment of DNA repair-related signatures (HRD, BRCAness and BC p53), increased BC proliferation (adj $p<0.05$), along with higher CDK4 expression and genomic risk ($p<0.05$). Interestingly, when we analysed the subgroups independently, the tumor-immune profile of PABC-BF tumours stood out, showing significantly higher immune infiltration indicated by increased immune activity and cell abundance signatures (cytotoxicity, CD8+ T-cells, Tregs) (adj $p<0.05$), as well as higher inflammatory chemokines levels and TIGIT expression ($p<0.01$). The CIBERSORTx analysis supported these findings, demonstrating a significantly higher abundance of several immune cells in PABC-BF compared to all other groups, notably CD8+ T-cells and Tregs ($p<0.05$). Our study confirms that PABC tumours display aggressive molecular features across all subgroups, contributing to their poor prognosis. Remarkably, it also uncovers that breastfeeding patients exhibit a particularly active tumour-immune microenvironment, highlighting potential for targeted immunotherapy.

Funding: PI22/00969.

SESSION II.

CHRONIC AND INFLAMMATORY DISEASES I

IIa. Integrative Multi-Omics Stratification of Rheumatoid Arthritis Reveals Disease Stage–Specific Profiles and Predictors of Treatment Response.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: **Arthritis** Rheumatoid, Biomarkers, Genomics and Proteomics, Disease-Modifying Antirheumatic Drugs (DMARDs).

Abstract:

Objectives: To characterize molecular profiles of RA patients through multi-omics integration and assess their associations with disease status and therapeutic response to csDMARDs, TNF inhibitors (TNFi), and JAK inhibitors (JAKi). **Methods:** Transcriptomic profiling was performed on PBMCs from established RA patients (n=206; 177 starting TNFi or JAKi), early RA (n=53; 30 initiating csDMARDs), and healthy donors (HD, n=42) using RNA-seq. Serum levels of 92 inflammatory proteins were measured via Proximity Extension Assay (Cobiomic/Olink). Six-months treatment response was evaluated using EULAR criteria. Unsupervised clustering and machine learning identified molecular subgroups and predictive biomarkers. **Results:** Transcriptomic clustering revealed three molecular groups, with cluster 1 (CL1) showing strong activation of immune and metabolic pathways. Proteomic profiles confirmed this inflammatory signature, identifying 38 differentially expressed proteins in CL1. These molecular profiles correlated with clinical parameters such as DAS28, autoantibody titers, and cardiovascular risk, with CL1 patients exhibiting more severe disease. Established RA displayed more pronounced molecular alterations than early RA, indicating increased immune dysregulation over time. Associations between molecular profiles and clinical features were stronger in established RA. Machine learning models predicted treatment response with high accuracy (AUC > 0.8), based on distinct transcriptomic signatures: i) csDMARDs: high metabolic and low oxidative stress gene expression; ii) TNFi: high inflammatory and low cytotoxicity gene expression. iii) JAKi: elevated interferon-related and decreased mitochondrial gene expression. Clinically applicable predictive models combining proteomic and clinical data achieved high accuracy. i) Baseline inflammatory burden and disease activity were key predictors of csDMARDs and TNFi response. ii) Lymphocyte-related immune activity played a more prominent role in JAKi response prediction. **Conclusions:** Molecular profiles allow stratification of RA patients based on disease stage and clinical features. Progression involves increased molecular complexity, and treatment responses correlate with specific pre-treatment signatures. These findings highlight the potential of integrative omics for personalized therapy in RA.

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IIb. FGF23 Neutralization Leads to Impaired Vascular Dysfunction Through Modulation of Arterial Stiffness and Vascular Remodeling.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: FGF23; Vascular remodeling; arterial stiffness; blood pressure; extracellular matrix.

Abstract:

Introduction: Chronic kidney disease (CKD) is frequently associated with increased arterial stiffness and hypertension. Vascular remodeling alterations play a pivotal role in the development of these complications. Previous research from our group demonstrated that fibroblast growth factor 23 (FGF23) increases arterial stiffness and vascular dysfunction. This study aims to assess the effect of FGF23 blockade on arterial stiffness and vascular remodeling in a rat model characterized by hypertension, arterial stiffness and high levels of FGF23. **Materials and Methods:** Spontaneously hypertensive rats (SHR) serve as an established model of increased arterial stiffness, exhibiting elevated FGF23 levels. SHR were treated with anti-FGF23 antibodies (1 mg/kg body weight) for 14 days. Wistar Kyoto (WKY) rats were used as normotensive controls. Blood pressure was evaluated at 7 and 14 days. Wire myography was used to measure arterial stiffness in thoracic aortic rings. Vascular remodeling was analyzed through electron microscopy, immunohistochemistry, and immunofluorescence studies targeting Fibrillin-1, Fibronectin, Fibulin-4, and Fibulin-5. **Results:** FGF23 neutralization led to a 40 mmHg reduction in systolic blood pressure in SHR, accompanied by significant structural changes in the thoracic aorta. Wire myography studies indicated increased arterial stiffness in SHR compared to WKY rats; however, FGF23 blockade significantly reduced pathologically arterial stiffness. Histologically, FGF23 neutralization markedly decreased collagen content and its distribution, as well as the expression of key proteins involved in vascular remodeling, including Fibrillin-1, Fibronectin, and Fibulin-5. Conversely, Fibulin-4 expression increased following FGF23 blockade. **Conclusion:** FGF23 directly influences the regulation of arterial stiffness and blood pressure. Thus, FGF23 neutralization induce pathological changes in vascular remodeling, leading to decreased arterial stiffness and impaired vascular function.

IIc. Integrative Lipidomic and Inflammatory Profiling in Rheumatoid Arthritis: Links to Disease Activity, Therapeutic Response, and Hepatic Mechanisms.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Metabolomics; Proteomics; biologic DMARDs; JAK inhibitors.

Abstract:

Background and objectives: Lipid metabolism plays a key role in immune cell activation, differentiation, and function. Inflammation disrupts this balance, contributing to rheumatoid arthritis (RA) progression. We aimed to analyze circulating lipid and inflammatory profiles in RA patients, explore their association with disease activity and therapeutic modulation, and identify mechanisms underlying altered lipid metabolism. **Methods:** Clinical data and blood samples were collected from 362 RA patients and matched healthy donors (HDs). Serum lipid profiles were analyzed using NMR spectroscopy and inflammatory proteins were measured by PEA (Olink/Cobiomic). A 6-month follow-up was conducted in patients receiving TNFi (n=80), IL6Ri (n=27), or JAKi (n=46). *In vitro* studies in HepG2 cells treated with patient serum -in the presence or absence of the above cited drugs-, included Bodipy staining and gene expression analyses. **Results:** Patients were classified into high (n=96), moderate (n=191) and low (n=75) disease activity (DAS28). Approximately 100 lipid markers differed significantly between groups, with high activity associated with reduced levels of apolipoproteins, fatty acids, phospholipids, and total lipid content. LDL and VLDL markers were also reduced. Many negatively correlated with CRP, ESR, ACPAs, cardiovascular risk factors and liver enzymes. Proinflammatory proteins were elevated in high activity, correlating with clinical parameters and altered lipids, suggesting a shared dysregulation. At follow-up, treatment significantly reversed lipid and inflammatory changes, paralleling clinical improvement. *In vitro*, HepG2 cells treated with active RA serum exhibited altered lipid accumulation and lipid transport genes expression. These effects were partially reversed by therapy mirroring in vivo findings. **Conclusion:** Active RA is characterized by reduced circulating lipids and proinflammatory dysregulation, which are partially reversed by therapy. Our findings suggest a hepatic adaptation to inflammation that may promote metabolic dysfunction and cardiovascular risk. Ongoing studies aim to clarify these mechanisms.

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IId. Clinical and Ultrasonographic Evaluation in Patients with Early-Onset Rheumatoid Arthritis: Treatment Response and Histological Pathotypes in Synovial Biopsy.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: ultrasonography, treatment, pathotypes.

Abstract:

Rheumatoid arthritis (AR) is a chronic and disabling inflammatory disease. In recent years histological analysis of synovial tissue has emerged as a potential predictor of therapeutic response, promoting the development of personalized medicine.
We accomplished a retrospective descriptive study involving 74 patients with early-onset RA (ARRI) (<6 months) and 11 with pre-RA (patients with seropositive arthralgias and ultrasoundconfirmed synovitis or tenosynovitis), from the cohort of the Reina Sofía University Hospital in Córdoba. Clinical, laboratory and ultrasound data were collected, including inflammatory markers (CRP, ESR), disease activity index (DAS28, CDAI, SDAI), and semi-quantitative ultrasound evaluation of synovitis and power Doppler activity according to EULAR-OMERACT criteria. Patients were divided in two groups based on their response to first-line synthetic DMARDs (Disease-Modifying Anti-Rheumatic Drugs) after one year of diagnosis, excluding those who changed or discontinued treatment due to side effects. Synovial biopsies were performed in 22 patients, identifying three histological pathotypes by immunohistochemistry: lympho-myeloid (B and myeloid cells), diffuse myeloid (mainly myeloid cells), and pauci-immune (low immune cell infiltration). We analyzed if clinical, analytical, or ultrasound variables differed significantly across these pathotypes. Significant differences were found in disease duration [2.16 (0.61) vs 1.68 (0.94); p=0.01] and diagnostic delay [1.27 (11.77); p= 0.4] between responders and non-responders. Non-responders showed higher seropositivity and more wrist synovitis and tenosynovitis, though not statistically significant. The lympho-myeloid group had higher baseline inflammation [baseline CRP: 46.59 (26.19); p=0.02 and baseline ESR: 49.2 (24.74); p=0.01]. The pauci-immune group showed more interstitial lung disease, lower treatment response, and greater need for biologics, without statistical significance. In conclusion, longer disease duration, diagnostic delay, seropositivity, and baseline ultrasound activity may be associated with therapeutic failure. Additionally, synovial histological analysis could help predict treatment failure, highlighting the potential value of early biologic therapy in selected patient.

IIe. Multi-Omic Characterization of Systemic Lupus Erythematosus Endotypes: Advancing Precision Understanding of Cardiovascular and Renal Involvement.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Systemic lupus erythematosus, Multi-omics, Cardiovascular risk, Lupus nephritis, Proteomics, Metabolomics.

Abstract:

Background and Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with significant clinical variability, complicating diagnosis and treatment. Cardiovascular complications and lupus nephritis are among the most severe manifestations, contributing to increased morbidity and mortality. Traditional biomarkers often fall short in capturing the molecular intricacies, emphasizing the need for integrative multi-omic strategies. This study combined proteomic and metabolomic analyses to identify molecular signatures related to cardiovascular risk and lupus nephritis. **Methods:** Serum from 199 SLE patients was analyzed using proximity extension assays for proteomics and nuclear magnetic resonance spectroscopy for metabolomics. In vitro assays involved treating HUVECs and HK2 cells with SLE patient serum to assess endothelial and renal proteomic responses. Ex vivo, rat kidney slices were cultured with serum to evaluate inflammatory signaling using p65 immunofluorescence. **Results:** Unsupervised clustering of proteomic data revealed two patient subgroups: high disease severity (HDS) and low disease severity (LDS). The HDS group exhibited elevated inflammatory proteins (e.g., IL6, CD40, CXCL9) and metabolites (e.g., creatinine, citrate), linked to cardiovascular risk and renal involvement. Machine learning accurately classified patients into HDS and LDS groups (AUC = 0.77), highlighting biomarkers like citrate and LDL subclasses. Validation in an independent cohort confirmed the robustness of these molecular patterns. In vitro, HDS serum induced endothelial dysfunction in HUVECs and activated inflammatory responses in HK2 cells, signaling tissue damage and immune activation. Ex vivo experiments indicated NF-$\varkappa$B pathway activation in rat kidney tissues exposed to HDS serum. **Conclusions:** The study provides compelling evidence that cardiovascular risk and lupus nephritis in SLE are associated with distinct proteomic-metabolomic signatures, reflecting underlying disease mechanisms. Integrating omics data with functional assays furnishes valuable insights into the molecular drivers of organ-specific damage in SLE, underscoring the potential of multi-omic strategies in enhancing disease understanding and treatment.

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IIf. Ferroptosis is involved in renal damage associated to hemoglobin overload in a murine model of Sickle Cell Disease.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Kidney, Sickle Cell Disease, CKD, Ferroptosis.

Abstract:

Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by chronic hemolysis, which promotes persistent oxidative stress, systemic inflammation, and progressive organ damage. The kidney is particularly affected, with patients often developing chronic kidney disease (CKD), marked by iron and hemoglobin accumulation, microalbuminuria, and tubular-glomerular injury. Despite its clinical relevance, the molecular mechanisms underlying sickle cell nephropathy remain unclear. Ferroptosis, an iron-dependent, lipid peroxidation-driven form of regulated cell death, has been implicated in kidney injury but has not been studied in the context of SCD. We evaluated ferroptosis in the Townes-humanized SCD mouse model, using healthy (HbAA), trait (HbAS) and SCD mice (HbSS) (n=8 per group). Mice were sacrificed at 6 months of age. Blood, urine, and kidney tissues were collected for hematological and renal assessments. Renal proteomics was performed via LC-MS/MS, while ferroptosis and oxidative stress markers were analyzed by RT-qPCR, Western blotting, and confocal immunofluorescence. HbSS mice exhibited classic SCD features, including anemia, splenomegaly, and severe hemolysis. Histology showed iron and hemoglobin deposition in tubules and glomeruli, glomerular congestion, and tubular injury. The albumin/creatinine ratio was elevated in HbSS vs. HbAA mice. Proteomic analysis revealed 288 upregulated and 19 downregulated proteins in HbSS kidneys, enriched in pathways linked to iron metabolism, oxidative stress, ferroptosis, and nephron damage. Molecular analysis confirmed increased oxidative stress (HO-1, Ferritin), inflammation, and glomerular injury (Nephrin, Synaptopodin, WT-1). We also found altered expression of iron transport markers (decrease in *Tfrc* and increased *Slc40a1* expression) and changes in proteins involved in ferroptosis (downregulated GPX4 and increased ACSL4 expression). Finally, we found elevated renal malondialdehyde (MDA) levels further confirmed lipid peroxidation, a key marker of ferroptosis. Conclusion: Our findings suggest that hemolysis-driven iron and hemoglobin overload in SCD promotes ferroptosis and renal damage. Targeting ferroptosis may offer a novel therapeutic approach for preserving kidney function in SCD.

POSTER
SESSION I.

PSI.a. Assessment of the neuroendocrine landscape in metabolic liver disease and cancer through the somatostatin system.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: hepatocellular carcinoma; metabolic dysfunction-associated steatotic liver disease; somatostatin receptors; neuroendocrine profiling; somatostatin analogues.

Abstract:

Liver cancer is the sixth most incident and third most lethal cancer type worldwide. Hepatocellular carcinoma (HCC) is the most predominant subtype (90% of cases) and shows a high heterogeneity that severely hampers systemic treatment. Preceding HCC, metabolic dysfunction-associated steatotic liver disease (MASLD) also exhibits a rapidly growing prevalence. Despite the liver's role as a neuroendocrine hub, classic neuroendocrine profiling and approaches [i.e., somatostatin (SST) system receptor expression and ligand response] have been severely underexplored in liver disease. This work aimed to provide molecular and functional insights on the SST system in the MASLD-HCC progression. Gene expression was evaluated using 2 internal retrospective cohorts [R1 (n=93), R2 (n=102)], 7 MASLD *in silico* cohorts [n=(45-109)/cohort], 6 HCC *in silico* cohorts [n=(65-369)/cohort] and 4 human liver cell lines. Sample clustering in TCGA-LIHC was implemented using Python (YellowBrick package). In a subset of R1 (n=25), immunohistochemistry (IHC) was performed. Cell lines were subjected to *in-vitro* functional assays (proliferation, colony and hepatosphere formation). SST receptors (SSTRs) expression was lower in MASLD compared to control tissue. This profile was reproduced in HCC, where it was associated to complex patterns of tumor aggressiveness and complemented by histological and subcellular localization (IHC). Cell lines mimicked this expression pattern, with HepG2 (low) and Hep3B (intermediate tumoral aggressiveness) showing the highest SSTRs expression. Clustering discriminated between SSTR1-expressing (more benign) and SSTR2-expressing (neuroendocrine-leaning, more aggressive) HCC samples. Consequently, differential antitumoral responses were observed in cell lines functional assays for cortistatin, classic SST synthetic analogues (octreotide, lanreotide and pasireotide) and novel synthetic analogues (BIM-23926 and BIM-23120, IPSEN). In conclusion, neuroendocrine profiling in MASLD-HCC offers a novel framework for understanding these diseases, providing new potential avenues for tumor assessment and personalized therapeutic options.

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PSI.b. Dissecting the roles of Kiss1AVPV neurons in the control of reproduction by functional genomics.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: AVPV, kisspeptins, preovulatory LH surge, ovulation, puberal onset.

Abstract:

Kisspeptins (Kp), essential for reproductive control, are synthesized through distinct populations of Kiss1 neurons mainly located in the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV) of the hypothalamus. While $Kiss1^{ARC}$ neurons are well defined as components of the GnRH/LH pulse generator, the role of $Kiss1^{AVPV}$ neurons in triggering the preovulatory gonadotropin surge remains less understood. We report herein a comprehensive series of analyses of the function of $Kiss1^{AVPV}$ neurons by combining virogenetic approaches with the generation of a congenital *Kiss1* KO model to induce conditional and congenital inactivation of *Kiss1* expression in the AVPV, respectively. Histochemical analyses documented that there is a high expression of tyrosine hydroxylase (TH) in $Kiss1^{AVPV}$ neurons, and virtually all are estrogen sensitive. Thus, we generated a TH-specific Kiss1 KO (TyKKO) mouse line, by crossing Th-Cre and $Kiss1^{fl/fl}$ mice, which displays blunted *Kiss1* but preserved *Th* mRNA expression in the AVPV. TyKKO females, but not males, showed delayed pubertal development, with trends for deferred vaginal opening and first estrus, and displayed longer and more irregular estrous cycles in adulthood. Estrogen-mediated LH surge protocols failed to induce the typical preovulatory rise in LH levels in TyKKO females, despite successful induction in controls. In good agreement, TH-specific Kiss1 KO resulted in anovulation. Additionally, inactivation of Kiss1 expression was carried out also in adult $Kiss1^{fl/fl}$ female mice, by bilateral injection of viral vectors expressing Cre-recombinase (AAV5_CMV:Cre). Effective ablation was documented by RNAscope and qPCR of AVPV micro-punches. In line with TyKKO data, Kiss1fl/fl females injected with viral Cre exhibited disrupted estrous cycles, lack of estrogen-induced LH surges, and halted ovulation. Interestingly, adult females with virogenetic inactivation of AVPV Kiss1 maintained LH pulsatility, suggesting preserved $Kiss1^{ARC}$ neuronal function. In conclusion, $Kiss1^{AVPV}$ neurons are essential for female puberty, preovulatory LH surges, and ovulation, but not for LH pulsatility.

PSI.c. Early Lifestyle Intervention Based on the Mediterranean Diet and Physical Activity: A Preventive Strategy for Childhood Obesity in At-Risk Preschoolers.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: childhood, exercise, diet, metabolism.

Abstract:

Introduction: Childhood obesity increases the risk of developing metabolic diseases in adulthood. Promoting physical activity and healthy eating habits from an early age is essential to support proper development and prevent excess weight. This study aimed to evaluate the impact of an early-life intervention promoting the Mediterranean diet and regular physical activity in comparison to a control group with no intervention. **Methods:** A randomized controlled multicenter trial was conducted with 206 children aged 3 to 6 years, all of normal weight but with a familial risk of obesity due to parental overweight or obesity. The intervention group received nutritional education focusing on the Mediterranean diet, including the use of olive oil and fish consumption twice a week. They also participated in a physical activity program consisting of three 60-minute sessions per week of moderate to vigorous exercise, aligned with international recommendations. The control group received no intervention. Annual evaluations included body composition and physical fitness measurements, lifestyle questionnaires, blood tests, and a one-week accelerometer assessment. **Results:** BMI, body composition, and metabolic markers remained within normal ranges in both groups. At baseline, 66.43% of participants met physical activity recommendations, increasing slightly to 68.8% after one year. Sedentary time was negatively associated with lean mass. Light activity correlated with BMI, lean mass, and fat mass index after one year. Moderate and vigorous activity showed associations with glucose, HDL, triglycerides, and lean mass at baseline, and vigorous activity remained correlated with favorable metabolic and body composition parameters after one year. **Conclusion:** Encouraging physical activity and healthy eating from early childhood may help support a healthier metabolic profile and reduce future obesity risk. Early intervention in at-risk children can be an effective strategy for long-term health promotion.

PSI.d. Cytokine-Induced Memory-Like NK Cells. A New Strategy for Cancer Immunotherapy.

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Scientific Program: Cancer (oncology and oncohematology).
Keywords: CAR-NK cells, Cytokines, Cytotoxicity, Immune checkpoints, Immunotherapy, Memory.

Abstract:

Natural killer (NK) cells are integral components of the innate immune system, essential for defending the host against virus-infected cells and in tumor surveillance. *In vitro*, exposure to interleukin-12/15/18 can induce NK cells to adopt a memory-like phenotype, characterized by increased survival and enhanced cytotoxicity. To achieve this, we expanded human "memory-like" (CIML) NK cells through pre-activation with IL-12/15/18. Subsequently, multiparametric flow cytometry analyses were performed to evaluate the phenotypic profiles of CIML NK cells. To obtain human CIML NK cells from healthy donors (n=15), NK cells were isolated from peripheral blood, pre-activated with IL-12/15/18 for 16 hours, and then expanded for 7 days with IL-15. The phenotypic profiles of CIML NK cells were evaluated at three time points: before stimulation (Day 0), after 16 hours of pre-activation (Day 1), and after 7 days of expansion (Day 7). The results revealed that, on Day 7, CIML NK cells showed a significant increase in the frequency of subsets co-expressing the inhibitory receptors TIM-3 and LAG-3, compared to control and unstimulated NK cells. At the same time, a significant increase was observed in the percentage of subsets co-expressing NKp30, NKp46 and NKG2D, as well as the activation markers CD25 and CD69 in CIML NK cells. This increase was also evident in subpopulations of CIML CD56^{bright} NK cells, which expressed TIM-3, NKp46, NKG2D and CD69. This study supports the potential of CIML NK cells as an innovative alternative in cancer immunotherapy. *In vitro* activation of these cells induces a “memory-like” phenotype characterized by increased cytotoxicity and cytokine production. In this context, we highlight the importance of analyzing NK cell expression patterns at different time points, as this allows for a more precise understanding of the cellular maturation process. These findings contribute to the development of antitumor therapies by prioritizing the expansion of CIML NK cell subpopulations.

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PSI.e. Exploring the redox status in Pseudomyxoma Peritonei: Insights from proteomic and functional analyses.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Cancer, Pseudomyxoma peritonei, redox homeostasis, oxidative stress, proteomic, cell viability.

Abstract:

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignancy characterized by the accumulation of mucinous implants, for which cytoreductive surgery with hyperthermic intraperitoneal chemotherapy remains the only effective treatment. However, due to the frequent relapses and poor early diagnosis, which are common events in this disease, understanding the molecular mechanisms underlying PMP is critical. In this context, this study aims to improve the understanding of PMP by defining the redox state of its tissues, as well as to investigate the role of oxidative stress in PMP pathophysiology using 2D cell cultures. Thus, we determined the cellular redox state in human mucin from PMP patients by measuring the ratio of oxidized/reduced thiol groups by mass spectrometry. Based on the results obtained, *in vitro* functional studies using antioxidants [Resveratrol (RSV) and N-acetylcysteine (NAC)] and prooxidants [dihydrogen peroxide (H_2O_2)] were carried out in PMP cell lines to unveil the contribution of oxidative stress to this malignancy. Our results demonstrated significant alterations in the oxidized/reduced protein ratios of PMP human tissues compared to controls, suggesting a disrupted redox state. Regarding functional assays, our results demonstrated post-treatment alterations in cell viability, indicating differential sensitivity to redox modulation. It is noteworthy that NAC reduced proliferation dose-dependently at early times, while RSV and H_2O_2 effects were dose and/or time-dependent according to the cell line. Furthermore, catalase activity assays confirmed an altered enzymatic response in PMP after treatment with H_2O_2. In conclusion, these findings support the hypothesis that PMP cells develop adaptive mechanisms to withstand oxidative stress, contributing to tumour persistence and progression. Therefore, targeting oxidative stress pathways may constitute a promising and innovative therapeutic avenue for PMP patients.

