15TH IMIBIC YOUNG INVESTIGATORS MEETING

ABSTRACT BOOK

IMIBIC

UNIVERSIDAD D CÓRDOBA

HURS

15TH IMIBIC YOUNG INVESTIGATORS MEETING

IMIBIC BUILDING
ASSEMBLY HALL
CÓRDOBA, 14-15 OCTOBER, 2024

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Acknowledgements

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.

PROGRAMME

Day 1 (14th OCT)

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

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

09:00 – 10:15 – SESSION I. Cancer I (IMIBIC Assembly Hall)

Chairs: Dr. Miguel Ruiz Cruz and Dr. Pedro Gómez Arias

Ia. 09:00 – 09:15	Defining the clinical value of circulating splicing factors in prostate cancer: SRRM1 as a novel predictive biomarker and exploitable therapeutic target. **Antonio Prats Escribano.**
Ib. 09:15 – 09:30	Shedding light on heterogeneity in small intestine neuroendocrine neoplasms: comprehensive characterization of the spliceosomic landscape in siNENs. **Victor García Vioque.**
Ic. 09:30 – 09:45	Unleashing the Diagnostic, Prognostic and Therapeutic Potential of the somatostatin/cortistatin system in Glioblastomas. **Ana S. De la Rosa-Herencia.**
Id. 09:45 – 10:00	Lack of PRDX6 alters lipid composition and traffic in hepatocarcinoma SNU475 cells and sensitizes to ferroptosis. **Ángel Ortiz-Alcántara.**
Ie. 10:00 – 10:15	Biliary brush cytology by ERCP for malignancy diagnosis, tertiary center experience from 2016-2022. **Paloma Alañón Martínez.**

10:15 – 11:15 – Coffee Break

11:15 – 12:30 – SESSION II. Chronic and inflammatory diseases (IMIBIC Assembly Hall)

Chairs: **Dr. Mª Belén Pastor Villaescusa and Dr. Hatim Boughanem**

IIa. 11:15 – 11:30	High levels of FGF23 cause hypertension: Clinical and Experimental Studies. **Raquel María García Sáez.**
IIb. 11:30 – 11:45	Clinical Effectiveness and Molecular Cardiovascular Effects of Baricitinib in Biologic-Naïve Rheumatoid Arthritis Patients: A Comparative Study with TNF Inhibitors and Traditional DMARDs. **Laura Muñoz Barrera.**
IIc. 11:45 – 12:00	Clustering Algorithm as an Exploratory Analysis of Different Clinical Phenotypes in Systemic Sclerosis. Data from the PRECISESADS Study. **Andrea Cid Chaves.**
IId. 12:00 – 12:15	The lipidomic and proteomic profiles in Antiphospholipid Syndrome patients are intricately linked to disease pathogenesis and modulated by Ubiquinol supplementation. **Beatriz Vellón García.**

IIe. 12:15 – 12:30 Ceftriaxone Administration Reduces Vascular Calcification Associated with an Experimental Model of Chronic Kidney Disease. **Teresa Obrero Sojo.**

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

Rafael Estévez, (BIOMOL Chief Executive Officer); Victoria García (BIOMOL Key Account Manager); María Barrero (BIOMOL Marketing)

13.30 - 15.00 – Lunch

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

Chairs: **Dr. Fernando Leiva Cepas and Dr. Alexander Batista Duharte**

PSI.a. The effect of the fourth dose of Pfizer COVID-19 vaccine. **Ester Irene Reina Alfonso.**

PSI.b. Transition from Psoriasis to Psoriatic Arthritis: Does Family History Influence the Time to Onset of Arthritis in Psoriasis Patients? **Marta Flores de Francisco.**

PSI.c. Longitudinal Study of the Neuropsychological Profile in Severe Mental Disorder. **Ana Jiménez Peinado.**

PSI.d. Immobilisation with compression bandage vs. antebraquial splint in distal radius fractures operated by open reduction and locking plate. Randomised clinical trial. **José Ignacio Miró Jiménez.**

PSI.e. Analysis of circulating immune cell gene expression profiles and their relationship with the severity of patients with alopecia areata. **Irene Suárez Vergne.**

PSI.f. Contribution of contrast-enhanced mammography in a population-based breast cancer screening programme: a prospective study including 860 consecutively recalled women. **Margarita Pedrosa Garriguet.**

PSI.g. Understanding the contribution of the redox state to the pathophysiology of Pseudomyxoma Peritonei: proteomic and functional analysis. **María Torres Martínez.**

PSI.h. Novel circulating natural killer cell subsets as biomarkers in alopecia areata progression. **Pablo Alvarez Heredia.**

PSI.i. Likelihood of respiratory disease in people with bipolar disorder: A systematic review and meta-analysis. **David Laguna Muñoz.**

PSI.j. Beyond the obstruction: immunological perspectives on aortic stenosis and coronary artery disease. **Antonio Costa.**

PSI.k. Incidence, mutational spectrum and prognostic impact of cebpa-bzip mutations in aml patients treated with semi-intensive regimens. **Esther Prados de la Torre.**

PSI.l. Molecular characterization and functional role of serpins in hepatocellular carcinoma. **María Serrano Jiménez.**

PSI.m Liquid biopsy methylation patterns enable effective risk stratification and monitoring of metastatic pancreatic cancer patients. **Pablo Francisco Cano Ramírez.**

PSI.n. Alteration in the molecular components of cellular machineries that control gene expression in thyroid cancer and their association with tumor behavior and/or clinical features. **Andrea Martínez Vara.**

PSI.ñ. Evaluation at real time of the repair of abasic sites in DNA using molecular beacons. **Ariadna Muñoz Fernández.**

PSI.o. Chronic kidney disease-related cognitive impairment is associated with lower abundance of membrane-bound Klotho in the cerebral cortex. **Daniel Jurado Montoya.**

PSI.p. Analysis of epigenetic factors regulating the circulating immune cells network in patients with mild and severe alopecia areata. **Carmen Mochón Jiménez.**

PSI.q. Acute non-traumatic neurological injury linked to rat hepatitis E virus infection. **Lucía Ríos Muñoz.**

PSI.r. Machine learning algorithms in controlled donation after circulatory death under normothermic regional perfusion: Role of Machine Learning classifiers as predictive models of graft survival. **Rafael Calleja Lozano.**

PSI.s. Tac1-expressing cells in the ventral premammillary nucleus and ventromedial hypothalamus are essential for induction of the pre-ovulatory LH surge. **Marta Navarro Torrente.**

PSI.t. DYRK2 promotes apoptosis in chemotherapy-resistant lung tumor cells through its USP28-mediated stabilization. **Irene Aguilera Ventura.**

PSI.u. Uncovering the Microbiome of Pseudomyxoma peritonei with novel omics approaches. **Rafaela Rocha Pezzopane.**

PSI.v. Efficacy and safety of Dalbavancin in the outpatient parenteral antimicrobial treatment of complex infections. **Cristina Molina Gutierrez.**

PSI.w. RASSF1A methylation analysis in Lung Cancer. **Carmen María Ayala Roldán.**

PSI.x. Development and validation of 3D-cell culture models generated from patients-derived xenografts with Pseudomyxoma Peritonei. **Ana Martínez López.**

PSI.y. VCE-005.1: A promising vasculogenic B55α/HIF activator that prevents endothelial cells damage and enhances wound healing. **Isabel Lastres Cubillo.**

PSI.z. Influence of high-impact physical activity on lumbopelvic muscle mechanical properties in asymptomatic nulliparous women: a case-control study. **Ines Cruz Medel.**

PSI.aa. Normothermic Regional Perfusion in Donation After Cardiac Death Liver Transplantation for Primary Sclerosing Cholangitis. **Manuel Durán Martínez.**

PSI.bb. Metabolic disorders and lifestyle behaviours in adolescents from under-resourced families in the context of E-DUCASS study. **Esther Porras Pérez.**

PSI.cc. LRG1, a potential therapeutic target in obesity. **Olga García Ruiz.**

PSI.dd. Developmental changes in the hypothalamic fat-sensing and ceramide pathways in a mouse model of Prader-Willi syndrome. **Álvaro Aranda Torrecillas.**

PSI.ee. Prevalence between type 2 diabetes mellitus and depression in older adults. **Francisco Javier Sánchez Jiménez.**

PSI.ff. Optimization of a Rabbit Corneal Endothelial Dysfunction Model for Pre-Clinical Studies. **Laura Ortega Llamas.**

PSI.gg. GPC1, an adipose extracellular matrix protein associated with obesity and inter-organ communication. **Beatriz González Almécija.**

PSI.hh. Study of the immune system changes during bee venom immunotherapy. **Nadine Blanco Toledano.**

PSI.ii. Nutritional Assessment and Adherence to the Mediterranean Diet in Schoolchildren from Cordoba. **María del Mar Uclés Torrente.**

PSI.jj. Enzymatic nanoparticles driven in situ drug synthesis for disease treatment. **Irene Bruque Monge.**

PSI.kk. Influence of revascularization in the diabetic-ischemic foot. **Avencia Arévalo Garcia.**

PSI.ll. Inclusive Virtual Training of Healthcare Providers for Migrant Pregnant Women. **Alessia Bisio.**

PSI.mm. Uncovering new molecular signatures in psoriatic arthritis by employing high-throughput proteomic analysis of immune cells. **Eduardo Martín-Salazar.**

PSI.nn. Dolutegravir, an antiretroviral compound that promotes adipose tissue metabolic dysfunction. **Samuel Lorenzo Pino.**

PSI.ññ. Characterization of outer membrane proteins in isolates of Klebsiella pneumoniae by SDS-PAGE, MALDI-TOF and whole genome sequencing. **Cristina Elías López.**

15:45 – 17:00 – SESSION III. Nutrition (IMIBIC Assembly Hall)

Chairs: **Dr. Cristian Rodelo Haad and Dr. Rafael González Manzanares**

IIIa. 15:45 – 16:00 Cannabidiol induces apoptosis of hepatic stellate cells and alleviates liver inflammation and fibrosis in a murine model of androgenic obesity. **Francisco José Ponce Díaz.**

IIIb. 16:00 – 16:15 Metabolic and transcriptomic insights into obesity-induced hypogonadism: Unveiling the role of Kiss1 neurons. **Manuel Jiménez Puyer.**

IIIc. 16:15 – 16:30 Relationship Between Liver Fibrosis Degree and the Incidence of Cardiovascular Events in Secondary Prevention Patients. CORDIOPREV Study. **Esperanza Sastre Menor.**

IIId. 16:30 – 16:45 Lifestyle habits according to the chronotype among a vulnerable population at risk of food insecurity. **Alejandro Serrán Jiménez.**

17:00 – 17:30 – Biomedicine & Bioengineering: a practical case (IMIBIC Assembly Hall)

17:30 – 18:45 – SESSION IV. Multidisciplinary (IMIBIC Assembly Hall)

Chairs: **Dr. Alejandro Ibáñez Costa and Dr. Álvaro Arjona Sánchez**

IVa. 17:30 – 17:45 Short term outcomes of a Patient-tailored Residual Cardiovascular Risk Reduction Program for Post-Acute Coronary Syndrome Patients. **Javier Herrera Flores.**

IVb. 17:45 – 18:00 Defining Early and Established Rheumatoid Arthritis Through Multi-Omic Profiling: Links to Disease Status and Treatment Response. **Ismael Sánchez Pareja.**

IVc. 18:00 – 18:15 Exploring the role of the metabolic factor LEAP-2 on puberty onset. **Carmen Torres Granados.**

IVd. 18:15 – 18:30 The relevance of the Nonsense-Mediated Decay and RNA-Exosome cellular machineries in the pathophysiology of pituitary tumours. **Miguel Eduardo García García.**

IVe. 18:30 – 18:45 BIORICA10- A longitudinal metabolic study in young adult with extrauterine growth restriction. **Laura Palomino-Fernández.**

Day 2 (15th OCT)

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

08:30 – 09:45 – SESSION V. Cancer II (IMIBIC Assembly Hall)

Chairs: Dr. Lucía Beltrán Camacho and Dr. Mª Ángeles Puche Larrubia

Va. 08:30 – 08:45 Targeting metabolism overcomes immune evasion and improves immunotherapy efficacy in GSNOR-deficient colorectal cancer tumors. María Teresa Sánchez Montero.

Vb. 08:45 – 09:00 Exploring the role of NOP10 in pancreatic ductal adenocarcinoma: Implications for telomere stability and tumor progression. María Trinidad Moreno Montilla.

Vc. 09:00 – 09:15 Pathophysiological dysregulation of the inflammasome machinery in glioblastoma. Ignacio Gil Duque.

Vd. 09:15 – 09:30 NK cell profiling predicts cetuximab efficacy in metastatic colorectal cancer and highlights TIGIT as a potential therapeutic target. Carmen Navarrete Sirvent.

Ve. 09:30 – 09:45 SMG7 as a potential driver of chronic liver disease progression to HCC. Betsaida Ojeda Pérez.

09:45 - 10:30 – Coffee Break

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

Chairs: Dr. Iván Arias de la Rosa and Dr. Silvia Fernández Álvarez

PSII.a. The administration of anti-FGF23 normalizes iron metabolism and erythropoiesis alterations associated with high FGF23 levels with normal kidney function. Karen Valdés-Díaz.

PSII.b. Role of regulatory T cells in the cellular immune response to influenza vaccine in older adults. Mónica Espinar García.

PSII.c. Assessing the Effects of a Basketball Program on Children's Physical Fitness and Cardiometabolic Health: The BIPIC Study. **Cristina Castro Collado.**

PSII.d. Age-dependent modulatory role of diet on the expression of miRNAs involved in aging-associated processes in patients with coronary heart disease: From CORDIOPREV study. **Maite Sánchez Giraldo.**

PSII.e. Linking Synovial Protein Signatures to Inflammation and Early Treatment Response in Rheumatoid Arthritis patients. **Sagrario Corrales Díaz-Flores.**

PSII.f. Metastatic prostate cancer prediction model based on telomeres. **Juan Manuel Rubio Galisteo.**

PSII.g. Phenotypic and Functional Analysis of Cytokine-Induced Memory-Like Natural Killer Cells. **Isabel Maria Vallejo Bermudez.**

PSII.h. Nox4 modulates erythropoiesis in response to massive intravascular hemolysis. **Cristina García Caballero.**

PSII.i. Impact of treatment of anemia on the quality of life in patients with chronic kidney disease. **Raquel Ojeda López.**

PSII.j. Optimization of adipose tissue fibrosis model based on 3D cell culture platforms. **María González Ruiz.**

PSII.k. Proteogenomic approaches reveal novel pathogenic splicing variants in hepatocellular carcinoma: the RBM22-PNKD axis. **Natalia Herman Sánchez.**

PSII.l. DYRK2 protein kinase as an unknown main member of MAPK pathway and its implications in cancer. **Lucía Suanes Cobos.**

PSII.m. VIRADS, is the new RADS really useful? **Jose Enrique Gordillo Arnaud.**

PSII.n. Lack of peroxiredoxin 6 in colon cancer cell line HCT116 alters cell proliferation, migration and invasion. **Antonio Manuel Montes Osuna.**

PSII.ñ. Characterization of the rna-exosome machinery component exosc4 in the development and progression of hepatocellular carcinoma. **Maria Isabel Pozo Relaño.**

PSII.o. Association between mortality and serum phosphorus in incident dialysis older patients. **Isabel López López.**

PSII.p. Optimization of a Rabbit Severe Corneal Disease Model for Pre-Clinical Studies. **Mayelín Pérez Perdomo.**

PSII.q. Human Leukocyte Antigen class II susceptibility for non-specific Lipid Transfer Proteins allergy. **Paula Álvarez Romero.**

PSII.r. Effect of re-exposure to repeated mismatches in kidney retrasplant. **Casimiro A. Valle Domínguez.**

PSII.s. How affect caloric restriction and nutritional supplementation in diabetic rat wound healing? **Victoria Pulido Escribano.**

PSII.t. The dual role of SNW1 in splicing and transcription as an approach to explore pancreatic neuroendocrine tumors progression. **Clara González-Pérez.**

PSII.u. Exploring The Relationship Between Hormonal Contraceptive Use And Ulcerative Colitis Flares: A Longitudinal Analysis. **Beatriz Gros Alcalde.**

PSII.v. Use of proton pump inhibitors in chronic patients: evaluation of quality of life. **María José Reyes Medina.**

PSII.w. Efficacy an Safety of Intraoperative Hyperthermic Intraperitoneal Chemotherapy for Locally Advanced Colon Cancer. A Phase 3 Randomized Clinical Trial. **María Esther Espinosa Redondo.**

PSII.x. Validation of diagnostic nomograms based on mass spectrometry-based urinary biomarkers to distinguish clinically significant prostate cancer: complementing MRI pathway. **Ana Cristina Morillo Tejedor.**

PSII.y. Effectiveness of two different Exergaming Systems in addition to Conventional Treatment for Physical Therapy in Patients with Multiple Sclerosis: A Study Protocol for a Multicenter, Assessor-Blind, 24-Weeks, Randomized Controlled Trial. **Alvaro Alba Rueda.**

PSII.z. Gender differences in the initiation and persistence of the first bDMARD in Spondyloarthritis: An 18-year follow-up study. **Diana Maria Margareta Moldovan.**

PSII.aa. Metabolic Gateways to Puberty: Unraveling the Role of Hypothalamic Lipid-Sensing Mechanisms. **Elvira Rodríguez Vázquez.**

PSII.bb. Validation of a CRISPR-Cas9 system for genetic manipulation of multi-drug resistant Klebsiella pneumoniae. **Víctor Gálvez Soto.**

PSII.cc. Analysis of SHOX2 and LINE-1 methylation and expression profiles in non-small cell lung cancer. **Litzy Gisella Bermudez Liscano.**

PSII.dd. Interaction of extracorporeal circulation with the degradation of the endothelial glycocalyx. **Luna López Coleto.**

PSII.ee. Aerobic Exercise Prescription for Pain Reduction in Fibromyalgia: A Systematic Review and Meta-Analysis. **David Casanova Rodríguez.**

PSII.ff. Diabetes produces changes in serum composition that compromise the differentiation and viability of mesenchymal stem cells to osteoblasts. Possible effect of sitagliptin treatment. **Bárbara Torrecillas Baena.**

PSII.gg. Planning-navegation assisted surgical treatment of orbital fractures. **Ana Isabel Fortis Ballesteros.**

PSII.hh. Kisspeptins centrally modulate food intake and locomotor activity in mice independently of gonadal steroids in a sexually dimorphic manner. **Silvia Daza Dueñas.**

PSII.ii. Role of hyperandrogenism in the pathogenesis of metabolic dysfunction-associated fatty liver disease (MAFLD) linked to polycystic ovary syndrome. **Andrea Rodríguez Martín.**

PSII.jj. Exploring the interplay between RNA methylation and splicing dysregulation in neuroendocrine tumors. **Laura Gutiérrez Camacho.**

PSII.kk. Potential use of ceftazidime-avibactam in patients with KPC-producing Klebsiella pneumoniae with low-risk of death: ¿when is it indicated? **Patricia Cosano Pérez.**

PSII.ll. Deciphering pulmonary tumor microenvironment through MALDI Imaging Mass Spectrometry: new approaches for tumor expansion inhibition. **Cristina María López Vázquez.**

PSII.mm. Relationship of glycosylated haemoglobin levels to cognitive impairment in the geriatric population. **María Morales-Cabanillas**.

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 – 12:30 – Session VI. Infectious and immunological diseases, organ transplantation (IMIBIC Assembly Hall)

Chairs: **Dr. Juan Antonio Moreno Gutiérrez and Dr. Henning Kirst**

VIa. 11:15 – 11:30 The role of central pulmonary venous gas measurement in extending donor lungs criteria for transplantation: a multicenter analysis of the European Society of Thoracic Surgeons (ESTS) lung transplant working group. **Benito Cantador Huertos.**

VIb. 11:30 – 11:45 Metabolic Reprogramming Induced by SARS-CoV-2 Accessory Proteins in Lung Epithelial Cells. **Raúl Fernández Rodríguez.**

VIc. 11:45 – 12:00 Refining the QuantiFERON-CMV cut-off: the Quanti-CMV study enhances CMV non-replication prediction in kidney and lung transplant recipients. **Elisa Ruiz-Arabi.**

VId. 12:00 – 12:15 Analysis of surgical indication and time to surgery in infective endocarditis and its relationship with prognosis. **Jorge Perea Armijo.**

VIe. 12:15 – 12:30 Serological and molecular survey of rat hepatitis E virus (Rocahepevirus ratti) in drug users. **María Casares Jiménez.**

12:30 – 13:30 – Plenary Lecture: "Unlocking cancer's metabolic code: a path toward novel therapeutic windows". Dr. Patricia Altea Manzano (CABIMER - Andalusian Molecular Biology and Regenerative Medicine Centre). (IMIBIC Assembly Hall)

13:30 – 14:00 – 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 109 abstracts were received. The Organizing Committee distributed all abstracts received amongst 36 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 5 (very good). It should be noted that the Organizing Committee has not evaluated or scored any of the submitted abstracts.

On September 16th, 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 one session for Multidisciplinary, Nutrition, Chronic and Inflammatory diseases, 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 5, 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 10 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 previous editions will be excluded from the process.

ORAL COMMUNICATIONS
Abstracts

SESSION I.

CANCER I.

Ia. Defining the clinical value of circulating splicing factors in prostate cancer: SRRM1 as a novel predictive biomarker and exploitable therapeutic target.

Authors: Antonio Prats-Escribano1,2,3, Antonio J. Montero-Hidalgo1,2,3, Enrique Gómez-Gómez1,3,4, Manuel Galán-Cañete1,2,3, Francisco Porcel-Pastrana F1,2,3, Jesús M. Pérez-Gómez1,2,3, María Ortega-Bellido1,2,3, Julia Carrasco-Valiente1,3,4, Laura Chamorro-Castillo1,3,4, Juan P. Campos-Hernández1,3,5, Oriol A. Rangel-Zuñiga1,3,5, Teresa González-Serrano1,3,6, Rafael Sánchez-Sánchez1,3,6, André Sarmento-Cabral1,2,3, Manuel D. Gahete1,2,3,7, Juan M. Jiménez-Vacas1,2,3, Raúl M. Luque RM1,2,3,7.
Affiliations: 1. Maimonides Institute for Biomedical Research of Cordoba (IMIBIC), Cordoba, Spain; 2. Department of Cell Biology, Physiology, and Immunology, University of Córdoba, Cordoba, Spain; 3. Hospital Universitario Reina Sofía (HURS), Cordoba, Spain; 4. Urology Service, HURS/IMIBIC, Cordoba, Spain; 5. Lipids and Atherosclerosis Unit, Internal Medicine Unit, HURS, Cordoba, Spain; 6. Anatomical Pathology Service, HURS, Cordoba, Spain. 7. Network Biomedical Research Center for Physiopathology of Obesity and Nutrition, (CIBERobn), Cordoba, Spain.
Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Splicing factors; SRRM1; SNRNP200; SRSF3; prostate cancer; biomarker.

Abstract:

Prostate cancer (PCa) is the second most prevalent cancer among men. The main screening method, based on prostate-specific antigen (PSA) determination, exhibits significant limitations (including poor sensitivity/specificity). Thus, more accurate non- invasive diagnostic biomarkers, with potential utility as prognostic and therapeutic targets, are required in PCa. In this context, dysregulation of the splicing process has emerged as a key feature in PCa development/progression, and several splicing factors (SFs; including SRRM1, SNRNP200, and SRSF3), have been found to be implicated in PCa pathophysiology. However, despite some SFs have been reported to be secreted by cancer cells, this event has not been addressed in PCa. Therefore, we aimed to explore the presence and potential clinical value of SRRM1, SNRNP200, and SRSF3 in human plasma samples. Thus, plasma levels of these SFs were measured (using ELISAs) in control individuals (n=41) and PCa patients (n=175). We identified, for the first time, that these SFs were detectable in human plasma samples, being corroborated in an independent cohort (n=313). Notably, plasma levels of SRRM1 and SNRNP200, but not SRSF3, were significantly higher in PCa patients vs. controls. Plasma SRRM1 levels were associated with relevant features of castration-resistant PCa (CRPC), a lethal disease stage. Moreover, SRRM1 levels positively correlated with androgen receptor (AR) and AR splicing variant 7 (AR-V7) expression/activity in PCa tissues. Furthermore, in vivo SRRM1 silencing in CRPC-derived xenografted tumors reduced aggressiveness features and AR/AR-V7 activity. Taken together, our findings suggest that circulating levels of SRRM1 may serve as a valuable diagnostic and prognostic non-invasive biomarker for PCa. Additionally, SRRM1 may hold a promising therapeutic value, offering a clinically relevant opportunity for further exploration in human studies.

Fundings: ISCIII (DTS20/00050), MICIIN (FPU18/02485, FPU18/06009, PRE2020- 094225, PRE2022-000741, PID2022-1381850B-I00).

Ib. Shedding light on heterogeneity in small intestine neuroendocrine neoplasms: comprehensive characterization of the spliceosomic landscape in siNENs.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: splicing, small intestine, neuroendocrine neoplasms, survival.

Abstract:

Small intestine neuroendocrine neoplasms (siNENs) are one of the most prevalent NENs subtypes (18% of all diagnosed NENs). Despite this, most of the molecular mechanisms responsible for the progression of siNENs remain unknown, in part due to their high heterogeneity. In this regard, alternative splicing has been shown to be a key molecular layer, which could contribute to this heterogeneity, but its dysregulation in siNENs and its possible connection to tumour biology is currently unexplored. Therefore, the aim of this study was to evaluate the spliceosomic landscape —splicing machinery components and alternative splicing variants— of siNENs to identify putative novel biomarkers in order to improve the prognosis of these patients. Thus, we carried out a comprehensive spliceosomic characterization employing RNA-seq data of 43 siNEN FFPE samples, dividing them into long (> 5 years) or short (< 5 years) survival groups. First, we quantified gene expression (htseq-count) and identified differentially expressed genes (DESeq2), as well as quantified splicing events (rMATS). Downstream analyses were performed using different R packages, Metaboanalyst and SpliceTools software. Expression analysis of the splicing machinery indicated that some components are differentially expressed in both groups and with important clinical parameters, like metastasis or invasion. Additionally, 158 differential splicing events emerged between these two groups, and were enriched in key cancer processes such as migration, splicing or KRAS signalling. Moreover, these events were associated to relevant clinical parameters such as the Ki67 index or metastasis. Notably, 33 of these events implied a drastic shift in transcript fate regarding nonsense-mediated decay. In conclusion, this work provides, for the first time, a comprehensive and insightful vision of the spliceosomic landscape in siNENs aimed at helping to unravel the heterogeneity of these tumours and to identify molecules that favour the prognosis and development of personalised therapeutic strategies.

Ic. Unleashing the Diagnostic, Prognostic and Therapeutic Potential of the somatostatin/cortistatin system in Glioblastomas.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Glioblastoma; Somatostatin/Cortistatin Receptors, Biomarkers; Therapeutic Tool.

Abstract:

Glioblastoma (GBM) remains the deadliest brain tumor, with a median survival of about 14 months post-diagnosis, largely due to late-detection and resistance to standard treatments based on surgery followed by radiotherapy and/or chemotherapy. These clinical challenges and the ambiguous follow-up emphasize the need for the identification of novel and effective diagnostic/prognostic and therapeutic approaches to combat this pathology. In this sense, the somatostatin/cortistatin (SST/CORT) system represent a valuable therapeutic target for various cancers. Therefore, our objective was to comprehensively characterize (clinically and molecularly) the expression of the SST/CORT-system components [ligands/receptors (SSTRs)] using five cohorts of patients and tested the in vitro therapeutic response of different SSTR-agonists in primary patient-derived glioblastoma cells. A clear downregulation of the whole SST/CORT-system (except for SSTR5) in glioblastoma vs. non-tumour brain samples was demonstrated (with high discriminatory capacity) using our internal cohort of patients (employing microfluidic technology based on qPCR methodology), and validated in four different human external cohorts (RNA-seq and microarray data). The downregulation of the main receptor (SSTR2) was also validated at protein levels by immunohistochemistry. Notably, poor survival and other critical parameters related to aggressive phenotype (i.e., mesenchymal/classical subtype, non-G-CIMP and IDH1 wildtype phenotype) were robustly associated to SSTR1/SSTR2 downregulation. Treatment with different SST-analogues [first and second generation (octreotide and pasireotide, respectively)], and specific agonists for SSTR1/2/5 significantly reduced cell-proliferation in primary patient-derived GBM-cells. Molecularly, octreotide and pasireotide exerted their antitumour effects through key signaling factors related to glioblastoma-aggressiveness (i.e., JAK-STAT/NF-κB/TGF-β-pathways) and cell cycle markers (i.e., CDKN-1A/1B). Altogether, this study demonstrated that SST/CORT-system is drastically altered in GBM representing a potential source of useful diagnostic and prognostic biomarkers, and that SSTR-agonists might represent an efficient therapeutic strategy to treat patients with glioblastoma.

Id. Lack of PRDX6 alters lipid composition and traffic in hepatocarcinoma SNU475 cells and sensitizes to ferroptosis.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: hepatocellular carcinoma, peroxiredoxin 6, oxidative stress, ferroptosis, lipid peroxidation.

Abstract:

Peroxiredoxin 6 (PRDX6) is a multifunctional enzyme provided with peroxidase, phospholipase A2 and lysophosphatidilcoline acyltransferase activities, being involved, among other processes, in phospholipid peroxide repair and metabolism. In this work we report a comparative study between SNU475 cell lines with (WT) or without (KO) PRDX6 at the level of global lipid composition and lipid-related cellular processes. Human hepatocarcinoma SNU475 cells lacking PRDX6 have shown modified lipid composition and lipid-related cellular processes presenting a general decrease in all kinds of lipids. Among these modifications, the formation of lipid droplets accumulating various polyunsaturated fatty acids (PUFA) and PUFA-containing triacylglycerols has been described, indicating an altered fatty acid flux in absence of PRDX6. An increment in arachidonic acid (AA) containing phosphatidylcholines was also observed, suggesting a preference of the PLA2 activity of this enzyme for these AA-storing glycerophospholipids. SNU475-KO cells also showed increased total lipid hydroperoxide levels, which reverted to the levels of SNU475-WT cells after transfection with PRDX6. Moreover, lack of PRDX6 enhanced sensitivity to erastin-induced ferroptosis, leading to changes in morphology and survival of SNU475-KO cells, which could be explained by an alteration in plasmalogen homeostasis. The results presented here show that all three enzymatic activities of PRDX6 contribute to the role of this enzyme in a variety of cellular processes, from membrane phospholipid remodelling and functional diversity of glycerophospholipids to the fate of lipid peroxides and modulation of AA levels. These contributions explain the complexity of the changes that loss of PRDX6 exerts on cellular functionality.

Ie. Biliary brush cytology by ERCP for malignancy diagnosis, tertiary center experience from 2016-2022.

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Keywords: ERCP, biliary brushing, pancreatic adenocarcinoma.

Abstract:

Background: Biliary brushing cytology during endoscopic retrograde cholangiopancreatography (ERCP) is used to assess the nature of a biliary stricture. Its eThe aim was to evaluate the diagnostic yield of brush cytology in biliary strictures and to identify predictive factors associated with a positive diagnosis of malignancy. Methods: Observational retrospective study in a tertiary center. All adult patients undergoing a biliary brushing during ERPC from 2016 to 2022 were included. **Results**: A total of 5309 patients underwent ERCP within the evaluated period. Out of these, biliary brushing was performed in 518 patients including 568 cytologies, 57.7% (299) men, median age 74 (64-84) years old. There were 24% (126) benign strictures and 76% (392) malignant of which the most common etiology were pancreatic adenocarcinoma 56% (220) and extrahepatic cholangiocarcinoma 19.4% (76). There were 4.4% (25) early post-ERCP complications: pancreatitis 1.9% (11), bleeding 1.7% (10), bacteriemia 0.5% (3) and perforation 0.2% (1). The sensitivity, specificity, positive predictive value, and negative predictive value were 48%, 98%, 98% and 37%, respectively. Sensitivity was 45% and 52% in pancreatic adenocarcinoma and cholangiocarcinoma, respectively. In the univariate analysis, age, leukocytes, total bilirubin, alanine transaminase (ALT), alkaline phosphatase and gamma-glutamyl transferase (GGT) were higher in malignant than in benign pathology. However, in multivariate analysis only age (p=0.005), leukocytes (0.017) and bilirubin (p <0.0001) were significant. **Conclusions**: Biliary brushing cytology during ERCP is a safe procedure with low sensitivity but high specificity. Age, bilirubin and leukocytes are associated to positive biliary cytology.

SESSION II.

CHRONIC AND INFLAMMATORY DISEASES.

IIa. High levels of FGF23 cause hypertension: Clinical and Experimental Studies.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: FGF23, Hypertension, Calcium entry, VSMC, Vascular function, chronic kidney disease.

Abstract:

Introduction: Ongoing studies suggest a potential connection between FGF23 and hypertension. Elevated FGF23 changes VSMCs phenothype that may aggravate arterial stiffness promoting vascular dysfunction. This study aimed to demonstrate in patients with chronic kidney disease (CKD) and in experimental models that high levels of FGF23 have a direct effect on vessels inducing hypertension. **Methods**: For the clinical studies, 159 g5 non-dialysis CKD patients were selected to analyze the association between FGF23 and blood pressure (BP). We used generalized additive models to analyze the possible non-linear association between iFGF23 and BP. In rats, recombinant FGF23 (15µg/day) was administered for 28 days via Alzet pumps to elucidate the pro-hipertensive effects and the mechanisms. In VSMCs, intracellular calcium entry stimulated by Ang2 (100nM) or Thapsigargin (2.5µM) was measured after the administration of high levels of recombinant FGF23 (2ng/ml) for 9 days. To elucidate the mechanisms, we used inhibitors targeting FGF Receptors (1-4) and Erk1/2 phosphorylation. We measured alterations in vascular remodeling, calcium channels and proteins associated with vascular contraction. Results: In CKD patients, the values of systole, diastole and pulse pressure were positively associated with FGF23 levels. These correlations were independently of other parameters such as age, GFR or gender. In vivo, elevated FGF23 led to hypertension and changes in the aorta expression of AGTR1 and SERCA2a. In VSMCs, FGF23 promoted calcium entry after Ang2 and Thapsigargin stimulation. The inhibition of FGFR1-3, Erk1/2 phosphorylation but not FGFR4 reduced calcium entry suggesting to FGFR1-3 and Erk1/2 as potential therapeutical targets. In vitro, high FGF23 levels increased AGTR1 and SERCA2a as compared to control cells. **Conclusions**: In summary, this study shows a direct association between elevated FGF23 levels and hypertension in patients with CKD and experimental models. These findings underscore FGFR1-3, Erk1/2, SERCA2a, and AGTR1 as potential therapeutic targets to treat FGF23-induced hypertension.

IIb. Clinical Effectiveness and Molecular Cardiovascular Effects of Baricitinib in Biologic-Naïve Rheumatoid Arthritis Patients: A Comparative Study with TNF Inhibitors and Traditional DMARDs.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Rheumatoid Arthritis, Biological therapies, JAK inhibitors, Cardiovascular disease.

Abstract:

The main objective of this study was to analyse the specific effects of the JAK-STAT inhibitor Baricitinib compared to other disease-modifying antirheumatic drugs (DMARDs) on the pro-inflammatory, pro-thrombotic, and cardiovascular (CV) risk profile of RA patients. A longitudinal prospective study included 75 DMARDs-naïve RA patients divided into three groups (25 each) starting: conventional DMARDs, TNF-alpha inhibitors (TNFi), and Baricitinib (4 mg/day). A control group of 25 age- and sex-matched healthy donors was included. Patients over 65 years, with BMI>30 or thrombotic disorders were excluded. Clinical and demographic data were collected before and after 6 months of treatment. The study assessed hypercoagulability status and CV-risk profiles using carotid intima-media thickness (CIMT); thrombotic activation molecules: D-dimer, Von-Willebrand factor, and thrombin-antithrombin complex; and 92 CV-related proteins using proximity extension assay technology (Olink). At baseline, disease activity levels, CV-risk scores and atherogenic indexes were similar among treatment groups, with a pathological CIMT prevalence of 30-35%. After six months, remission rates were 75% for Baricitinib, 58% for TNFi, and 42% for DMARDs. Elevated baseline D-dimers were significantly reduced in all groups. CV proteome analysis revealed changes in 32 proteins with Baricitinib treatment, 26 with TNFi, and 23 with conventional DMARDs. Eight proteins were commonly modified by all treatments, related to inflammation, vascular remodeling, chemotaxis, and apoptosis. Baricitinib uniquely modulated 21 proteins, affecting inflammation, cell adhesion/signalling, coagulation, atherosclerosis and lipid metabolism. While Baricitinib increased certain pro-atherogenic and pro-inflammatory proteins (without exceeding the levels in HDs), it also reduced others that might counterbalance these effects, including inflammatory cytokines and oxidative stress, atherosclerosis development, and vascular inflammation regulators. In conclusion, Baricitinib demonstrates higher clinical efficacy in treating DMARD-naïve RA patients, compared to TNF-alpha inhibitors and conventional DMARDs, while it also uniquely modulates the CV proteome by balancing CV-risk factors through specific protein adjustments.

Fundings: Lilly (I4V-NS-0032), ISCIII (PI21/0591, CD21/00187, RICOR-21/0002/0033), RYC2021-033828-I; co-financed by European Union.

IIc. Clustering Algorithm as an Exploratory Analysis of Different Clinical Phenotypes in Systemic Sclerosis. Data from the PRECISESADS Study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Systemic sclerosis, phenotypes, organic damage.

Abstract:

Background: Systemic sclerosis is a systemic autoimmune disease with multiorgan involvement. Its pathophysiology is based on three pillars: vasculopathy, fibrosis, and autoimmunity. Despite advances in recent decades and a clear improvement in prognosis, there remains a subset of patients who develop early organ involvement. Therefore, patient stratification is essential to identify those most susceptible to organ involvement and to potentially anticipate its development. The objective of this study was to determine the existence of different groups in systemic sclerosis based on a clustering algorithm using clinical and serological variables. **Methods**: An observational cross-sectional study was conducted with 402 patients diagnosed with systemic sclerosis, using data from the multicentric PRECISESADS study. Clinical (sex, age, interstitial lung disease, smoking...) and serological variables (autoantibody positivity) were collected from all patients. Clustering algorithm following the k-means technique was applied to our participants, integrating age, ILD, smoking, sclerodactily, sex, PAH, calcinosis, arthritis, esophageal dismotility, Raynaud, telangiectasias, muscular weakness, GERD, digital ulcers and pitting scars. The optimal number of clusters was determined using the silhouette width method. Then, univariate analysis was performed to assess the differences between the clusters. **Results**: Two groups were identified (Cluster 1 = 221 (54,97%) and Cluster 2 = 181 (46,03%)). The results of the univariate analysis are presented in Table 1. In the first cluster, we observed a slightly younger population (57.16 vs. 59.15 years), although this difference does not reach statistical significance ($p = 0.12$). Generally, patients in Cluster 2 exhibited a significantly higher prevalence of organ involvement, such as ILD (14.48% vs. 59.67%), PAH (9.05% vs. 30.94%), esophageal dysmotility (34.84% vs. 67.96%), and inflammatory joint involvement (20.81% vs. 39.78%). Other systemic sclerosis characteristics were also more prevalent in Cluster 2, notably the presence of calcinosis (6.79% vs. 43.09%), digital ulcers (4.98% vs. 15.47%), and telangiectasias (39.82% vs. 83.43%). We also conducted an analysis of the serological characteristics of the patients. Anti-centromere 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%). The graphical distribution of the clusters is shown in Figure 1. Comorbidities such as hypertension, dyslipidemia, smoking, and obesity did not show significant differences between both clusters. **Conclusion**: These results suggest that identifying clusters may exhibit distinct clinical and serological profiles, suggesting the presence of heterogeneous subgroups within the systemic sclerosis population. This stratification could be pivotal in tailoring patient management and predicting disease progression. Further research is required to validate these findings and explore their clinical implications.