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PSI.f. Type 2 Diabetes and Immune-Related Genetic Variants Modulate Etanercept Drug Survival in Psoriasis Patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Pharmacogenetics, Psoriasis, Etanercept, Single-nucleotide polymorphisms (SNPs), Type 2 diabetes mellitus (T2DM).

Abstract:

Background: Drug survival is a key surrogate of treatment effectiveness in real-world psoriasis cohorts. While obesity and metabolic comorbidities are known to impact biologic persistence, the role of genetic variability in modulating these effects remains poorly understood. **Objectives:** To evaluate whether single-nucleotide polymorphisms (SNPs) in immune-related genes influence drug survival of biologics in patients with psoriasis and type 2 diabetes mellitus (T2DM), with a focus on etanercept. **Methods:** We analyzed a cohort of 1,014 biologic-treated psoriasis patients, of whom 345 had available genotyping data. We performed Cox regression models including interactions between T2DM, biologic type, and 200+ SNPs from candidate genes in IL-17, IL-23, TNF, and metabolic pathways. Interaction terms were tested for significance, and hazard ratios (HR) with 95% confidence intervals were estimated. **Results:** Multiple SNPs showed significant interaction with etanercept in the context of T2DM. Notably, carriers of minor alleles in IL17RA_rs882643, TNFRSF1B_rs683240, TNFRSF1B_rs590977, and TNFRSF1B_rs5746051 displayed markedly reduced drug survival (HRs ranging from 2.1 to 2.9, $p < 10^{-14}$). These effects were specific to etanercept and were not observed with other TNF or IL-17 inhibitors**. Conclusions:** We report a robust pharmacogenetic signal for reduced etanercept survival in psoriasis patients with T2DM carrying specific SNPs in TNFRSF1B and IL17RA. These findings support the integration of metabolic and genetic profiling to optimize biologic selection, particularly in complex patients with metabolic syndrome or diabetes.

PSI.g. Integrating machine learning and proteomics to predict response to anti-TNFα therapy in psoriatic arthritis: insights into drug-modulated proteins.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Proteomic, Machine Learning, Psoriatic Arthritis, Biomarkers.

Abstract:

Psoriatic arthritis (PsA) poses treatment challenges due to clinical heterogeneity and variable therapeutic responses. Identifying reliable biomarkers is essential for optimizing and personalizing anti-TNFα therapy. Proteomics combined with machine learning offers promising tools for uncovering treatment-responsive molecular signatures. The objectives of the study were to identify proteomic biomarkers predictive of anti-TNFα response in peripheral blood mononuclear cells (PBMCs) from PsA patients, and to evaluate protein modulation after six months of therapy. We conducted a cross-sectional study with 71 PsA patients treated with anti-TNFα agents were classified as responders or non-responders based on >50% DAPSA score reduction at 6 months. Proteomic profiling of 384 inflammation-related proteins was performed on PBMCs using the Olink platform. Machine learning algorithms were applied to identify proteins associated with treatment response. Additionally, longitudinal analysis was conducted in a subset of 20 patients to assess therapy-induced proteomic changes over six months. Eight proteins showed significant differential expression between responders and non-responders. A machine learning model incorporating two of these proteins achieved an AUC of 0.80 and an accuracy of 0.92 in distinguishing non-responders. Longitudinal analysis identified 65 proteins modulated by anti-TNFα therapy: 57 were upregulated and 8 downregulated. Enrichment analysis revealed upregulation of B cell-related pathways and downregulation of neutrophil-associated pathways. CD200, the most significantly upregulated protein, is expressed by B cells and regulates neutrophils—consistent with observed increases in lymphocyte counts and reductions in neutrophils post-treatment. Notably, CD200 elevation was specific to responders. Our findings highlight the utility of proteomics and machine learning in identifying predictive biomarkers of anti-TNFα response in PsA. The results support the role of B cell-associated proteins, particularly CD200, as potential indicators of therapeutic efficacy, offering insights for personalized treatment strategies.

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PSI.h. Impact on work capacity in post-covid syndrome patients: Analysis of sociodemographic and clinical factors.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Post-COVID, workers, persistent symptoms, severity, work ability.

Abstract
COVID-19, caused by SARS-CoV-2, is primarily transmitted through respiratory droplets and aerosols. The symptoms can affect the ability to carry out daily activities, and those affected may have difficulties returning to work. Workers, especially older adults or those with comorbidities, suffer long-term effects (post-COVID) such as fatigue and respiratory problems. A comprehensive and multidisciplinary approach in medical care is essential for their recovery. To analyze the perceived work capacity of workers with post-COVID in Spain, assessing its impact and effect on their work performance. A cross-sectional study using a questionnaire to collect sociodemographic and work-related data, and another specific one to analyze work capacity (WAI) in 281 workers diagnosed with post-COVID. The variables have been described with measures of central tendency, frequency tables, and 95% confidence intervals (CI). The chi-square test has been used to relate qualitative variables. The majority of participants are women (79%), with an average age of 47.97 years. 97.5% remain actively employed, although many had sick leave due to COVID-19, with the unvaccinated being the most affected. 83.3% report persistent symptoms, especially musculoskeletal disorders and mental health issues. Only 25.3% are considered fit to return to work, while 31% feel incapable, and 37.4% have no hope for the future. It is observed that work capacity is more closely related to working women ($p=0.039$). There is a significant relationship between being female and experiencing cardiac symptoms ($p=0.041$) and musculoskeletal disorders in the lower back ($p=0.032$), and workers aged 46 to 55 rated their work capacity as poor or very poor ($p=0.011$). The analysis reveals a significant impact on the work performance and well-being of workers with post-COVID. Most experience limitations that affect productivity, with persistent symptoms influencing performance and causing setbacks. Many feel unable to perform their job as before, while others must adjust their pace or work methods.

PSI.i. Influence of psychological variables on adherence to the Mediterranean diet and its impact on health: analysis of blood biomarkers in a pediatric endocrinology sample.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: pediatric endocrinology; Mediterranean diet; overweight and obesity; blood biomarkers.

Abstract:

Obesity in children and adolescents is a current health issue, often associated with various types of pathologies identifiable by blood biomarkers. Adherence to the Mediterranean diet (AMD), which has been shown to be a healthy eating pattern, could improve levels in these biomarkers. Research also suggests that healthy behaviors, such as AMD, may be modified by psychological variables. Therefore, this study aimed to evaluate how psychological variables (well-being, positivity and self-efficacy) may influence the AMD, and to test whether there are differences in various biomarkers according to the levels of AMD in a clinical endocrinological population of children and adolescents. A total of 175 patients aged 6 to 17 years (mean = 11.27, *SD* = 2.22; 47.7% girls, 50.6% boys, 1.1% non-binary) were evaluated at first (F1), and their blood tests were obtained at 6-12 months later (F2). The KIDMED scale on AMD was administered at F1, dividing the sample according to their scores [low (9.7%), medium (46.0%) and optimal adherence (30.7%)]. Measures of subjective well-being, positivity, and dietary self-efficacy were also administered at F1. Simple linear regression analyses showed that psychological variables were related to better KIDMED categories, although multiple linear regression analysis revealed that only positivity and dietary self-efficacy were significant. Analysis of variance showed significant differences in triglyceride (p = .036), alanine (p = .002) and vitamin D (p = .010), with the group with the highest ADM having better levels. These results suggest that AMD may have a positive impact on biomarker levels in the short-medium term in children and adolescents with endocrinological issues. Furthermore, the importance of addressing psychological factors to promote healthy behaviors (such as AMD) is emphasized. Thus, psychological interventions to target these factors could be beneficial to improve the well-being and physical health of pediatric endocrine patients.

PSI.j. RNA exosome complex is impaired in Oral Squamous Cell Carcinomas and linked to key pathophysiological features.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: RNA exosome, Oral squamous cell carcinoma, biomarker; therapeuticc target.

Abstract:

Oral squamous cell carcinoma (OSCC) incidence has increased by 50% over the last decade. Unfortunately, surgery and adjuvant radiotherapy and chemotherapy are still the mainstream modality of treatment, underscoring the need for alternative therapies and novel prognostic biomarkers. The dysregulation and implication of the RNA-Exosomecomplex (REC; cellular machinery controlling the 3'-5'processing/degradation of most RNAs) in different cancer-types, including OSCC, is poorly known. Herein, we aimed to characterize and compare the expression levels of REC in OSCC vs. adjacent non-tumour samples (n=32) with a microfluidic technology based on qPCR. Moreover, the relationship of the expression levels of REC components with clinical and histopathological features of OSCC was assessed (clinical follow-up ranging from 2 to 7 years). The direct effect of the pharmacological inhibition of REC activity on the proliferation rate of primary OSCC cell. The results revealed a significant dysregulation in several REC in OSCC vs. adjacent-healthy tissues, being EXOSC7 and EXOSC2 particularly relevant as diagnostic biomarkers [i.e. ROC curve analyses revealed AUC values of 0.724 and 0.719 (p-values of 0.005 and 0.04), respectively]. Notably, the expression levels of some REC were associated with clinical and histopathological features. Specifically, patients with overexpression of EXOSC1 in OSCC patients exhibited a lower mortality risk (logistic regression p=0.023, OR=0.26; ROC curve for EXOSC1 showed an AUC of 0.769). Moreover, we found that the inhibition of REC-activity decreased OSCC-cell proliferation. Our data revealed a significantly altered expression of several components of the REC in OSCC and a link to pathophysiological features, reinforcing a potential clinical and pathophysiological relevance of the REC dysregulation in OSCC. The inhibition of REC-activity might be a therapeutic avenue in OSCC, offering a clinically relevant opportunity to be explored in the future.

PSI.k. Genomic Evolution of Colistin-Resistance in Klebsiella pneumoniae ST512: Impact on Virulence and Fitness Cost.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Klebsiella pneumoniae sequence type ST512; colistin resistance; machine learning; phoQ; virulence; whole-genome sequencing.

Abstract:

Antimicrobial resistance in Klebsiella pneumoniae producing KPC-type carbapenemases (KPC-KP) poses a critical treatment challenge. The first sequence type ST512 KPC-KP outbreak in Spain was reported at Reina Sofía University Hospital in 2012. We analyzed a microbial collection of 314 ST512 clinical isolates collected from infection episodes at our hospital between 2012–2022 (195 colistin-resistant, 119 colistin-susceptible; MIC threshold 2 mg/L) by whole-genome sequencing. Single-nucleotide variants and small insertions/deletions across all coding regions were identified relative to the index 2012 outbreak strain and encoded in a binary presence/absence matrix. Five machine-learning classifiers confirmed phoQ mutations as central predictors of colistin-resistance reversion and produced a ranked shortlist of novel candidate loci (dedA, fucP, oppC). Preliminary genomic findings reveal multiple evolutionary pathways from colistin resistance to colistin sensitivity beyond phoQ alterations. We selected representative KPC-KP isolates spanning canonical and noncanonical mutation profiles to test the impact of genomic context on virulence and fitness. Ongoing in vitro experiments include macrophage infection assays to measure intracellular survival, antibiotic-free growth curves to quantify fitness costs, and broth microdilution to validate colistin MICs. By integrating machine-learning-driven genomic discovery with targeted functional assays, we aim to identify and validate new biomarkers of colistin-resistance. Such insights will improve prediction of emerging colistin-sensitive lineages and may inform more precise infection-control and antimicrobial-stewardship strategies.

PSI.1. Molecular and Functional Characterization of Aminoacyl-tRNA Synthetases in Hepatocellular Carcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: hepatocellular carcinoma; chronic liver disease; ARS; *HARS2*.

Abstract
The final stage of metabolic dysfunction-associated steatotic liver disease (MASLD) is hepatocellular carcinoma (HCC). Given the known disruption of RNA metabolism and protein synthesis processes in these pathologies, we investigated the dyseregulation of the aminoacyl-tRNA synthetase (ARS) family—enzymes essential for protein synthesis yet with unclear roles in cancer—throughout chronic liver disease and HCC. Expression profiles of 51 genes related to tRNA biogenesis, including 36 ARSs and 15 associated factors were analyzed using in silico cohorts of chronic liver disease and HCC (datasets: GSE_65485, GSE_76427, GSE_77314, GSE_82177, GSE_94660, GSE_104310, GSE_84598, GSE_89377, GSE_98383, GSE_105130, GSE_114564, GSE_135631, GSE_176271, GSE_121248, GSE_124535, GSE_184733). Functional effects of *HARS2* and *PARS2* silencing were evaluated in HCC cell lines (Hep3B and SNU-387). Transcriptomic analysis of both cytosolic and mitochondrial ARSs in HCC revealed significant deregulation, with mitochondrial ARSs—particularly *HARS2* and *PARS2*—standing out for their ability to distinguish tumor tissue from adjacent non-tumor tissue. CRISPR/Cas9-mediated knockout (KO) models were generated in SNU-387 and Hep3B cells. In Hep3B, a highly efficient *HARS2* KO (95%) was obtained. Functional impact was assessed through proliferation, migration, colony formation, and tumorsphere assays. *HARS2* depletion led to a marked reduction in all these parameters, supporting its critical role in HCC tumorigenicity. There is substantial deregulation of ARSs in chronic liver disease and HCC, with *HARS2* emerging as a potential driver in disease progression.

Fundings: ISCIII (PI23/00652; co-funded by the European Union), MINECO (FPU20/03957), Junta de Andalucía (PI-0046-2024, BIO-0139), FSEEN, and CIBERobn/CIBERehd.

PSI.m. A Sarcoma with late diagnosis.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Sarcoma, General Practitioners, Delayed Diagnosis.

Abstract:

Background: Sarcomas are tumors that represent 1% of all malignant neoplasms in adults. Despite well-defined referral guidelines, the diagnosis of sarcoma is often delayed, due to the rarity of the disease and inconspicuous presentation, as well as other patient- and physician-dependent factors. **Aim of the case report:** A 58-year-old male patient underwent minor surgery for a fibroid (2017) on the anterior aspect of the left thigh. Investigating the patient's medical history, the pathological anatomy of the removed piece is not found. In 2018, the patient came again because the fibroid had reappeared, being painful on palpation and presenting a purplish color suggestive of a keloid. It is treated with topical treatment without improvement. He consulted again a year later, 2019, for the same symptoms. **Case report:** Physical examination: tumor of about 2 cm in the left thigh. **Evolution:** Due to the persistence of the symptoms and the slow growth of the lesion, the patient was referred to the surgery service for evaluation. During the consultation, he suggests that it is a sebaceous cyst, but it was removed in 2020 and the lesion was sent for analysis. The pathological study describes a leiomyosarcoma measuring approximately 7 cm that affects the resection edges. **Conclusions:** Sarcoma must be managed by qualified professionals who achieve early diagnosis and treatment and are referred to expert reference centers. This management has a considerable time-dependent impact on the prognoses of these patients.

PSI.n. Understanding adipose tissue fibrosis: LRG1 as a mediator in the crosstalk between adipocytes and macrophages.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: obesity, proteomics, fibrosis, extracellular matrix, LRG1.

Abstract:

Introduction: Leucine-rich α-2-glycoprotein 1 (LRG1) is a novel adipokine consistently elevated in obesity. Beyond its association with obesity, LRG1 is implicated in fibrosis across various tissues. Concerning adipose tissue obesity, both macrophages and adipocytes are critical drivers of inflammation and emerging fibrosis, which contribute to metabolic dysfunction. While these cellular players are central to adipose tissue remodeling, the precise mechanisms by which LRG1 influences adipocyte function and modulates macrophage behavior within this complex environment, and how these interactions contribute to obesity-associated fibrosis, remain unknown. **Methods:** Cell cultures of key adipose tissue cell types – adipocytes, and M1/M2 macrophages – were exposed to obesity-like conditions to investigate LRG1 regulation. The impact of LRG1 on adipose tissue cells, including ECM production, fibrillogenesis, adipogenesis and macrophage polarization, was also assessed by different techniques. **Results:** We demonstrated that TNF-α enhances LRG1 production in mature adipocytes, which are the primary contributors along with M2-macrophages in obesity-like circumstances. In mature adipocytes, while acute exposure to high dose (150 ng/mL) LRG1 induced increased levels of collagens and ECM regulators, chronic exposure to LRG1, as would occur in obesity, significantly decreased expression of these ECM components, suggesting that LRG1 exposure in obesity downregulates adipose tissue homeostasis. Regarding macrophage polarization, LRG1 switched M2-macrophages towards a mixed activation phenotype, while inactivated M1-macrophages. Summing up, inflammation increases LRG1 production in mature adipocytes, which could then act on M2-macrophages, driving them towards a M2b/c-mixed phenotype that combines pro-inflammatory and pro-fibrotic characteristics. This situation might contribute to further inflammation and altered ECM remodeling, potentially releasing more TNF-α, amplifying the loop. **Conclusion:** LRG1 could modulate the crosstalk between adipocytes and macrophages, influencing ECM remodeling and inflammation. This suggests that LRG1 could be a promising therapeutic target for fibrosis.

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PSI.o. Task Engagement Patterns in a CBT-Based eHealth Intervention for Adolescents with Type 1 Diabetes: A Usability Analysis of the ERES App.

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Scientific Program: Endocrine and metabolic diseases.
Keywords: T1D; psychology; eHealth; App; CBT; minors.

Abstract:

The development of eHealth technologies has become a valuable resource to support treatment adherence and self-management, particularly in chronic conditions such as Type 1 Diabetes (T1D). Among this population, the use of continuous glucose monitors (CGMs), which provide real-time interstitial glucose readings, has become increasingly widespread. These devices often synchronize with mobile applications, enabling patients to access data that supports therapeutic decision-making. Concurrently, psychoeducational interventions targeting self-management have been developed, especially for pediatric and adolescent populations. This study examines the usability of the ERES mobile application, implemented as part of an 8-week intervention based on cognitive-behavioral therapy (CBT), and registered in ClinicalTrials.gov (NCT06450730). The intervention consists of five asynchronous online sessions and three in-person sessions. Online sessions include a variety of tasks designed to promote emotional self-regulation. The objective was to identify which task formats were most engaging, with the aim of reducing attrition. A total of 23 participants (10 males, 13 females; mean age = 13.83 years, SD = 3.14; age range: 9–18 years) used the ERES app over eight weeks. Each online session included multiple task formats: textual content (with/without images), interactive activities, slide presentations, short-format videos, and audio recordings. Completion rates were recorded for each task type. Slide presentations had the highest completion rate (54.03%), followed by text-based tasks (53.28%). Audio tasks were least completed (30.40%). Tasks involving active engagement (e.g., swiping or typing) showed higher completion than passive formats (e.g., listening or watching). These findings offer insights into the design of digital health interventions for youth with T1D, emphasizing the importance of interactive components to enhance engagement and support sustained use.

PSI.p. Clinical potential and non-canonical roles of the cytosolic aspartyl-tRNA synthetase (DARS1) in hepatocellular carcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: DARS1, Hepatocellular carcinoma, proteomics, SAGA, MYC, senescence.

Abstract:

Aminoacyl-tRNA synthetases (ARSs) catalyze the transfer of amino acids to tRNAs for protein synthesis. Here, we explored the clinical potential and the molecular implications of the cytosolic aspartyl-tRNA synthetase (DARS1) in hepatocellular carcinoma (HCC). DARS1 levels were analyzed in cytosolic/nuclear protein fractions of HCC patients ($n = 42$ patients), tissues of seven *in silico* cohorts, and plasma samples of two cohorts. Aspartate "substitutants" were identified in HCC patients by peptide mapping against virtual aspartate-substituted proteomes. Functional assays were performed in three liver cancer-derived cell lines after DARS1 modulation. *DARS1*-overexpressing Hep3B cells were used for *in vivo* orthotopic tumor formation. Immunoprecipitation of DARS1 and quantitative proteomics were performed in cytosolic/nuclear Hep3B fractions. DARS1 abundance was higher in HCC tissues, in plasma samples of HCC patients [Area Under Curve (AUC) HCC *vs.* controls: 0.8376], and in aggressive tumors. Consistently, *DARS1* silencing/pharmacological inhibition reduced, while *DARS1* overexpression increased, aggressiveness *in vitro*, while orthotopic tumors formed by *DARS1*-overexpressing Hep3B cells showed increased growth *in vivo*. A re-analysis of proteomic data of patients revealed a reduction of aspartate "substitutants" in HCC samples, suggesting a better efficiency of aspartate incorporation into proteins. Also, 132 nuclear DARS1 interactors were identified by immunoprecipitation and mass spectrometry, among them three members of the SAGA complex, which regulates MYC acetylation and stability. This interaction was confirmed by docking of DARS1/SAGA crystal structures. Consistently, *DARS1* silencing reduced MYC protein levels but increased its phosphorylation, and reduced drug-induced senescence, suggesting a link between DARS1-SAGA interaction and MYC-regulated senescence. Therefore, DARS1 is overexpressed in HCC, representing a potential biomarker in liquid biopsy and a therapeutic target that modulates MYC activity and senescence.

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PSI.q. Deciphering the contribution of hyperandrogenism to metabolic dysfunction-associated steatotic liver disease (MASLD) development in the context of polycystic ovary syndrome.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: PCOS, MASLD, hyperandrogenism, liver, androgen receptor.

Abstract:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among premenopausal women, characterized by hyperandrogenism and reproductive abnormalities. Beyond its reproductive alterations, PCOS is frequently associated with metabolic disorders, and women living with PCOS are four times more prone to developing metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD is a widespread liver condition, affecting 35-70% of women with PCOS. MASLD encompasses a range of hepatic manifestations that begin with liver fat accumulation, which may progress to non-alcoholic steatohepatitis (NASH); a more severe stage that may lead to cirrhosis, liver failure and hepatocellular carcinoma. Cumulative evidence suggests that the higher incidence of MASLD in women with PCOS may be linked to their metabolic comorbidities. However, recent findings indicate that chronic hyperandrogenism may be an independent risk factor for developing MASLD in these patients. In our study, we analyzed the role of hyperandrogenism on the development of MASLD by using a well-validated murine model of PCOS and a liver-specific androgen receptor knockout model generated in our group. We evaluated the effect of chronic androgen excess, alone or in combination with an obesogenic diet, on the metabolic and hepatic profile during 15, 18 and 23 weeks of exposure in the PCOS model. Chronic hyperandrogenism altered metabolic parameters and increased hepatic lipid and collagen accumulation at 15 weeks. These parameters were exacerbated when the animals were fed a high-fat diet (HFD) and/or exposed to androgens for a longer period (18 and 23 weeks). Interestingly, mice devoid of the androgen receptor in the liver were partially protected, as they showed better metabolic and hepatic profile when exposed to chronic hyperandrogenism, especially in HFD-fed animals. Our findings set the basis for understanding the pathophysiology of PCOS-bound MASLD and the potential role of hyperandrogenism in its development through activation of the hepatic androgen receptor.

PSI.r. Deciphering Systemic Sclerosis Phenotypes: A Novel Approach Using Clustering Algorithms and Proteomic Insights. Results from the PRECISESADS Study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Autoimmune Diseases; Proteomics; Scleroderma; Systemic sclerosis.