Variable	Cluster 1 (n = 221)	Cluster 2 (n = 181)	p-value
Age, mean (SD)¶	57.16 (13.24)	59.15 (12.38)	0.12
Sex (female), n (%)¶	188 (85.06)	151 (83.43)	0.75
ILD, n (%)¶	32 (14.48)	108 (59.67)	< 0.01
Sclerodactyly, n (%)¶	118 (53.39)	170 (93.92)	< 0.01
PAH, n (%)¶	20 (9.05)	56 (30.94)	< 0.01
Raynaud phenomenon, n (%)¶	209 (94.57)	180 (99.45)	0.01
Ever smoking, n (%)¶	32 (14.48)	23 (12.71)	0.71
Hypertension, n (%)	72 (32.58)	57 (31.49)	0.90
Centromere positivity, n (%)	96 (43.44)	53 (29.28)	< 0.01
Scl-70 positivity, n (%)	44 (19.91)	70 (38.67)	< 0.01
Arthritis, n (%)¶	46 (20.81)	72 (39.78)	< 0.01
Calcinosis, n (%)¶	15 (6.79)	78 (43.09)	< 0.01
Digital ulcers, n (%)¶	11 (4.98)	28 (15.47)	< 0.01
Telangiectasias, n (%)¶	88 (39.82)	151 (83.43)	< 0.01
GERD, n (%)¶	117 (52.94)	150 (82.87)	< 0.01
Dyslipidemia, n (%)	57 (25.79)	41 (22.65)	0.54
Pitting scars, n (%)¶	65 (29.41)	133 (73.48)	< 0.01

Current immunosuppressants, n (%)	32 (14.48)	74 (40.88)	< 0.01
Obesity, n (%)	23 (10.41)	16 (8.84)	0,72
Esophageal dysmotility, n (%)¶	77 (34.84)	123 (67.96)	< 0.01
Puffy fingers, n (%)	116 (52.49)	109 (60.22)	0.14
Muscle weakness, n (%)¶	21 (9.50)	51 (28.18)	< 0.01

Table 1. Clinical and serological characteristics of patients by cluster. SD refers to Standard Deviation. ¶ stands for variables used in the clustering algorithm.

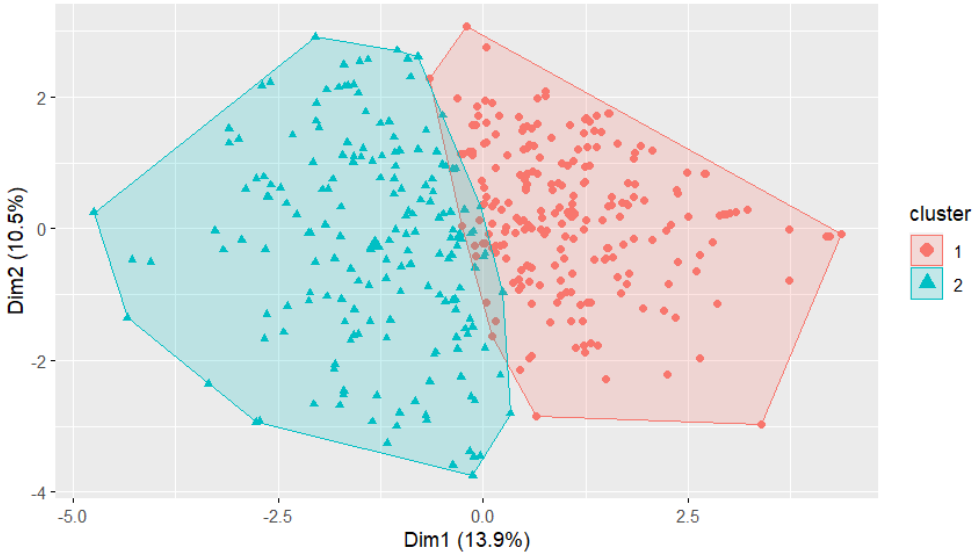

Figure 1. Graphical representation of clusters in systemic sclerosis.

IId. The lipidomic and proteomic profiles in Antiphospholipid Syndrome patients are intricately linked to disease pathogenesis and modulated by Ubiquinol supplementation.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Biomarkers, metabolomics, proteomics, Atherosclerosis, Complementary Therapy.

Abstract:

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by antiphospholipid antibodies and a hypercoagulable state. This study characterized the circulating lipidomic and proteomic profiles of APS patient, investigate the effects of ubiquinol (reduced coenzyme Q10) supplementation, and asses the impact of the circulating alterations on macrophages and endothelial cells (HUVECs). 129 APS patients and 43 healthy donors (HD) underwent clinical and molecular characterization. Serum levels of 92 cardiovascular-related proteins were assessed using proximity extension assay (Olink/Cobiomic) and over 250 metabolites using nuclear magnetic resonance metabolomics (Nightingale). Unsupervised clustering analysis was conducted to stratify patients based on molecular and clinical features. Changes in molecular profile of 15 APS patients receiving Ubiquinol supplementation were evaluated. In vitro studies exposed macrophages and HUVECs to APS serum combined with CoQ. Proteomic analysis identified 33 altered CVD-related proteins in APS serum, linked to clinical features. APS patients exhibited significant alterations in 53 metabolites, including reduced atheroprotective lipids and increased pro-atherogenic mediators. Unsupervised clustering analysis identified two patient subgroups. Cluster 2 (C2), compared to cluster 1 (C1), had higher levels of VLDL, LDL, triglycerides, fatty acids, and higher prevalence of arterial thrombosis, elevated aGAPSS, and traditional CVD risk factors. Correlations among altered proteins and metabolites were identified. In vivo ubiquinol treatment partially reversed altered lipidomic and proteomic profiles, reducing pro-atherogenic and increasing anti-atherogenic markers. In vitro, pre-treating macrophages and HUVECs with CoQ prior to exposing them to serum from highest CVD risk C2 patients, prevented the induction of CVD markers in both cell types and the formation of foam cells in monocytes. Conclusively, APS patients exhibit altered lipidomic and proteomic profiles associated with increased CVD risk. In vivo, ubiquinol supplementation restored these altered profiles in APS patients, highlighting its cardiovascular benefits. In vitro, APS-related molecular changes amplify the pro-atherogenic profile of macrophages and HUVECs, which was mitigated by CoQ.

IIe. Ceftriaxone Administration Reduces Vascular Calcification Associated with an Experimental Model of Chronic Kidney Disease.

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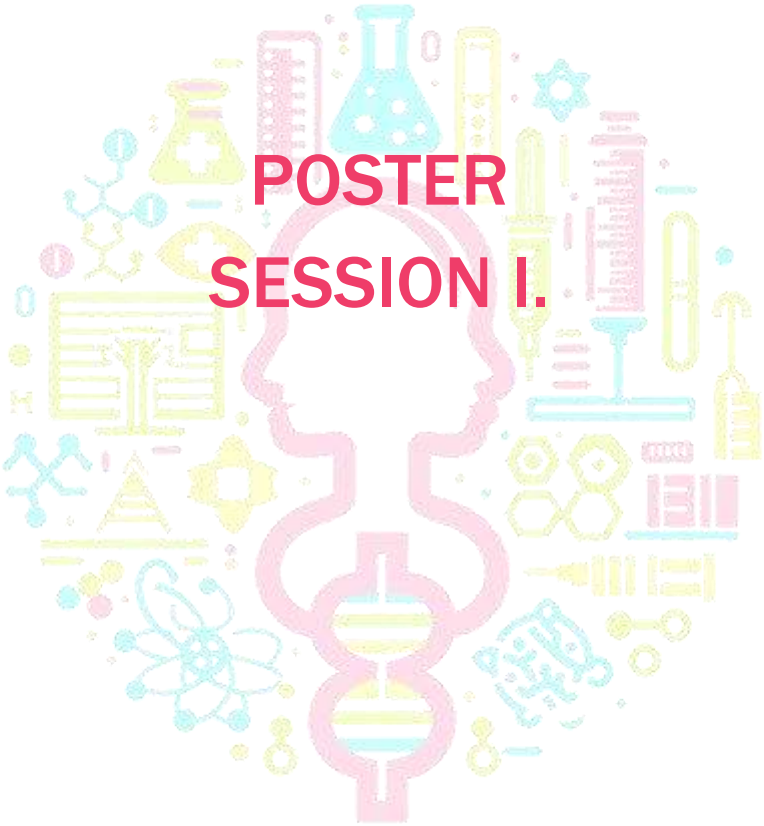
Scientific Program: Chronic and Inflammatory diseases.
Keywords: Vascular calcification, gut microbiota, ceftriaxone.

Abstract:

In chronic kidney disease (CKD), there is a persistent microinflammatory state associated with disease progression and the development of vascular calcification (VC). Changes in the gut microbiota have been linked to an increased inflammatory state, which may contribute to CKD progression and VC. This study aimed to investigate the impact of microbiota depletion, through the antibiotic ceftriaxone, on inflammation, renal function, and VC in an experimental uremia model. Oral ceftriaxone (400 mg/kg/day) was administered for 7 days. Subsequently, 5/6 nephrectomy (Nx) was performed, and a diet containing 1.2% phosphorus and 60 ng/kg/48h calcitriol was administered for 14 days. The animals were divided into three groups: control (n=7), Nx (n=7), and Nx+ATB (n=7). Parameters of mineral metabolism, renal function, VC, and the composition of fecal microbiota (V3-V4 region of 16S rRNA gene, Illumina MiSeq 300×2) were measured. Interestingly, animals treated with the antibiotic had significantly lower serum phosphorus levels and reduced calcium and phosphate content in the thoracic aorta, as confirmed von Kossa staining. Regarding the microbiota, a significant state of dysbiosis was observed in the Nx group compared to the control. Bacteria belonging to the Erysipelotrichaceae, Oscillospiraceae and Peptostreptococcaceae families increased, while bacteria from the Xantobacteraceae and Pseudomonadaceae decreased. Compared to the Nx group, antibiotic administration reduced the presence of bacterial genera such as Colidextribacter and Escherichia-shigella, which are linked to inflammation, fever, and diarrhea. Both genera showed a positive correlation with serum phosphorus levels, and Colidextribacter was also positively correlated with phosphorus and calcium levels in the thoracic aorta. Additionally, antibiotic administration increased the presence of the butyrate-producing genus Lachnoclostridium. In conclusion, the depletion of the microbiota by ceftriaxone administration reduced hyperphosphatemia and the degree of VC. This finding suggests that altering the microbiota by ceftriaxone could be a promising therapeutic strategy to prevent VC in patients with CKD.



POSTER SESSION I.

PSI.b. Transition from Psoriasis to Psoriatic Arthritis: Does Family History Influence the Time to Onset of Arthritis in Psoriasis Patients?

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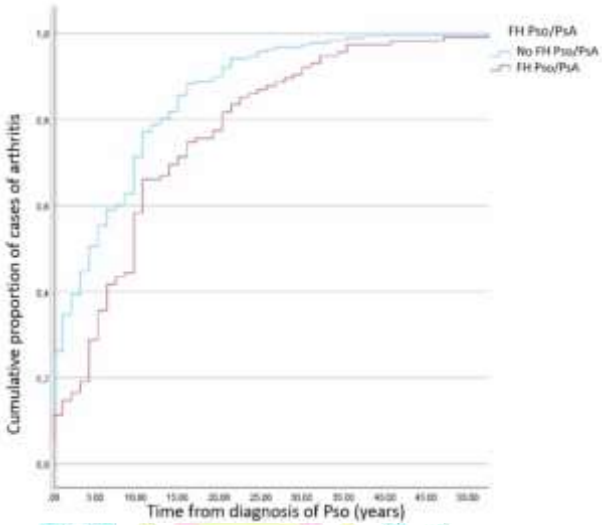
Scientific Program: Chronic and Inflammatory diseases.
Keywords: psoriatic arthritis, family history, latency, Kaplan-Meier, Cox, Hazard ratio.

Abstract:

Psoriatic arthritis (PsA) is a debilitating disease that occurs in up to one-third of patients with psoriasis (Pso), generally manifesting after the onset of Pso. Numerous studies have analyzed the risk factors for the development of PsA in patients with Pso, highlighting family history. However, there is little evidence about what determines the latency period between the onset of Pso and the development of arthritis. **Objectives**: a) To analyze the clinical phenotype of PsA based on the presence or absence of a family history of Pso or PsA (FH Pso/PsA). b) To determine which factors (including FH Pso/PsA) influence the speed of onset of arthritis after the initial presentation of Pso. Methods: We conducted a retrospective analytical study including 359 patients diagnosed with PsA according to the "Classification Criteria for Psoriatic Arthritis" (CASPAR). These patients were divided based on the presence or absence of a family history of Pso/PsA (FH Pso/PsA). We collected clinical, radiographic, and treatment variables for each patient, as well as the dates of onset of Pso and arthritis. For the comparison of variables, Student's t-test (for quantitative variables) and Chi-square test (for qualitative variables) were used. We designed a survival analysis with Cox multiple regression to determine which factors influence the speed of onset of arthritis after the initial presentation of Pso. **Results**: Of the 359 patients included, 37.5% had a family history of Pso/PsA (FH Pso/PsA). Patients with FH showed cutaneous-onset forms of PsA more frequently than those without FH (86.4% vs. 70%; $p<0.001$), as well as a younger age at disease onset (Table 1). The latency period between the onset of Pso and the development of arthritis was longer in patients with FH (median time: 9.6 vs. 4.3 years; log-rank: $p<0.001$; Figure 1). In the multivariable analysis, FH Pso/PsA (HR 0.88 (95% CI 0.78–0.99)) and a younger age at Pso onset (HR 1.03 (95% CI 1.02–1.04)) were associated with a delay in the onset of arthritis relative to Pso (Omnibus test: $p<0.001$). **Conclusion**: Family history of Pso/PsA in patients with Pso is associated with a longer time until the onset of arthritis. Therefore, patients with FH not only require a higher index of suspicion for PsA but also need longer follow-up periods to detect it. Collaboration between Dermatology and Rheumatology will be essential for early diagnosis and optimal management.

Variable	FH Pso/PsA	No FH Pso/PsA	P value	Variable	FH Pso/PsA	No FH Pso/PsA	P value
Gender (male)	57.6%	60.9%	0.537	PsA starting type DIP Polyarticular Oligoarticular Spondylitis	 6.8% 17.4% 62.1% 13.6%	 4.5% 22.3% 62.7% 10.5%	 0.483
Starting age of psoriasis (years)	30.18 ± 13.24	39.94 ± 15.39	0.001	Inflammatory lumbar pain	36.4%	29.1%	0.156
Starting age of arthritis (years)	40.69 ± 14.17	45.94 ± 13.38	<0.001	DIP inflammation	36.4%	27.9%	0.095
PsA starting type Cutaneus type Joint type Both types	86.4% 3% 10.6%	70% 6.8% 23.2%	<0.001 0.128 0.003	Aquilean entesitis	8.3%	10%	0.604
Pso body surface <10% 10-25% >25%	14.6% 16.9% 68.5%	13.2% 3.6% 73.2%	0.615	Dactilytis	25.8%	32.3%	0.196

Nail injury	50.8%	49.1%	0.762	Radiographic sacroiliitis	40.9%	31.8%	0.084
HLAB27 +	6.1%	11.5%	0.097	Radiographic DIP injury	26.7%	21.8%	0.296
Dactilytis	25.8%	32.3%	0.196	Treatment tsDMARD bDMARD	 49.2% 18.3%	 57.1% 11.2%	 0.167 0.073



PSI.c. Longitudinal Study of the Neuropsychological Profile in Severe Mental Disorder.

Authors: Ana Jiménez-Peinado, MD, MSc1,2,3, David Laguna-Muñoz, MD1,2,3, María José Jaén-Moreno, MD,PhD1,2,3, Fernando Sarramea, MD,PhD 1,2,3,4.
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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Schizophrenia, Bipolar Disorder, Neuropsychology, Executive Function, Memory, Attention.

Abstract:

Neuropsychological impairments are common in both schizophrenia and bipolar disorder. Studies have shown that cognitive capacity can predict clinical and functional outcomes. However, few studies have analyzed neurocognitive performance in these patients using comprehensive neuropsychological batteries, and the results have been inconsistent. This study assessed the longitudinal trajectory of cognitive performance in patients with schizophrenia and bipolar disorder (BD), the two main diagnoses among severe mental disorders (SMI). We conducted a longitudinal, prospective study of 63 patients diagnosed with schizophrenia and BD. The mean follow-up period was 43.38 months, with evaluations at baseline and at three years using a neuropsychological test battery (Trail Making Test (TMT) and Verbal Span (forward and backward digits) from WAIS III, assessing executive functions, working memory, verbal memory, visual memory, visuomotor processing), clinical scales (scale for Positive and Negative Symptoms of Schizophrenia, Hamilton Depression Rating Scale, Young Mania Rating Scale), and functional outcome measures (Global Assessment of Functioning scale). Neuropsychological, clinical, and functional performances were compared at baseline and 3 years. The sample included 63 patients, with 48 diagnosed with schizophrenia (76.2%) and 15 with BD (23.8%). The mean ages were 48.93 and 53.14 years, respectively. The cross-sectional cognitive profiles were similar for both groups. After controlling for age, illness duration, and antipsychotic medication burden, cognitive function did not differ significantly over time for most tests, except for the TMT-B test, where schizophrenia patients showed significant improvement at 3 years. This preliminary study suggests that clinical stability and cognitive performance are closely linked in severe mental disorders. Recognizing this relationship is crucial, as these factors can be fundamental in achieving functional recovery.

PSI.d. Immobilisation with compression bandage vs. antebraquial splint in distal radius fractures operated by open reduction and locking plate. Randomised clinical trial.

Authors: J.I. Miró, A. García Vaquero-pina, A. Sierras Cristiá , J.I. Duca a, A. García Bensi , G.L. Gómez Rodríguez , A. Galán Novella , A. Izquierdo Fernández.
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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Schizophrenia, Bipolar Disorder, Neuropsychology, Executive Function, Memory, Attention.

Abstract:

Introduction: Currently, there is a lack of prospective studies to unify criteria about type and time for postoperative immobilisation in surgical distal radius fractures. The aim of this study is to compare functional and radiological results in two groups of distal radius fractures treated with internal fixation with locking plate, and immobilised with antebrachial splint or compression bandage for 3 weeks. **Material and methods:** A randomised clinical trial was carried out with two parallel groups with 3, 6, and 12 weeks of follow-up. Main and secondary functional variables were measured, such as pain on VAS scale, values on PRWE, DASH and MRS scale, range of motion in flexion—extension, complications, etc. In addition, some radiological variables were measured at preoperative period and one week after surgery, such as union time, dorsal displacement, shortening, ulnar variance, etc. **Results:** A total of 62 patients were evaluated: 27 immobilised with bandage and 35 with splint. Analysis of the results obtained showed significant differences in both groups for almost all radiological variables from pre to postoperative period, and for all functional variables from 3 to 12 weeks after surgery. No significant differences were found between the two groups for any of the radiological and functional variables evaluated (VAS 3—12 weeks: p = .584; PWRE 3—12 weeks: p = .248; flexion range of motion 3—12 weeks: p = .959; extension range of motion: p = .50; union time: p = .89). **Conclusions:** We do not find clinical or radiological differences between immobilisation with antebrachial splint or compression bandage for distal radius fractures operated with locking plate. A greater number of patients and follow-up are necessary to extrapolate the results to the general population and to establish criteria for good postoperative management of these fractures.

PSI.e. Analysis of circulating immune cell gene expression profiles and their relationship with the severity of patients with alopecia areata.

Authors: Irene Suárez-Vergne, MD1,2; Carmen Mochón-Jiménez, MD1,2; Juan de Luque-Fernández, MD1,2; Macarena Aguilar-Luque, BSc1; Pedro J. Gómez-Arias, MD1,2; Pablo Álvarez-Heredia4; Alexander Batista-Duharte, PhD4; Alejandra Pera, PhD4; Beatriz Isla-Tejera, PharmD, PhD1,3.
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Scientific Program: Chronic and Inflammatory diseases.
Keywords: alopecia areata; micro RNAs; pathway enrichment analysis; therapeutic repositioning.