Abstract:

Introduction: Systemic sclerosis (SSc) is a multi-organ autoimmune disease characterized by three main pathological hallmarks: vasculopathy, fibrosis, and autoimmunity. Despite advances in treatment and prognosis, some patients develop early organ involvement. Patient stratification is critical to identifying individuals at higher risk of organ damage, enabling earlier detection and potentially preventing its progression. **Objectives**: 1) To identify distinct clinical subgroups in SSc using a clustering algorithm based on clinical and serological variables. 2) To compare the proteome of the identified clinical clusters to explore biomarkers associated with organ damage. **Methods:** A cross-sectional observational study was conducted with 402 patients diagnosed with SSc, utilizing data from the international multicenter PRECISESADS study. Clinical and serological variables were collected. A k-means clustering algorithm was applied, integrating various clinical and serological variables. The optimal number of clusters was determined using the silhouette width method. Subsequently, a univariate analysis was performed to compare the clusters. Following the identification of clinical clusters, a random sample of 144 patients (77 from each cluster) was selected for proteomic analysis of 92 proteins associated with organ damage using OLINK technology. **Results:** Two clusters were identified (Cluster 1 = 221 (55%) and Cluster 2 = 181 (45%)). The results of the univariate analysis are shown in Table 1. Cluster 1 included a slightly younger population (57.2 vs. 59.1 years) and a shorter disease duration (10.2 vs. 11.6 years), although these differences were not statistically significant. Patients in Cluster 2 exhibited a higher prevalence of organ involvement, including ILD (14.48% vs. 59.67%), PAH (9.05% vs. 30.94%), and esophageal dysmotility (34.84% vs. 67.96%). Serologically, anticentromere antibody positivity was more frequent in Cluster 1 (43.44% vs. 29.28%), whereas anti-Scl70 positivity was more common in Cluster 2 (19.91% vs. 38.67%). Proteomic comparison between the two clusters (Figures 1 and 2) revealed significant differences, with 7 proteins elevated in Cluster 2 compared to Cluster 1 (NOS3, PON2, MAP4K5, AIFM1, NUB1, STX8, and PDGFC) and 1 decreased protein (HPGDS). These proteins are involved in various metabolic pathways, with MAP4K5 being relevant to the interferon pathway, while PON2, AIFM1, and NUB1 are implicated in the regulation of apoptosis, a dysregulated process in SSc. **Conclusions:** These findings suggest the presence of distinct clinical, serological, and proteomic clusters, indicating heterogeneous subgroups within SSc. The proteomic analysis also identifies potential biomarkers associated with organ damage, providing key insights into the underlying mechanisms of the disease. This stratification could be instrumental in tailoring patient management, predicting disease progression, and guiding targeted therapeutic strategies.

Variable	Cluster 1 (n = 221)	Cluster 2 (n = 181)	p-value
Age (years), mean (SD)¶	57.2 (13.2)	59.2 (12.4)	0.12

Disease duration (years), mean (SD)	10.2 (9.6)	11,6 (7.5)	0.10
Sex (female), n (%)	188 (85.1)	151 (83.4)	0.75
ILD, n (%)	32 (14.5)	108 (59.7)	< 0.01
Sclerodactyly, n (%)	118 (53.4)	170 (93.9)	< 0.01
PAH, n (%)	20 (9)	56 (30.9)	< 0.01
Raynaud phenomenon, n (%)	209 (94.6)	180 (99.4)	0.01
Ever smoking, n (%)	32 (14.5)	23 (1.7)	0.71
Hypertension, n (%)	72 (32.6)	57 (31.5)	0.90
Centromere positivity, n (%)	96 (43.4)	53 (29.3)	< 0.01
Scl-70 positivity, n (%)	44 (19.9)	70 (38.7)	< 0.01
Arthritis, n (%)	46 (20.8)	72 (39.8)	< 0.01
Calcinosis, n (%)	15 (6.8)	78 (43.1)	< 0.01
Digital ulcers, n (%)	11 (5)	28 (15.5)	< 0.01
Telangiectasias, n (%)	88 (39.8)	151 (83.4)	< 0.01
GERD, n (%)	117 (52.9)	150 (82.9)	< 0.01
Dyslipidemia, n (%)	57 (25.8)	41 (22.6)	0.54
Pitting scars, n (%)	65 (29.4)	133 (73.5)	< 0.01
Current bDMARD, n (%)	2 (0.9)	8 (4.4)	0.04
Current immunosuppressants, n (%)	32 (14.5)	74 (40.9)	< 0.01
Obesidad, n (%)	23 (10.4)	16 (8.8)	0.72
Esophageal dysmotility, n (%)	77 (63.6)	123 (68)	< 0.01
Statins use, n (%)	42 (19)	42 (23.2)	0.36
Puffy fingers, n (%)	116 (52.5)	109 (60.2)	0.14
Muscle weakness, n (%)	21 (9.5)	51 (28.2)	< 0.01

Table 1. Clinical and Serological Characteristics of Patients by Cluster, stand for variables used in the clustering algorithm.

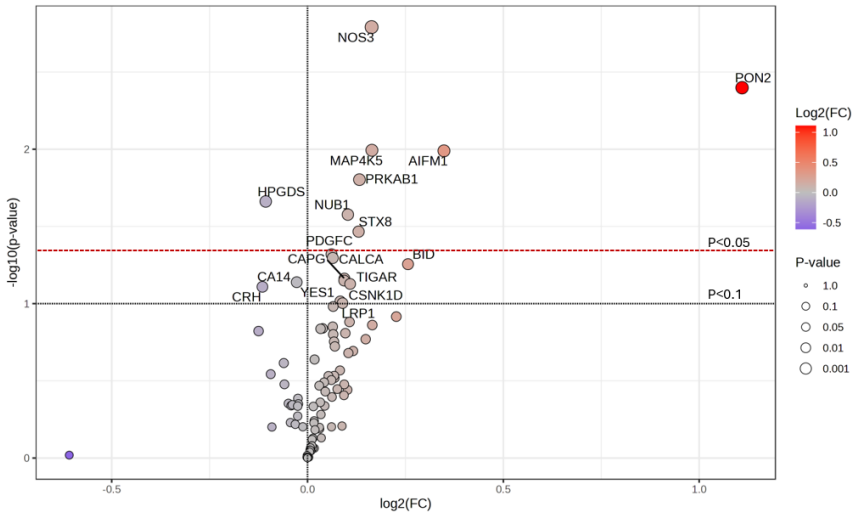

Figure 1. Volcano plot of differentially expressed protein levels between the identified clusters. Color indicates the magnitude of change, and point size reflects the level of statistical significance.

PSI.t. Innovation in the study of alopecia areata: tape strips as a noninvasive tool for transcriptional characterization.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Alopecia Areata, Tape Strips, Biomarkers of Severity.

Abstract:

Background and Objectives: Tape strips are a minimally invasive technique that allows for the simple and reproducible collection of skin samples. While they have proven useful in skin diseases such as psoriasis, atopic dermatitis, and ichthyosis, their applicability in inflammatory disorders of the hair follicle, such as alopecia areata (AA), has not been explored. This pilot study evaluated the feasibility of using tape strips to capture the molecular signatures of AA and characterize its pathophysiology. **Methods:** Sixteen participants were included and distributed into four groups: healthy controls (n=4), mild AA (n=3), moderate AA (n=4), and severe AA (n=5). A total of 20 tape strips were collected per subject for RNA extraction and RNA-seq analysis using IonTorrent technology. Differentially expressed genes (DEGs) (fold change > ±2; adjusted p-value < 0.05) were analyzed using GSVA and GSEA to explore molecular processes. These were also correlated with SALT scores and analyzed by PCA according to disease severity. **Results:** A total of 1,203 DEGs were identified in AA patients compared to controls (fold change > ±2; adjusted p-value < 0.05). Tape strips demonstrated their ability to detect changes in known AA markers, such as IL15, IL15RA, CXCL10, PRF1, and TBX21/T-bet (overexpressed), as well as S100A6, S100A8, KRT34, and KRT85 (underexpressed). Activation of immune pathways including Th1 (CCR5, IL12A), Th2 (IL4, IL5, IL13), and Th17 (IL17A, IL17RA, IL26) was observed, along with inflammatory chemokines (CCL5, CCL18, CXCR3) and tissue damage markers (S100A6, S100G). Functional analysis highlighted cellular damage processes such as exhaustion, senescence, and apoptosis. PCA revealed a clear separation between severe/moderate AA and controls/mild cases, indicating lower inflammatory involvement in the latter. Additionally, genes such as IL5, FGF10, CXCR3, and CCL5 were significantly correlated with SALT scores, positioning them as potential biomarkers of disease severity. **Conclusions:** Tape strips are established as an effective tool for identifying inflammatory and structural alterations in lesional areas of AA, demonstrating their potential for characterizing disease pathophysiology and discovering non-invasive severity biomarkers. This innovative approach opens new avenues for research into inflammatory diseases of the hair follicle.

PSI.u. Effectiveness of Nintendo Wii Fit© for Physical Therapy in Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: multiple sclerosis; exergaming; exercise; physical therapy; neurological rehabilitation; meta-analysis.

Abstract:

Multiple sclerosis (MS) is a chronic, inflammatory, and autoimmune disease that mainly affects the central nervous system and currently has no cure. Exergaming is considered a nonimmersive approach to improving functional and motor skills in the treatment of MS. The aim of this systematic review was to evaluate the effectiveness of the Nintendo Wii Fit© (NWF) on physical outcomes compared with control regimes in patients with MS. The search was performed in seven databases including articles published up to June 2024. The PICOS model was used to establish the study eligibility criteria. The Cochrane Collaboration tool and the PEDro scale were used to assess the risk of bias and evaluate the methodological quality of the studies, respectively. A meta-analysis using the standardized mean difference (SMD) and confidence interval (95% CI) was developed using the Review Manager 5.4 software. Seven articles were included in the systematic review. The statistical analysis showed favorable overall results for the NWF on functional mobility (SMD = 0.25; 95% CI = 0.09, 0.41) and fatigue (SMD = 0.41; 95% CI = 0.00, 0.82). In conclusion, this systematic review suggests that the NWF has shown favorable effects compared to control regimes on functional mobility and fatigue outcomes in patients with MS.

PSI.v. Impacts of COVID-19 and Antimicrobial Stewardship on Nosocomial and Nonnosocomial KPC-producing Klebsiella pneumoniae Infections: A Ten-Year Longitudinal Cohort Study with Interrupted Time Series Analysis.

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Scientific Program: Infectious and Immunological diseases.
Keywords: KPC-producing *Klebsiella pneumoniae* infections, Antimicrobial stewardship program (ASP), COVID-19 infection control, Incidence trends, Genomic epidemiology, Multidrug-resistant organisms (MDRO).

Abstract:

Infections caused by carbapenemase-producing *Klebsiella pneumoniae* (KPC-KP) represent a major public health threat. In this prospective cohort study, we evaluated ten-year trends (2012–2022), clinical characteristics and molecular epidemiology of both nosocomial and non-nosocomial KPC-KP infections at a tertiary referral hospital, and assessed the impact of an antimicrobial stewardship program in 2014 (ASP) and COVID-19 infection-prevention measures. We analysed incidence density using interrupted time-series and ARIMA models, finding a significant post-ASP decline with a four-month lag between nosocomial and non-nosocomial infections, remaining stable rates during the COVID-19 period. Cross-correlation analyses examined temporal links between interventions and infection rates. Among 467 patients, 33.2% had non-nosocomial infections (0.53/1,000 admissions/month) and 66.8% nosocomial infections (0.30/1,000; p=0.39). Urinary tract infections comprised 52.9% of nonnosocomial and 25.6% of nosocomial cases; bacteremia occurred in 23.0% overall (14.2% non-nosocomial, 28.2% nosocomial). Whole-genome sequencing revealed sequence type ST512/KPC-3 as the dominant clone, persisting over time and disseminating from hospital to community. Multivariable regression showed similar 30-day mortality (33.0%) and comparable clinical and microbiological responses across both groups. Our findings demonstrate that sustained ASP and rigorous COVID-19 controls help maintain low KPC-KP rates, while genomic data underscore the hospital-to-community spread of ST512/KPC-3. The substantial burden and outcomes of non-nosocomial infections highlight the need for continued, targeted public-health interventions.

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PSI.w. Constructing enzymatic nanoparticles for in situ drug synthesis.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Nanomedicine, Synthetic biology, cancer treatment.

Abstract:

Specifically targeting cancer cells for therapies is inherently difficult as they originate from the body's own cells. Here we aim to exploit the tumor microenvironment with its hallmarks of high lactate and ATP concentrations and utilize them as substrates for *in situ* drug synthesis offering a unique safety mechanism, as drug synthesis is specifically linked to the environment of the tumor. Bridging synthetic biology and metabolic engineering with nanomedicine we present the design rational of novel nanoparticles, encapsulating a synthetic biosynthesis pathway utilizing the high lactate and ATP concentrations in the tumor microenvironment to produce the anti-cancer molecule hydrogen peroxide. We have produced prototype nanoparticles and tested their immunogenicity as well as cytotoxicity. Currently we are testing nanoparticle stability under different physiological conditions and load them with cargo enzymes for drug synthesis. The novel concept of encapsulating a metabolic pathway into a nanoparticle might find broad application to treat diseases in which local metabolite differences can be exploited to drive therapeutic molecule production or to correct enzymatic defects.

PSI.x. Dietary modulation of advanced glycation end products metabolism and its influence on peripheral artery disease in coronary heart disease patients.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: arteriopathy, AGEs, Mediterranean diet.

Abstract:

Peripheral artery disease (PAD) increases cardiovascular risk and mortality in patients with coronary heart disease (CHD), especially when both conditions coexist. Advanced glycation end products (AGEs), known for their proinflammatory and cytotoxic roles, are elevated in chronic conditions such as type 2 diabetes and cardiovascular disease. Most AGEs derive from dietary sources, and recent evidence suggests that the Mediterranean diet is low in AGEs. This study, conducted within the CORDIOPREV clinical trial (NCT00924937), evaluated whether a Mediterranean diet or a low-fat diet more effectively reduces the incidence or progression of PAD in CHD patients by modulating AGE metabolism. A total of 1002 patients were followed for five years, with diet assignments randomized. PAD presence was assessed via the ankle-brachial index. Parameters measured included circulating AGEs (methylglyoxal), receptor expression (RAGE, AGER1), and enzymatic degradation activity (GloX1). Results showed that non-incident PAD patients had improved lipid profiles and AGE metabolism after dietary intervention. Specifically, the Mediterranean diet enhanced GloX1 and AGER1 expression while limiting methylglyoxal levels, suggesting a protective role through reduced AGE accumulation and inflammatory receptor signaling. These findings highlight the Mediterranean diet as a promising strategy for PAD risk reduction in CHD patients through modulation of AGE-related pathways.

PSI.y. Development of a 3D Human Hepatic Spheroid Model to Investigate Obesity-Associated Liver Disease.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: 3D culture, liver disease, obesity, steatosis, fibrosis.

Abstract:

Obesity represents a major health problem and significantly increases the risk of metabolic comorbidities, most notably metabolic dysfunction-associated steatotic liver disease (MASLD). The pathophysiology of MASLD is significantly influenced by white adipose tissue (WAT) dysfunction; however, it is still unclear how exactly obese WAT-derived signals contribute to hepatic alterations. This study focuses on the development and optimization of a physiologically relevant 3D human hepatic spheroid model to investigate the consequences of obesity, with a particular emphasis on hepatic steatosis and fibrosis. The model is based on the co-culture of HepG2 hepatocytes with hepatic stellate LX-2 cells, aiming to recapitulate key parenchymal and non-parenchymal interactions within the liver microenvironment. Spheroid formation was optimized by testing different seeding densities, with 2000 cells per spheroid proving the best model based on viability and spheroid morphology assessments using optical and confocal microscopy. To investigate how obese adipose-derived factors influence hepatic function, these hepatic spheroids will be stimulated with steatotic agents such as oleic and palmitic acid, as well as conditioned media derived from 3D human adipocyte spheroids (generated from normoglycemic and insulin-resistant individuals with obesity). Functional outcomes were assessed using RT-qPCR and immunoblotting to track gene and protein expression related to lipid and glucose metabolism, inflammation, oxidative stress, and extracellular matrix dynamics. In addition, histological (H&E, Picrosirius Red) and ultrastructural (electron microscopy) analyses were performed to evaluate tissue architecture, fibrosis, and cellular integrity. Our results support that this optimized 3D hepatic model is a strong platform for dissecting the molecular mechanisms underlying obesity-associated liver disease and shows promise as a preclinical tool for metabolic drug screening.

PSI.z. Tumour-intrinsic GSK-3β drives a fibrotic immunosuppressive microenvironment in colorectal cancer and emerges as a target to overcome immunotherapy resistance.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: GSK-3β; tumor microenvironment; TGFβ; CAFs.

Abstract:

Colorectal cancer (CRC) is a heterogeneous disease with limited response to conventional therapies. While glycogen synthase kinase-3 (GSK-3) is key in cancer development, its impact on tumor microenvironment (TME) remains unclear. Therefore, this study aimed to investigate the role of GSK-3 isoforms in TME regulation. GSK-3 α and β expression was evaluated in 115 CRC clinical samples and correlated with clinicopathological factors. PD-L1 expression was evaluated by conventional IHC and TME cell populations were characterized in samples from 12 patients using a Multiplex IHC assay. RNA-seq data from 32 CRC clinical samples were analyzed using Gene Set Enrichment Analysis (GSEA). GSK-3 isoforms were silenced in HCT116 cells and epithelial-mesenchymal transition (EMT) markers, tumorsphere formation, and inflammatory secretion profiles were assessed. GSK-3-silenced tumor cells were co-cultured with fibroblasts, with or without TGF-β neutralization, and α-SMA expression was evaluated. Finally, humanized PDX models derived from GSK-3βHIGH and GSK-3βLOW CRC tumors were treated with GSK-3 inhibitor, anti-PD-1, or both. GSK-3βHIGH tumours correlated with poor survival, aggressive clinicopathological features, and an immunosuppressive TME enriched in CAFs, M2 macrophages, and high PD-L1 expression. GSEA analysis revealed an enrichment of several signaling pathways, including TGFβ signaling, in GSK-3βHIGH tumors. Notably, GSK-3β silencing in HCT116 cells reversed their EMT phenotype, impaired their tumorsphere formation capacity and decreased their secretion of pro-inflammatory and pro-fibrotic mediators, including TGFβ and LIF. Accordingly, fibroblast activation decreased in co-cultures with GSK-3β-silenced tumor cells or upon TGFβ neutralization in control co-cultures, implicating TGFβ signaling in this effect. In vivo, GSK-3βHIGH tumors responded synergistically to GSK-3 inhibition combined with anti-PD-1, while GSK-3βLOW tumors only responded to anti-PD-1 treatment, with responses correlating with T-cell infiltration. In conclusion, our findings identify GSK-3β as a poor-prognosis biomarker and a key driver of immunosuppressive remodeling in CRC, underscoring its potential as therapeutic target in GSK-3βHIGH tumors. Funding: PI23-00489.

PSI.aa. Regenerative medicine applications of sustainable hydrogel from cellulose nanofibers.

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Scientific Program: Active aging and frailty.
Keywords: Regenerative medicine and waste-derived cellulose hydrogel.

Abstract:

The growing need for sustainable strategies has driven the development of advanced materials from agricultural waste, in line with the principles of the circular economy. This work presents the obtaining of cellulose nanofibres (CNF) by means of biorefinery processes applied to agro-food by-products, and their subsequent use in the formulation of functional hydrogels, combined with alginate, for applications in regenerative biomedicine. The use of CNF derived from waste plant biomass not only allows its revalorisation, but also gives the hydrogels biomedical properties superior to those of many synthetic hydrogels. These include biocompatibility, biodegradability and adjustable mechanical properties. Some of these properties are biocompatibility, biodegradability and tunable mechanical properties. The incorporation of alginate improves gelation and structural stability. This hybrid formulation has been shown to effectively simulate the native extracellular matrix environment, allowing for more realistic results when simulating in vivo conditions. Cell cultures were performed in the CNF-alginate hydrogel to assess the distribution and viability of umbilical cord-derived mesenchymal stem cells by staining with calcein and resazurin assays, respectively. The results confirmed a homogeneous distribution of the cells throughout the matrix, as well as a high viability maintained during several days of culture; confirming the suitability of the hidrogel as a 3D biomimetic support. We are currently evaluating the capacity of this hydrogel for the production of exosomes, with the aim of improving their properties compared to those obtained by other techniques and thus enhancing their functionality in advanced regenerative therapies. Furthermore, its versatility allows it to be adapted to other therapeutic applications, such as the release of drugs, consolidating it as a polyvalent and environmentally friendly platform.

PSI.bb. Workers' satisfaction with health surveillance: Development and validation of a new scale.

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Scientific Program: Active aging and frailty.
Keywords: Occupational health; Occupational health nursing; Occupational medicine; Patient satisfaction; Surveys and questionnaires.

Abstract:

Background: Health surveillance in the workplace involves conducting occupational health examinations of workers based on the risks to which they are exposed. The objective is to protect their health and proactively identify potential harm resulting from occupational activities. However, there is no assessment tool which focuses on workers' satisfaction with this activity. Therefore, having a validated instrument for measuring workers' satisfaction with health surveillance would enable the optimization of the care provided in occupational health services. **Objective:** To develop and validate a questionnaire to assess the satisfaction of the working population with health surveillance. **Design:** A cross-sectional psychometric validation study. **Setting:** Data were collected from an occupational health service in Spain. **Participants:** A total of 600 participants were included. **Methods:** The research was carried out in four phases: i) Design: review and selection of the questionnaire items. ii) Content validation: participation of a group of 12 experts, using Delphi methodology. iii) Pilot study: running a pilot study (n = 30 workers). iv). **Construct validation:** with a sample of 600 workers, performing an exploratory factor analysis (EFA) and confirmatory factor analysis (CFA), both on sample of 300 workers. **Results:** The final version of the scale comprised 17 items distributed in 4 factors, explaining 63.4% of the total variance. Content validity (Aiken's V coefficient = 0.904, Lawshe's content validity index = 0.868) and construct validity (Cronbach's alpha = 0.870, McDonald's omega = 0.872, intraclass correlation coefficient = 0.861) were demonstrated. The factors obtained in the EFA with half of the sample were confirmed in the other half, with the CFA indices suggesting an acceptable model fit. **Conclusions:** The psychometric properties showed a valid, reliable instrument to assess workers' satisfaction with health surveillance. It is therefore a useful tool for occupational health professionals and can improve the care provided to workers.

PSI.cc. Multicenter Experimental Study to Evaluate the Efficacy of Targeted Exercise in Combination with Cytisinicline in Smoking Cessation (MEDSEC-CTA).

Authors: Sofia Ruiz-Salcedo[1,2], Antonio Ranchal-Sanchez[1,3], Javier Ruiz-Moruno[1,2], Jaime Monserrat-Villatoro[1,4], Jose Manuel Jurado-Castro[1,5,6] , Esperanza Romero-Rodriguez[1,2] .
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Scientific Program: Active aging and frailty.
Keywords: Tobacco Use Cessation; Cytisine; Exercise; Multicenter Studies as Topic.

Abstract:

Background: Tobacco use is one of the leading causes of preventable death in our country, contributing to a multitude of health problems. Despite various interventions to assist in smoking cessation, success rates remain modest. Cytisinicline has shown promising results in the treatment of nicotine addiction. Additionally, physical exercise has been recognized for its potential to reduce tobacco withdrawal symptoms, as well as improve mood and weight barrier. **Objectives:** The primary objective of this study is to evaluate the efficacy of the adjuvant effect of targeted physical exercise in smoking cessation in patients treated with cytisinicline. The secondary objectives are to evaluate the efficacy of its adjuvant effect in reducing tobacco use and reducing mean blood pressure (BP), mean heart rate (HR), and mean body mass index (BMI). **Methods:** We propose a multicenter, randomized, controlled experimental study to be carried out in primary care centers. Patients aged 18–65 years who smoke ≥ 10 cigarettes per day, with high dependence on nicotine, and motivation to quit smoking will be included. Participants will be randomized into two groups: one receiving very brief advice (VBA), targeted physical exercise and cytisinicline (experimental) and the other receiving VBA, cytisinicline and general physical exercise instructions (control). The intervention's efficacy will be assessed through various outcomes, including daily cigarette consumption, smoking abstinence, changes in BP, HR, body weight, and BMI. **Expected results and Conclusions:** The findings of this study could significantly contribute to public health strategies, offering a potentially more effective solution for smoking cessation.