Abstract:

Objectives: Alopecia areata (AA) is a chronic, immune-mediated inflammatory disease that reversibly affects the hair follicle. We set out to identify deregulated microRNAs in peripheral blood, compare mild and severe forms, with the aim of identify the metabolic pathways that remain altered, and predict candidate drugs that can reverse these alterations. **Methods**: Cross-sectional observational study. Plasma levels of 754 miRNAs were analysed using RT-PCR, comparing severe (n=9) and mild (n=12) forms of AA versus healthy controls (n=5). With the list of differentially expressed miRNAs, metabolic pathways enrichment (GeneCodis) and drug repositioning (CMaps LINCS) analyses were carried out. **Results**: We identified 19 downregulated miRNAs in the plasma of patients with severe AA compared to healthy controls, with the degree of dysregulation observed in mild forms being minimal. The enrichment analysis showed a greater alteration of pathways related to the immune system, the cell cycle, the DNA damage repair, the cellular response to stress, and post-translational modification of proteins. Some of the specific pathways represented were p53, GFR, NOTCH1, PIP3/AKT, FGFR1, and PDGFR. Finally, 39 drugs potentially capable of reversing this state of dysregulation were predicted, the most important group being JAK kinase inhibitors. **Conclusions**: Severe forms of AA present various altered metabolic pathways due to downregulation of miRNAs in peripheral blood. Its identification in early phases could facilitate more precise therapeutic strategies.

PSI.f. Contribution of contrast-enhanced mammography in a population-based breast cancer screening programme: a prospective study including 860 consecutively recalled women.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: breast neoplasms; contrast media; mammography; breast screening.

Abstract:

Objective: The main objective of our study is to evaluate the contribution of contrast-enhanced mammography in the care of women referred to the breast cancer screening programme, by comparing its diagnostic accuracy with that of digital mammography. **Methods**: We performed a prospective analytical observational study in which we consecutively included all women referred to the breast cancer screening programme from june 2021 to march 2022. In our unit, all women underwent digital mammography and contrast-enhanced mammography. A group of radiologists with experience in breast imaging evaluated the findings and assigned a BI-RADS assesment independently for each technique. We defined positive studies as those with BI-RADS assessments of 3, 4 or 5. Negative studies were defined as BI-RADS assessments 1 or 2. Sensitivity, specificity, positive and negative predictive values were calculated and compared between both techniques using the McNemar test for paired data, and the ROC and AUC curves using the DeLong test. Results: A total of 860 women were included. Overall diagnostic rates for contrast-enhanced mammography have been superior to those for digital mammography: sensitivity 100% (+7.8%), specificity 77% (+23.8%), negative predictive value 100% (+2.2%) and positive predictive value 40.4% (+16.9%). All increases were statistically significant (p<0,001). This difference is maintained regardless of breast density. **Conlusions**: Our results suggest that contrast-enhanced mammography improves the diagnostic performance of digital mammography in the care of referred women, streamlining the diagnostic process and avoiding the need to perform breast biopsies or other unnecessary complementary tests.

PSI.g. Understanding the contribution of the redox state to the pathophysiology of Pseudomyxoma Peritonei: proteomic and functional analysis.

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

Abstract:

Pseudomyxoma peritonei (PMP) is a rare disease in which mucus accumulates in the abdomen, usually originating from the appendix. The current treatment option is radical cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. Although outcomes are favourable after surgery, many patients experience tumour recurrence and progression. Indeed, this pathology has been poorly characterised at the molecular level, drawing special attention to the proteome, due to its low incidence and the difficulty posed by the mucin-rich mucus. In this context, this study aims to improve the understanding of both aetiopathogenesis and pathophysiology of PMP by defining the redox state of its tissues, both low-grade (LG) and high-grade (HG), in comparison with control tissues (C). This study assessed the cellular redox state by measuring the ratio of oxidised/reduced thiol groups using an optimised protocol involving cysteine alkylation with N-ethylmaleimide, quantification by mass spectrometry and data analysis. Based on the results obtained, in vitro functional studies using antioxidants (i.e. Resveratrol) and prooxidants (i.e. dihydrogen peroxide) are being used to unveil the contribution of the redox status to this malignancy, analysing changes such as cell proliferation rate, enzyme activities, or the expression levels of key genes. The results showed several significant changes in the oxidised-reduced Cys ratio. Bioinformatic analyses using different software tools identified associations between the observed changes and intracellular apoptotic pathways, protein phosphorylation, and responses to stress, among others. In conclusion, the results of the present study, together with the ongoing in vitro assays, indicate that the redox state is significantly altered in PMP patients, paving the way for further research to understand in depth the functional significance of the observed changes.

Fundings: This work is supported by “Instituto de Salud Carlos III (ISCIII)” (PI22/001213), co-funded by the European Union and by “Asociación Española contra el Cáncer” (PRYES223170ARJO).

PSI.h. Novel circulating natural killer cell subsets as biomarkers in alopecia areata progression.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: NK cells, alopecia areata, flow-cytometry, innate immunity, immunology, dermatology.

Abstract:

Alopecia areata (AA) is a disorder characterized by non-scarring hair loss, affecting the scalp and other areas of the body. This condition arises when the immune system mistakenly attacks hair follicles, leading to hair loss. NK cells are a key component of the innate immune system that can influence both innate and adaptive immune responses through their cytokine production and cytotoxic functions, playing a crucial role in initiating and perpetuating inflammatory and/or autoimmune processes. Some studies have already suggested the possible contribution of NK cells to AA through direct cytotoxic effects on hair follicles, cytokine production, and interactions with other immune cells. This study aims to further investigate the role of NK cells in the pathogenesis of AA and to identify potential peripheral blood biomarkers for disease risk or progression. For this porpoise, we measured the AA severity through the SALT score and collected peripheral blood from AA patients and controls. We performed a detailed phenotypical characterization of NK cells and their subsets in isolated PBMCs by multiparametric flow cytometry. A significant increase in the frequency of CLA and CD38 co-expression clusters in CD56dim NK cells was observed in AA patients compared to controls. Remarkably, the frequency of NKG2A and CD38 co-expression clusters in CD56dim NK cells decreased in AA. Additionally, we identified four CD56bright NK cell clusters, which did not show significant differences between patients and controls. Furthermore, significant correlations were identified between CD56dim clusters and the SALT score. These findings provide valuable insights into the understanding of alopecia areata immunopathogenesis and identify potential peripheral blood biomarkers for disease risk or progression.

Fundings: PI23/01590 & FI20/00194, funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

PSI.i. Likelihood of respiratory disease in people with bipolar disorder: A systematic review and meta-analysis.

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Affiliations: 1 Maimónides Biomedical Research Institute of Córdoba (IMIBIC), Córdoba, Spain 2 Psychiatry Resident, Reina Sofía University Hospital, Córdoba, Spain 3 Psychiatry Department, Reina Sofía University Hospital, Córdoba, Spain.
Scientific Program: Chronic and Inflammatory diseases.
Keywords: Bipolar Disorder, Respiratory disease, meta-analysis.

Abstract:

Background: Individuals diagnosed with bipolar disorder (BD) experience a decrease in life expectancy by 15 years, with an elevated risk of premature death and a respiratory mortality rate that exceeds that of the general population. However, to date, no meta-analysis has been conducted on respiratory illnesses within this specific demographic. Material and Methods: We systematically review and meta-analyze the prevalence of respiratory diseases (asthma, chronic obstructive pulmonary disease (COPD), pneumonia, lung cancer and tuberculosis) in patients with BD, comparing the frequency and odds ratio (OR) with the general population. The systematic literature search was conducted in Pubmed, PsycINFO, Scielo and Scopus, with snowball search of reference and citation lists. Results: In individuals diagnosed with BD (nearly 1 million) at a mean age of 54.4 years and 44.7% being male, the occurrence of COPD was 9.14% (95%CI: 6.61%-12.5%), asthma 6.4% (95%CI: 4.56%-8.91%), pneumonia 2.78% (95%CI: 2.51%-3.08%), and lung cancer 0.44% (95%CI:0.23%-0.84%). When compared to the general population (over 37 million), those with BD exhibited notably higher rates of COPD (OR: 1.73; 95% CI: 1.40-2.14), particularly among younger individuals and females; asthma (OR: 1.91, 95% CI: 1.25-2.94), with a higher prevalence among younger patients; and pneumonia (OR: 2.82, 95% CI: 1.33-5.99). Conclusions: In the first meta-analysis conducted on this subject, BD was linked to a higher likelihood of respiratory illness compared to the general population. In COPD and asthma, young people and women are at particular risk. This represents a novel opportunity to reiterate the necessity of initiatives designed to facilitate improved access to timely preventive and diagnostic healthcare, with particular emphasis on younger individuals.

Fundings: by the Carlos III Health Institute (P120/01657) and the European Union via FEDER (European Regional Development Fund), "A way of making Europe".

PSI.j. Beyond the obstruction: immunological perspectives on aortic stenosis and coronary artery disease.

Authors: Antonio Costa1, 2*, Pablo Álvarez-Heredia1*, Jose Joaquín Domínguez-del-Castillo3, Irene Reina-Alfonso1, Mónica Espinar-Garcia1, Isabel Maria Vallejo-Bermúdez1, Carmen Gutiérrez1, Fakhri Hassouneh1, Alexander Batista-Duharte1, Rafael Solana-Lara1, 2, Ignacio Muñoz3, Alejandra Pera Rojas1, 2.
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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Effector T cells, Lymphocytes, Flow Cytometry, Inflammation, Senescence, Innate Immunity.

Abstract:

Aortic valve calcification process occuring in aortic stenosis (AS) shares similarities with the systemic vascular atherosclerotic process leading to coronary artery disease (CAD), indicating a common pathogenesis. Moreover, traditional cardiovascular risk factors like hypertension, hypercholesterolemia, smoking, or diabetes are associated with both AS and CAD. The progression of AS and CAD, like atherosclerosis, involves inflammatory processes, highlighting the complex immunological interplay between these conditions. We performed an immunological characterization of immune populations in peripheral blood from sex/age matched AS patients (n=58), CAD patients (n=20) and healthy donors (HD, n=55). Our analysis revealed distinct immune profiles between AS and CAD cohorts. CAD patients exhibited an overall increase in the frequencies of terminally differentiated effector memory T cells (CD4, CD8 and TcRγδ) when compared to AS and HD individuals ($p<0.001$). Additionally, both frequencies and absolute numbers of CD14+CD16+ monocytes and CD56bright NK cells were increased in CAD patients ($p<0.01$). In contrast, AS patients exhibited an increased CD4:CD8 T cell ratio compared to CAD patients and HD ($p<0.01$). Furthermore, AS patients had higher frequency of CD4+CD28null and CD8+CD28null T and an enhanced expression of CX3CR1 and CD57 surface markers in all T cell subsets ($p<0.01$) in comparison with HD and CAD patients. Moreover, we found lower absolute numbers of dendritic cells (DCs) and their subsets ($p < 0.01$) in AS when compared to CAD patients and HD. Although AS and CAD share the same pathogenic mechanisms, our research reveals significant differences regarding the immune populations present in the peripheral blood of these patients. Our analysis suggests that CAD patients exhibit an expansion of immune populations associated with inflammation, whereas, AS patients show higher level of immunosenescence than CAD patients. These differences suggest the necessity to further investigate the role played by the immune system in the atherosclerotic progress, which varies between these diseases.

PSI.k. Incidence, mutational spectrum and prognostic impact of cebpa-bzip mutations in aml patients treated with semi-intensive regimens.

Authors: Esther Prados de la Torre1 , Josefina Serrano1, David Martínez-Cuadrón2,3 , Laura Torres2,3, Claudia Sargas4 , Rosa Ayala5 , Cristina Bilbao-Sieyro6 , María Carmen Chillón7 , María José Larráyoz8 , Elena Soria9 , Alfredo Pacheco1, Juan M. Bergua10 , Teresa Bernal11, Cristina Gil12, Mar Tormo13, Lorenzo Algarra14, Juan M. Alonso Domínguez15, Eduardo Rodriguez-Arbolí9 , Pilar Martínez-Sanchez5 , Ana Oliva16 , Ana M. Colorado-Araujo17, Carlos Rodríguez-Medina6 , Susana Vives18, Lourdes Hermosín19, Joaquín Martínez-López5 , Ramón García-Sanz7 , José A. Pérez-Simón9 , María José Calasanz8 , María Teresa Gómez-Casares6 , Eva Barragán3,20, Joaquín Sánchez-García1 , and Pau Montesinos2,3 , on behalf of the PETHEMA group.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: AML, NGS, CEBPA, NON-INTENSIVE TREATMENT, CO-MUTATIONS, PROGNOSIS.

Abstract:

AML patients' prognosis is defined by the presence of specific genetic abnormalities and CEBPA mutations (CEBPAmut) have classically been classified as having a favorable prognosis. Recently, a narrower definition of the bZIP CEBPAmut has been proposed as a favorable prognostic category by ELN2022 restricted to intensively treated patients. In this study we analyzed the incidence, co-mutations and prognostic impact of CEBPAmut in 504 AML patients treated with non-intensive treatment (NIT) [hypomethylating agents (Decitabine/Azacitidine+Venetoclax), FLUGA (Fludarabine+Ara-C), FLAG-IDA-LITE

(Fludarabine+Ara-C+Idarubicin) or low-dose Ara-C] in the national PETHEMA registry. We performed NGS analysis with 32 genes included in a commercial panel using IonTorrent/Illumina platforms, and all data obtained were analyzed with RStudio (v4.1.2). A total of 40 patients (7.9%) had CEBPAmut: 19 bZIP-domain (11 were in-frame mutations) and 21 outside bZIP-domain (other CEBPAmut). Patients without CEBPAmut (CEBPAwt) were mostly >60 years old (99.1% vs. 90.6% CEBPA-bZIP-inf, P=0.044). 33.1% of CEBPAwt patients had an unfavourable karyotype, while all CEBPA-bZIP-inf patients had a normal karyotype. The 3-year survival rates were 12.5% (95%CI, 2-78.2), 23.7% (95%CI, 10.1-55.7) and 6.5%(95%CI, 4.2-10.18) for CEBPA-bZIP-inf, other CEBPAmut and CEBPAwt, respectively, with no statistical significance. Similar results were observed pooling all bZIP-domain mutations. The main co-mutations with CEBPAmut were: SRSF2 (52.5%), TET2 (47.5%) and ASXL1 (35%). We compared the mutational spectrum with CEBPAmut patients who received intensive treatment (n=82), we observed a larger cluster of dysplasia-related genes in those with NIT. We performed a Bradley-Terry model to infer the timing of mutations, finding that mutations in TP53, dysplasia-related genes and, epigenetic regulators occur earlier than signaling genes mutations (NRAS, KRAS, and FLT3). In conclusion, we report that 8% of AML patients with NIT harbored CEBPAmut; however, they did not show better survival than CEBPAwt. These patients had normal karyotype and frequent mutations in dysplasia-related genes and epigenetic regulators that occur early in leukemogenesis.

PSI.I. Molecular characterization and functional role of serpins in hepatocellular carcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: hepatocellular carcinoma; chronic liver disease; “matrisome”; serpins; SERPINF2.

Abstract:

Hepatocellular carcinoma (HCC) is an aggressive tumour tightly associated with the existence of an underlying liver disease, mainly cirrhosis. The importance of extracellular matrix remodelling in hepatic pathologies is broadly known; however, the dysregulation of the proteins controlling the remodelling process in chronic liver disease is controversial. This work aimed to characterize the dysregulation of the serpins, a family of serin-proteases inhibitors, in different stages of the chronic liver disease. We analysed the dysregulation of 23 serpins in quantitative proteomics data from an HCC cohort (42 HCC vs. 42 non-tumour adjacent tissue) and validated in in silico chronic liver disease and HCC cohorts from the HCCBD (6 controls, 40 cirrhosis, 1469 adjacent tissue, 2048 HCC) and GEO [27 control, 22 hepatic steatosis (MASLD), 465 fibrosis/cirrhosis, 408 HCC]. The functional effect of genetic modulation (silencing and overexpression) or treatment with SERPINF2-enriched medium was evaluated in HCC-derived cell lines (Hep3B and SNU-387). Thirteen serpins were detected and quantified in the quantitative proteomics. Nine of them (70%) were overexpressed in tumour tissues compared to controls. In the in silico cohorts, most of the serpins were altered in MASLD and fibrosis/cirrhosis samples, as well as in HCC, where serpins expression comprises a molecular fingerprint discriminating tumour and control tissues. Particularly, SERPINF2 was consistently downregulated and associated with clinical parameters of MASLD severity and tumour aggressiveness. In vitro, SERPINF2 silencing reduced, while its overexpression increased, functional parameters (proliferation, migration, colony/tumorsphere formation, invasion) in HCC-derived cell lines. However, SERPINF2-enriched medium induced different functional alterations compared to SERPINF2 overexpression, suggesting different intra-extracellular actions of SERPINF2. There results reveal a strong dysregulation of serpin family in chronic liver disease and HCC, where SERPINF2 could play a relevant role in disease progression.

Fundings: ISCIII (PI20/01301, PI23/00652; co-funded by the European Union), MINECO (FPU20/03957), JdA (PEMP-0036-2020, BIO-0139), FSEEN and CIBERobn/ehd.

PSI.m. Liquid biopsy methylation patterns enable effective risk stratification and monitoring of metastatic pancreatic cancer patients.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Liquid Biopsy, pancreatic cancer, methylation array, cfDNA methylation, ddPCR.

Abstract:

Introduction: Pancreatic cancer is the most lethal cancer due to its late diagnosis, and the ineffectiveness of current treatments. Optimizing the follow-up of patients, and treatment response evaluation would improve clinical decision-making, allowing for the most appropriate therapeutic strategy at each time of the disease. Circulating CA19-9 levels and computed tomography (CT) imaging are the standard available tools for assessing disease progression. However, liquid biopsy-based methylation analysis has recently been emerged as a non-invasive method for developing epigenetic biomarkers with diagnostic and prognostic potential. **Objective:** Identification of liquid biopsy-based epigenetic biomarkers in cell-free DNA (cfDNA) from patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) for monitoring disease progression and to establish prognostic biomarkers based on early changes in cfDNA methylation. **Methods:** An Illumina Infinium EPIC 850K methylation array was performed with cfDNA samples to compare methylation patterns between healthy individuals and mPDAC patients. Subsequently, array results were validated both in TCGA database and by digital droplet PCR methylation analysis on plasma samples. **Results:** The methylation array revealed nineteen differentially methylated CG positions between mPDAC patients and healthy individuals, most of them located in gene regions, at the genes body or at their promoter region. Data from the TCGA database and ddPCR analysis in plasma confirmed the differential methylation of two of these targets (LAX1 and RCAN3). Moreover, we found that combining circulating methylation levels of LAX1 and RCAN3 allowed efficient monitoring of disease progression, providing more effective prediction than other circulating markers such as CA19-9 or RAS mutational status. Importantly, we further observed that early changes in circulating LAX1-RCAN3 methylation levels can predict response to treatment. **Conclusions:** Our results confirm a distinct and differential methylation pattern in cfDNA from metastatic pancreatic cancer patients, highlighting the clinical utility of liquid biopsy-based epigenetic biomarkers for the management of this disease.

Fundings: Junta de Andalucía ProyExcel_00734.

PSI.n. Alteration in the molecular components of cellular machineries that control gene expression in thyroid cancer and their association with tumor behavior and/or clinical features.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: thyroid cancer, gene expression machineries, splicing, RNA metabolism, aggressiveness.

Abstract:

Emerging evidence indicates that the cellular machineries controlling gene expression mechanisms are altered in several endocrine-related cancers (ERC), leading to some oncogenic events associated with tumor progression/aggressiveness. However, whether this phenomenon also occurs in thyroid cancer (TCa) has not been yet explored. Therefore, this study was focused on: 1) investigating the potential alteration and functional role of key molecular components of the cellular machineries controlling RNA metabolism [Splicing machinery, RNA-Exosome complex, Non-sense Mediated Decay (NMD)] in clinically well-characterized human papillary and medullary TCa samples vs. its adjacent non-tumour tissue; and 2) whether these alterations might be associated with relevant clinical parameters. Results revealed a clear dysregulation of several components of these machineries in papillary and medullary TCa samples, wherein the expression of specific components was associated with key clinical parameters (e.g. metabolic status, aggressiveness, multifocality, etc). Then, we explored different functional (e.g. proliferation, migration, and tumour-spheres and colonies formation) and mechanistic (gene expression/signalling pathways) assays in response to the modulation in the expression (e.g. silencing) of key components of these machineries using a human TCa cell-line (TCP1). These in vitro studies revealed that different molecular components of splicing, RNA-exosome and NMD machineries significantly modulated cell aggressiveness features in TCP1 cells. Altogether, our data demonstrate a drastic dysregulation of key components of the molecular machineries controlling gene expression mechanisms (particularly splicing) in papillary and medullary TCa samples that might be associated to the development and progression of this pathology.