SESSION III.
NUTRITION.

IIIa. Alterations of the hypothalamic Kiss1 neuronal activity in the arcuate nucleus in response to different diets.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Intermittent fasting, caloric restriction, fiber photometry, kisspeptin neuron.

Abstract:

Kiss1 neurons in the hypothalamus play a major role in the reproductive axis by providing indispensable excitatory transmission to gonadotropin-releasing hormone (GnRH) neurons for the synchronized release of gonadotropins (LH and FSH), thereby controlling puberty and fertility. It is well known that metabolic conditions influence this physiological process in mammals. Currently, different nutritional interventions, including intermittent fasting (IF) and caloric restriction (CR), have been studied in rodents and humans to determine their benefits and downsides in terms of health. Nevertheless, little is known about the effects of these conditions on the activity of kisspeptin neurons, as key hub for reproductive control. The objective of this study was to monitor *in vivo* the activity of hypothalamic Kiss1 neurons in the arcuate nucleus (ARC) under different metabolic conditions in adult male mice (3 to 8 months) for 8 to 9 weeks. Four experimental groups were included: control (fed ad libitum), 20% caloric restriction (CR), intermittent fasting and 50% cellulose diet (aka, caloric dilution; equivalent to a 20% CR). In our approach, we used fiber photometry to monitor the activity in our target neuronal population *in vivo* by tracing fluorescence changes from a genetically encoded calcium indicator, named GCaMP. Moreover, key metabolic and reproductive parameters, including LH, food intake, body weight and metabolic hormones, were monitored. Our data unveiled differences in the activity of Kiss1 neurons, denoted by modifications in the amplitude and number of calcium peaks, in response to the different diets. Interestingly, in some scenarios, adaptive mechanisms appear to adjust Kiss1 neuron activity based on anticipated nutrient availability, rather than actual body nutrient and energy levels. In conclusion, our data opens a new dimension to be considered in order to measure the impact of modern weight loss strategies, based on changes in feeding patterns, on overall health, including a reproductive perspective.

IIIb. Preventing Sepsis in Preterm Infants with Bovine Lactoferrin: A Randomized Trial Exploring Immune and Antioxidant Effects.

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Scientific Program: Nutrition, Endocrine and Metabolic Diseases.
Keywords: lactoferrin; newborn infants; prematurity; sepsis; antioxidants; immunity.

Abstract:

Background & Aim: Very-low-birth-weight (VLBW, <1500 grams and/or gestational age (GA) <32 weeks) infants have immature immune and antioxidant systems, predisposing them to late-onset sepsis (LOS; ≥72h post-birth) and related morbidities. Bovine lactoferrin (bLf) combines antimicrobial, immunomodulatory, antioxidant, iron-handling, and bifidogenic properties. We assessed its impact on LOS, mortality, morbidities, plasma cytokines, total antioxidant capacity (TAC), and hemoglobin (Hb) levels. **Methods:** In a randomized, double-blind, placebo-controlled trial, 103 VLBW infants received enteral bLf (150 mg/kg/day; n=50) or placebo (n=53) within 72h post-birth during four weeks or until discharge. Culture-confirmed LOS, mortality, and morbidities (bronchopulmonary dysplasia; necrotizing enterocolitis; patent ductus arteriosus; retinopathy of prematurity; brain injury) were analyzed by unadjusted RR (χ^2/Fisher-test), and if ≥25 events, adjusted RR (modified Poisson regression) by GA, human milk, and ventilatory support. Pre/post-intervention changes in various cytokines, TAC and Hb levels, were analyzed, including *timexTreatment* (t×T) effects, and, when relevant, interactions with LOS or transfusion. Two-tailed significance $p<0.05$. **Results:** BLf reduced LOS by 46% (aRR:0.54 [95%CI:0.31–0.93]; NNT=6). There were no differences in other morbidities or mortality. Overall, bLf preserved MCP-1, whereas placebo declined (txT p=0.022). Among LOS infants receiving bLf, IL-6 remained stable, while MCP-1 levels increased, versus cytokine declining in all other groups (txT×LOS p=0.007 for IL-6 and p=0.052 for MCP-1). TAC showed a non-significant txT interaction (p=0.108); In Post-hoc, placebo declined (p=0.002), whereas bLf remained unchanged (p=0.400). Hb's txTxTransfusion interaction was not significant (p=0.913); non-transfused bLf infants had higher post-intervention Hb levels than non-transfused controls (11.1±1.9 vs 10.2±1.3 g/dL; $p<0.028$). **Conclusions:** Early bLf supplementation for four weeks safely reduces LOS, accompanied by MCP-1-centred immunomodulation, preserved TAC, and a favorable Hb profile in non-transfused infants.

IIIc. Hypothalamic SIRT1-mediated regulation of the hormonal trigger of ovulation and its repression in energy deficit.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: SIRT1, Kisspeptins, Kiss1, GnRH, Ovulation, Female Reproduction.

Abstract:

Female reproduction is highly sensitive to body energy stores; persistent energy deficit, as seen in anorexia or strenuous exercise, is known to suppress ovulation via ill-defined mechanisms. We report herein that hypothalamic SIRT1, a key component of the epigenetic machinery that links nutritional status and puberty onset via modulation of *Kiss1*, plays a critical role in the control of the preovulatory surge of gonadotropins, i.e., the hormonal trigger of ovulation, and its repression by conditions of energy deficit. Kiss1 neurons in the preoptic area, with proven roles in the control of ovulation, express *Sirt1* mRNA. Reciprocal changes in hypothalamic SIRT1 content and *Kiss1* expression were observed during the pre-ovulatory phase in adult female rats. Central activation of SIRT1 reduced *Kiss1* expression in the rostral hypothalamus, and attenuated the preovulatory surge, while blockade of central SIRT1 augmented it. Conditions of energy deficit enhanced hypothalamic SIRT1 activity and caused suppression of the pre-ovulatory surge and ovulation, which could be rescued by central SIRT1 inhibition. In turn, virogenetic induction of SIRT1 in rostral hypothalamic Kiss1 neurons in adult female mice disrupted ovarian cyclicity and suppressed reproductive indices, despite preserved body weight. Our data document the prominent function of hypothalamic SIRT1 as a key modulator of Kiss1 neurons and the hormonal surge driving ovulation in adulthood, with a major role in its inhibition during conditions of energy insufficiency.

IIId. 3D spheroid models as a novel strategies to analyze obesity-associated adipose tissue dysfunction and fibrosis.

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Scientific Program: Endocrine and metabolic diseases.
Keywords: Adipose Tissue, Obesity, fibrosis, extracellular matrix, spheroids.

Abstract:

Obesity is a highly prevalent, multifaceted condition characterized by excessive and/or abnormal accumulation of adipose tissue. This pathological state disrupts the balance between synthesis and degradation of the extracellular matrix (ECM), contributing to tissue fibrosis. In this study, three-dimensional (3D) spheroid culture models were developed using either the 3T3-L1 adipocyte cell line or primary preadipocytes isolated from subcutaneous (SAT) and visceral (VAT) adipose tissues of individuals with obesity, aiming to better replicate the obese microenvironment in vitro. 3T3-L1 cells were seeded into low-attachment plates, differentiated over 10 days, and exposed to obesogenic conditions, including TNFα, palmitate, and high glucose/high insulin levels to mimic obesogenic conditions. In parallel, stromal vascular fraction (SVF) cells isolated from SAT and VAT of bariatric surgery patients were cultured, seeded into low-attachment plates to form spheroids and treated with a differentiation cocktail. Samples were collected at day 0 and day 14 for molecular and imaging analysis. The spheroids exhibited sustained growth, viability and capacity to differentiate throughout the experimental period. Notably, human derived adipocytes, which showed limited differentiation capacity in traditional 2D cultures, successfully differentiated in 3D spheroids. Optical, confocal and electron transmission microscopy, confirmed that the spheroids were composed of tightly packed cells forming cohesive 3D structures and lipid droplet accumulation increased progressively. In addition, gene expression and proteomics analyses showed significant changes in adipogenic, senescence and ECM-related genes and proteins between early and late differentiation stages. Overall, 3D adipocyte spheroid models provide a more physiologically relevant in vitro system than traditional 2D cultures. These models offer a valuable platform for studying obesity-related molecular mechanisms, particularly ECM remodeling and fibrosis, and have strong potential to enhance translational research in obesity and metabolic disorders.

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IIIe. Analysis of the role of hepatic kisspeptin system in energy and metabolic homeostasis: Influence of sex and feeding status.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Kiss1, liver, fasting, iLiKKO.

Abstract:

The ability to ensure correct energy balance is a fundamental requirement for organism survival. Therefore, there are physiological adaptations that regulate body energy balance and metabolic state. Kiss1 neurons not only play a key role in reproduction, one of the most energy-demanding processes, but also are sensitive to changes in metabolic state. Furthermore, *Kiss1* and its receptor, *Gpr54*, are also expressed in key peripheral tissues involved in metabolic control, such as the liver. However, the actual physiological relevance of hepatic kisspeptins remains largely unknown. Here, we report that the kisspeptin system (*Kiss1* and *Gpr4*) is expressed in the mouse liver in a sexually dimorphic manner, with females showing higher levels. The expression of this system is also influenced by nutritional state, with a substantial increase of liver *Kiss1* mRNA levels after 12-hours of fasting in males, but at least 15-h in females. This response was completely reversed after 24-hour re-feeding, even after 1 month of intermittent fasting days. Additionally, liver *Kiss1* and *Gpr54* expression was affected by metabolic hormones, being up-regulated by glucagon. To explore the physiological function of hepatic kisspeptin, we have generated an inducible, liver-specific Kiss1 knockdown (iLiKKO) mouse, using viral-driven hepatic Cre-expression in a Kiss1$^{loxP/loxP}$ line. Initial experiments verified selective downregulation of liver *Kiss1* expression, with no reproductive effects. While no major metabolic changes have been observed in iLiKKO mice under ad libitum conditions, studies addressing the impact of iLiKKO in conditions of fasting, as well as high-fat-diet- or androgenic-induced obesity, are currently in progress to fully clarify the metabolic role of liver Kiss1. Our study defines for the first time the sex- and nutritional-dependent pattern of expression of Kiss1/Gpr54 in the liver, and develops novel tools for addressing the physiological relevance of hepatic kisspeptins in the peripheral control of metabolism.

IIIf. Nimacimab, a Peripherally Restricted CB1R Inverse Agonist, Alleviates Diet-Induced Obesity and Improves Metabolic Function in Humanized CB1R Mice.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Obesity, MASLD, CB_1R inverse agonism, humanized mice.

Abstract:

The endocannabinoid system (ECS), particularly the cannabinoid receptor type 1 (CB_1R), plays a key role in regulating appetite, fat storage, glucose metabolism, and inflammation. CB_1R is expressed in both the central nervous system and peripheral tissues such as the liver, adipose tissue, and skeletal muscle. Rimonabant, a CB_1R inverse agonist, showed clinical efficacy in obesity management but was withdrawn due to severe psychiatric side effects. This has spurred growing interest in peripherally restricted CB_1R inverse agonists, which aim to retain metabolic benefits while avoiding central nervous system-related risks. One such candidate is Nimacimab, a humanized monoclonal antibody that selectively targets peripheral CB_1R without crossing the blood–brain barrier. It is currently being evaluated in a Phase 2 clinical trial for obesity (ClinicalTrials.gov: NCT06577090). In this study, we confirmed that Nimacimab effectively antagonizes CB_1R signaling measured by cAMP induction and β-arrestin recruitment in cell lines overexpressing the receptor. Its therapeutic potential was then assessed in a diet-induced obesity (DIO) model using CB_1R humanized (knock-in) mice, treated either alone or in combination with tirzepatide, a dual GIP/GLP-1 receptor agonist. Nimacimab significantly reduced body weight and fat mass, effects that were further enhanced by tirzepatide co-treatment. It also increased thermogenesis, improved glucose and lipid metabolism, and reduced adipocyte size, adipogenesis, and macrophage infiltration in adipose tissue. In the liver, Nimacimab effectively prevented steatosis, inflammation, and fibrosis. Peripheral biomarkers analyzed by ELISA and multiplex assays, along with liver proteomic profiling via LC-MS, confirmed its anti-obesity, anti-inflammatory, and hepatoprotective effects. Finally, by laser Doppler imaging we observed that obese mice exhibited a marked reduction in peripheral blood flow, a defect that was significantly improved following Nimacimab treatment. Collectively, these findings underscore the therapeutic potential of Nimacimab in the treatment of obesity and related metabolic and vascular complications.

SESSION IV.

INFECTIOUS AND IMMUNOLOGICAL DISEASES. ORGAN TRANSPLANTATION

IVa. Mortality of Bloodstream Infections Caused by ESBL-Producing Enterobacterales in Solid Organ Transplant Recipients Versus Non-Transplant Patients: A Multicentre, International, Retrospective Matched Cohort Study (INCREMENT vs INCREMENT-SOT).

Authors: Elisa Ruiz-Arabi[1,2,3], Belén Gutiérrez-Gutiérrez[3,4], Juan Antonio Marín-Sanz[2], Miriam Marín-Sanz[2], Juan José Castón[1,2,3], Angela Cano[1,2,3], Isabel Machuca[1,2,3], Víctor Gálvez-Soto[2], Elisa Vidal[1,2,3], Elena Pérez-Nadales[2,3,5,*,¥], Julián Torre-Cisneros[1,2,3,¥].

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Scientific Program: Infectious and Immunological Diseases. Organ transplantation.

Keywords: Bloodstream infection; ESBL-producing Enterobacterales; Solid organ transplant; mortality; INCREMENT-SOT.

Abstract:

Background/objective: Despite advances in solid organ transplantation, infectious complications remain a significant challenge. Recent data suggest that Solid Organ Transplant (SOT) recipients may experience lower mortality following severe infections. We evaluated 30-day mortality in patients with ESBL-producing Enterobacterales bloodstream infections (BSI) by comparing SOT and non-SOT recipients from two large multinational retrospective cohorts. **Methods:** In this matched-cohort study, SOT recipients with ESBL-E BSI from the INCREMENT-SOT cohort (38 hospitals in 16 countries, 2004–2016, NCT02852902) were matched to non-SOT patients from the INCREMENT cohort (37 European hospitals in 15 countries, 2004–2013, NCT02709408). Multivariable and stratified Cox regression analyses were performed. **Results:** A total of 512 matched patients (256 SOT and 256 non-SOT) were included. The 30-day mortality was 10.6% (95% CI, 7.2–15.1%) in SOT recipients versus 20.3% (95% CI, 15.7–25.9%) in non-SOT patients, yielding an absolute difference of –9.7% (95% CI, –16.4 to –3.2%) and a crude hazard ratio (HR) of 0.42 (95% CI, 0.26–0.70; $p<0.001$). The population attributable fraction for 30-day mortality for SOT versus non-SOT was -2.5% under a 5% SOT prevalence scenario. In the high-risk subcohort (INCREMENT-ESBL ≥11), SOT was independently associated with lower mortality (HR 0.54, 95% CI, 0.31–0.95; $p=0.031$). **Conclusion:** ESBL-E BSI is associated with significant mortality. Our findings suggest that SOT may confer a survival benefit, especially among high-risk patients, warranting further investigation into the underlying mechanisms.

IVb. Decoding tissue-specific virulence mechanisms of Salmonella Typhimurium in porcine hosts.

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Scientific Program: Infectious and Immunological diseases.
Keywords: *Salmonella* Typhimurium, TraDIS, porcine infection, neutrophile, virulence factor.

Abstract:

Non-typhoid salmonellosis is one of the main contributors to foodborne gastrointestinal diseases, with pigs being a major reservoir of Salmonella Typhimurium. The increasing difficulty in treating Salmonella infections in pigs underscores the urgent need to understand the mechanisms of virulence and persistence in hosts. To achieve this, we employed Transposon Directed Insertion Sequencing (TraDIS) to identify essential genes for a highly virulent Salmonella Typhimurium DT104 isolate during infection in porcine neutrophils, ileum, and lymph nodes. A high-density mutant library (~1.2 million mutants) of Salmonella was generated using the pBAM1 plasmid. After validation of the input library, porcine neutrophiles were infected (MOI 1:25) and five weaned pigs (4 weeks old) were challenged with 109 CFUs. Output libraries from neutrophils, ileum, and lymph nodes were sequenced on an Illumina NovaSeq 6000, and analyzed using the Bio-Tradis pipeline. A total of 2082 genes were identified as essential for Salmonella pathogenesis, with 44,5% unique to lymph nodes, revealing tissue-specific adaptations. Notably, 169 genes were universally essential (essential across all three conditions), including 16 type III secretion system genes, that comprise structural components such as *prgI*, *prgJ*, *prgK*, *invC* or invI and secretion regulators and effectors like *invE*, *invF* or *avrA*. Additionally, these universally essential genes included 9 lipopolysaccharide biosynthesis genes, and 10 stress response genes. Moreover, 39 universally essential genes have a predicted function but are not characterized, opening up the opportunity on the characterization of new genes involved in *Salmonella* infection. Functional enrichment highlighted metabolic gene dominance in the ileum, reflecting nutrient acquisition, while neutrophils and lymph nodes showed enrichment in immune evasion and regulatory genes, indicating survival strategies under host pressure. These findings reveal Salmonella's genetic adaptations across host environments, identifying tissue-specific virulence mechanisms, and offering novel targets for interventions against non-typhoidal salmonellosis.

IVc. Gut microbiome diversity predicts mortality in carbapenemase-producing Klebsiella pneumoniae colonized patients.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Gut microbiome diversity, Carbapenemase-producing Klebsiella pneumoniae; Intestinal colonization; Shotgun metagenomics; Prognostic biomarkers; 90-day mortality prediction.

Abstract:

Carbapenemase-producing Klebsiella pneumoniae (KPC-KP) colonization disrupts gut microbiota, increasing infection risk and mortality. In a prospective cohort of 81 patients with first-time KPC-KP rectal colonization (ST512/KPC-3) at Reina Sofia University Hospital (Jan 2018‑Mar 2019), we performed shotgun metagenomics on rectal swabs to calculate alpha-diversity (Shannon index) and beta-diversity (Bray‑Curtis, weighted/unweighted UniFrac; PERMANOVA) and identify differentially abundant taxa (ANCOM-BC2). Logistic regression adjusted for Giannella Risk Score (GRS), which predicts the risk of subsequent infection in KPC-KP-colonized patients, Charlson index, and sex tested microbiome predictors of infection, and Cox regression assessed predictors of 90-day mortality. Of the cohort, 39.5% developed infection and 38.3% died within 90 days. Beta-diversity differed by mortality (unweighted UniFrac p=0.046) and high GRS (≥7) (unweighted UniFrac p=0.036; Bray‑Curtis p=0.03); several taxa varied with both outcomes. After adjustment, microbiome diversity did not predict infection, but higher Shannon diversity independently reduced mortality risk (adjusted hazard ratio 0.67; 95% CI 0.46‑0.96; p=0.032), controlling for sex and comorbidity. These findings link lower intestinal alpha-diversity to higher mortality in KPC-KP colonized patients and suggest.

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IVd. Emergence of infections caused by carbapenemase-producing Proteus mirabilis: OXA-48: analysis of the PROTECOR cohort.

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Scientific Program: Infectious and Immunological diseases.

Keywords: OXA-48*; Proteus mirabilis*; carbapenemase; mortality; multidrug-resistant.

Abstract:

Background: *Proteus mirabilis* producing OXA-48 and extended-spectrum beta-lactamases (ESBL) is emerging as a clinically significant pathogen due to its ability to harbor broad-spectrum resistance genes that often go undetected by conventional phenotypic testing. This underdiagnosis may delay appropriate treatment and worsen clinical outcomes. **Methods:** We included patients with *P. mirabilis* infections between January 2017 and January 2024. Cases involving OXA-48/ESBL-producing strains were compared to those caused by susceptible strains, including a matched subcohort (2:1) based on age, comorbidity, infection site, and clinical severity. Thirty-day mortality, clinical response, and associations with antibiotic treatment were evaluated. **Results:** Of 1,254 infections, 79 (6.3%) were due to OXA-48/ESBL-producing strains. These infections were significantly associated with older age, greater comorbidity, and increased clinical severity ($p < 0.001$). Thirty-day mortality was markedly higher in the OXA-48/ESBL group (30.38% vs. 7.32%, $p < 0.001$), with a population attributable fraction of 17.9%. In multivariable analysis, late-phase infection (day 7–30) with OXA-48/ESBL strains was strongly associated with increased mortality (HR = 14.5, $p = 0.001$). Carbapenem treatment was linked to higher mortality (57.1% vs. 24.6%, $p = 0.03$), even after adjusting for clinical severity (HR = 3.36, $p = 0.01$). An INCREMENT score >7 was a consistent predictor of mortality across all models. **Conclusion:** Infections caused by OXA-48/ESBL-producing *P. mirabilis* are associated with high mortality, especially during late phases of infection. Carbapenem therapy may be inadequate in this setting, highlighting the urgent need for alternative treatment strategies and improved early detection of resistant strains.

IVe. Surveillance of Rat Hepatitis E Virus in Nigeria: Serological and Molecular Evidence and Associated Risk Factors.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.

Keywords: Rat HEV, Animal Handlers, Risk factors, Emerging Infectious Diseases, RNA.

Abstract:

Background and Aim: Rat hepatitis E virus (ratHEV) is an emerging zoonotic pathogen of global concern. While human cases have been reported worldwide, no infections have been documented in Africa. Transmission routes and risk factors remain poorly understood. This study aimed to assess the prevalence and potential risk factors for ratHEV infection in different population groups in southwestern Nigeria. **Methods:** A cross-sectional study included 627 from southwestern Nigeria, categorized into three groups: students (control group), villagers, and individuals with occupational animal contact (butchers, pig farmers, and animal handlers). Anti-ratHEV IgG antibodies were detected using an in-house dot-blot assay. Active ratHEV infection was evaluated by detecting viral RNA in serum samples, with positive cases confirmed by sequencing. **Results:** Overall seroprevalence of anti-ratHEV IgG was 3.2% (95% CI: 2.0-4.9%), highest in the animal contact group (2.6%), particularly animal handlers (2.0%). Logistic regression identified higher odds of seropositivity in individuals aged 31–40 vs. >50 (OR=6.00; 95% CI: 1.23–29.14; p=0.026) and lower odds in villagers vs. animal handlers (OR=0.096; 95% CI: 0.01–0.77; p=0.027). No gender association was found. RatHEV RNA was detected in 0.8% (5/627; 95% CI: 0.3–1.9%), with 0.3% in villagers and 0.5% in the animal contact group. Students had no infections. **Conclusion:** This is the first report of ratHEV exposure in Africa, providing both serological and molecular evidence of infection. The higher seroprevalence among animal handlers suggests a possible occupational risk and highlights the need for further research into transmission dynamics and zoonotic potential.

IVf. Immunometabolic remodeling in the porcine ileum during *Salmonella* infection: Insights from Single-Cell RNA sequencing.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Salmonellosis; pig; immunity; zoonosis; Single-Cell.

Abstract:

Salmonella Typhimurium is a major zoonotic pathogen, with pigs acting as important subclinical reservoirs. To characterize the intestinal immune response, we applied single-cell RNA sequencing (scRNA-seq), enabling high-resolution analysis of epithelial and immune cell subsets during infection. We identified twelve T/ILC subtypes and five B cell subtypes, along with monocytes/macrophages, dendritic cells, and enterocytes, revealing significant infection-driven changes in cellular composition and gene expression. Naive $CD4^+$/$CD8^+\alpha\beta$ T cells and cytotoxic $CD8^+\alpha\beta$ T cells expanded upon infection, suggesting early adaptive immune activation. In contrast, decreases in cycling $CD8^+\alpha\beta$ T cells, activated $CD8^+\alpha\beta$ T cells, $CD2^-\gamma\delta$ T cells and group 1 ILCs may reflect altered cell survival, functional exhaustion, or migration. B cell analysis showed increased activated B cells and reduced other subtypes, indicating strong antigenic stimulation and a possible shift toward effector differentiation. Pathway analysis revealed broad immunometabolic remodeling, with activated T cells showing upregulation of oxidative phosphorylation and IL6/JAK/STAT3 signaling, consistent with effector activation. Cycling T cells exhibited stress signatures and reduced proliferation, suggesting homeostatic disruption. Group 1 ILCs activated IFNγ and apoptosis pathways while suppressing PI3K/AKT-mTOR signaling, supporting their role in inflammatory amplification. B cell subtypes also reacted to infection: transitioning B cells overactivated IFNγ and oxidative phosphorylation; resting B cells upregulated glycolysis and MYC targets; activated B cells showed strong TNFα, ROS and complement signaling; and antibody-secreting cells enhanced NF-κB signaling. Monocytes/macrophages upregulated key inflammatory and effector pathways highlighting their role as frontline immune effectors. Dendritic cells downregulated classical cytokine signaling while upregulating metabolic and cell cycle pathways, indicating a regulatory or post-activation state. Enterocytes showed downregulation of epithelial integrity and metabolic pathways, and upregulation of stress, glycolysis, and inflammatory responses. This study provides the first scRNA-seq landscape of the porcine ileum during *Salmonella* Typhimurium infection, offering new insights into host immune cell dynamics and immunometabolic responses.

SESSION V.

CANCER II

Va. The role of RNA methylation and splicing dysregulation in neuroendocrine neoplasms biology.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: RNA methylation, splicing, neuroendocrine neoplasms, m^{6}A.

Abstract:

RNA processing and post-transcriptional modifications constitute key elements in cancer. In particular, alternative splicing dysregulation has been shown to play an important role in the development neuroendocrine neoplasms (NENs). In this context, a less known post-transcriptional alteration, *N*^{6}-methyladenosine, or m^{6}A, has been recently shown to be involved in the development of various cancers. However, its role in NENs remains unexplored. The m^{6}A methylation is catalyzed by a set of proteins known as writers, while its removal is mediated by the demethylases FTO and ALKBH5, referred to as erasers. The functional impact of these RNA modifications is mediated by readers, which influence RNA biogenesis, translocation, splicing, translation, decay and/or stability. In this line, we hypothesize that m^{6}A modification may be linked to alternative splicing dysregulation in NENs, leading to increased tumor development and aggressiveness. To test this hypothesis, we conducted a biocomputational analysis in two NEN cohorts, comprising 281 lung and 174 pancreatic NENs, exploring synergies between m^{6}A regulators with clinical features and splicing alterations. Additionally, we have studied the functional role of writers, erasers and readers *in vitro* using lung and pancreatic NEN cell lines. We observed a clear relationship between expression levels of several m^{6}A components, specific to NEN subtype, with mutations in key genes, metastatic status and differentiation grade. We also found strong correlations between abnormal levels of m^{6}A components and alternative splicing events linked to tumorigenesis, tumor development, and aggressive biological behavior. *In vitro* assays showed that the effects of the inhibitors are cell line-dependent, highlighting the heterogeneity of these tumors. Overall, our results suggest that lung and pancreatic NENs exhibit an additional level of RNA processing dysregulation involving m^{6}A alteration. This study could reveal novel therapeutic strategies targeting m^{6}A, offering innovative approaches for the future treatment of these challenging tumors.

Vb. A Novel Feedback Loop Between DYRK2 and USP28 Regulates Cancer Homeostasis and DNA Damage Signaling.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: DYRK2; USP28; DNA damage; Ubiquitination.

Abstract:

Posttranslational modifications, such as ubiquitination and phosphorylation, play pivotal roles in regulating protein stability in response to cellular stress. Dual-specificity tyrosine phosphorylation-regulated kinase 2 (DYRK2) and ubiquitin-specific peptidase 28 (USP28) are critical regulators of cell cycle progression, DNA damage response, and oncogenic signaling. However, their functional interplay remains largely unexplored. Here, we describe a novel bidirectional regulatory mechanism between DYRK2 and USP28 that integrates DNA damage response and ubiquitin-mediated protein degradation. We demonstrate that DYRK2 phosphorylates USP28, promoting its ubiquitination and proteasomal degradation in a kinase activity-independent manner, thereby contributing to the maintenance of oncogenic protein homeostasis. Conversely, USP28 functions as a deubiquitinase for DYRK2, stabilizing its protein levels and enhancing its kinase activity. Notably, we show that DYRK2 interacts and co-localizes with USP28, with the 521-541 DYRK2 region, particularly residue T525, playing a crucial role in USP28-mediated DYRK2 stabilization. Functionally, this reciprocal regulation modulates p53 signaling, influencing apoptotic responses to DNA damage. DYRK2-mediated phosphorylation of p53 at S46 is significantly reduced upon USP28 depletion, suggesting that USP28 facilitates DYRK2-dependent apoptosis. Additionally, our results highlight a complex regulatory axis involving USP28 and DYRK2, with implications for oncogenic cell death and genomic stability. Overall, our findings uncover a novel feedback loop in which DYRK2 and USP28 dynamically regulate each other to control protoonco-proteins homeostasis and DNA damage signaling. This interplay offers potential therapeutic opportunities for targeting cancers with dysregulated ubiquitination and genomic instability.

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Vc. Exploring MUC13 as potential therapeutic target in pseudomyxoma peritonei.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Cancer, Pseudomyxoma peritonei, molecular characterization, mucin, MUC13.

Abstract:

Pseudomyxoma peritonei (PMP) is a rare malignant disease characterized by a massive accumulation of mucin and secreting tumour cells inside the peritoneal cavity. The only therapeutic option is a complex surgery combined with chemotherapy. However, many patients suffer tumour relapse with fatal outcomes due to the absence of effective treatments and limited molecular knowledge of these tumours. In this sense, we previously developed the first protocol that allowed us to break the mucin barrier and described the first PMP proteome profile. This revealed a unique mucin isoform profile and identified MUC13 as a potential tumour marker. Here, our main objective is to explore the importance of MUC13 in PMP pathophysiology using 2D and 3D (organoids) cell cultures. First, we examined MUC13 expression levels in a PMP cell line (N14A) and organoids. Next, to examine the functional relevance of MUC13, a monoclonal anti-MUC13 antibody was developed and evaluated in cell cultures. Our results demonstrated that MUC13 was highly expressed in PMP cell cultures and confirmed the presence of MUC13 in the cell surface. Moreover, our results showed that anti-MUC13 significantly reduced cell proliferation in N14A cells but not in the colon cancer cell line HT29, which also presented high MUC13 expression levels. Finally, long-term treatment of PMP organoids revealed a clear decrease in cell viability and organoid size when treatment began on day 0, before organoids formed. However, this effect was reduced when treatment was administered on day 6, suggesting that MUC13 may be relevant in the initial stages of tumour development. Overall, our results evidence that targeting MUC13 could be a potential therapeutic option for treating PMP patients and preventing recurrences after surgery.

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Vd. Dysregulation of the matrisome in periprostatic adipose tissue drives prostate cancer progression: oncogenic role of LAMB1/RPSA-receptor axis.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: Matrisome; Periprostatic Adipose Tissue; Prostate Cancer; Laminin B1; Laminin Receptor; RPSA.

Abstract:

Prostate cancer (PCa) remains one of the leading causes of cancer-related mortality among men. Despite substantial advances in elucidating the molecular mechanisms driving PCa onset and progression, the specific role of periprostatic adipose tissue (PPAT) remains insufficiently characterized. In this study, we explored the contribution of dysregulated matrisome components in PPAT to PCa development and progression by employing an integrative multi-omic approach across several well-defined PCa patient cohorts and cellular/preclinical models. Our analyses revealed a marked dysregulation of PPAT matrisome components in PCa patients compared to control subjects [with benign prostate-hyperplasia (BPH)]. Among these, LAMB1 emerged as a critical oncogenic factor, exhibiting significantly elevated transcript levels in the PPAT of PCa patients and correlating with key clinical features of tumor aggressiveness. In parallel, LAMB1 protein levels were notably increased in the PPAT secretome of PCa patients. Further, we identified laminin-411 (LAN411)—a LAMB1-containing laminin isoform—as a key mediator of the PPAT-PCa interaction, acting via RPSA, the laminin receptor. Interestingly, RPSA was consistently overexpressed across six independent PCa cohorts and associated with key aggressiveness features. Notably, RPSA silencing in vitro and in vivo, along with in vivo application of LAN411-enriched basement membrane extracts, demonstrated the impact of LAMB1/RPSA-axis modulation on critical cancer hallmarks including proliferation, migration, invasion, adhesion, colonies and tumorspheres formation, and tumor growth. Molecularly, RPSA dysregulation was linked to alterations in critical oncogenic pathways (such as c-MYC activation, energy homeostasis and mitotic spindle regulation) and was associated with changes in RPSA intracellular localization after silencing. Taken together, our findings highlight the functional relevance of the PPAT-derived LAMB1/RPSA-axis in driving PCa pathogenesis, offering an unique opportunity for novel therapeutic research targeting PPAT matrisome-components in PCa.

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Ve. Relevance of mRNA metabolism dysregulation in glioblastoma.

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Keywords: RNA-exosome; glioblastoma; biomarker; therapeutic target.

Abstract:

Glioblastoma (GBM) stands as the most prevalent and lethal brain tumour due to the late-stage diagnosis and the resistance to gold-standard therapy. Recent studies indicate that alterations in mRNA metabolism mechanisms are involved in key pathophysiological processes in a wide variety of cancers including brain tumours. Nevertheless, some mRNA metabolism machineries, such as RNA-Exosome, have not been explored yet. Therefore, we characterized the expression levels of RNA-Exosome components in GBM (n=60) and non-tumour samples (n=7) with a microfluidic technology based on qPCR. Moreover, other external cohorts were used to bioinformatically select the most clinically relevant factor. Then, we performed several bioinformatic approaches and functional/molecular assays in primary derived cell cultures, cell lines and an *in vivo* xenograft model to reveal the potential role of a selected factor. First, we observed a clear dysregulation of multiple RNA-Exosome components in GBM. EC1* was selected for further analyses due to the consistent upregulation across different human cohorts (transcriptomic and proteomic data). Interestingly, samples with higher levels of EC1 showed a worse prognosis and were associated with the most aggressive Verhaak subtype (classical). A deeper *in silico* characterization revealed that EC1 levels were higher in tumour cells than stroma cells in GBM microenvironment at single cell level and that samples with higher levels were enriched with key signalling pathways in classical subtype (*e.g.,* NOTCH, SHH, etc.). Therefore, EC1 silencing in different GBM-cell models decreased aggressiveness features (*i.e.,* proliferation, migration, invasion, VEGF secretion, colony formation) and induced apoptosis. As proof of concept, we overexpressed this factor and we obtained opposite results. Finally, we also observed a reduction in tumour growth in a xenograft-preclinical model after EC1 silencing. This study provides evidence indicating the drastic alteration of RNA-Exosome in GBMs, which could represent a novel source of diagnostic/prognostic biomarkers and therapeutic targets in this devastating pathology.

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Vf. Differential gene expression analysis according to the CEBPA gene mutational status in Acute Myeloid Leukemia patients.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: AML, CEBPA, RNA-Seq, favorable prognosis, differential gene expression.

Abstract:

Acute myeloid leukemia (AML) is a neoplasm characterized by high genetic-molecular heterogeneity. Among AML recurrent alterations, mutations in bZIP domain of *CEBPA* (*CEBPA*bZIP) have been classified as favorable prognosis. However, molecular mechanisms underlying this better outcome are not clarified. Our aim was to study the RNA expression patterns between *CEBPA*bZIP *vs.* other*CEBPA*mut *vs. CEBPA*wt patients, to elucidate the biological-molecular basis for this favorable prognostic. We used the public BEAT-AML dataset, selecting RNA-seq data from 450 diagnostic patient samples and split into 3 groups: *CEBPA*bZIP (n=9), other*CEBPA*mut (n=14), and *CEBPA*wt (n=423). Statistical analyses were performed using R (v4.3.2). PLS-DA was used for pairwise comparisons of RNA-seq expression, with VIPscores identifying group-discriminating genes. Differential expression analyses were performed using volcano-plots. STRING and lncSEA were used to explore functional interactions and molecular mechanisms associated with differentially expressed genes. We first validated 5-year survival probability obtaining: 71.4%(95%CI:44.7-100)-*CEBPA*bZIP, 35.7%(95%CI:17.7-72.1)-other*CEBPA*mut, and 33.6%(95%CI:28.5-39.6)-*CEBPA*wt patients. *CEBPA* expression was statistically different (P<0.001) between *CEBPA*bZIP *vs. CEBPA*wt and other*CEBPA*mut *vs. CEBPA*wt. Regarding pairwise comparisons, we identified several genes that discriminated between groups with a VIPscore>1.5: 2745-*CEBPA*bZIP *vs. CEBPA*wt, 3199-*CEBPA*bZIP *vs.* other*CEBPA*mut, and 2957-other*CEBPA*mut *vs. CEBPA*wt. In volcano-plots, we significantly found 761-*CEBPA*bZIP *vs. CEBPA*wt, 299-*CEBPA*bZIP *vs.* other*CEBPA*mut, and 717-other*CEBPA*mut *vs. CEBPA*wt upregulated genes; and 914-*CEBPA*bZIP *vs. CEBPA*wt, 192-*CEBPA*bZIP *vs.* other*CEBPA*mut, and 890-other*CEBPA*mut *vs. CEBPA*wt downregulated genes. To identify genes differentially expressed specifically in *CEBPA*bZIP patients, we performed Venn diagrams of previous comparions and selected genes presented in both *CEBPA*bZIP *vs.* other*CEBPA*mut and *CEBPA*bZIP *vs. CEBPA*wt, but absent or unique in others. Among up- and down-regulated genes, we sorted only those with VIP>1.5, resulting in 50 up- and 64 down-regulated genes. Significantly, downregulated genes in *CEBPA*bZIP patients were associated with citrullination, chromatin structural components, cancer phenotypes linked pathways, and metastasis. Genes overexpressed in *CEBPA*bZIP group were related to granulocyte differentiation, tumor suppression, transcriptional repression, and cell proliferation. These molecular signatures may uncover new insights related to the leukemogenic mechanisms, favorable prognosis as well as potential therapeutic new targets.

POSTER
SESSION II.

PSII.a. Systemic Cytokine Signatures Associated with Disease Activity and IL-17A Inhibitor Response in Spondylarthritis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Spondyloarthritis; Biomarkers, Il17A inhibitors, Proteomics.

Abstract:

Objectives: a) To analyze the inflammatory proteome of Spondyloarthritis (SpA) patients; b) To evaluate the molecular effects of IL-17A inhibitors. **Methods:** 33 patients with SpA were included. A panel of 45 cytokines was analyzed in serum using "Proximity Extension Assay". In parallel, 17 of these patients initiated IL-17A inhibitor therapy (Secukinumab), and clinical and molecular evaluations were performed after 6 months. Additionally, affinity chromatography was used to discriminate between free and drug-conjugated IL-17A after treatment. **Results:** Unsupervised cluster analysis based on the inflammatory proteome identified two distinct molecular subgroups. Cluster 2 displayed significantly higher expression of multiple cytokines compared to Cluster 1, including IL-6, -8, -2, -18, -7, -1B and -15, CXCL9, CCL-3, -4, -7, -8 and -19, CSF1, VEGFA, OSM, and EGF. Clinically, C2 was associated with higher CRP levels, a greater proportion of radiographic forms, and elevated levels of tissue turnover and organ function markers (ALP, LDH, GGT, etc). Furthermore, patients with high disease activity (ASDAS > 3.5) showed increased levels of IL-17A, IL-6, IL-1β, and CCL4. In the subgroup treated with IL-17A inhibitors, high baseline levels of IL-17C, HGF, CCL13, CCL3, IL-8, IL-1β, and EGF—and low levels of CSF3—were significantly associated with better clinical response. Interestingly, total serum IL-17A levels increased significantly after therapy and correlated positively with clinical improvement. Further analysis showed that only conjugated IL-17A, and not the free form, increased post-treatment, suggesting that antibody-bound cytokines remain in circulation longer due to reduced clearance. **Conclusions:** SpA patients are clinically and molecularly heterogeneous, with distinct inflammatory profiles that correlate with disease severity. / A specific baseline inflammatory protein signature is associated with favorable response to IL-17A inhibitors, supporting its potential as a predictive biomarker. / Measuring total IL-17A after treatment may help monitor therapeutic response, as increased detection likely reflects effective cytokine neutralization by the drug.

PSII.b. Corneal incision contracture: literature review and report of a novel therapeutic strategy using intrastromal corneal ring segments.

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Keywords: Corneal incision contracture; Phacoburn; Corneal burn; Phacoemulsification; Intrastromal corneal ring segment; Cataract surgery; Refractive surgery.

Abstract

Purpose: This review summarizes key aspects of corneal incision contracture (CIC), also known as wound burn. CIC is a rare complication of phacoemulsification, which can significantly compromise surgical outcomes, leading to delayed healing, suboptimal functional results, and patient dissatisfaction. **Methods:** A comprehensive literature review was conducted across multiple databases, encompassing full-length studies, case series, and reports. A total of 52 studies were selected, focusing either on the etiopathogenesis and risk factors of CIC or on different treatment strategies. **Results:** Although preventing CIC remains challenging, key risk factors include excessive ultrasound energy, the use of high-viscosity ophthalmic viscosurgical devices (OVDs), and narrower, longer incisions, particularly in shallow anterior chambers. Additionally, this review highlights therapeutic approaches for managing both the acute and chronic phases of CIC. A critical analysis of previous reports reveals a lack of consensus on management and limited attention to long-term rehabilitation, contributing to suboptimal visual outcomes in the majority of patients. Finally, we propose a novel treatment for the chronic phase of CIC: the implantation of intracorneal ring segments (ICRS), a technique not previously described. This method was successfully applied in a patient with severe CIC-induced astigmatism (>23 diopters), achieving a plano spherical equivalent and a final visual acuity (VA) of 0.8 decimal (0.1 logMAR). This outcome surpasses those reported in previous literature. **Conclusion:** This study highlights the significant challenges associated with CIC and introduces a promising therapeutic strategy using ICRS implantation, potentially improving outcomes for these complex cases.

PSII.c. Cefiderocol resistance in clinical isolates of KPC-Producing *Klebsiella Pneumoniae* resistant to ceftazidime-avibactam: molecular insights.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: KPC, ceftazidime-avibactam, cefiderocol.

Abstract:

Introduction: Ceftazidime-avibactam (CAZ/AVI) and cefiderocol (FDC) are active against most clinical isolates of KPC-producing *Klebsiella pneumoniae* (KPC-Kp). However, cross-resistance to both drugs has been reported. The aim of this study was to investigate cefiderocol resistance in clinical isolates of CAZ/AVI-resistant KPC-Kp. **Methods:** Pre- (CAZ/AVI-S; n=9) and post-therapy (CAZ/AVI-R; n=13) isolates from 9 patients treated with CAZ/AVI for infections caused by KPC-3-Kp in the period 2014-2023 were analysed. Susceptibility to FDC was determined twice by reference microdilution (CLSI-2023, M100) and interpreted according to EUCAST breakpoints. Whole genome sequencing (WGS) was performed with the Illumina Novaseq 6000 system. Genomes were screened for antimicrobial resistance genes with Resfinder (CGE). Parental genomes were annotated by Prokka and relevant single nucleotide polymorphisms (SNPs) were identified using CLC Genomics Workbench (Qiagen). *OmpK35* and *ompK36* were also independently analysed. **Results:** MICs of FDC increased ≥4 times in all post-therapy isolates in comparison with the MICs for the corresponding parental isolates. In isolates from 6/9 patients, this increase resulted in FDC resistance (MICs: 4 to >32 mg/L). All 9 pre-therapy isolates contained *bla*$_{\text{OXA-9-like}}$, *bla*$_{\text{SHV-11}}$, *bla*$_{\text{TEM}}$ variants and *bla*$_{\text{KPC-3}}$. All 13 post-therapy isolates had different *bla*$_{\text{KPC}}$ variants (Table 1) and 8 of them also presented mutations in other genes related to beta-lactam resistance: peptidoglycan synthesis (*mrdA*/*mrcA*/*ftsI*/*ycfS*) (n=7), iron transport (*fhuA*/*fepG*/*fecA*/*tolQ*) (n=4) and/or permeability/efflux system (*envZ*/*acrB*) (n=3). Differences in *ompK35* or *ompK36* of pre- and post-therapy isolates were not found. **Conclusions:** Treatment of KPC-Kp with CAZ/AVI can select mutants resistant to FDC. Some of these isolates present SNPs in genes related to PBPs, iron transport or permeability/efflux, together with mutations in *bla*$_{\text{KPC}}$ genes. Further studies are required to understand the independent role of these mechanisms.

PSII.d. Major cardiovascular events in patients with atrial fibrillation and active lung cancer: data from the CANAC-FA registry: a multicentre, retrospective, observational study.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Lung cancer, Atrial fibrillation, Cardiovascular events, Major bleeding, Mortality, Anticoagulation.

Abstract:

Background: Lung cancer has a poor prognosis for most patients, as it is frequently diagnosed in advanced tumor stages. Real observational data about major cardiovascular events (MACE) in patients with atrial fibrillation (AF) and active lung cancer are very limited. **Objetive:** Our aim was to investigate the prevalence of AF and active lung cancer in the outpatient oncology clinic and to describe the clinical profile, management and the incidence of MACE in this population. **Methods:** We used data from CANAC-FA Registry, an observational, multicentre, retrospective study. The medical records of all subjects attended from January 1st, 2017 to December 31st, 2019 in five hospitals were reviewed. The first visit to the oncology clinic with AF diagnosis during the first year after the lung cancer detection was considered the basal visit. End points were stroke/systemic embolism, thrombotic events, major bleeding, and cardiovascular events (hospital admission for cardiovascular reasons or cardiovascular death). **Results:** Among 6984 patients, 269 presented active lung cancer and atrial fibrillation (3.7%). Mean age was 71±8 years, and 91% were male. Charlson, CHA_2DS_2VASc and HAS-BLED indexes were 6.7±2.9, 2.9±1.5 and 2.5±1.2 respectively. Anticoagulants were prescribed to 84% of the patients: direct anticoagulants (44%), low molecular weight heparins (30%) and vitamin K antagonists (26%). After up to 46 months of maximum follow-up, 7 patients presented a stroke, 18 had a thrombotic event, 16 presented a major bleeding, 33 had a cardiovascular event and 186 died. Cumulative incidences of major events at one, two and three years of follow-up were 2.4±1.0%, 3.3±1.3% and 3.3±1.3% for stroke; 4.7±1.3%, 8.0±2.1% and 8.9±2.2% for thrombotic events; 2.7±1.0%, 6.7±1.9% and 9.9±2.6% for severe bleeding, and 9.5±1.8%, 13.4±2.5% and 15.9±3.0% for cardiovascular events. **Conclusion:** Cumulative incidence of cardiovascular events was 15.9% at three years. These data could suggest an unmet need for more effective preventive strategies in this population.