Fundings: Grupo Español de Tumores Neuroendocrinos (GETNE G211), Junta de Andalucía (PEER-0048-2020).

PSI.ñ. Evaluation at real time of the repair of abasic sites in DNA using molecular beacons.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Base excision repair, Abasic Sites, AP lyases, AP Endonucleases, Molecular Beacons.

Abstract:

The stability of DNA can be compromised when it is exposed to different agents that cause damage to the genetic material. These agents include several drugs used in chemotherapy such as alkylating agents. One of the most important is temozolomide (TMZ), which is used as an antitumour agent in different types of cancer including glioblastoma. However, it has been described that a high percentage of cancer patients treated with TMZ relapse due to the generation of resistance to treatment. This resistance has been associated with a greater capacity of tumour cells to repair the damage generated by this alkylating agent. The main DNA damage caused by TMZ is the modification of guanine to generate N7-methylguanine, which represents 70% of the total lesions produced by this drug. This lesion can undergo spontaneous or enzymatic depurination, generating abasic sites (AP). AP sites are generally repaired by DNA base excision repair (BER) through the AP Endonuclease and/or AP Lyase-dependent pathway. Our starting hypothesis is that resistance to TMZ is related to a greater repair capacity of abasic sites that are generated from the depurination of N7meG. To check this hypothesis, we analysed the repair of abasic sites in glioblastoma-derived cells from TMZ-sensitive and TMZ-resistant cell lines at real time by using molecular beacons containing abasic sites. The results showed that the use of molecular beacons is a very effective tool to study the BER activity of abasic sites, both through the AP Endonuclease pathway and the AP Lyase pathway. Furthermore, our data indicate that there are differences in repair efficiency between TMZ-sensitive and TMZ-resistant cells, suggesting that the capacity to repair DNA abasic sites is an important factor to consider in the response to treatment with such alkylating agent.

PSI.o. Chronic kidney disease-related cognitive impairment is associated with lower abundance of membrane-bound Klotho in the cerebral cortex.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: chronic kidney disease, cognitive impairment, Klotho.

Abstract:

Cognitive impairment (CI) is a complication of chronic kidney disease (CKD) that is frequently observed among patients. The aim of this study was to evaluate the potential crosstalk between changes in the cognitive function and the levels of Klotho in the brain cortex in an experimental model of CKD. To induce renal damage, Wistar rats received a diet containing 0.25% adenine and 0.9% phosphorus for six weeks. A group of animals that served as controls fed a standard diet. Before sacrifice, animals underwent different tests for the assessment of cognitive function. At sacrifice, changes in the parameters of mineral metabolism and the expression of Klotho in the kidney and frontal cortex were evaluated. The animals with CKD exhibited impaired behavior in the cognitive tests in comparison with the rats with normal renal function. At sacrifice, CKD-associated mineral disorder was confirmed by the presence of the expected disturbances in the plasma phosphorus, PTH, and both intact and c-terminal FGF23, along with a reduced abundance of renal Klotho. Interestingly, a marked and significant decrease in Klotho was observed in the cerebral cortex of the animals with renal dysfunction. In sum, the loss of cerebral Klotho observed in experimental CKD may contribute to the development and progression of cognitive dysfunction frequently observed among patients. Although further studies are required, Klotho might have a relevant role in the development of CKD-associated CI and represent a potential target in the management of this complication.

PSI.p. Analysis of epigenetic factors regulating the circulating immune cells network in patients with mild and severe alopecia areata.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Alopecia areata; scRNAseq; ATAC-seq; immune cells.

Abstract:

Objectives: Alopecia areata (AA) is a chronic, immune-mediated inflammatory disease that reversibly affects the hair follicle. We aimed to conduct an RNA sequencing (scRNAseq) and chromatin accessibility (ATACseq) analysis on peripheral blood mononuclear cells (PBMCs) from individuals with AA at a single-cell level. **Methods**: This is an observational cross-sectional study. Using scRNAseq and ATAC-seq, we analyzed PBMCs from 11 patients with AA and 5 healthy individuals. The 10X Genomics Chromium controller and advanced processing methods were employed to assess sample quality and generate a robust dataset. We identified cell subtypes and performed comparative analyses of gene expression and chromatin accessibility to identify molecular markers and significant differences between mild and severe cases of AA, utilizing advanced statistical and bioinformatic approaches. **Results**: We identified 11 main cell types and multiple subgroups, highlighting notable differences in gene expression and chromatin accessibility between patients and controls. CD14+ proinflammatory monocytes showed the greatest alterations, including genes such as DUSP1, FOS, ZFP36L2, and NR4A2. These findings suggest a dysregulated innate immune response in AA, with implications for pathophysiology and potential therapeutic targets. Additional analyses indicated the presence of key transcription factors and possible affected developmental and immune response pathways. **Conclusions**: Our findings reveal the systemic involvement of immune cells in alopecia areata, emphasizing cellular heterogeneity and genetic differences in mild and severe forms. CD14+ monocytes, NK cells, and CD8+ T cells are key players in the pathogenesis.

PSI.q. Acute non-traumatic neurological injury linked to rat hepatitis E virus infection.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Rat hepatitis E virus; Spain; neurological injury; viruses; zoonoses.

Abstract:

Background and Aim: The rat hepatitis E virus (ratHEV) is an emerging zoonotic virus, currently considered a significant global public health issue. Despite being linked to both acute and chronic hepatitis, the full extent of its clinical impact remains unclear. In this context, the aim of the study is to assess the prevalence of ratHEV in a population with acute non-traumatic neurological injury (ANTNI). **Methods**: Retrospective longitudinal unicentric observational study including patients with ANTNI with available serum samples between 2021 and 2023. The presence of active infection by ratHEV RNA was analyzed using qPCR, and the positive samples were confirmed by sequencing. Whenever possible, the presence of viral RNA in cerebrospinal fluid (CSF) was analyzed in ratHEV cases. **Results**: The study comprises 117 patients with acute non-traumatic neurological injury. Patients had both central nervous system (CNS) and peripheral nervous system (PNS) disorders, with most of them suffering CNS injury (90/117, 76.9%). ratHEV RNA was confirmed in six patients, supposing a prevalence of infection of 5.1% (95% CI: 2.1-11%). All six sequences belonged to ratHEV, and they were similar to those identified in patients with acute and chronic hepatitis and in rodents, the main reservoir of the virus. CSF could be analyzed in three cases, and viral RNA was confirmed in one patient. Infected patients were suffering from multiple Sclerosis, acute sensory-motor polyneuropathy, Parsonage- Turner syndrome, Guillain-Barré syndrome, lymphocytic meningoencephalitis, and idiopathic benign intracranial hypertension, respectively. None of them had liver disorders. **Conclusions**: Our study constitutes the first report of a likely causal association between neurological disorders and ratHEV in Europe. Our results provide robust evidence to consider ratHEV in the differential diagnosis of acute non-traumatic neurological injury, even in the absence of liver injury.

PSI.r. Machine learning algorithms in controlled donation after circulatory death under normothermic regional perfusion: Role of Machine Learning classifiers as predictive models of graft survival.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Organ allocation; circulatory death; prediction model; liver transplantation; regional normothermic perfusion; machine learning.

Abstract:

Several scores have been developed to stratify the risk of graft loss in controlled donation after circulatory death (cDCD). However, their performance is unsatisfactory in the Spanish population, where most cDCD livers are recovered using normothermic regional perfusion (NRP). Consequently, we explored for the first time the role of different machine learning-based (ML) classifiers as predictive models for graft survival. This retrospective multicenter cohort study used 543 D-R pairs of cDCD livers recovered with NRP including 17 donor and recipient variables. The following ML classifiers were explored: logistic regression (LR), ridge classifier (RC), support vector classifier (SVC), multilayer perceptron (MLP), and random forest (RF). The endpoints were the 3- and 12-month graft survival rates. Among all ML algorithms, LR yielded the best performance at 3 months (AUC-ROC=0.838) and 12 months (AUC-ROC=0.884). The model developed outperformed the UK-DCD score in our study population (C-index: 0.837 vs. 0.565; $p<0.05$). The satisfactory performance of our score within the study population suggests significant potential to support liver allocation; nonetheless, prospective validation is imperative.

PSI.s. Tac1-expressing cells in the ventral premammillary nucleus and ventromedial hypothalamus are essential for induction of the pre-ovulatory LH surge.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: LH surge, Tac1 neurons, Substance P, DREADD.

Abstract:

Infertility/subfertility is a growing challenge in reproductive medicine. The most common cause of subfertility in females is ovulatory dysfunction. Conditions linked with oligo-/anovulation include polycystic ovary syndrome, hypothalamic amenorrhea and premature ovarian insufficiency. However, the central neuroendocrine defects affecting the pre-ovulatory LH surge that drives ovulation remain ill defined. While hypothalamic GnRH neurons are the major output pathway for the brain control of ovulation, upstream Kiss1 neurons, particularly in the anteroventral periventricular area (AVPV) of the hypothalamus in rodents, are thought to be crucial for the timed activation of GnRH neurons and generation of the preovulatory surge of gonadotropins. Yet, the major upstream regulators of this Kiss1/GnRH pathway are largely unknown. Substance P (SP, encoded by Tac1), a member of the tachykinin (TAC) family that acts via the receptor, NK1R (encoded by Tacr1), has been shown to centrally regulate gonadotropin release, and, according to our initial data, might modulate the pre-ovulatory surge in mice through its direct action on AVPV Kiss1 neurons. We report herein that Tac1-expressing cells in the ventral premammillary nucleus (PMV) and ventromedial hypothalamus (VMH) become activated during the preovulatory surge, as denoted by co-expression of c-Fos. Moreover, we document here that the neurons in the PMV project to key reproductive areas, including the rostral preoptic area (rPOA), AVPV, arcuate nucleus (ARC), and the medial posterodorsal amygdala (MePD). Furthermore, the chemogenetic inhibition of Tac1-expressing neurons with a Cre-dependent AAV inhibitory DREADD in the PMV and in the VMH dramatically decreases the magnitude of the pre-ovulatory LH surge, but has no influence on tonic LH pulsatility. Overall, our findings strongly support a relevant stimulatory role of SP originating from Tac1 neurons at the PMV and VMH in the generation of the pre-ovulatory surge of gonadotropins, responsible for ovulation.

PSI.t. DYRK2 promotes apoptosis in chemotherapy-resistant lung tumor cells through its USP28-mediated stabilization.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: DYRK2, USP28, DNA damage, apoptosis, cell signalling.

Abstract:

All cellular processes are regulated by complex signaling pathways that ensure their proper functionality, allowing the control of crucial processes such as apoptosis or cell cycle. In this context, post-translational modifications play a crucial role, among the most important of these is ubiquitination, allowing a balance between protein synthesis and degradation. Counteracting the activity of E3 ligase enzymes, de-ubiquitinase enzymes (DUBs) participate in this process, and their deregulation has been linked to pathologies like cancer. USP28 ranks as one of the most significant deubiquitinating enzymes, being a key protein in the control of oncoproteins such as c-Myc or NOTCH1. On the other hand, DYRK2 is a kinase that has been related to carcinogenesis, due to its role in the control of apoptosis or angiogenesis, among others. In this work we identified USP28 as the first DUBs described for DYRK2 kinase. We demonstrate that USP28 interacts with DYRK2, causing a stabilization in the kinase levels. In response to DNA damage, USP28 stabilizes DYRK2, affecting important substrates of the kinase such as p53. The interaction between the two proteins causes changes in the phosphorylation of serine-46 of the tumor suppressor p53, leading to cell death. Consequently, our results demonstrate a novel mechanism for controlling apoptosis through the stabilization of DYRK2 by USP28. Furthermore, we describe a dual regulatory mechanism in which DYRK2 would also be regulating USP28 levels, causing its degradation. Interestingly, USP28 degradation is independent of DYRK2 kinase activity, suggesting a novel role for DYRK2 as a protein scaffold. The results shown in this work are of particular interest, as we demonstrate that the USP28-DYRK2 axis has direct effect on carcinogenesis, altering cell proliferation and sensitivity of tumor cells to apoptosis. This opens the door to new therapeutic strategies aimed at promoting apoptosis in chemotherapy-resistant cells, thereby improving the efficacy of standard treatments.

PSI.u. Uncovering the Microbiome of Pseudomyxoma peritonei with novel omics approaches.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pseudomyxoma peritonei; bioinformatic analysis; metaproteomics; microorganisms.

Abstract:

Pseudomyxoma peritonei (PMP) is a rare malignancy and the paradigm of peritoneal mucinous carcinomatosis, causing continuous accumulation of mucus-secreting cells and glycoprotein-rich mucus in the abdomen. The only available treatment is complete cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. Despite this aggressive treatment, relapses are common in PMP, leading to debilitating symptoms and a fatal outcome. It is therefore essential to explore ways to improve treatment and to better understand the pathogenesis of the disease. Microorganisms have previously been identified in PMP using genomic approaches and antibacterial treatment has been suggested, but data are limited. Our group aimed to develop the first method based on a "proteomic approach" to test and characterise the presence of microorganisms in mucinous tumour tissues. Samples obtained from patients during CRS-HIPEC surgery were treated with our pioneering protein isolation protocol and then analysed by nanoHPLC-MS/MS. A new human and microbial protein database was created to identify and describe the presence of microorganisms in the tumour tissue. Our results demonstrate for the first time the presence of fungal proteins in mucin samples from both low and high grade PMP tumours, validated by cytology analysis by our pathology service. In addition, our group has performed a metagenomic study of PMP, analysing different tumour grades for bacterial 16S rRNA and ongoing studies for fungal identification by next-generation sequencing. This work presents a novel proteomic and bioinformatic approach to identify the presence of microbiota. This is consistent with the literature where different genera of bacteria and fungi have been identified by genomic approaches in different types of cancer. However, further research is needed to determine the role of these microorganisms in the pathogenesis of mucinous tumours, to understand the mechanisms of oncogenesis and to develop better therapeutic strategies for these patients.

Fundings: This work is supported by “Instituto de Salud Carlos III (ISCIII)” (PI22/001213), co-funded by the European Union and by “Asociación Española contra el Cáncer” (PRYES223170ARJO).

PSI.v. Efficacy and safety of Dalbavancin in the outpatient parenteral antimicrobial treatment of complex infections.

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Scientific Program: Infectious and Immunological diseases.

Keywords: Infectious Diseases, Dalbavancin, multidrug-resistant bacteria, Outpatient parenteral antimicrobial treatment (OPAT).

Abstract:

Introduction: Outpatient parenteral antimicrobial treatment (OPAT) can be very versatile when safe and easy-to-administer antibiotics are available. Objectives: Evaluate efficacy and safety of Dalbavancin in the maintenance treatment of complex infections caused by gram-positive bacteria. **Methods**: An observational, descriptive study of a retrospective cohort of Outpatient parenteral antimicrobial treatment with Dalbavancin after a hospitalization period at the Hospital (HURS), from December 2016 to the present. Patient characteristics, isolated microorganisms, and administered treatments were studied. An induction dose (1,000 mg) followed by weekly doses (500 mg) was administered. Inclusion criteria for the program were established. Nephrotoxicity was defined as a doubling of baseline creatinine levels. **Results**: 58 patients were analyzed: 47 were men (73%) and 17 were women (27%), with a median age of 58 years. The most prevalent underlying condition was cardiovascular disease, present in 58.8% (30 cases). 11 patients with chronic renal failure were treated without requiring a dosage change during treatment. The most frequently treated condition was osteoarticular infections, with Staphylococcus epidermidis being the most frequently isolated microorganism in this condition, and Staphylococcus aureus sensible a meticilina overall. 49 patients received another antibiotic prior to Dalbavancin, with a median treatment duration of 11 days. In most cases, 49 of 58, Dalbavancin was administered as targeted therapy. The most common reasons for using this treatment were resistance to other antibiotics and patient's comfort in the moments of the administration. The most commonly used induction therapy: Vancomycin. In 58 patients treated with this drug, 51 were treatment continuation (median duration of 3 weeks) and 7 as suppressive therapy (median duration of 18 weeks, range 4-24 weeks). Clinical cure was achieved in 84.5% of patients, and microbiological cure in 87.5%. **Conclusion**: Dalbavancin is effective and safe for Outpatient parenteral antimicrobial treatment of complex infections by susceptible microorganisms after hospital induction therapy.

PSI.w. RASSF1A methylation analysis in Lung Cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: lung cancer, RASSF1A, biomarker, DNA methylation, minimally invasive samples, cell lines.

Abstract:

RASSF1A is a protein with three main domains: the C1/DAG domain, the Ras association domain (RA) and a Sav/RASSF/Hpo interaction domain (SARAH). Through the RA domain, RASSF1A interacts with members of the Ras GTPase family to exert its tumour suppressor function. It is involved in the processes of cell proliferation, apoptosis, migration and adhesion. The regulation of RASSF1A gene expression is epigenetically controlled by DNA methylation. In many human tumours, methylation of its promoter has been described in association with inhibition of its expression. In particular, it has been described in lung cancer, which is a major health problems due to its high incidence and mortality. In this context, the aim of this project was to investigate the methylation status of RASSF1A in minimally invasive samples (blood plasma) from lung cancer patients and people with risk factors (smokers and chronic obstructive pulmonary disease or COPD), and lung cancer cell lines. The plasma samples were classified into four groups: healthy, smokers as a risk factor, COPD risk factor and lung cancer group. The cell lines used were: BEAS-2B from healthy lung epithelium and A549, H23, H727, H292 and PC9 from lung cancer. DNA was extracted from all samples and modified with sodium bisulphite. Methylation status specific PCR (qMSP) was performed to determine the methylation status of the RASSF1A promoter. We detected RASSF1A methylation in all blood plasma groups, with a higher frequency in lung cancer patients where 38.5% was detected. These results were confirmed in lung cancer cell lines. These preliminary data suggest that methylation of RASSF1A may be a useful epigenetic biomarker for diagnosis of lung cancer using minimally invasive samples.

PSI.x. Development and validation of 3D-cell culture models generated from patients-derived xenografts with 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 clinical entity characterized by progressive accumulation of mucin in the peritoneal cavity. It most commonly originates from the appendix and the only treatment currently available is an aggressive cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. However, tumor relapse with subsequent progression and death is frequent. To date, functional and molecular characterization of this disease is scarce, mainly due to its low incidence, the barrier generated by the extreme excess of mucus production and the lack of appropriate in vitro and in vivo models. Here, we aimed to develop and validate 3D-cell culture models (organoids) from patient-derived xenografts (PDX) with low and high grade PMP. To this end, tumor tissues from these PMP PDXs were homogenized into single cells and seeded with a specific media and growth factor mix to develop the organoids. After three weeks, the organoids were formalin-fixed, paraffin-embedded and immunostained against MUC2, CK7, CK20, P53, Ki67, and CDX2. To validate the organoids, the results were compared with the original patient tumor tissue. The results showed that MUC2 expression was strongly positive in both low and high-grade PMP organoids in line with the original human tumor tissues (HT), confirming a clear PMP phenotype. Additionally, CK7 and CK20 were negative and CDX2 showed a positive signal in both organoids and HT. The Ki67 proliferation index was similar between organoids and HT in both low and high-grade PMP, but the P53 marker was only validated in the high-grade samples, which could be due to the low cellularity observed in the organoids compared to the HT. In conclusion, immunohistochemical analyses showed that the expression patterns of specific markers were maintained and consistent in the organoids compared to the original human samples, suggesting that are a valuable resource for the development and testing of more personalized treatments.

Fundings: This work is supported by "Instituto de Salud Carlos III (ISCIII)" (PI22/001213), co-funded by the European Union and by "Asociación Española contra el Cáncer" (PRYES223170ARJO).

PSI.y. VCE-005.1: A promising vasculogenic B55α/HIF activator that prevents endothelial cells damage and enhances wound healing.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Vascular Endothelium, angiogenesis, diabetic foot.

Abstract:

Diabetic foot disease (DFD) is a severe complication of diabetes, resulting in significant morbidity due to poor wound healing and a high risk of infection. Despite standard of care treatment 70% of diabetic wounds remain unhealed. This underscores the critical need for novel therapeutic targets and pharmacological approaches to address underlying endothelial dysfunction and impaired vasculogenesis. This study examines the pharmacological profile of VCE-005.1 (Betulinic Acid Hydroxamate) and its efficacy in a preclinical model of DFD, focusing on its potential to promote angiogenesis, enhance wound healing, and reduce inflammation. VCE-005.1 is an activator of the B55α subunit of protein phosphatase 2A (PP2A), which stabilizes hypoxia-inducible factor (HIF). In this study, we further explored the mechanism of action of VCE-005.1 and evaluated its ability to promote neovascularization and wound healing in vivo. Our findings show that VCE-005.1 induces AMPK and eNOS phosphorylation, upregulates Sirt1 expression concluding that VCE-005.1 acts as a dual activator of the intersecting B55α/AMPK/Sirtuin-1/eNOS and B55α/PHD2/HIF-1α pathways. Furthermore, VCE-005.1 prevents H2O2-induced cellular senescence and cytotoxicity. To investigate the efficacy of topical VCE-005.1 in DFD, we utilized db/db mice as a model of type-2 diabetes mellitus and db/+ as control. In both mice groups, VCE-005.1 induced the expression of B55α+/CD31+ and CD31+/Sirt1+ cells, reepithelization, prevented the accumulation of macrophages and neutrophils, promoting wound healing. This was accompanied by increased expression of Sirt1 and B55α, proangiogenic factors such as Hgf, Epo, and Cav1, and the formation of new blood vessels (CD31+/αSMA+) and (CD31+/CD34+), which are essential for effective wound healing. In conclusion, VCE-005.1 enhances wound healing by promoting angiogenesis, epidermal regeneration, reducing inflammation and granulation, making it a promising treatment for diabetic foot disease and other types of wounds.

PSI.z. Influence of high-impact physical activity on lumbopelvic muscle mechanical properties in asymptomatic nulliparous women: a case-control study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: intense physical activity; muscle rest assessment.

Abstract:

To identify whether the muscle mechanical properties (MMPs) of the lumbopelvic region are different between continent nulliparous women depending on whether they practice high-impact physical activity. Secondarily, correlations between lumbopelvic MMPs and sociodemographic data were evaluated. **Methods**: Fifty women were included in the high-impact group, and 50 women who did not practice high-impact activity were included in the control group. Data collection for both groups included sociodemographic data and lumbopelvic MMPs, which were externally assessed using a hand-held tonometer device. Between-groups comparison of the MMPs were calculated, together with intra-group correlations between outcomes. **Results**: The MMPs of pelvic floor muscles (PFM) had less tone (0.76Hz, 95%CI=0.04, 1.48) and stiffness (23.76N/m, 95%CI=1.10, 46.42) and were more viscoelastic (relaxation: -1.04ms, 95%CI=-1.98,-0.11; creep: -0.04De, 95%CI=-0.07,-0.02) in women who practiced high-impact physical activity. Women in the control group showed greater and higher correlations between MMPs of PFM and lumbar MMPs, and age and BMI compared to those who practiced high-impact physical activity. **Conclusions**: High-impact physical activity alters the MMPs of PFM in nulliparous women, although not lumbar spinal MMPs, even before the appearance of signs or symptoms.

PSI.aa. Normothermic regional perfusion in donation after cardiac death liver transplantation for primary sclerosing cholangitis.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: transplantation, liver, primary sclerosing cholangitis, donation after circulatory death.

Abstract:

Normothermic regional perfusion (NRP) may mitigate the risks of using donations after circulatory death (DCD) grafts in patients with primary sclerosing cholangitis (PSC). This study aimed to compare the liver transplantation outcomes using DCD and donations after brain death (DBD) grafts. **Methods**: This retrospective, multicenter cohort study was conducted between 2016 and 2022. The primary endpoints were graft and patient survival rates. The secondary endpoints were incidences of early allograft dysfunction (EAD), primary nonfunction (PNF), biliary and vascular complications, and recurrence. **Results**: The DCD-NRP and DBD groups comprised 32 and 123 grafts, respectively. No significant differences were observed between the groups regarding donor and recipient characteristics. The 1- and 3-year graft survival rates in the DCD-NRP group were 94% and 86%, respectively (DBD group: 87% and 86%, respectively; p = 0.89). The patient survival rates at 1- and 3-years in the DCD-NRP group were 94% and 86%, respectively (DBD: 89% and 87%, respectively; p = 0.67). No differences were observed between the groups regarding the incidence of anastomotic biliary strictures, ischemic-type biliary lesions, PNF, EAD, hepatic artery thrombosis, or disease recurrence. **Conclusions**: The safety and outcomes of NRP-DCD and DBD grafts are comparable in patients with PSC; therefore, their use can improve their access to transplantation.

PSI.bb. Metabolic disorders and lifestyle behaviours in adolescents from under-resourced families in the context of E-DUCASS study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Cardiovascular health, metabolic disorders, vulnerable population, food insecurity; educational program.

Abstract:

Cardiovascular health (CVH) status of adolescents could be negatively influenced by adverse social determinants of health. Particularly in under-resourced communities at risk of food insecurity, the study of CVH could offer valuable insights for early intervention and targeted public health initiatives. Therefore, the aim is to evaluate CVH status, metabolic disorders and lifestyle behaviours of adolescents from families at risk of food insecurity from the E-DUCASS study (NCT05379842). CVH, metabolic disorders and lifestyle behaviours were assessed at baseline in 141 adolescents (12-19 years) from the E-DUCASS study. CVH was evaluated by the Life's Essential 8 (LE8) score from the AHA; healthy diet adherence was evaluated by Mediterranean Diet Adherence Screener; metabolic disorders, physical activity and screen time were evaluated based on WHO recommendations. The mean of CVH in adolescents was 70.3 (95% CI, 68.6-72.1), categorizing 16.7% with high CVH, 79.7% with moderate and 3.6% with low. The Mediterranean diet adherence was 5.8 +- 1.7, classifying 44.2% with low adherence, 53.6% with medium and 2.2% with high. According to metabolic disorders, 19.1% had overweight, 21.3% obesity, and 42.6% high body fat percentage. Moreover, 31% of participants showed metabolic syndrome with hypertension (61%), hypertriglyceridemia (45.6%) and abdominal obesity (42.8%) as predominant criteria. According to physical activity recommendations, only the 7.9% reached both physical activity (60 min/day and 3 days/week) recommendations. Weekly screen time recommendation was not accomplished by 62.6% of the adolescents, spending more than 120 minutes/day. Adolescents from under-resourced families showed poor adherence to healthy diet and lifestyle behaviours, along with high overweight and obesity rates (40.4%) exceeding the data reported from PASOS study (29.3%). Worryingly, despite the youth of the participants, a low percentage had high CVH. The E-DUCASS program could be a good strategy to improve the cardiometabolic health in an economically, sustainable and maintainable way over time.

PSI.cc. LRG1, a potential therapeutic target in obesity.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Obesity, insulin resistance, fibrosis, LRG1.

Abstract:

Leucine-rich α-2 glycoprotein 1 (LRG1) is a member of the leucine-rich repeat family of extracellular matrix (ECM) proteins that has been related with several diseases including obesity and diabetes. Recently, LRG1 has been shown to be secreted by mature adipocytes, acting as an adipokine that ameliorates insulin resistance in obesity by mediating the crosstalk between adipocytes and hepatocytes. LRG1 also plays an important role in skin repair and fibrosis stimulating TGF-β signaling. Previous data from our group highlighted the potential use of LRG1 as an adipose tissue marker in weight gain. However, the regulation and precise function of this protein in the adipose tissue are still unknown. Herein, we aimed at investigating LRG1 production and potential role in ECM remodeling and fibrosis in the adipose tissue. **Methods**: Cell cultures of main adipose tissue cell types, preadipocytes, mature adipocytes and macrophages were exposed to conditions mimicking hyperglycemia/hyperinsulinemia, inflammation and lipid overload. Molecular studies including qPCR, western blot and ELISA were used to evaluate LRG1 under obesogenic conditions, and the effect of LRG1 administration on adipose tissue cells and ECM production was analyzed. Finally, fibrillogenesis and electron microscopy studies were carried out to assess the role of LRG1 on ECM fibril organization. **Results**: Our results show that LRG1 is produced by mature adipocytes as well as by M2 macrophages which could be consistent with M2a profibrotic phenotype. Inflammation increased LRG1 expression by mature adipocytes, while palmitate decreased expression in macrophages. Exposure of mature adipocytes to LRG1 decreased the expression of ECM regulators, MMP2 and TIMP2. Finally, no significant changes in COL-I fibril organization were observed in presence of LRG1. **Conclusions**: LRG1 exhibits a complex, cell type-specific regulation in the adipose tissue under obesogenic conditions. LRG1 can disrupt tissue homeostasis affecting ECM remodeling which could contribute to fibrosis and insulin resistance in the adipose tissue.

PSIdd. Developmental changes in the hypothalamic fat-sensing and ceramide pathways in a mouse model of Prader-Willi syndrome.

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Scientific Program: Nutrition, Endocrine, and metabolic diseases.
Keywords: Prader-Willi; metabolism; hypothalamus, Magel2, fat-sensing.

Abstract:

Prader-Willi syndrome (PWS) is a rare condition with significant metabolic alterations. Infants show decreased feeding behavior, while children and adults display excessive overeating and obesity. Similarly, Magel2-null mice, an animal model of PWS, show reduced body weight before weaning and increased adiposity and weight gain in adulthood. Mounting evidence suggests that hypothalamic fat-sensing pathways play a role in controlling energy balance. However, their influence on the developmental metabolic changes linked to PWS has not been assessed. Here, we examined the hypothalamic expression of relevant fatty acid transporters (CD36, FATP1, and FATP4), free fatty acid receptors (FFAR4), and lipid transducers (PPAR-γ), as well as the hypothalamic content of key lipid-signaling molecules (ceramides), in Magel2-null mice at different postnatal (P) development stages (P7, 14, 23, 35, and 42), covering the infantile-to-pubertal transition. Additionally, we analyzed gene expression of relevant neuropeptides in the control of energy balance, as Pomc and Npy, and metabolic phenotypes. In male Magel2-null mice, we observed reduced mRNA levels of Ppar-γ at P23, a stage when their body weight was decreased, and a decline of Pomc mRNA expression at P35, a period when the animals experienced more significant weight gain. In female Magel2-null mice, Ppar-γ mRNA levels decreased at P14, while Fatp1 and Fatp4 mRNA expression increased at P23. These changes were associated with reduced body weight. At P35, when female Magel2-null mice display increased weight gain, Pomc mRNA levels declined, a phenomenon that was associated with higher Ppar-γ mRNA levels. Moreover, unlike Magel2-null male mice, female Magel2-null mice exhibited significant changes in certain ceramide species at P35 and P42. Our findings suggest that male and female Magel2-null mice display similar metabolic changes during development. However, the mechanisms driving these changes differ, with remarkable alterations in hypothalamic Ppar-γ and ceramide signaling pathways in female Magel2-null mice.

PSI.ee. Prevalence between type 2 diabetes mellitus and depression in older adults.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Depression, Diabetes Mellitus.

Abstract:

The relationship between Type 2 Diabetes Mellitus (T2DM) and depression is complex and multifactorial, involving mechanisms biological factors such as inflammation, insulin resistance, and lifestyle, among others. Moreover, this relationship is bidirectional, since the presence of one of these conditions can worsen the other. In this sense, the aim was to determine the prevalence of depression in people with T2DM. To this aim, a cross-sectional study was conducted between January and April 2024. The study subjects were patients aged 60 years or older with T2DM selected by simple random sampling from among those under follow-up within the Integrated Care Process for Diabetes Mellitus. The study setting was the Basic Health Area of Peñarroya-Pueblonuevo, province of Cordoba. Sociodemographic variables and clinical history were collected by interviewing individuals and reviewing medical records. The descriptive and bivariate statistical analysis was performed using SPSS version 22. Of the 258 subjects in the sample, 58.91% (n=152) were men, with a mean age of 69.78 (SD=6.22) years. In addition, 68.09% (n=147) were married, 6.02% (n=13) were single, 5.56% divorced-separated (n=12) and 20.37% (n=44) were widowed. 12.79% (n=33) were depressed. In this regard, 5.26% (n=8) of the men were depressed compared to 23.58% (n=25) of the women ($p<0.001$). In turn, 7.69% (n=1) of single people, 8.16% of married people (n=12), 16.67% (n=2) of separated/divorced people and 25% (n=11) of widowed people had depression ($p<0.02$). Therefore, the overall prevalence of depression and its higher presence in women and widowed/divorced may be connected to hormonal factors, caregiving burden, stress of partner loss and complications of T2DM.

PSI.ff. Optimization of a Rabbit Corneal Endothelial Dysfunction Model for Pre-Clinical Studies.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Animal model, corneal endothelial dysfunction, descemetorhexis.

Abstract:

Corneal endothelial dysfunction (CED) lead to stromal edema, bullous keratopathy, pain, and loss of vision due to the limited regenerative ability of the human corneal endothelium. The most common treatment for CED is corneal transplantation; however, its limitations recently led to the development of novel therapeutic approaches like tissue engineering or cell therapies. In order to facilitate this development, it is precise to generate relevant and translatable animal models of CED for preclinical studies. Herein, we explored the potential of an adult rabbit descemetorhexis model to recapitulate for at least 3 months the damage to the endothelium and Descemet's membrane seen in humans. Corneal transparency analyzed by slit lamp demonstrated a reduction of red pupillary reflex post-surgery, with severe corneal edema at week 1. Adult rabbit model displayed grade 3 corneal opacity at 2-week that was reduced and maintained to grade 2-3 until the end of the study. Corroborating these results, quantitative analysis of macro images showed a statistically significant reduction in corneal transparency during the follow-up period, with remarkable effect at 2-week ($P<0.05$ vs. pre-surgery). In addition, optical coherence tomography (OCT) showed a significant increase in corneal thickness and fibrosis at 4 and 8-week post-surgery ($P<0.05$ vs. pre-surgery). By 12-week, rabbits maintained remarkable fibrosis ($P=0.011$ vs. pre-surgery). Finally, histological and immunohistochemical analysis were performed to study endothelium regeneration. Absence of Descemet's membrane – endothelium complex in adult rabbits was displayed in the surgical center, which was associated to non-expression of corneal endothelium-related markers [Na+/K+-ATPase and ZO-1]. Related to this finding, a myofibroblast layer along with an altered collagen matrix in the posterior stroma was found in the injury area in the descemetorhexis group. Overall, our results indicate that descemetorhexis in adult rabbits could be an adequate corneal endothelial disease model for studying the safety and efficacy of treatments for CED.

PSI.gg. GPC1, an adipose extracellular matrix protein associated with obesity and inter-organ communication.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Adipose tissue, extracellular matrix, weight gain, insulin resistance, muscle, liver.

Abstract:

Introduction: Glypican-1 (GPC1) is a cell surface heparan sulfate proteoglycan involved in cell division, growth, and differentiation through the regulation of multiple signaling pathways. While other glypican family members have been identified as potential biomarkers for metabolic diseases, the specific role of GPC1 remains unclear. Previous proteomic studies from our laboratory have suggested GPC1 as a potential marker of subcutaneous adipose tissue (SAT) in relation to weight gain, but its role in tissue function has not been examined. Therefore, this study aims to investigate the regulatory network of GPC1 using a preclinical model which overexpresses this proteoglycan in SAT. **Methods**: C57BL/6 mice at 8 weeks of age were injected in SAT (inguinal pads) adeno-associated viral vectors serotype 8 (AAV8) encoding GPC1 sequence for protein overexpression (AAV8-OE) or non-encoding null vectors (AAV8-null). Mice were fed ad libitum with either a normal diet (ND) or a high fat diet (HFD) for 11 and 7 weeks, respectively. Characterization studies including molecular techniques for protein/gene expression analysis and image studies of adipose tissue, muscle and liver were performed. **Results**: A significantly reduction in body weight was observed in animals expressing GPC1, either fed with ND or HFD. In HFD mice, this reduction was attributed to changes in the liver and SAT, whereas in ND mice it was related with muscle mass. These results are consistent with the bioinformatics analysis of the Quantitative Endocrine Network Interaction Estimation (QENIE), which proposes GPC1 as an inter-organ protein associated with liver-SAT interactions and indicates a high correlation with the mitochondrial protein Serine Beta-Lactamase-Like Protein (LACTB). **Conclusions**: Our findings suggest that GPC1 is a molecular marker of weight gain and may play a key role in inter-organ cross-talk in obesity. However, its exact function remains unclear.

Fundings: MICINN/FEDER (PID2019-108403RB-I00). CIBERobn (ISCIII).

PSI.hh. Study of the immune system changes during bee venom immunotherapy.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Adipose tissue, extracellular matrix, weight gain, insulin resistance, muscle, liver.

Abstract:

Specifically targeting cancer cells for therapies is inherently difficult, because it is an abnormal growth of the body's own cells. Instead of trying to deliver drugs to cancer cells which often have severe off target effects, I aim to take a different approach by exploiting the tumor microenvironment with it hallmarks of high lactate and ATP concentrations. Bridging synthetic biology and metabolic engineering with nanomedicine I 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. Thus, the cytotoxic activity of the nanoparticle is primarily linked to the location of the cancer. Prototype nanoparticles labeled with the fluorescent protein iLOV and firefly luciferase have been produced to test the nanoparticle loading mechanism. 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.ii. Nutritional Assessment and Adherence to the Mediterranean Diet in Schoolchildren from Cordoba.

Authors: María del Mar Uclés Torrente1, Manuel Vaquero Abellán1, Pilar Aparicio Martínez1, Isabel María Blancas Sánchez2, Manuel Vaquero Álvarez2, Gema Esperanza Ruíz3, Laura Montaño Azor4, Enrique Yeguas Bolivar5.
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Scientific Program: Nutrition and endocrine and metabolic diseases.
Keywords: obesity, pediatrics, mediterranean diet, lifestyle, technology.

Abstract:

Background: Childhood overweight is a public health issue influenced by cultural, social, and socioeconomic factors. In Spain, 4 out of 10 school children are overweight. The causes range from maternal and gestational factors to lifestyle during the early years. To combat this, healthy habits are promoted, and strategies such as "the Mediterranean diet" and the use of technologies to assess nutritional status are applied. **Main objective**: To analyze the prevalence of childhood overweight and consumption habits in school children, to assess anthropometric indicators and blood pressure values in a group of school children, and to estimate adherence to the Mediterranean diet and determine its relationship with sociodemographic variables. **Methodology**: A cross-sectional observational study was conducted in a school population to evaluate their nutritional status and adherence to the Mediterranean diet. Non-probabilistic sampling was carried out, excluding those with pre-existing medical conditions or without informed consent. Sociodemographic, anthropometric, and blood pressure data were collected, and questionnaires were administered to assess diet. The data were analyzed using descriptive and inferential methods to interpret the results. **Results**: Significant differences in anthropometric values by sex were found in the sample of 58 school children. The most consumed foods were whole milk, fresh fruits, and pasta. The prevalence of overweight was 24.14%, with intermediate adherence to the Mediterranean diet, higher in those who ate in the school canteen and those with a high socioeconomic level ($p<0,05$). **Conclusion:** The study showed significant differences in anthropometric measures by sex, with a lower prevalence of overweight than the national average. KIDMED scores were better in school children who ate in the canteen and those from high socioeconomic levels, highlighting the influence of socioeconomic level on child health.

PSI.jj. Enzymatic nanoparticles driven in situ drug synthesis for disease treatment.