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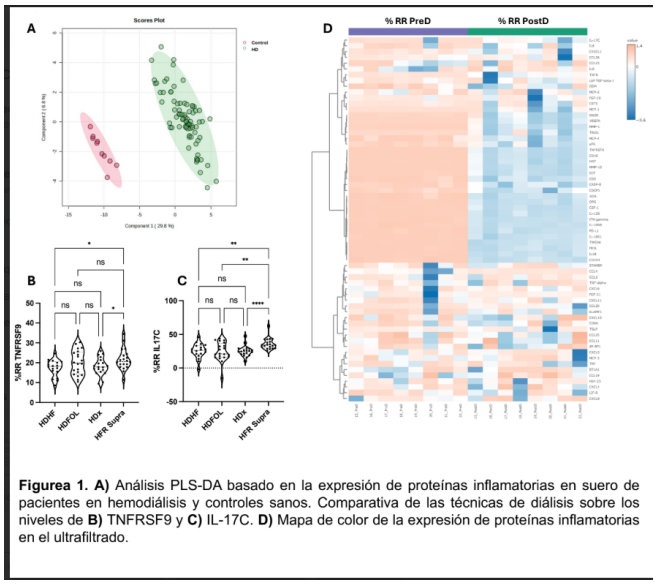
Scientific Program: Chronic and Inflammatory diseases.
Keywords: Inflammation, uremia, hemodialysis.

Abstract:

Introduction: Hemodialysis (HD) is based on the physical principles of diffusion, convection, and adsorption. Understanding how these principles influence not only solute clearance but also inflammation modulation is essential for optimizing dialysis techniques and improving clinical outcomes. **Objective:** To evaluate the effects of different dialysis techniques on the inflammatory process and cardiovascular risk. **Methodology:** A prospective, randomized study was conducted in 25 prevalent HD patients undergoing dialysis using different techniques: high-permeability HD (HFHD), post-dilution online hemodiafiltration (OLHDF), extended HD (HDx), and hemodiafiltration with ultrafiltrate reinfusion (HFR). Levels of 92 inflammatory proteins were quantified using a proximity extension assay (PEA). The results were compared with 10 controls with normal renal function. **Results:** HD patients showed significantly elevated levels of 43 inflammatory proteins (FDR <0.01) compared to controls (Fig. 1A). Convective techniques (OLHDF and HFR) showed increased clearance of TNFRSF9 compared to diffusive techniques (HFHD and XHD) (Fig. 1B). Furthermore, the technique combining diffusion + convection + adsorption (HFR) showed significantly improved IL17C removal compared to other modalities (Fig. 1C). Analysis of the HFR ultrafiltrate after passage through the resin revealed that both TNFRSF9 and IL17C are removed by adsorption (Fig. 1D). However, while TNFRSF9 clearance decreases significantly at the end of dialysis, the IL17C removal rate remains stable throughout the HD session. **Conclusions:** This study highlights the impact of HD on systemic inflammation, as evidenced by the increase in proinflammatory markers. The technique, which integrates diffusion, convection, and adsorption, offers significant advantages in the elimination of inflammatory mediators, which could translate into better control of the chronic inflammatory state associated with uremia.



Figurea 1. A) Análisis PLS-DA basado en la expresión de proteínas inflamatorias en suero de pacientes en hemodiálisis y controles sanos. Comparativa de las técnicas de diálisis sobre los niveles de **B)** TNFRSF9 y **C)** IL-17C. **D)** Mapa de color de la expresión de proteínas inflamatorias en el ultrafiltrado.

PSII.f. Genetic Markers for the Evaluation of Cardiovascular Event Recurrence Risk. CORDIOPREV-HERITAGE.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Cardiovascular Disease; Recurrence; Genetics; Prediction; PRS.

Abstract:

Introduction: Cardiovascular diseases (CVD) are one of the leading causes of morbidity and mortality worldwide. Despite advances in treatment and secondary prevention, the risk of recurrence after a first event remains high, ranging between 20–35% over 7 years. Various studies have identified genetic variants associated with cardiovascular risk, and polygenic risk scores (PRS) have been proposed as tools for predicting the incidence of atherosclerotic cardiovascular disease. However, evidence regarding their utility in predicting recurrence remains limited. **Objective:** To evaluate the area under the curve (AUC) for sensitivity and specificity in identifying long-term recurrence (7 years) of three risk models: a PRS, a clinical score, and a combined score of the two. **Materials and Methods:** Fifty previously validated SNPs for cardiovascular disease were genotyped to generate a PRS score (previously validated) based on 50 genetic polymorphisms in 945 participants from the CORDIOPREV study (using the Axiom_SpainBA2.r1 array), and a clinical score (based on age, gender, smoking, hypertension, LDL, and diabetes). A Combined Score was also determined by combining the values of both scores. Data processing was performed using PLINK 2.0 and the R statistical software. The corresponding ROC curves for sensitivity and specificity of 7-year events were compared using DeLong tests. **Results:** The PRS score model achieved an AUC of 0.624 (95% CI: 0.580–0.669), the clinical score an AUC of 0.583 (95% CI: 0.540–0.627), and the combined model reached an AUC of 0.649 (95% CI: 0.606–0.691). In DeLong tests, the combined model proved superior to the currently used clinical model (p=0.002).

PSII.g. Lung health predicts mortality in SMI.

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Scientific Program: Chronic and Inflammatory disease.
Keywords. Schizophrenia, bipolar disorder, lung function, mortality, Serious mental illness.

Abstract:

Background: The population with a serious mental illness (SMI) shows a high risk of premature mortality. Overexposed to multiple health risks throughout life, their main threat is physical illness, which starts earlier and is not diagnosed in time. Developing preventive actions is a public health priority. **Methods:** This longitudinal prospective study evaluated the predictive value of lung function on all-cause mortality in patients with schizophrenia or bipolar disorder. Patients aged 40-70, active smokers, and without pre-existing respiratory disease underwent spirometry following ATS/ERS 2021 standards. Mortality data was collected through December 2022. Cox proportional hazards models and Kaplan-Meier survival curves analyzed the association between lung function, forced expiratory volume (FEV1), forced vital capacity (FVC), and mortality, adjusting for relevant confounders (age, gender, abdominal circumference and comorbidities). **Results:** Of 107 participants (mean age 49.3 years, 63.3% male) with SMI (72% schizophrenia) and active smokers, 8 (7.5%) died during the six-year follow-up (5 cardiovascular, 3 cancer). Lower FEV1 and FVC z-scores were significantly associated with increased mortality risk (p=0.002 and p=0.009, respectively). Kaplan-Meier analysis confirmed this association for FEV1 (p=0.039) and FVC (p=0.007) but not for gender, comorbidities (hypertension, diabetes, dyslipidemia), or FEV1/FVC. A multivariate Cox regression model, adjusting for age and abdominal circumference, confirmed the independent predictive value of lower FEV1 z-score for mortality (HR 0.473, 95% CI 0.220-0.979, p=0.044). **Conclusions:** Poorer lung function, especially lower FEV1, was independently associated with all-cause mortality in SMI. Spirometry, an easily implementable technique, could help to detect at-risk individuals and favor prevention initiatives.

PSII.h. Peripubertal changes in the hypothalamic transcriptome of a Prader-Willi syndrome mouse model with altered metabolic and pubertal phenotype.

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Scientific Program: Nutrition, Endocrine, and metabolic diseases.
Keywords: Prader-Willi; hypothalamus; *Magel2*; puberty; transcriptomics.

Abstract:
Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder that is associated with various endocrine manifestations, including metabolic and pubertal abnormalities. Notably, puberty and metabolism are closely linked, and their hypothalamic regulation relies on the coordination and integration of complex signaling pathways involving intricate gene programs. Although hypothalamic dysfunction has been proposed as a major contributor to the metabolic and pubertal changes associated with PWS, the underlying molecular pathways remain unknown. Here, we examined the pubertal and metabolic phenotype of Magel2-null mice, a PWS animal model, along with their hypothalamic transcriptomic signature during the peripubertal period. To this end, differential gene expression and functional enrichment analyses were performed using a standardized RNA-Seq pipeline combining Fastp, Salmon, DESeq2, and GOseq. Magel2-null male mice, but not females, exhibited a marked increase in insulin levels, a significant decrease in adiposity percentage during the early peripubertal period, and a marked pubertal delay. These alterations were associated with an increase in the number of hypothalamic genes that were differentially expressed in these animals from the early peripubertal period, consisting of 163 genes, to the late peripubertal period, which included 674 genes. Functional enrichment analysis of these genes across both peripubertal ages revealed their involvement in relevant signaling pathways for the neuroendocrine control of puberty and metabolism, including glutamatergic and GABAergic synapses, the PI3K-Akt signaling pathway, and gonadotropin-releasing hormone secretion pathways critical for triggering puberty. Remarkably, the puberty-activating genes Kiss1 and Tac2 were among the top ten genes that showed the most significant reduction in Magel2-null mice during the late peripubertal period, providing a novel molecular insight into the pubertal delay observed in this PWS model. Collectively, our findings unveil a molecular framework for understanding hypothalamic dysfunction in PWS during the peripubertal period, which may guide future therapeutic strategies for addressing the associated metabolic and pubertal alterations.

PSII.i. Transcriptomic characterization of primary lymphocytic cicatricial scarring alopecia: systematic review and meta-analysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: scarring alopecia; transcriptomics; meta-analysis; fibrosis; immunopathogenesis; therapeutic targets.

Abstract:

Introduction: Primary lymphocytic cicatricial scarring alopecia including frontal fibrosing alopecia (FFA), lichen planopilaris (LPP), and central centrifugal cicatricial alopecia (CCCA) are chronic scalp diseases with complex etiology. Despite the growing availability of transcriptomic studies, there is no systematic integration of their molecular profiles to guide pathogenic understanding or the search for therapeutic targets. **Objective:** To synthesize and integrate available transcriptomic data on LPP, FFA, and CCCA through a systematic review and meta-analysis, identifying common and specific differential gene profiles, altered functional signatures, and possible therapeutic implications. **Methods:** A systematic search was performed in public databases (GEO, ArrayExpress), selecting transcriptomic studies of scalp biopsies. Microarray and RNA-seq (bulk) data were normalized and harmonized, correcting for batch and platform effects. Mixed linear models and LOSO sensitivity analysis were applied. This was complemented by functional analysis (GO, Reactome), signature enrichment (GSVA), cell deconvolution, and protein interaction maps (PPI). **Results:** Six studies with 141 samples were included. A total of 682 differentially expressed genes common to all three entities were identified, as well as modules specific to each subtype. LPP and FFA shared immune activation and epithelial inhibition, while CCCA showed a more metabolic, mitochondrial, and proteostasis signature. Dysregulation of fibrogenic, IFN, senescence, and oxidative damage pathways was detected. Sensitivity analyses and metaregression showed the robustness of these findings. Drug repurposing suggested potential antifibrotic and immunomodulatory candidates. **Conclusions:** This meta-analysis reveals a common core of transcriptomic dysregulation in lymphocytic scarring alopecias, along with distinctive biological profiles by subtype. The integrated findings offer new insights into pathogenic mechanisms and therapeutic opportunities that need to be validated experimentally.

PSII.j. Defining the clinical value of MYD88, a component of the inflammasome machinery, as a diagnosis, prognosis and therapeutic tool in brain endocrine cancers.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Inflammasome, glioblastoma, hallmark, diagnostic, prognostic, therapeutic target.

Abstract:

Glioblastoma (GBM) stands as the most prevalent and lethal brain cancer due to the late-stage diagnosis and the resistance to gold standard therapy, which results in a low survival rate after diagnosis (8-9 months) and poor prognosis. Consequently, the identification of diagnosis/prognosis biomarkers and therapeutic targets becomes critical to improve GBM management. Herein, we focused on the study of the inflammasome machinery, activated by cellular stress and damage, triggering the maturation and release of proinflammatory cytokines, and being closely associated to the modulation of immune-responses, cell-death and tumor microenvironment (TME), a well-known hallmark of cancer. We initially characterized the expression levels of the inflammasome components in a well-characterized cohort of GBM patients (*n=63*) vs non-tumor brain (NTB; *n*=19) samples by using a qPCR array based on microfluidic technology. Our results revealed a profound dysregulation of the expression pattern of the inflammasome machinery in our cohort of GBM samples, which was later validated in different external cohorts using RNA-seq and microarrays data. Remarkably, the expression of key inflammasome components, especially *MYD88*, was associated to several clinical parameters of aggressiveness/poor-prognosis (e.g. survival rate, recurrence, EGFR amplification and MGMT methylation status). Moreover, MYD88 expression was found to be associated with diverse pathways of relevance in GBM pathophysiology (e.g. epithelial to mesenchymal transition, hypoxia, angiogenesis or NFkB-signaling). The modulation of the expression of *MYD88* (through transitory silencing or pharmacological inhibition) significantly reduced several key tumor functional parameters *in vitro*, including cell-proliferation, tumorspheres or colonies formation and migration rate. Taken together, this study demonstrates the critical role of inflammasome machinery in GBM pathophysiology, highlighting the importance of *MYD88* as a potential driver of GBM aggressiveness. Therefore, *MYD88* could serve as a novel diagnostic and/or prognostic biomarker, and potential therapeutic target that might be useful to improve the quality of life of GBM patients.

Fundings: ISCIII (DTS23/00055), MICINN (FPU23/02246, FPU20/03954); CIBERobn, and AECC.

PSII.k. Optimizing QIIME2 workflows for 16S metagenomics of clinical samples from patients colonized by KPC-carbapenemase-producing *Klebsiella pneumoniae*.

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Scientific Program: Infectious and Immunological diseases.
Keywords: QIIME2, 16S metagenomics, pipeline optimization, ASV vs OTU, Gut microbiota, *Klebsiella pneumoniae* infection.

Abstract:

The initial outbreak of the *Klebsiella pneumoniae* producing KPC-3 carbapenemase (KPC-KP) of sequence type ST512 was detected in 2012 at Reina Sofía University hospital in Córdoba, Spain, involving 67 infected patients and traced to an index case from Italy. The KLEBCOM cohort is a prospective observational study conducted between 2018 and 2019. Its primary aim was to determine whether the relative intestinal load of KPC-KP in colonized patients could predict subsequent infection and crude 90-day mortality. In this context, we optimized QIIME2 workflows to analyze 16S rRNA metagenomics data obtained from rectal swabs of 81 prospectively enrolled patients. Several analytical strategies were explored, including initial sequence filtering with fastp and comparison of amplicon sequence variants (ASVs) *versus* operational taxonomic unit (OTU) clustering. Taxonomic classification, including machine learning classifiers trained on SILVA and GreenGenes2 databases within QIIME2, and a comprehensive set of alpha and beta diversity metrics was applied to assess microbial community structure and variation. Our results demonstrate that preprocessing, denoising, and taxonomic classification choices significantly influence the detection of microbial taxa and diversity estimates. These findings inform our understanding of the gut microbiota's role in *K. pneumoniae* colonization and infection and provide practical guidelines for applying 16S metagenomics to clinical microbiome research in antimicrobial-resistant infections.

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PSII.1. Hepatic artery atherosclerosis is a risk factor for biliary strictures after liver transplantation.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: liver transplantation, hepatic artery, atherosclerosis, biliary stricture.

Abstract:

Background and Aims: The aging of liver donors and transplant candidates, along with the growing prevalence of metabolic comorbidities, may increase the prevalence of hepatic artery (HA) atherosclerosis. Since the biliary epithelium relies exclusively on hepatic arterial flow, HA atherosclerosis could increase the risk of biliary complications after liver transplantation (LT). **Method:** Retrospective observational study including all adult patients undergoing LT in a single institution between 2012 and 2023 who had a blinded pathological evaluation of the donor and recipient hepatic arteries. Patients receiving a retransplantation, combined organ transplantation, or showing HA thrombosis after transplantation were excluded. Risk factors for biliary complications were analyzed using univariate and multivariate Cox's regression, censoring events at 24 months post- transplantation. **Results:** Among 322 included patients, 63 (19.6%) developed biliary complications after a median follow-up of 44 months (IQR 17-22 months). The incidence of biliary strictures was 14.3% (n=46) at 24 months. Liver grafts from donation after circulatory death were associated with higher risk of developing biliary strictures at 24 months compared to grafts from brainstem-death donors (23.6% vs. 12.4%, p=0.03). Patients with histological atherosclerosis either in the donor or the recipient hepatic arteries (58.4%) showed a higher risk of biliary complications (17.6 vs 9.7%, p=0.047). After controlling for age, sex, transplantation indication (hepatocellular carcinoma), donor steatosis, and cardiovascular comorbidities in the multivariate Cox's regression analysis, hepatic artery atherosclerosis (HR= 2.18 [95%CI 1.12-4.21; p = 0.021]) and donation after circulatory death (HR= 2.43 [95%CI 1.25-4,76; p = 0.009) were the only independent predictors of biliary complications after LT. **Conclusion:** Donor or recipient hepatic artery atherosclerosis is associated with an increased risk of biliary strictures after liver transplantation. In such patients, the use of antiplatelet therapy could be considered to reduce the risk of biliary complications.

PSII.m. Regulatory T-Cell Response in Young and Older Healthy Adults Vaccinated Against Influenza: Impact of Human Cytomegalovirus Infection.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Regulatory T cells, influenza vaccine, aging, human cytomegalovirus, immunosenescence, vaccine response.

Abstract:

Influenza poses a serious health risk to older adults and is often associated with reduced vaccine efficacy. Regulatory T cells (Tregs) are essential for maintaining immune balance but may also dampen vaccine-induced responses. Some studies have reported increases in Tregs following influenza vaccination, potentially limiting immune activation, though definitive evidence remains limited. Human cytomegalovirus (hCMV) infection is a major contributor to immune aging and may influence both Treg activity and vaccine responsiveness. In this study, we examined Treg responses in young and older healthy adults after influenza vaccination, taking hCMV serostatus into account. Peripheral blood samples were collected before and after vaccination to analyze Treg subsets—assessing frequency and activation status—using flow cytometry. Additional immunogenicity endpoints, including antibody titers, Th1 polarization, and CD8 T-cell activation, were also evaluated. We found that antigen-specific Tregs increased post-vaccination in both age groups, with only minor differences when comparing young versus older adults. However, stratifying by hCMV serostatus revealed distinct patterns. hCMV-positive individuals showed higher IFN-γ production following vaccination, particularly in older adults. This effect was most evident after hemagglutinin stimulation, while responses in unstimulated conditions were less pronounced. In contrast, hCMV-negative older adults had lower IFN-γ levels than their hCMV-negative younger counterparts, suggesting a reduced vaccine response in the absence of hCMV-driven immune modulation. As the impact of hCMV on vaccine-induced immunity continues to be debated, our findings provide new evidence of its regulatory influence. These results underscore the complexity of immune aging and support the need for more personalized vaccination strategies in older populations, taking into account latent viral infections such as hCMV.

PSII.n. Histopathological Analysis of Synovial Biopsies in Patients with Early-Onset Rheumatoid Arthritis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: rheumatoid arthritis, early-onset, synovial biopsy, histopathology, immunohistochemistry.

Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by persistent inflammation of the synovial joint tissue. Although early diagnosis and the development of new therapies have improved the prognosis and management of the disease, a significant proportion of patients still fail to achieve adequate disease control or respond favorably to available treatments. In this context, synovial biopsy has been proposed as a strategy to predict disease progression and treatment response, enabling more personalized and optimized management. **Methods**: Synovial tissue samples were obtained through ultrasound-guided biopsies of clinically affected joints. The samples were fixed in 4% formaldehyde, embedded in paraffin, and stained with hematoxylin and eosin (H&E). Histomorphological evaluation included the Krenn score for diagnosing and grading synovitis, as well as the scoring of inflammatory aggregates. Immunohistochemical staining was performed using a semiquantitative scoring system (0 = absent to 4 = very severe) for CD68, CD3, CD20, and CD138 to characterize the synovial "pathotype" as one of the following: lympho-myeloid, diffuse myeloid, or pauci-immune. **Results:** Non-representative synovial biopsy samples and those from patients with a disease duration exceeding one year were excluded. As a result, the final study cohort consisted of 25 patients. Epidemiologically, 68% were women, with a median age at diagnosis of 57 years (range: 36–82 years). Morphologically, based on the Krenn score, 52% of patients were diagnosed with high-grade synovitis (Krenn score > 4). Additionally, 52% exhibited a lympho-myeloid pathotype, which was the most frequently observed profile. **Conclusions:** In conclusion, synovial biopsy of clinically affected joints in patients with rheumatoid arthritis allows for the histopathological evaluation of specific parameters. This approach may help predict the clinical course and treatment response, thereby enabling a more personalized therapeutic strategy. Such stratification could reduce the risk of missed treatment opportunities and unnecessary exposure to adverse effects.

PSII.o. Establishment and validation of animal models and 3D-cell culture models of Pseudomyxoma Peritonei.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: cancer, Pseudomyxoma Peritonei, mucin, organoids, cell culture, tumor markers.

Abstract:

Pseudomyxoma peritonei (PMP) is a rare malignancy characterized by an excessive accumulation of mucin in the abdomen. The current treatment involves aggressive cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. However, tumor recurrence is frequent. To date, functional/molecular characterization of this disease is scarce, mainly due to its low incidence, the barrier generated by the extreme mucus production and the lack of appropriate *in vitro* and *in vivo* models. Here, we aimed to establish/validate patient-derived xenograft (PDXs) and 3D-cell culture (organoids) models able to replicate the disease. Thus, tumor tissues obtained from PMP patients during surgery were implanted intraperitoneally in immunosuppressed mice. We successfully established two PDX models: one high-grade with appendix origin and one high-grade with mucinous colon origin. In addition, to establish/validate organoids, tumor tissues from our PDXs were homogenized into single cells, seeded with a specific media and growth factor mix and cultured for three weeks. Then, mucinous tumor tissues from the patient's original tumors, tumor-bearing mice, and organoids were formalin-fixed, paraffin-embedded, and immunostained against MUC2, CK7, CK20, P53, Ki67, and CDX2. We compared the results from the PDXs and organoids with those from the original human tumor tissues (HTTs). The results showed that MUC2 expression was strongly positive in both types of PMP organoids in line with PDXs tumors and HTTs. Additionally, CK7 and CK20 were mainly negative and CDX2 showed a positive signal in all samples. The Ki67 proliferation index and P53 marker were similar between organoids, PDXs and HTTs in both high-grade PMP subtypes, confirming a clear PMP phenotype. In conclusion, immunohistochemical analyses showed that the expression patterns of specific markers were maintained and consistent in the PDXs and organoids compared to the original human samples, suggesting that are a valuable resource for the development and testing of more personalized treatments.

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PSII.p. Endothelial-to-Mesenchymal Transition in Calcific Aortic Valve Disease: a Single-Cell Transcriptomics Approach.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: CAVD, blood flow, endothelium, scRNA-seq, Endothelial-Mesenchymal transition.

Abstract:

The Calcific Aortic Valve Disease (CAVD) is an increasingly widespread condition which provokes the deposition of calcium salts in the aortic valve, resulting in valvular dysfunction, with potentially fatal consequences. Currently, the absence of pharmacological therapies renders CAVD the most common indication for cardiac valve surgery, a lengthy and complex procedure which poses serious health risks for elderly patients. The aortic valve comprises several specialized cell types, such as valvular endothelial cells (VECs), which form a protective monolayer on the valve surface; and valvular interstitial cells (VICs), which primarily maintain its structural integrity. In this context, the haemodynamic forces exerted on the VECs induce distinct effects depending on whether the incident blood flow is laminar or turbulent. While the former affects the ventricular side of the valve and preserves endothelial function, the latter impacts the aortic side, promoting an inflammatory VEC phenotype, ultimately leading to VEC dysfunction, VIC differentiation and valve calcification. Therefore, this differential VEC response to flow influences angriocrine or cell-cell signalling to other valvular cell types, contributing to CAVD initiation and progression. Given the inherent cellular heterogeneity of the valve and the different cell types implicated in the disease, high-resolution technologies such as scRNA-seq prove essential. By reanalyzing publicly available raw scRNA-seq datasets from CAVD patients, we were able to identify the numerous valvular cell types and distinguish between ventricular and aortic VECs based on the expression of flow-sensitive markers. Additionally, trajectory analysis and functional enrichment uncovered a VEC subtype which appeared to undergo endothelial-to-mesenchymal transition. This new cell type was only present in calcified valves and possibly derives from aortic VECs. These findings suggest an active role of the valvular endothelium in the progression of CAVD and open new avenues for the development of novel therapeutic strategies which may prevent the progression of the disease.

PSII.q. Circulating miRNA profiling for improved molecular diagnosis of obesity-induced hypogonadism in men.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Obesity, hypogonadism, miRNAs, testosterone, insulin resistance.

Abstract:

Severe Overweight is a major factor for triggering insulin resistance and Obesity-Induced Hypogonadism (OIH) in men. This gonadal dysfunction is associated with low testosterone levels and increased co-morbidity and mortality. Our recent evidence suggests that specific hypothalamic miRNAs control the reproductive axis, contributing to OIH pathogenesis and representing potential targets for intervention. Notably, miRNAs are also detectable in plasma, of potential use as biomarkers. Yet, characterization of putative alterations of circulating miRNAs in OIH is missing. To assess whether OIH is associated with dysregulated circulating miRNAs, we applied NanoString technology for direct, large-scale miRNA determination in plasma samples from a cohort of 272 men with obesity, with or without low testosterone (T). The cohort was classified into four groups: eugonadal (n=99; T=107.06±29.4 (SD) pg/mL; mean HOMA index=2.35), eugonadal with insulin resistance (n=103; T=96.39±23.9 (SD) pg/mL; HOMA index=6.49), hypogonadal (n=27; T=58.03±9.2 (SD) pg/mL; HOMA index=2.47) and hypogonadal with IR (n=43; T=56.19±9.5 (SD) pg/mL; HOMA index= 7.44). Large-scale analyses on representative plasma samples from each group (n=11) identified three miRNA candidates (*anonymized due to pending patent protection*) with differential expression in the OIH group. Expression analyses by qPCR were then conducted in the whole cohort, using a combination of these candidates and others selected by literature research and bioinformatics. We have already validated three miRNAs deregulated in OIH that have been additionally confirmed in a second cohort, comprising lean, obese, and hypogonadal obese individuals. Furthermore, three potential candidates related to insulin resistance have been identified in the first cohort, and correlations have been found between these miRNAs and circulating levels of LH and estradiol. Altogether, our results document the existence of a molecular signature of deregulated miRNAs in OIH, which may help to better diagnose and stratify patients living with obesity, with or without low testosterone levels and/or insulin resistance.

PSII.r. Role of the RNA-Exosome Machinery and the EXOSC4 Component in Hepatocellular Carcinoma.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: RNA-Exosome, EXOSC4, preclinical models, hepatocellular carcinoma, biomarker.

Abstract:

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, with increasing incidence and high aggressiveness. However, its pathophysiology and molecular drivers remain poorly defined. Although recent studies suggest a possible involvement of RNA processing machinery in HCC, its role has not been fully explored. The aim of this study was to characterize the dysregulation and putative role of the RNA-exosome machinery, specifically the component EXOSC4, in HCC progression to identify new diagnostic/prognostic biomarkers and/or potential therapeutic targets. To this end, bioinformatic approaches were implemented to analyse the dysregulation of the RNA-exosome machinery and to characterize, *in silico*, the expression of EXOSC4 at mRNA/protein levels in HCC and control (normal or adjacent tissue) samples in 13 cohorts (2 retrospective and 11 *in silico*). Correlations between EXOSC4 expression and clinical parameters relevant to HCC progression were evaluated. Pathway enrichment analyses were performed to identify associated cellular and molecular processes. Finally, the functional role of EXOSC4 was characterized *in vitro* (proliferation, migration, etc) by modulating its expression (silencing and overexpression) in HCC lines, and *in vivo* through a preclinical model of Hep3B-induced xenograft tumors. These studies revealed that EXOSC4 was consistently overexpressed in HCC samples from the cohorts analyzed, and associated with poorer survival, higher invasion and recurrence, and with the enrichment of oncogenic pathways (cell cycle regulation or DNA repair). Consistently, *in vitro* assays demonstrated that EXOSC4 silencing induced a reduction in key functional parameters, while its overexpression was associated with increased tumor aggressiveness. Indeed, *in vivo* studies confirmed the pro-tumorigenic potential of EXOSC4 by inducing tumor growth in murine models. Therefore, EXOSC4 seems to be involved in the development and progression of HCC and could have potential diagnostic/prognostic and therapeutic utility.

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PSII.s. Sex-Based Differences in Secondary Prevention Following Acute Coronary Syndrome at One-Year Follow-Up: Are Current Strategies Adequate?

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Acute Coronary Syndrome, Sex-differences, cardiovascular prevention.

Abstract:

Acute Coronary Syndrome (ACS) remains one of the leading causes of morbidity and mortality worldwide. Although age- and sex-adjusted incidence rates of ACS have been declining, multiple studies have highlighted persistent sex-related disparities in the management of this condition. Compared with men, women often experience diagnostic delays and are less likely to receive timely coronary revascularization.The objective of our study was to evaluate the outcomes of implementing a long-term (12-month) personalized residual cardiovascular risk programme, stratified by sex, in patients discharged following an ACS event. We aimed to assess the association between circulating lipid fractions, particularly LDL-C levels, and the incidence of major adverse cardiovascular events (MACE) after one year of follow-up. From January to December 2023, all consecutive male and female patients discharged from our cardiology department following an ACS were prospectively identified and enrolled. Patients were monitored through scheduled virtual consultations at 1, 6, and 12 months to assess sex-specific differences in outcomes and detect the occurrence of MACE at one year. MACE was defined as all-cause mortality, cardiovascular death, non-fatal myocardial infarction, stroke, hospitalization for heart failure, readmission for unstable angina, or unplanned revascularization. Lipid targets were defined according to the 2023 ESC guidelines for the management of ACS. Clinical characteristics of the cohort are shown in Figure 1. Women were significantly older than men (70.8 ± 11.8 years vs. 64.8 ± 12.6 years, p = 0.002) and were less frequently active smokers (23 vs. 153, p < 0.001). The incidence of MACE was comparable between sexes (13.7% in women vs. 10% in men, p = 0.363). Only four deaths occurred during follow-up (2 in each group, p = 0.684), all of non-cardiovascular origin. At 12 months, the lipid profiles were similar across sexes (Table 1). No significant differences were observed in the proportion of patients achieving the LDL-C target of <55 mg/dL (84.9% in women vs. 85.3% in men, p = 0.750), nor in the lipid-lowering therapies prescribed. In our cohort, no sex-related differences were found in the incidence of new MACE at 12 months. LDL-C control among women was comparable to that of men, indicating effective lipid management irrespective of sex.

	Mujeres (n= 73)	**Varones (n= 252)**	***P***
Características clínicas			
Edad, años	70,8 ± 11,8	64,8 ± 12,6	**0,002**
Hipertensión arterial, n (%)	25 (34,3)	165 (65,5)	0,492
Hipercolesterolemia, n (%)	40(54,8)	117 (46,5)	0,254
Historia previa de tabaquismo, n (%)	23 (31,7)	153(60,7)	**<0,001**
Diabetes, n (%)	26 (35,9)	93 (36,8)	0,841
Hipertrigliceridemia, n (%)	3 (4,1)	17(6,7)	0,303
Presentación clínica del SCA			
IAMCEST, n (%)	30 (41,1)	83 (32,9)	0,282

IAMSEST, n (%)	27 (37)	84 (33,3)	0,585
Angina inestable, n (%)	16 (21,9)	85 (33,8)	0,264
Terapia hipolipemiante al alta			
Estatinas de alta intensidad, n (%)	73 (100)	252 (100)	0,651
Ezetimibe, n (%)	73 (100)	228 (90,5)	0,391
Ácido Bempedoico, n (%)	4 (5,5)	24 (9,5)	0,957
Anticuerpos anti-PCSK9, n (%)	1 (1,4)	3 (1,2)	0,829
Inclisiran, n (%)	1 (0,9)	1 (0,8)	0,668
Terapia hipolipemiante en el 12º mes			
Estatinas de alta intensidad, n (%)	72 (98,6)	248 (98,4)	0,245
Ezetimibe, n (%)	73 (100)	228 (90,5)	0,391
Intolerantes a estatinas, n (%)	1 (1,4)	4 (1,6)	0,251
Ácido Bempedoico, n (%)	21 (29,2)	45 (17,9)	0,866
Anticuerpos anti-PCSK9, n (%)	5 (6,8)	20 (7,9)	0,091
Inclisiran, n (%)	3 (4,1)	3 (1,2)	0,323
Objetivo LDL-c < 55 mg/dL *, n (%)	62 (84,9)	215 (85,3)	0,750
MACE, n (%)	10 (13,7)	25 (9,9)	0,364
Muerte			
No cardiovascular, n (%)	2 (2,7)	2 (0,8)	0,684
Cardiovascular, n (%)	0	0	-

	Mujeres (n= 73)	**Varones (n= 252)**	***P***
Perfil lipídico en el 12º mes			
Colesterol total, mg/dL	115.8 ± 22.8	109.1 ± 21.5	0.337
HDL-C, mg/dL	49,4 ± 21,2	45,2 ± 13	0.199
LDL-C, mg/dL	44.1 ± 18.6	44.1 ± 14.1	0,157
Lp (a), mg/dL	27 (10-352)	31.8 (10-365)	0,100
ApoB, mg/dL	51.3 ± 14.1	50.5 ± 13.5	0,683
ApoA1, mg/dL	126.4 ± 24,7	123.6 ± 25.6	0.312
No-HDL-C, mg/dL	68.8 ± 20.5	68 ± 25.4	0,541
TG, mg/dL	98.5 (30-266)	91 (36-243)	0,670
VLDL-C, mg/dL	20 (9-53)	19 (7-49)	0,819
Colesterol remanente,mg/dL	21.8 ± 6,7	21.4 ± 6,9	0,713
LDL-C/ApoB	0,85 ± 0,2	0,83 ± 0,2	0,282
TG/HDL-C	2.3 ± 0,7	2.5 ± 0,7	0,492
Índice TyG	4,6 ± 0,2	4,6 ± 0,2	0,378
PCR us (mg/dL)	0.5 (0,5-10)	0.5 (0,5-6.2)	0,087

PSII.t. Induction with Thymoglobulin or Basiliximab versus no induction in kidney transplantation with low immune risk.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Renal transplantation, induction, Thymoglobulin, Basiliximax, immunological risk.

Abstract:

Introduction: In kidney transplantation of patients at low immunological risk, induction is used to reduce acute rejection rates and/or minimize exposure to calcineurin inhibitors. However, induction is associated with an increased risk of infectious complications. For this reason, its routine use in this patient group is controversial. **Objective:** To compare rejection-free survival and the occurrence of infectious complications between non-induced kidney graft recipients and those induced with basiliximab or thymoglobulin. **Methods:** We identified 174 kidney or pancreas-kidney transplant recipients without pretransplant anti-HLA antibodies. Rejection-free survival at 6 months post-transplant was compared between induced and non-induced patients, as well as the incidence of hospitalization due to infection, significant cytomegalovirus (CMV) replication or disease, viruria (≥10 million copies), and BK viremia (≥10,000 copies) at 6 and 12 months post-transplant, as well as kidney graft function. **Results:** 43.1% of patients did not receive induction, 23.6% received basiliximab, and 33.3% received thymoglobulin. Patients induced with thymoglobulin had a lower incidence of rejection in the first 6 months post-transplant compared to non-induced patients (30.7% vs. 15.5%, p = 0.043). This difference was not observed between patients induced with basiliximab and those not induced (30.7% vs. 29.3%, p = 0.88). After adjusting for donor type, the absence of induction was associated with a higher risk of rejection at 6 months post-transplant (p = 0.023, HR 0.35, 95% CI [0.14-0.87]). Induction with thymoglobulin reduced the risk of rejection by 76% compared to non-induction (p=0.030, HR 0.25, 95% CI [0.08–0.87], while induction with basiliximab did not show a protective effect (p=0.310). However, no differences in renal function were observed at 6 (creatinine 1.48 mg/dL, RI [1.3–1.9] vs. 1.52 mg/dL, RI [1.10–1.89], p=0.079) or 12 months post-transplant (creatinine 1.5 mg/dL, RI [1.3–1.85] vs. 1.5 mg/dL, RI [1.11–1.8], p=0.325) between induced and non-induced patients, respectively. Thymoglobulin induction was not associated with a higher incidence of hospitalization due to infection or CMV or BK replication compared to non-induced patients. Hospitalization due to infection was higher among patients induced with thymoglobulin compared to those induced with basiliximab at 6 (25.9% vs. 12.2%, p=0.095) and 12 months (34.5% vs. 22%, p=0.177) post-transplant, although statistical significance was not reached. **Conclusions:** Thymoglobulin significantly reduced the risk of rejection in low immunological risk patients, without increasing early infectious complications. Basiliximab did not reduce the risk of rejection, but may reduce hospitalization due to infection. There were no differences in graft function between induced and non-induced patients.

PSII.u. Measles immunity among users of HIV pre-exposure prophylaxis (PrEP).

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Scientific Program: Infectious and Immunological diseases.
Keywords: Measles, PrEP, immunity, screening, vaccination.

Abstract:

The resurgence of measles poses a growing global public health threat, particularly in socially connected populations. We aimed to assess measles immunity in HIV pre-exposure prophylaxis (PrEP) users, a key group with increased risk of viral transmission. A cross-sectional observational study was conducted in the HIGIA cohort at Reina Sofía University Hospital (Córdoba, Spain). Baseline serum samples from 155 participants were analyzed for anti-measles IgG using chemiluminescence immunoassay (CLIA). Negative or equivocal results were confirmed by plaque reduction neutralization test (PRNT). Overall, 4.5% (7/155) of participants lacked serological immunity despite documented or presumed childhood vaccination. CLIA showed a positive predictive value of 100% and a negative predictive value of 23.3% when compared to PRNT. Notably, immunosuppression was significantly associated with measles seronegativity (p=0.043). These findings suggest the existence of immunity gaps among PrEP users that may have epidemiological relevance. Given the high positive predictive value of CLIA and the technical complexity of PRNT, revaccination of individuals with negative or borderline IgG by CLIA could be a reasonable and cost-effective strategy, particularly in the current context of global measles resurgence. Systematic immunity screening in high-risk groups such as PrEP users may help strengthen herd immunity and prevent future outbreaks.

PSII.v. Caloric restriction: a new approach to improve regenerative capacity.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: diabetes; caloric restriction; nutritional supplementation; wound healing.

Abstract:

Nutrition plays an important role in wound healing, modulating inflammatory responses, supporting collagen synthesis, and promoting the function of regenerative cells. Diabetes significantly compromises wound healing, leading to the development of chronic ulcers. Moreover, caloric restriction can help to control the effects of diabetes. For this reason, the aim of this study is to evaluate how sera from diabetic rats subjected to periods of caloric restriction influences tissue regeneration. For that, streptozotocin-induced diabetic rats were divided into two groups: (C) unrestricted diet, (RC) 50% diet. After two weeks, two dorsal wounds were made on the animals and the group and the group 50% diet was divided into three subgroups: (RC50) continued with 50% diet, (RC100) *ad libitum* diet was added, (RC100pr) *ad libitum* protein-rich diet was added. After 14 days following these diets, sera were obtained, and evaluated *in vitro* experiments. Viability, wound healing, chemotaxis, and angiogenesis assays were carried out in presence of rat's sera, using cells involved in skin regeneration, such as fibroblast, keratinocytes (HaCaT), and human umbilical vein endothelial cells (HUVEC). The rats in group RC100 showed better healing after 14 days. Sera from these animals improved the viability of fibroblasts, HaCaT and HUVEC, which was superior to the viability of cells treated with sera from healthy rats. In addition, these sera improved chemotaxis compared to the diabetic control in all three cell models. In the wound healing assay, no changes were observed in HaCaT and HUVEC. However, fibroblasts treated with sera from rats subjected to caloric restriction and then fed a balanced diet ad libitum and a high-protein diet showed an increased migration capacity. In HUVEC angiogenesis assay, a balanced diet after a period of caloric restriction was shown to increase the number of tubular structures. In conclusion, periods of caloric restriction followed by a balanced diet can positively influence regenerative capacity, leading to an improvement in skin wound healing.

PSII.w. Identification of a translatable animal model for dry eye disease using comparative analysis of tear inflammatory-soluble factors across species.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Proteins, Tears, Dry eye disease, Animal model.

Abstract:

Dry eye disease (DED) is a multifactorial syndrome characterized by loss of tear film homeostasis. This disease is a chronic inflammatory condition that displays altered levels of tear-soluble factors such as pro-inflammatory cytokines, chemokines, proteases and neurotrophins. Several DED animal models have been developed and refined to both elucidate the different mechanisms involved in the initiation and perpetuation of DED. However, there still exists a lack of translational mimicry of the human disease. Therefore, our aim in the present study was to assess the similarity of five main tear-soluble factors [interleukin (IL)-6, tumor necrosis factor (TNF)-α, matrix metalloproteinase (MMP)-9, IL-8 and nerve growth factor (NGF)] involved in the DED inflammatory response between experimental animals and humans to identify the most translational animal model for dry eye disease. Eleven species were selected for a physicochemical comparison of five tear-soluble factors involved in the inflammatory response associated to DED in human. Amino acid sequences were compared using BLAST. Protein primary structure, isoelectric point (pI) and grand average of hydropathicity (GRAVY) were determined using ExPASy and compared with humans. Tear-soluble factor study revealed that the pig was the only species with high similarity for all proteins (>60 %). Amino acid content was similar for most species compared to humans, except mouse for IL-6 and rodents and pig for IL-8. The pI and GRAVY values varied across species, though the pig and sheep were the only ones with similar pI to humans for four out of five factors. The pig exhibited the highest similarity to humans in five tear-soluble factors involved in the DED inflammatory response analysis among non-primate mammals, suggesting that the porcine model may be the most translational for DED research.

PSII.x. Virtual reality and digital twins as tools for intervention in child health: a preventive approach to childhood overweight.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Pediatric, nutrition, mediterranean diet, childhood obesity.

Abstract:

Introduction: Childhood overweight is a major public health concern, influenced by a wide range of cultural, social, and socioeconomic factors. In Spain, the prevalence affects approximately 4 out of 10 schoolchildren, reflecting a worrisome trend. The causes are multifactorial, including maternal background, gestational conditions, dietary patterns, and lifestyle during early childhood. In response to this issue, the acquisition of healthy habits is promoted, with special emphasis on the Mediterranean diet and the use of technologies as tools to assess nutritional status. **Objectives:** This study aims to analyze the prevalence of childhood overweight and dietary habits in a sample of schoolchildren. It also seeks to identify key anthropometric indicators and blood pressure values, estimate the level of adherence to the Mediterranean diet, and explore its relationship with sociodemographic variables, school type, and use of the school dining service. **Methodology:** A cross-sectional observational was conducted in five schools in the city of Córdoba, including one private, one semi-private (charter), and three public schools, selected based on geographic location and socioeconomic level. A non-probabilistic sampling method was used, excluding participants with previous medical conditions or without informed consent. Nutritional status, adherence to the Mediterranean diet, and the quality of meals provided in school canteens were assessed. Data collection included sociodemographic variables, anthropometric measurements (weight, height, waist circumference), and blood pressure. Validated questionnaires were administered, such as the KIDMED test to assess adherence to the Mediterranean diet and a 24-hour dietary recall to evaluate dietary habits. Statistical analysis included both descriptive and inferential methods. **Results:** The sample consisted of 177 schoolchildren. Significant differences were found in nutritional status according to sex, socioeconomic level, and school type. Girls showed healthier dietary patterns compared to boys. Both adherence to the Mediterranean diet and fulfillment of nutritional requirements were more favorable among schoolchildren from higher socioeconomic backgrounds, those attending schools with a dining service, and those who regularly ate at school. A significant relationship was observed between school type, use of the school canteen, and students' nutritional status. **Conclusions:** The study highlights relevant differences in nutritional indicators and dietary habits based on sex, socioeconomic level, school type, and participation in the school dining service. The findings reveal greater adherence to the Mediterranean diet and better nutritional indicators in students attending private or semi-private schools and in those who used the school canteen. These results emphasize the need to implement health promotion strategies tailored to the socio-educational context. From a professional practice perspective, encouraging the use of the school canteen as a structured environment for healthy eating and promoting specific interventions in schools with higher levels of social vulnerability are recommended to reduce nutritional inequalities from an early age.

PSII.y. Digital twin and virtual reality in eating disorders: a multifactorial investigation.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Eating disorders, Adolescents, Habits.

Abstract:

Currently, there are a lot of studies about healthy habits and their multiple benefits, both physical and mental, at any age. Because of that, there are increasingly early attempts to introduce these habits, with the aim of making them from an early age. However, it has been found that healthy living habits are influenced by different factors such as socio-cultural, news, and magazines. One of the biggest influences is the media and, above all, has been studied in adolescents and how they affect, leading to eating disorders. They are usually divided into adolescents, between 12 and 16 years of age, and especially in girls. However, there is now more influence on young people, so that this trend may be changing starting in school children aged 9-10. Through the implementation of different questionnaires with EAT 21 among all and taking measures, to know the probabilities of development of a dietary behavior disorder and perform different interventions emphasizing healthy activities.

PSII.z. MiR-191-5p represents a potential personalized diagnostic and therapeutic tool in prostate cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Prostate cancer, obesity, microARN, PSA, therapeutic target.

Abstract

Prostate cancer (PCa) is a major cause of male cancer-related mortality worldwide, emphasizing the need for non-invasive diagnostic and prognostic biomarkers and therapeutic targets for this pathology. MicroRNAs (miRNAs) have emerged as promising diagnostic and therapeutic tools for various pathologies. In this study, we investigated the microRNA landscape in plasma samples from PCa patients and explored their potential diagnostic and therapeutic value. Initially, the miRNome of plasma samples from a discovery cohort of healthy subjects (n=18) and PCa patients (n=19) was determined using an Affymetrix-miRNA array. Subsequently, the major changes were validated in an independent validation cohort [n=202 (91 healthy subjects, and 111 PCa patients)]. In addition, *in silico* and *in vitro* approaches were performed on normal (RWPE-1 and PNT-2) and tumoral (LNCaP, DU145, and PC-3) prostate cell-models. The results from the discovery cohort revealed that the expression of 104 miRNAs was significantly altered. Among these, miR-191-5p emerged as a particularly noteworthy candidate due to its potential clinical utility and its role in the pathophysiology of PCa. Specifically, miR-191-5p levels were significantly elevated in PCa patients, highlighting a potential diagnostic value particularly within the Grey Zone of PSA, wherein PSA sensitivity and specificity for diagnosing PCa is drastically limited. Notably, the diagnostic capacity of miR-191-5p was further enhanced in PCa patients with obesity (BMI>30). Then, a bioinformatics approach was employed, to identify potential targets regulated by miR-191-5p, which showed 13 potential oncogenic targets. Further analyses in PCa cell models in response to miR-191-5p overexpression identified *TMOD2*, a migration-related gene, as the most consistently decreased target. Furthermore, *TMOD2* levels were also confirmed to be modulated by miR-191-5p by using a miRNA-target interaction blocker. Altogether, our findings demonstrate that miR-191-5p may serve as an effective personalized diagnostic biomarker in PCa, particularly among patients with obesity.

Fundings: MICINN (PID2022-1381850B-I00; PRE2020-094225) and CIBERobn.

PSII.aa. Relationship between knowledge of menopause and quality of life in women aged 40-60: a cross-sectional study.

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Scientific Program: Active aging and frailty.
Keywords: Menopause, Climacteric, Knowledge, Quality of life.