Authors: Irene Bruque Monge1, 2, Henning Kirst 1,2.
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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, because it is an abnormal growth of the body's own cells. Instead of trying to deliver drugs to cancer cells which often have severe off target effects, I aim to take a different approach by exploiting the tumor microenvironment with it hallmarks of high lactate and ATP concentrations. Bridging synthetic biology and metabolic engineering with nanomedicine I 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. Thus, the cytotoxic activity of the nanoparticle is primarily linked to the location of the cancer. Prototype nanoparticles labeled with the fluorescent protein iLOV and firefly luciferase have been produced to test the nanoparticle loading mechanism. 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.kk. Influence of revascularization in the diabetic-ischemic foot.

Authors: Avencia Arévalo García.
Affiliations: Endocrine and metabolic diseases.
Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Pediatry, diabetic-ischemic foot, amputation, ulcer.

Abstract:

Patients who suffer from diabetes mellitus (DM) throughout their lives, in 25% of cases suffer ulceration in the lower limb, with a high percentage requiring amputation of the latter; In 85% of patients who underwent amputation, they have previously suffered from a diabetic foot ulcer. Diabetic foot is defined, according to the WHO, as "the infection, ulceration and destruction of deep tissues of the lower extremity, associated with neurological and digestive alterations". The patient who suffers from the pathology identified as diabetic-ischemic foot is the one who has compromised the circulatory branch of the lower limb, with or without associated diseases. It is the consequence of the difficulty of the arterial blood, rich in nutrients, to irrigate the lower limb. The risk of amputations in the diabetic foot population is 15 times higher than in the general population. This is therefore the main motivation of the doctoral thesis described, to detect risk factors, and to try to make the population have a specialist in the field, to promote the preventive strategy. Hypothesis: differentiate between patients who have suffered an amputation due to diabetic neuropathy and have attended a podiatry clinic and those who have never visited a foot specialist, with patients who have had a higher amputation rate and worse prognosis.

PSI.II. Inclusive Virtual Training of Healthcare Providers for Migrant Pregnant Women.

Authors: Alessia Bisio, Enrique Yeguas Bolívar, Pilar Aparicio Martínez, Juri Taborri, Aurora Ruiz Mezcua.
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Scientific Program: Active aging and frailty.
Keywords: Primary care, Virtual Reality (VR), Pregnant Women, Vulnerable Group.

Abstract:

There is a significant gap in the training of primary care professionals regarding culturally sensitive care for migrant pregnant women. These women face significant health challenges and poor pregnancy outcomes due to restrictive legal entitlements, fear of deportation, social fragility, low health literacy, and barriers related to language and culture upon arriving in Europe. This project aims to fill this gap by designing and developing a virtual reality (VR) lab specifically tailored for primary care professionals. The VR lab will immerse professionals in realistic scenarios, highlighting the barriers faced by both sides and providing opportunities to overcome them in a controlled, simulated environment. By focusing on culturally sensitive and gender-specific approaches, through surveys and interviews useful to identify key barriers and training needs, the lab aims to empower healthcare professionals to deliver tailored services, raise awareness of minority issues, and provide essential cultural and linguistic tools. Ultimately, the goal of the laboratory is to enhance pregnancy outcomes and improve the overall health and well-being of migrant women.

PSI.mm. Uncovering new molecular signatures in psoriatic arthritis by employing high-throughput proteomic analysis of immune cells.

Authors: Eduardo Martín-Salazar1, Iván Arias-de la Rosa1, Laura Cuesta-López1, María Lourdes Ladehesa-Pineda1, Miriam Ruiz-Ponce, Antonio Barranco1, María Ángeles Puche-Larrubia1, Carlos Pérez-Sánchez1, 2, 3, Yasin Hanaee1, 2, María del Carmen Ábalos Aguilera1, Desirée Ruiz-Vilchez1, Pedro Ortiz-Buitrago1, Chary López-Pedrera1, Alejandro Escudero-Contreras1, Eduardo Collantes-Estevez1, Clementina López-Medina1, Nuria Barbarroja1, 2.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Psoriatic arthritis; proteomic; biomarkers.

Abstract:

Introduction. Diagnosing psoriatic arthritis (PsA) is challenging, making the discovery of novel biomarkers through proteomics crucial for early and accurate detection. Molecular clustering can reveal disease heterogeneity, aiding in the identification of subtypes and informing personalized treatments. In this way, the aims of our study are discover novel proteins involved in PsA pathogenesis and uncover molecular phenotypes of PsA patients through unsupervised analysis. **Methods**. This study involved 154 participants, including 104 PsA patients (diagnosed by CASPAR criteria) and 50 control subjects with musculoskeletal symptoms but no rheumatic disease. We analyzed 384 proteins in peripheral blood mononuclear cells (PBMCs) using Olink technology, exploring biological functions with the R platform and identifying molecular clusters with a self-organizing map algorithm. **Results**. PsA patients had an average disease duration of 7 ± 5 years and moderate disease activity, with elevated acute phase reactants compared to controls. Clinical manifestations included dactylitis, enthesitis, and onychopathy. We detected 338 proteins in PBMCs, with 73 significantly altered in PsA patients, enriched in inflammatory response, immune function, and osteoclast activity. Proteins altered were associated with disease activity and dactylitis. Unsupervised analyses identified three PsA clusters with distinct molecular patterns, involving proteins like DAPP1, CCN2, SPRY2, and others, and different levels of C-reactive proteins and monocytes. Moreover, we observed differences in the proteomic profile based on the disease duration (> 5 years or < 5 years). **Conclusions**. High-throughput proteomic analysis identified novel protein alterations in PsA related to inflammation, immune response, and osteoclast function. This study revealed distinct molecular clusters tied to clinical features and immune cell types. These findings pave the way for validation studies to confirm these proteins as robust biomarkers, seeking to improve PsA diagnosis.

Fundings: Supported the “Instituto de Salud Carlos III” (PI22/00539 and RICOR-RD21/0002/0033) co-financed by the European Union and “Junta de Andalucia” (PI-0243-2022).

PSI.nn. Dolutegravir, an antiretroviral compound that promotes adipose tissue metabolic dysfunction.

Authors: Samuel Lorenzo Pino1; M Carmen Soler-Vázquez1,2; Olga García-Ruíz1; Beatriz González-Almecija1; María González-Ruíz1; Elena Salido-Martínez1; Rocío Guzmán-Ruiz1; Mario Frias3; Antonio Rivero-Juárez3; Antonio Rivero3; María M. Malagón1,4; Ana Gordon1.
Affiliations: 1 Adipobiology Group. The Maimonides Institute for Biomedical Research of Cordoba (IMIBIC)/Department of Cellular Biology, Physiology and Immunology (University of Cordoba, Spain)/Reina Sofía University Hospital (HURS), Córdoba; 2 University of Barcelona, Spain; 3 Clinical Virology and Zoonosis, IMIBIC/HURS/UCO; 4 CIBER Physiopathology of Obesity and Nutrition (CIBERobn), ISCIII, Spain.
Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: adipose tissue, antiretroviral therapies, human immunodeficiency virus, thrombosposdin-1.

Abstract:

Antiretroviral therapies (ARTs) for human immunodeficiency virus (HIV) are mainly based on nucleoside reverse transcriptase inhibitors, integrase inhibitors (INIs) or protease inhibitors. Recent studies indicate that some INIs evoke body weight gain and development of metabolic diseases. Specifically, it has been proposed that exposure to Dolutegravir (DTG) could alter adipocyte function leading to adipose tissue fibrosis, thus contributing to the development of insulin resistance. With this background, the main objective of this work was to evaluate the in vitro effects of DTG on 3T3-L1 adipocytes at different stages of differentiation. Moreover, we analyzed serum proteomic samples from a cohort of HIV patients treated with DTG or other ARTs, to identify potential serum biomarkers of adipose dysfunction. For the in vitro studies, preadipocytes and mature adipocytes were exposed to DTG during differentiation or for 72 h, respectively. Adipocyte function was evaluated by molecular (inmmunoblotting, qRT-PCR…) and functional assays (lipid accumulation, viability, lactate production…). Proteomic analysis of serum samples was performed differentially expressed proteins were identified. DTG exposure reduced preadipocyte lipid content and differentiation and altered both mitochondrial protein complexes and lactate production. Moreover, DTG-treated mature adipocytes showed alterations in glucose and lipid metabolism and increased the secretion of an obesogenic adipokine, FABP4. Additionally, proteomic analysis pointed to Thrombospondin-1 (TSP1), a glycoprotein implicated in metabolic diseases, as a potential biomarker associated with adipose tissue damage in HIV patients treated with DTG. In conclusion, our studies show that DTG alters adipocyte functionality, acting mainly at the mitochondria as well as on lipid and glucose regulation Finally, TSP1 serum levels in DTG-treated patients could represent a potential biomarker of adipose tissue dysfunction.

Fundings: UCO/FEDER (202099901920128-R), CIBERobn (ISCIII), INVESTIGO. Margarita Salas (UB 2021-2023).

PSI.ññ. Characterization of outer membrane proteins in isolates of Klebsiella pneumoniae by SDS-PAGE, MALDI-TOF and whole genome sequencing.

Authors: Cristina Elías-López1,2, Montserrat Muñoz-Rosa1,3, Julia Guzmán-Puche1,3, Elena Pérez-Nadales1,2,5, Eduardo Chicano4, Luis Martínez-Martínez1,2,3,5.
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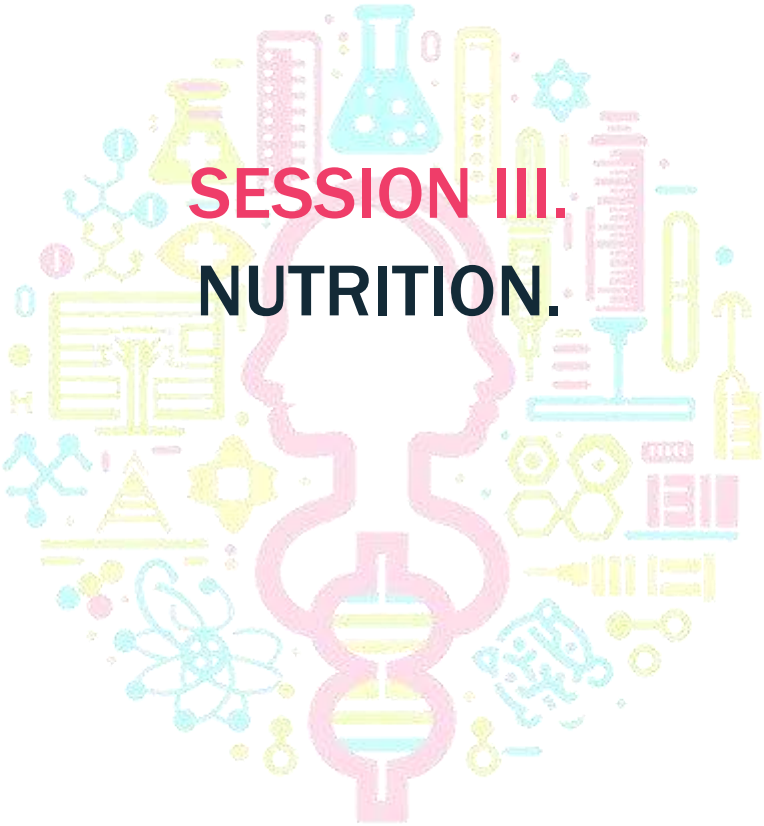
Scientific Program: Infectious and Immunological diseases.
Keywords: Klebsiella pneumoniae, antibiotic resistance, outer membrane protein.

Abstract:

Outer membrane proteins (OMPs) contribute to modulate the susceptibility of bacteria to many groups of antibiotics; their loss or structural alteration is a cause of resistance to different antimicrobials. The main OMPs in Klebsiella pneumoniae (Kp) are OmpA, OmpK35 and OmpK36. The objective of this study was to analyse OMPs in clinical isolates of Kp by SDS-PAGE, MALDI-TOF and whole genome sequencing (WGS). Twenty-six Kp isolates with different phenotypes were tested. Extraction of OMPs was performed using two broth cultures with low and high osmolarity, respectively. SDS-PAGE electrophoresis was performed using Mini-PROTEAN® TGX Stain-Free (Bio-Rad), protein bands were identified by liquid chromatography/mass spectrometry. A rapid extraction method was used to analyse OMPs by MALDI-TOF Sirius (Bruker). WGS was performed with Illumina Novaseq6000 and mutations were identified by BLAST (reference genome: NZ_KN046818.1). Bands at ~37, ~38 and ~39 kDa were detected by SDS-PAGE and identified as OmpA, OmpK36 and OmpK35, respectively. Peaks at ~35700, ~37000 and ~38000 m/z were identified by MALDI-TOF, corresponding to OmpA, OmpK35 and OmpK36, respectively. Osmoregulation was observed all wild-type strains, expressing only OmpK36 in the high osmolarity broth. OmpA was detected by SDS-PAGE and MALDI-TOF in all isolates and point mutations of the gene were identified in one of them. Ompk35 was detected by SDS-PAGE and MALDI-TOF only in wild-type Kp. Isolates producing KPC or OXA-48 showed a premature stop codon with the exception of an isolate with a point mutation. OmpK36 was detected by SDS-PAGE and MALDI-TOF in all but three isolates. MALDI-TOF is a rapid alternative for detecting OMPs in Kp, providing the same results that those obtained with the traditional SDS-PAGE method. Because of the complex regulation of OMP genes, the important information about them obtained by WGS cannot always anticipate the results on their expression obtained by SDS-PAGE or MALDI-TOF.



SESSION III.

NUTRITION.

IIIa. Cannabidiol induces apoptosis of hepatic stellate cells and alleviates liver inflammation and fibrosis in a murine model of androgenic obesity.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Cannabidiol, Non-alcoholic liver disease, obesity.

Abstract:

Polycystic Ovary Syndrome (PCOS) often leads to androgenic obesity (AO) that exacerbates metabolic perturbations, like dyslipidemia and type-2 diabetes, while hormonal imbalances disrupt ovulation, causing irregular cycles. Managing PCOS requires addressing both metabolic and reproductive health through lifestyle changes, pharmacological treatments and psychological support, since PCOS is often linked to anxiety and depression. Cannabidiol (CBD), a non-psychoactive compound from Cannabis sativa, shows potential in treating obesity, anxiety and depression. Herein, we examined CBD's efficacy in a murine AO model induced by chronic exposure of post-weaning female mice to dihydrotestosterone and high-fat diet for 18-weeks, before 21-day CBD treatments. CBD significantly reduced fat mass and weight gain, improved glucose intolerance and insulin resistance, and prevented liver inflammation, fibrosis, hyper-trophic adipocytes, and macrophage infiltration in fat tissues. Circulating ghrelin levels were downregulated in AO and this was counteracted by CBD. Other biomarkers, including IL-1, Ddah1, Prdx5, Map2k6, Plin1, Ca13, Eno2, and Itgb1pp2, were suppressed also by CBD. To explore CBD's hepatic effects, we performed LC/MS-based proteomics in the liver of control, AO and CBD-treated AO mice, quantifying 4,348 proteins, with 1,083 showing significant changes in at least one comparison against control mice. Deregulated proteins in AO were associated with oxidative phosphorylation, MYC-targets and adipogenesis-related genes. CBD down-regulated proteins related to oxidative phosphorylation and adipogenesis. Our AO model displayed ovarian failure, with decreased ovarian weight, disrupted follicular dynamics, lack of corpora lutea, and increased stromal fibrosis. CBD did not rescue ovulation but increased ovarian weight and reduced fibrosis. In vitro, CBD induced apoptosis in human hepatic stellate cells (HSCs) and reduced activated HSCs in the liver of AO mice. In summary, CBD has significant therapeutic potential for PCOS due to its multitarget effects, as anxiolytic, antidepressant, anti-obesity, and antifibrotic agent. This makes CBD a promising candidate for combination with ovulation-inducing therapies in PCOS.

IIIb. Metabolic and transcriptomic insights into obesity-induced hypogonadism: Unveiling the role of Kiss1 neurons.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Kiss1, Obesity, Hypogonadism, Reproduction, LC-MS/MS.

Abstract:

Obesity represents a global public health issue. One of the comorbidities of obesity is hypogonadism, an often overlooked condition that can affect up to 50% of obese men and is characterized by low levels of gonadal steroids, which may lead to sexual and metabolic problems. Kiss1 neurons have recently emerged as key regulators of the hypothalamic-pituitary-gonadal axis and research from our group has shown that manipulation of these neurons affects gonadal and metabolic function. In this study, we have developed a mouse model of obesity-induced male hypogonadism (OIH) to investigate the role of Kiss1 neurons in this condition. Our model specifically expresses the Td-tomato fluorescent protein in Kiss1 neurons, which allows us to isolate this cell type using cell sorting technology (FACS) after exposure to an obesogenic diet. Our model exhibits classic features of OIH, such as low luteinizing hormone levels, obesity, glucose intolerance and increased fat mass. To understand the potential involvement of Kiss1 neurons in OIH, FACS-isolated Kiss1 neurons from our OIH model have been characterized using RNA-seq. Our transcriptomic studies revealed a set of altered genes in the OIH mouse model, pointing to the deregulation of key biological processes closely related to reproduction and metabolism. In addition, we have carried out an LC-MS/MS analysis of serum in our OIH model, revealing several metabolites of interest whose levels are deregulated in the hypogonadal model when compared to control animals. The next studies will include conditional manipulation of target genes in Kiss1 neurons through gene-editing CRISPR/Cas9 technology, aiming to dissect out their specific contribution to the generation of OIH.

IIIc. Relationship between liver fibrosis degree and the incidence of cardiovascular events in secondary prevention patients. CORDIOPREV Study.

Authors: Esperanza Sastre Menor1,2, Antonio Pablo Arenas De Larriva1,2,3, Adelaida Fernández Navarro1,2, Juan Luis Romero Cabrera1,2,3, José David Torres Peña1,2,3, Laura Limia Pérez1,2, Juan Francisco Alcalá Díaz1,2,3 and José López Miranda1,2,3.
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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: liver fibrosis, fibrosis index, steatotic liver disease, cardiovascular events, secondary prevention, CORDIOPREV study.

Abstract:

Objectives: To assess the relationship between liver fibrosis degree and major cardiovascular events. **Material and Methods**: Analytical and retrospective study with 1002 participants of CORDIOPREV study, in which liver fibrosis degree was estimated by calculating the APRI, FIB-4, BARD, Forns, NFS and Hepamet indices, classifying participants into different groups for each. Cardiovascular events were collected from patients over 7 years of follow-up, calculating the difference in its mean and percentage. Kaplan-Meier test was used to analyse cardiovascular event-free survival in the different risk groups for each index using log-rank determination to compare survival curves and search for differences in the risk of cardiovascular events between them. **Results**: The mean number of cardiovascular events in the low-risk fibrosis group according to Hepamet index was 0.369; lower than the mean of 0.482 in the intermediate-high risk group; p=0.037. The percentage of cardiovascular events in the low-risk group, 17.6%, was lower than the percentage in the intermediate-high risk group, 24.8%; p=0.011. The mean event-free time in the low-risk fibrosis group was 2324.87 days compared to 2229.22 days in the intermediate-high risk group, with a log-rank p-value of 0.009. **Discussion**: Hepatic steatosis associated with metabolic dysfunction (MASLD) is widely linked to cardiovascular risk by interacting with all other risk factors, leading to an increase in cardiovascular events. Previous studies have suggested the need to incorporate liver fibrosis indices into daily clinical practice to adequately stratify cardiovascular risk of patients affected by MASLD and thus prevent the development of new events and reduce mortality. **Conclusions**: A higher degree of liver fibrosis estimated by the Hepamet index is related to a higher number of cardiovascular events and a decrease in event-free survival, so this index could be used to better stratify cardiovascular risk of patients, optimising their follow-up to prevent new events and reduce their mortality.

IIId. Lifestyle habits according to the chronotype among a vulnerable population at risk of food insecurity.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: chronotype, cardiovascular disease, food insecurity, vulnerable population.