Abstract:

Introduction: with the increase in life expectancy of women in Spain, the menopause is becoming more relevant. During this stage, symptoms such as hot flushes, anxiety, increased cardiovascular risk and osteoporosis can occur, the severity of which can be affected by lifestyle habits. However, for being a natural physiological process that all women go through, it is still little studied. It is essential for women to be aware of this stage so that can live in the best possible way, applying health promotion measures during the climacteric period. **Objectives**: to find out the relationship between women's knowledge of the menopause and their quality of life. **Methodology:** cross-sectional study, using two specific questionnaires aimed at women aged between 40 and 60 years attending health services in the health area of Cordoba. These questionnaires collected variables related to quality of life according to somatic, psychological, urogenital and total domains and the level of knowledge about menopause. **Results:** there was a participation of 231 women in this study. In terms of quality of life, the somatic domain is the most affected; impacting on physical well-being and being associated with age and the presence of climacteric. In addition, 58.4% of respondents had a high or very high level of knowledge about menopause, although this varied according to age, educational level and climacteric stage. **Conclusions:** women's quality of life during the climacteric period does not correspond to the level of knowledge about menopause.

PSII.bb. Identifying Musculoskeletal Risk Profiles in Athletes with Patellar Tendinopathy: A Cross-Sectional Study.

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Scientific Program: Active aging and frailty.
Keywords: Patellar tendinopathy, Risk factors, Lower limb biomechanics, Neuromuscular performance, VISA-P, Ultrasound assessment.

Abstract:

Patellar tendinopathy is a degenerative overuse injury frequently observed in athletes engaged in sports involving repetitive jumping, sprinting, or abrupt directional changes. Despite its prevalence, the multifactorial etiology of this condition remains insufficiently understood. The present study aims to analyze the relationship between various lower limb biomechanical and neuromuscular risk factors and symptom severity in athletes clinically diagnosed with patellar tendinopathy. Sixty-six athletes with confirmed patellar tendinopathy underwent a comprehensive musculoskeletal assessment including tendon morphology (ultrasound imaging), ankle dorsiflexion range of motion, plantar pressure distribution, muscle flexibility (quadriceps and hamstrings), and lower limb length discrepancy. Additionally, neuromuscular performance was evaluated through countermovement jump (CMJ), an incremental squat power test, and a 5RM knee extension task. Participants were stratified into tertiles based on perceived pain levels (VISA-P scores) to compare functional and structural variables between subgroups. Statistical analysis included normality testing, ANOVA, and post hoc comparisons as appropriate. Our findings aim to identify modifiable risk factors associated with increased symptom severity, offering valuable insights for individualized injury prevention and rehabilitation strategies. This investigation may contribute to the refinement of screening protocols and inform targeted interventions in athletic populations at risk of patellar tendinopathy.

PSII.cc. Aerobic exercise prescription for the management of pain in fibromyalgia patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: chronic pain; endurance training; exercise therapy; fibromyalgia; pain intensity.

Abstract:

Background and Objective: Fibromyalgia is a condition characterised by disabling levels of pain of varying intensity. Aerobic exercise may play a role in reducing pain in these patients. The aim of this review is to assess the dose of aerobic exercise needed, based on the frequency, intensity, type, time, volume and progression (FITT-VP) model, to obtain clinically relevant reductions in pain. **Databases and Data Treatment:** A systematic review and meta-analysis of randomized clinical trials was conducted in the Web of Science (WoS), PEDro, PubMed and Scopus databases, the search having been conducted between July and October of 2023. Risk of bias was assessed with the Cochrane Risk of Bias assessment tool 2**. Results:** Seventeen studies were included. The risk of bias varied, with six studies showing low risk; five, some concerns; and six, high risk. Aerobic exercise interventions were analysed using the FITT-VP model. Frequency ranged from 1 to 10 times per week, intensity varied from light to vigorous, and the types of exercise included music-based exercise, interval training, pool-based exercise, stationary cycling, swimming and walking. The intervention durations ranged from 3 to 24 weeks, with session lengths ranging from 10 to 45 min. Most of the studies presented significant differences, favouring aerobic exercise (MD -0.49; CI [-0.90, -0.08; p = 0.02]), with moderate to low heterogeneity in subgroup analyses. **Conclusions:** The study findings underscore the efficacy of aerobic exercise in alleviating pain among fibromyalgia patients, advocating for tailored exercise dosing to optimize adherence and outcomes.

PSII.dd. Risk scores for predicting incident heart failure admission in patients with chronic coronary syndromes: validation in a prospective, monocentric, long-term, cohort study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Chronic coronary syndrome, heart failure, risk factors.
Abstract:

Background: Heart failure (HF) admission is a serious event in the follow up of patients with chronic coronary syndromes (CCS). Stratification schemes have been described for predicting this end-point but none of them has been externally validated. **Purpose:** To develop point-scores for predicting incident HF admission with data from previous studies, to perform an external validation in an independent prospective cohort study, and to compare their discriminative ability for this event. **Methods:** We performed a literature review searching for prospective studies including patients with CCS, excluding patients with HF at baseline, with data on HF admission incidence in follow up and predictive variables. If undescribed previously, scores were developed including those variables independently associated with this outcome, and score points were assigned based in the relative magnitude of the coefficients of Cox regression models. The resulting scores were validated and their discriminative ability compared in a prospective, monocentric, 17-years cohort study, that included consecutive outpatients with CCS. **Results**: Four studies were included: two post-hoc analysis of clinical trials (CARE and PEACE) and two observational registries (CORONOR and CLARIFY). The validation cohort included 1212 patients (mean age 67±11 years, 74% male) followed for up to 17 years (median 12 years, p25-75 5-15 years), with 171 patients suffering at least one HF admission in follow-up. The proportions of the variables needed for scores calculation available in the database of the study were 75% (6/8), 88% (15/17), 100% (8/8) and 85% (17/20) respectively, for each of these study-derived scores. Discriminative ability for predicting HF admission was statistically significant for all (C-statistic 0.72, 95%CI 0.68-0.75, p<0.0005; 0.72, 95%CI 0.68-0.76, p<0.0005; 0.73, 95%CI 0.69-0.76, p<0.0005; and 0.69, 95%CI 0.65-0.73, p<0.0005 for CARE, PEACE, CORONOR and CLARIFY scores, figure 1) and paired comparison among them were all non-significant except for CORONOR and CLARIFY scores (p=0.03). The CORONOR score (Age [each year] 2 points, ejection fraction [each percentage point] -1 point, hypertension 11 points, diabetes 10 points, atrial fibrillation 14 points, body mass index [each kg/m2 unit] 1 points, symptomatic angina 11 points and multivessel disease 7 points) identified subgroups of patients with 12 years-HF admission free survival probabilities of 97%, 87 and 62% (p<0.0005, first, second and third tertile of the score, figure 2). **Conclusions:** All tested scores showed significant discriminative ability for predicting incident HF admission in this independent validation study. Their discriminative ability was similar, except that CORONOR score performed significantly better than CLARIFY score.

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PSII.ee. Rewiring Tumor Vulnerability: Targeting SAMHD1 to Boost VACV Oncolysis and Chemotherapy.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Vaccinia virus, oncolytic virotherapy, combinatorial therapy, chemoresistance.

Abstract:

In the fight against cancer, conventional treatments often fall short of clinical expectations, making oncolytic virotherapy a versatile and promising alternative. Among oncolytic viruses, Vaccinia virus (VACV) stands out due to its exceptional immunogenic properties and antitumor potential, which can be enhanced by deleting certain genes to improve safety and inserting heterologous genes to boost cytotoxicity.

However, translating oncolytic viruses into effective clinical cancer therapies faces key challenges, including the tedious process of generating viral variants, the risk of infecting non-tumor cells, and limited efficacy. Regarding this last issue, cancer's plasticity and resilience make monotherapies, including oncolytic virotherapy, often insufficient. Therefore, combination treatments, especially with chemotherapy, are crucial for tackling aggressive, poor-prognosis tumors. Yet, many current combination regimens yield only additive effects without the synergy needed for significantly improved clinical outcomes.

Thus, we propose a VACV-based virotherapy strategy that synergistically enhances chemotherapy's and oncolytic's effectiveness, facilitating its clinical translation with better results. A key element in this approach is SAMHD1, an enzyme regulating dNTP homeostasis and acting as a viral restriction factor. SAMHD1 is also linked to resistance to certain chemotherapeutic agents. Our strategy involves designing a recombinant VACV expressing the viral protein Vpx, which targets SAMHD1 for proteasomal degradation to increase, on one hand, tumor cell susceptibility to viral replication and, on the other hand, to sensitize them to nucleoside analogs. This innovative combination could significantly improve the treatment for poor-prognosis tumors, offering a promising path for more effective oncolytic + chemotherapy combinations. Two recombinant VACV-Vpx candidates, WRΔ3Vpx251 and WRΔ3Vpx239, were developed. Western blot analysis after multiple passages confirmed the stability of Vpx expression. Replication kinetics, plaque size experiments and infectivity assays showed that Vpx doesn't affect viral infectivity. Furthermore, the inserted Vpx is functional, and phenotypic analysis revealed an increased viral replication capacity during infection.

PSII.ff. Exploring the protective role of miR-191-5p in the development Institof early obesity and metabolic comorbidities.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: microRNAs, childhood obesity and metabolic syndrome.

Abstract:

Child obesity affects more than 390 million individuals aged 5 to 18 years worldwide, being also a contributing factor to the development of metabolic comorbidities in adulthood. MicroRNAs (miRNAs) are short non-coding RNA sequences whose deregulation has been linked to the pathogenesis of various conditions, including obesity. In previous stages of our research, we identified a pattern of deregulated circulating miRNAs associated with obesity in prepubertal girls. Among those, different candidates were validated in a preclinical model of early obesity using female Wistar rats. For further functional analyses, we selected miR-191-5p based on its potential involvement in key metabolic processes as predicted by bioinformatic tools. In this context, we used locked nucleic acid (LNA) technology to specifically block miR-191-5p in our preclinical model of early obesity. Systemic blockade of miR-191-5p revealed a worsening of the obesogenic state and related metabolic parameters, associated with increased food intake and diminished brown adipose tissue thermogenesis, suggesting that miR-191-5p may play a protective role against the development of obesity and its metabolic comorbidities. Interestingly, our KEGG analysis identified PLCD1 as a specific target of miR-191-5p, a protein previously linked to thermogenesis and adipogenesis. In addition, validation analysis by Western Blot in tissues from LNA-treated animals and miRNA-target mRNA *in vitro* luciferase assay confirmed the interaction between miR-191-5p and PLCD1. Furthermore, functional analyses using target site blockers technology to block specifically the miR-191-5p/PLCD1 interaction, in our preclinical model of early obesity, partially recapitulated the effects observed with miR-191-5p LNA treatment. In conclusion, our analyses unveiled a protective role for miR-191-5p in the development of early obesity and its metabolic comorbidities that is mediated, at least partially, through its interaction with PLCD1.

SESSION VI.

CHRONIC AND INFLAMMATORY DISEASES II

VIa. Safety and tolerability of diuretics withdrawal in patients with heart failure with reduced ejection fraction. REDICAE trial.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: heart failure, diuretic, congestion.

Abstract:

Introduction: Patients with heart failure with reduced ejection fraction (HFrEF) are often on chronic diuretic treatment. Our aim was to demonstrate that the withdrawal of diuretics without prognostic benefit in stable, euvolemic outpatients with HFrEF is a safe and feasible strategy (REDICAE trial; ClinicalTrials.gov identifier: NCT05964738). **Methods:** In this single-center, phase II (prof-of-concept), open-label trial, we randomized stable euvolemic outpatients with chronic HFrEF receiving guideline-directed medical therapy (GDMT) to diuretic withdrawal or diuretic maintenance. The primary outcome was to assess dyspnea by a visual analogue scale. Secondary outcomes assessed: congestion grade by plasmatic biomarkers (NT-proBNP and CA-125), ultrasound congestion parameters (pulmonary and venous excess ultrasound score) and bioimpedance analysis; quality of life status (Kansas City Cardiomyopathy Questionnaire) and functional capacity (6-minute walk test). **Results:** We randomized 98 patients (male 75%, 62±9 years-old, left ventricular ejection fraction 33±8%) during a median follow-up of 28 weeks. No significant difference in the primary outcome of dyspnea visual analogue scale was observed (least-square mean difference 2; 95% confidence interval [CI], -1.8 to 4.9; p=0.37). There were 3 (6.3%) and 5 (10%) acute decompensated heart failure events in the diuretic withdrawal and diuretic maintenance groups respectively (hazard ratio 0.59; 95% CI 0.1 to 2.5; p=0.47). We did not find any significant differences among parameters that assess volemic status. Likewise, there were no significant differences in quality of life status (p=0.67) or functional capacity (p=0.82). **Conclusions:** Diuretic withdrawal in stable euvolemic outpatients with chronic HFrEF and GDMT did not increase dyspnea nor worsen volume status.

VIb. Distinct Ex Vivo Immune Signatures Modulated by JAK and TNF Inhibitors Predict Treatment Response in biologic and targeted synthetic DMARDs-Naïve Rheumatoid Arthritis Patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Rheumatoid Arthritis, Targeted synthetic drugs, Biologic synthetic drugs, -omics, Cytokines and Chemokines, Biomarkers.

Abstract
Background: Despite therapeutic advances, 20–40% of Rheumatoid Arthritis (RA) patients do not respond to biologic or targeted synthetic DMARDs (b/tsDMARDs). Understanding the molecular effects of each drug may help identify responders to specific therapies. **Objectives:** 1) Characterize the *ex vivo* molecular and cellular effects of JAK (JAKi) and TNF (TNFi) inhibitors on RA immune cells. 2) Identify, *in vivo*, RA patient subgroups with distinct baseline drug-specific proteomic signatures and their association with clinical response. **Methods:** Peripheral blood mononuclear cells (PBMCs) and neutrophils from 48 b/tsDMARD-naïve RA patients were cultured with autologous serum and Baricitinib (JAKi) or Etanercept (TNFi)(10μM) for 24 and 12 hours, respectively. Proliferation, adhesion, and NETosis were measured using commercial kits, and protein changes assessed via proximity extension assay targeting 92 inflammatory proteins in the supernatant. Baseline serum from 193 RA patients (36 JAKi-naïve, 32 non-naïve JAKi, 125 TNFi-naïve) was analyzed to evaluate the association between proteomic signatures and treatment response. **Results:** Baricitinib and Etanercept reduced proliferation, adhesion, and NETosis in PBMCs and neutrophils from naïve RA patients, each modulating distinct inflammatory signatures: Baricitinib mostly affected Th17/adaptive immunity, while Etanercept targeted acute inflammation. Unsupervised clustering based on JAKi-regulated protein signature identified two subgroups among JAKi-naïve patients; high baseline expression correlated with greater ΔDAS28-CRP reductions at 3, 6, and 12 months. This stratification was not predictive in non-naïve JAKi or TNFi-naïve patients, indicating specificity. Similarly, TNFi-regulated signature stratified TNFi-naïve patients, with high baseline levels predicting improved response at 6 and 12 months. It showed no association with response in JAKi-naïve patients, confirming its treatment-specific relevance. **Conclusions:** JAKi and TNFi have distinct effects on RA immune cells, and their *ex vivo*-modulated protein signatures stratify patients, as each correlates with response to its corresponding treatment but not the other, supporting their use in guiding personalized therapy.

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VIc. Percutaneous revascularization of chronic total coronary artery occlusions reduce pro-inflammatory and hypoxic status in cardiac microenvironment.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: coronary artery disease, chronic total occlusion, percutaneous coronary intervention, angiogenesis, hypoxia, oxidative stress.

Abstract:

Introduction: Chronic total occlusions (CTO) are common in patients with coronary artery disease. They constitute an in vivo model of chronic ischemia where the stimulation of compensatory local responses (increase of oxidative stress, liberation of proinflammatory chemokines and increase of vascular endothelial growth factors) promote angiogenesis and myocardial tissue survival. This study aimed to evaluate the acute effect of percutaneous revascularization of CTO (CTO-PCI) in the hypoxia and inflammatory status of cardiac microenvironment. **Material and methods:** Prospective observational study performed at Reina Sofia University Hospital including 33 patients. The main inclusion criteria were the presence of one single CTO and proven myocardial viability by cardiac magnetic resonance imaging. Patients underwent CTO-PCI and blood samples from coronary sinus were collected before and just after reaching TIMI flow 3 in the occluded artery. Samples were immediately processed and stored at -85 ºC. A total of 28 biomarkers related to oxidative stress, inflammation, hypoxia and angiogenesis were measured using ELISA method. Besides, baseline peripheral blood samples were harvested to measure conventional biomarkers related to inflammation and myocardial damage. The follow up period was six months, and a control peripheral blood sample test was performed at the end of follow up. **Results:** There was a significant decrease in inflammatory chemokines (CXCL8, IL1B), angiogenesis-related growth factors (ANGP 1, VEGFA, VEGFD, KDR, EGF, THPO), oxidative stress molecules (OLR1), cellular damage-related molecules (CASP8) and hypoxia-related factors (EPO). Besides, a significant increase in anti-inflammatory chemokines was evidenced (IL-10). At six months, the level of conventional inflammatory (CRP, homocysteine) and myocardial damage biomarkers (BNP, Troponin I) were significantly lower than baseline. **Conclusion:** The results of our study suggest that CTO-PCI has an acute beneficial effect in cardiac microenvironment, reducing inflammatory and hypoxic status. It might be related to the decrease in systemic inflammation and myocardial damage evidenced in follow-up.

VId. FGF23 as a Bridge Between Energy Metabolism and Hypertension in Chronic Kidney Disease.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Chronic Kidney Disease; AMPK; Energy metabolism; FGF23; Hypertension.

Abstract:

Our group is uncovering a key role of FGF23 in the development of hypertension associated with chronic kidney disease (CKD). FGF23 is a bone-derived cytokine whose levels are markedly elevated in CKD patients. The kidney is the second most energetic-demandant organ in the human body. Most of its energy is derived from mitochondrial oxidative phosphorylation (OXPHOS) in renal tubules. A significant decrease of OXPHOS in CKD patients has been reported. Alterations in energy metabolism may contribute to hypertension through the new renal and vascular actions of FGF23. In this study, we will explore the role of FGF23 on energetic metabolism and hypertension. To achieve this aim we have performed in vivo and in vitro experiments. Changes in energetic parameters such as AMPK and Seahorse studies were performed in human proximal tubular cells (HK2) and vascular smooth muscle cells (VSMC). In vivo, we used two different experimental models. In the first one, Hyp mice (with high levels of FGF23) were used to analyze changes in oxylet. In the second one, we used rats with elevated levels of recombinant FGF23 for 4 weeks using Alzet pumps. Here, we performed metabolomic, Seahorse and bioenergetic sensors studies in renal tissue. High levels of FGF23 induce hypertension and an increment in oxygen consumption and energy expenditure. Measurements of mitochondrial respiration showed an augment of the oxygen consumption rate supporting our findings. This increase was accompanied by changes in metabolites and regulator proteins related to energetic metabolism affecting to OXPHOX. Interestingly, AMPK phosphorylation ratio showed a positive correlation with the values of blood pressure in the rats with high FGF23. While additional research is required, FGF23 seems to act as a critical nexus connecting energy metabolism, hypertension, and the progression of CKD, potentially serving as a therapeutic target to delay disease advancement and related complications.

VIe. Therapeutic Modulation of NAD+ Metabolism in Inflammatory Rheumatic Disorders by TNFi and NAD+ Precursors.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Biomarkers, Complementary Therapy, Genomics and Proteomics, Inflammation, Anti-TNF Drugs.

Abstract:

This study investigates the NAD+ metabolome in chronic inflammatory and rheumatic diseases (CIRDs), its association with clinical traits, TNFi therapy effects, and NAD$^+$ boosters' potential to restore pathway alterations and reduce inflammation. Whole blood samples were collected from 70 healthy donors (HDs), 80 rheumatoid arthritis (RA), 80 psoriatic arthritis (PsA), and 80 spondyloarthritis (SpA). NAD$^+$ pathway metabolites (NAD+, NADH, NAM, NMN, NR, NADP and Tryp) were analyzed using two-dimensional NMR. A longitudinal analysis in 30 patients per disease assessed NAD$^+$ metabolome changes after TNFi therapy. Peripheral blood mononuclear cells (PBMCs) from 15 patients per disease were treated *ex-vivo* with NAD+ boosters (NR, NMN, NRT, NRH, and NAR), and intracellular NAD+/NADH levels and secreted inflammatory mediators (Olink Inflammation Panel, Cobiomic) were evaluated. CIRDs showed a reduced NAD$^+$/NADH ratio and elevated NAM and NMN versus HDs. RA displayed decreased NAD$^+$, while PsA and SpA increased NADH; SpA also had reduced NADP and elevated Trp. These disease-specific alterations correlated with distinct clinical features: in RA, the NAD$^+$/NADH ratio was negatively associated with DAS28, while NADH and NMN positively with CRP, tender/swollen joint counts (TJC, SJC) and autoantibodies with NADH. In PsA, the NAD$^+$/NADH ratio and NAD+ levels correlated negatively with TJC and SJC, and disease activity respectively. Uveitis correlated positively with NAD$^+$, and psoriasis with NAM. In SpA, axial forms had a lower NAD+/NADH ratio, with positive correlations between ESR and NMN, entesitis and NADH, and dactylitis with Trp. TNFi therapy restored levels toward HDs. Boosters increased intracellular NAD$^+$ in PBMCs, with NRH being the most effective. Boosters reduced inflammatory mediator secretion, showing disease and booster specific effects. Conclusively, The NAD$^+$ metabolome was altered in CIRDs, displaying disease-specific disruption patterns associated with key clinical manifestations. TNFi treatment normalized NAD$^+$ pathway metabolites, suggesting a role during therapeutic response. NAD$^+$ boosters increase intracellular NAD$^+$ and attenuate inflammation, supporting a therapeutic target in CIRDs.

VIf. Design of 3D scaffolds for hypoximetic drugs-controlled release and their application in wound healing.

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Keywords: diabetic foot, 3D-scaffolds, drug release, hypoximetic compounds (HMMs) and angiogenesis.

Abstract:

Chronic wounds have become a significant burden for both patients and healthcare systems around the world. Severe complications induced by these wounds can lead to limb amputation or even death and urgently require more effective treatments. In this context, 3D bioprinting offers an innovative approach to design functional scaffolds capable of controlled drug release and enhancing tissue repair. Hypoximetic compounds (HMMs) mimic hypoxic conditions by promoting HIF-1α expression, a key factor in new blood vessel formation. We developed HMMs that activate the B55α/PP2A/HIF/SIRT1/AMPK axis, which plays a key role in angiogenesis, protection against cellular stress and apoptosis, improvement of endothelial vascular function, and reduction of inflammation. This study aims to develop 3D-bioprinted scaffolds with HMM compounds, activators of the B55α/PP2A/HIF/SIRT1/AMPK pathway, to improve therapeutic efficacy and provide an alternative to standard formulations in the treatment of wound healing and diabetic foot ulcers. To this end, 3D-scaffolds were manufactured using the Bio X6 bioprinter (CELLINK), incorporating HMMs into their structure. Swelling and degradation analyses, along with Fourier-transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD), were performed to assess component interactions and evaluate the crystallinity of the materials. The release of HHM from the scaffold was monitored using the NIH-3T3-EPO-Luc cell line to evaluate HIF-1 activation. HHM-3D implants promoted sustained EPO gene transcription, indicating persistent HIF-1 activation throughout the two-month study period. *In vitro* studies showed biocompatibility, improving cell adhesion and proliferation. Subsequently, their efficacy was also evaluated in preclinical wound healing *in vivo* models, exhibiting that HMM scaffolds increased the expression of proangiogenic factors such as *Hgf, Epo, Vegf-a* and *B55a* at the injury site, induced angiogenesis, reduced inflammation and promoted the repair of damaged tissue. Therefore, the design of drug delivery 3D-scaffolds represents an innovative and promising strategy for treating chronic ulcers, improving clinical outcomes and patient quality of life.