Abstract:

Chronodisruption has been associated with cardiovascular risk. Evening chronotype individuals show a predisposition to suffer chronodisruption and unhealthy lifestyle habits. Our objective was to assess lifestyle habits according to the chronotype among a vulnerable population at risk of food insecurity, from the E-ducass study. We carried out a cross-sectional study including 460 subjects from the E-ducass study (NCT05379842), a health educational clinical trial. We classified the subjects as more morning-type or more evening-type, according to the Morningness-Eveningness Questionnaire. The participants filled out sociodemographic and lifestyle questionnaires including the Mediterranean Diet Adherence Score (MEDAS). Subjects classified as more evening-type had feeding timing such as breakfast (9:24 hours vs 8:42 hours, p<0.01), lunch (14:42 hours vs 14:30 hours, p=0.05) and dinner (21:42 hours vs 21:18 hours, p<0.01), in addition of sleep timing such as bedtime (23:54 hours vs 23:06 hours, p=0.01) and wake up (8:00 hours vs 7:18 hours, p<0.01) significantly later than more morning-type subjects. Interestingly, the more evening-type participants also had less duration of sleep (7.5 hours vs 8.1 hours, p=0.04), lower adherence to a Mediterranean diet (7.5 points vs 8.2 points, p=0.04), lower total weekly physical activity (4:48 hours vs 5:54 hours, p<0.01) and more sedentarism compared to more morning-type participants. More evening-type adult subjects had unhealthy lifestyle habits compared than more morning-type subjects. Therefore, to assess chronotype in a vulnerable population could help us to provide tailored recommendations focused on lifestyle habits to improve their cardiovascular health.

SESSION IV.

MULTIDISCIPLINARY.

IVa. Short term outcomes of a Patient-tailored Residual Cardiovascular Risk Reduction Program for Post-Acute Coronary Syndrome Patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Acute coronary syndrome. Cardiovascular disease. Residual cardiovascular risk. Lipoprotein (a).

Abstract:

Background: Acute Coronary Syndrome (ACS) remains one of the most frequent causes of morbidity and mortality in the world. Although the age- and gender-adjusted incidence of ACS is declining, the mortality associated to this condition remains elevated, particularly at one year after the acute event. A considerable percentage of major adverse cardiovascular events (MACE) occurs despite optimal LDL-C levels, underscoring the need to focus on the role of other lipid fractions with atherogenic potential in "residual cardiovascular risk". Among these fractions, notable components (including remnant cholesterol [RC], lipoprotein (a) and small and dense LDL-C) are now well-known residual risk targets as new strategies aimed at lowering their levels appear to decrease the occurrence of new MACE. **Purpose**: We aimed to describe the results of the implementation of a "residual cardiovascular risk personalised program" at short-term (1 month) in patients discharged after an ACS and to assess the association between 1-month LDL-C and others circulating lipid fractions levels with MACE. **Methods**: From January 2023 to December 2023, all consecutive patients discharged from our cardiology department after an ACS were identified and evaluated one month later to assess the occurrence of MACE (defined as all-cause death, cardiovascular death, non-fatal myocardial infarction, stroke, hospitalization because of heart failure, readmission due to unstable angina or unplanned revascularization). Lipid control targets were defined following 2023 guidelines on Acute Coronary Syndrome. **Results**: Figure 1A summarizes baseline clinical, lipid lowering therapy and echocardiographic characteristics of 325 patients discharged after an ACS. The incidence of MACE in our population was high, 4.9% (figure 2A), although no deaths related to cardiovascular events or other causes were recorded. Significant differences in circulating lipid levels were detected within the initial follow-up (Figure 1B). LDL-C goal lower than 55 mg/dL was reached by 69% of patients (Figure 2B). The achievement of LDL-C targets or maintenance of fasting RC levels below those recommended by ESC guidelines did not correlate with the occurrence of new MACE during the initial month of follow-up (Figures 2C and 2D). **Conclusion(s):** The implementation of a patient-tailored residual cardiovascular risk program resulted in a high percentage of patients achieving the recommended LDL-C targets, along with a significant improvement in the overall lipid profile at the first month of follow-up.

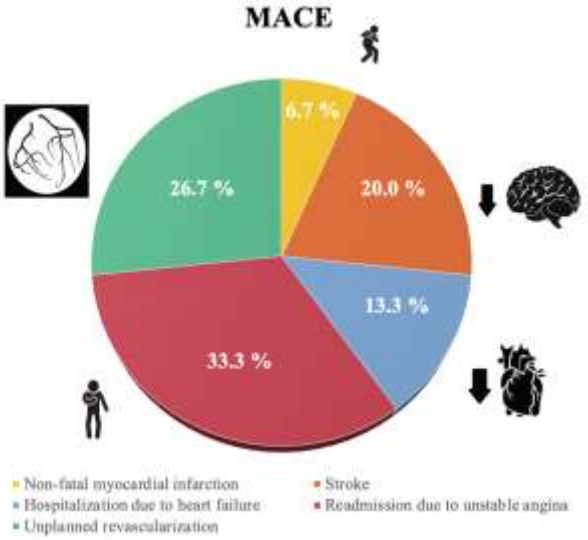

Figure 2A. Fifteen new major adverse cardiovascular events (MACE) appear during the initial month of follow-up.

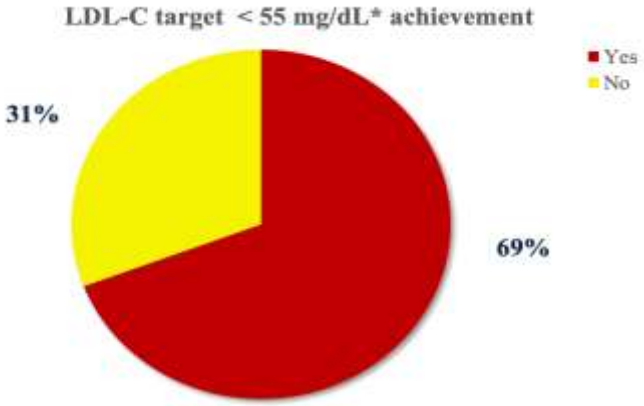

Figure 2B. Percentage of patients achieving low-density lipoprotein (LDL-C) goal of less than 55 mg/dL. * Goal of less than 40 mg/dL if history of multiple cardiovascular events.

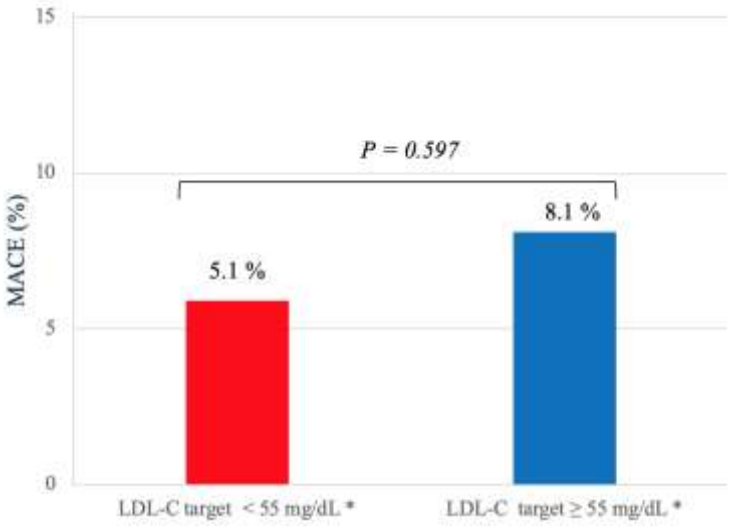

Figure 2C. Percentage of patients experiencing MACE and achieving low-density lipoprotein (LDL-C) goal of less than 55 mg/dL. * Goal of less than 40 mg/dL if history of multiple cardiovascular events.

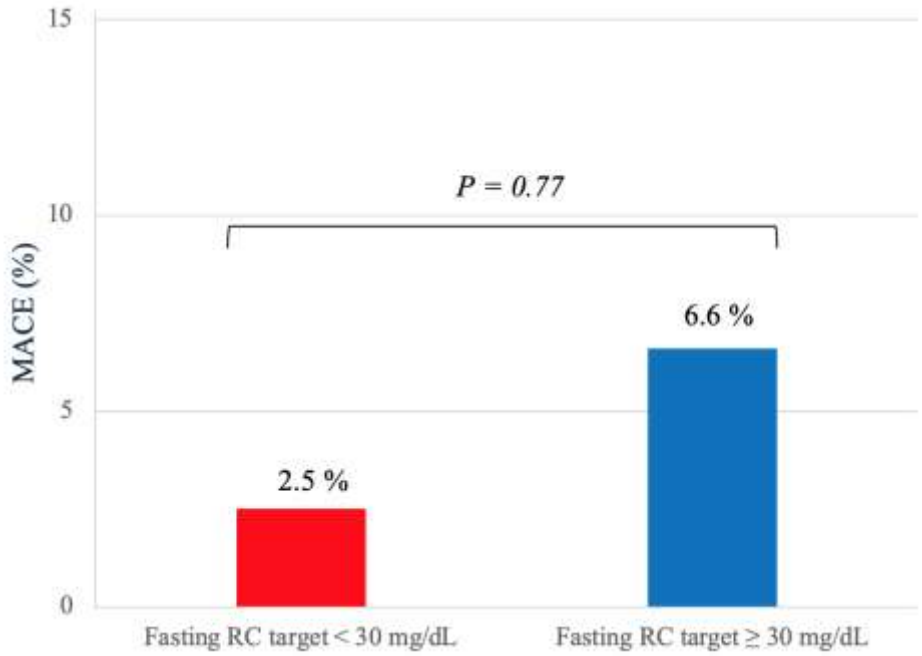

Figure 4. Percentage of patients experiencing MACE and achieving fasting remnant cholesterol (RC) goal of less than 30 mg/dL.

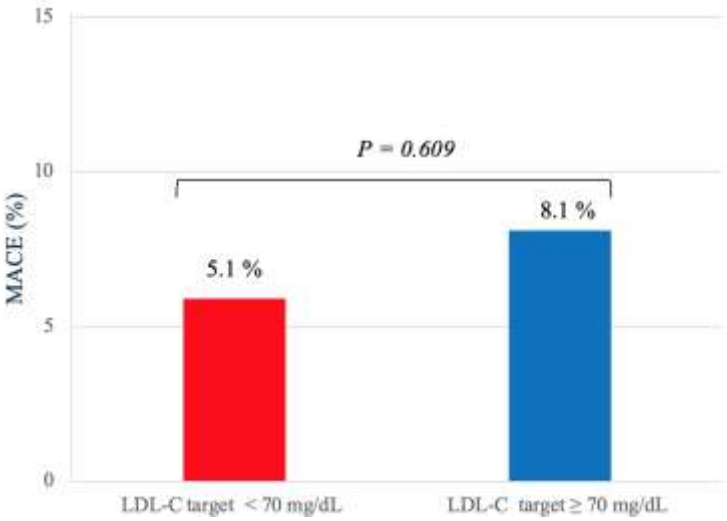

Figure 5. % patients experiencing MACE and achieving low-density lipoprotein (LDL-C) goal of less than 70 mg/dL. TABLES

Figure 1A. Baseline clinical, ACS presentation, echocardiographic and lipid-lowering treatment characteristics of 325 patients after ACS. Continuous variables shown as mean ± standard deviation. ACS: acute coronary syndrome. STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction.

Clinical characteristics	
Age, years	66.3 ± 12.6
Women, n (%)	73 (22.5)
Hypertension, n (%)	287 (88.3)
Dyslipidaemia, n (%)	159 (48.9)
Smoking (current or former), n (%)	171 (52.6)
Diabetes, n (%)	141 (43.4)
Hypertriglyceridemia n (%)	50 (15.4)
ACS clinical presentation	
STEMI, n (%)	106 (32.6)
NSTEMI, n (%)	73 (21.2)
Unstable angina, n (%)	158 (46.2)
LV dysfunction (FEVI < 50%), n (%)	89 (27.4)
Lipid-lowering therapy at discharge	
High dose statins, n (%)	325 (100)
Ezetimibe, n (%)	245 (75.4)
Bempedoic acid, n (%)	24 (7.4)
Anti-PCSK9 antibodies, n (%)	23 (7.1)
Inclisiran, n (%)	3 (0.9)

Figure 1B. Baseline and first month Lipid profile of 325 patients after ACS. Continuous variables shown as mean ± standard deviation or median and interquartile range. TC: total cholesterol; HDL-c: high-density lipoprotein; LDL-C: low-density lipoprotein; Lp(a): lipoprotein (a); ApoB: apolipoprotein B; ApoA1: apolipoprotein A1; Non-HDL-C: non-high-density lipoprotein; VLDL-C: very low-density lipoprotein; TG: triglycerides; TyG index: triglycerides-glucose index; Hs-CRP: high sensitivity C reactive protein.

	Baseline	**First month**	***P***
Lipid profile			
TC, mg/dL	162.4 ± 46.1	112.8 ± 26	< .001
HDL-C, mg/dL	39.9 ± 11	40.1 ± 11.6	.637
LDL-C, mg/dL	94.3 ± 37.3	49.7 ± 20.6	.005
Lp (a), mg/dL	36.2 (10-464)	32 (10-503)	.005
ApoB, mg/dL	86 ± 26.4	57.6 ± 17.1	< .001
ApoA1, mg/dL	113.8 ± 23.9	113.9 ± 23.7	.948
Non-HDL-C, mg/dL	117 ± 47.9	72.9 ± 22.5	< .001
TG, mg/dL	121.5 (9-631)	106 (10-710)	< .001
VLDL-C, mg/dL	26 (9-293)	21 (6-142)	< .001
Remnant cholesterol mg/dL	26.8 ± 14.7	17 ± 6.9	< .001
LDL-C/ApoB	1.2 ± 0.4	0.9 ± 0.3	< .001
TG/HDL-C	3.8 ± 0.7	3.2 ± 0.7	< .001
TyG index	4.8 ± 0.4	4.6 ± 0.3	< .001
Hs- CRP (mg/dL)	11.8 (.5-143.8)	1.9 (0.1-26.9)	< .001

IVb. Defining Early and Established Rheumatoid Arthritis Through Multi-Omic Profiling: Links to Disease Status and Treatment Response.

Authors: Ismael Sanchez-Pareja1, Carlos Perez-Sanchez1, Daniel Toro-Domínguez2, Laura Muñoz-Barrera1, Tomas Cerdó1, Elena Moreno-Caño1, Rafaela Ortega-Castro1, Jerusalem Calvo Gutierrez1, María Lourdes Ladehesa-Pineda1, Concepción Aranda-Valera1, María Carmen Ábalos-Aguilera1, Christian Merlo-Ruiz1, Maria Angeles Aguirre-Zamorano1, Nuria Barbarroja1, Marta Alarcon-Riquelme2, 3, Alejandro Escudero-Contreras1, Chary Lopez-Pedrera1.
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Scientific Program: Chronic and Inflammatory diseases.
Keywords: rheumatoid arthritis, -omics, biomarkers.

Abstract:

Objectives: Characterize the molecular landscape of RA patients using a multi-omic approach encompassing transcriptomics and proteomics and assess its association with disease stage and therapeutic outcomes. **Methods**: PBMCs from patients with early RA (EA-RA; diagnosis ≤ 1 year; n=31), stablished RA (ES-RA; diagnosis ≥ 5 years; n=66), and healthy donors (HDs; n=27) were profiled by RNAseq on Illumina platforms. Ninety inflammatory mediators were analyzed in serum using "Proximity extension assay" (Olink). EA-RA included 26 patients starting conventional disease-modifying antirheumatic drugs (DMARDs). ES-RA cohort comprised 47 biologics-naïve patients before receiving TNF-inhibitors (TNFi) or JAK-STAT-inhibitors (JAKi) DMARDs. Clinical outcomes were assessed after 6 months (EULAR-criteria). Computational analysis evaluated the relationship between transcriptomic and proteomic profiles, disease features, and therapy response. **Results**: Seventy gene-modules related to lymphocyte and myeloid cell activation and inflammation were altered in EA-RA compared to HDs. ES-RA displayed more pronounced alterations and specific changes in 58 additional gene modules concerning other immunoregulatory pathways. Significant inflammatory response changes were observed in ES-RA, with 49 proteins differentially expressed compared to HDs, contrasted with 32 in EA-RA. EA-RA patients showed a negative correlation between disease activity (DAS28, acute phase reactants) and T lymphocytes and NK cell activation modules, and a positive correlation with inflammatory and myeloid gene modules. Protein inflammatory mediators were linked with disease severity and autoantibodies positivity (RF and ACPAS). These correlations were more pronounced in ES-RA, highlighting increased molecular complexity over time. A significant relationship was noted between altered gene modules in PBMCs and circulating inflammatory proteins, indicating a sophisticated molecular network driving disease progression. Baseline transcriptomic signatures were linked with clinical response: increased lymphocyte activation-gene modules expression predicted a good response to conventional DMARDs in EA-RA but poor response to JAKi and TNFi in ES-RA. **Conclusions**: Distinct molecular signatures in EA-RA and ES-RA reflect disease progression and therapy response differences. Greater deregulation in ES-RA underscores the need for stage-specific therapeutic strategies. Identified gene modules and proteins could serve as biomarkers for disease activity and treatment response, supporting personalized RA treatment.

Fundings: EU/EFPIA IMI-JU 3TR, ISCIII (PI21/0591, CD21/00187 and RICOR-21/0002/0033),co-financed by European Union, and MINECO (RYC2021-033828-I/PID2022-1415000A-I00).

IVc. Exploring the role of the metabolic factor LEAP-2 on puberty onset.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: LEAP-2, ghrelin, puberty.

Abstract:

Puberty is a key maturational process, highly dependent on energy resources, that culminates with the acquisition of reproductive capability. In this context, a multitude of metabolic signals precisely regulate puberty onset based on energy availability. Among others, ghrelin -an orexigenic hormone secreted mainly by the stomach- plays a crucial role in controlling metabolism and puberty onset by activating the growth hormone secretagogue receptor (GHS-R1a). Recently, the hepatic peptide LEAP-2 has emerged as a potential GHS-R1a antagonist involved in the regulation of energy homeostasis. However, its impact on pubertal maturation remains unexplored. Thus, this project aimed to investigate the contribution of LEAP-2 to the metabolic control of puberty. To this end, we examined the impact of acute or chronic LEAP-2 administration during pubertal transition in female Wistar rats under different metabolic conditions and steroid milieu. Our findings revealed that acute central administration of LEAP-2 increases luteinizing hormone (LH) release in a dose-dependent manner in intact peripubertal rats fed ad libitum or subjected to 24-hour fasting, a condition known to elevate circulating ghrelin levels. Chronic central administration of LEAP-2 in prepubertal female rats, either fed ad libitum or subjected to 20% food restriction, significantly advanced puberty onset. This effect was characterized by earlier vaginal opening, increased LH levels, and accelerated ovarian maturation, regardless of the nutritional status, with a more pronounced effect in undernourished animals. A similar increase in LH levels was observed in ovariectomized peripubertal rats replaced with physiological levels of estradiol and treated with LEAP-2. Notably, central LEAP-2 treatment in the different experimental conditions increased Kiss1 mRNA levels, suggesting the participation of this neuropeptide as a potential transmitter of the effects of LEAP-2 on puberty onset. Therefore, our data provide the first evidence of the role of LEAP-2 in the metabolic control of pubertal maturation, potentially via Kiss1 neurons.

IVd. The relevance of the Nonsense-Mediated Decay and RNA-Exosome cellular machineries in the pathophysiology of pituitary tumours.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: Pituitary tumour; RNA metabolism; Nonsense-Mediated Decay; RNA-Exosome; biomarkers; therapy.

Abstract:

Pituitary tumours (PTs) represent more than 15% of Central Nervous System tumours and they are divided into hormonally active (with significant endocrine comorbidities associated), or clinically non-functioning (NFPTs; exhibiting mass effect-related comorbidities). Recent studies indicate that dysregulations in splicing machinery is a prevalent characteristic observed in several endocrine/tumour pathologies, including PTs. In this context, other mRNA metabolism machineries [i.e., Nonsense-Mediated-Decay (NMD) and RNA-Exosome] have also been associated with the pathophysiology of other endocrine-related cancers. Therefore, our objective was to characterize the pathophysiological role of these mRNA metabolism machineries in PTs. To that end, we evaluated the expression levels of NMD and RNA-Exosome components using a microfluidic array in an internal cohort [n=73 NFPTs; n=50 somatotropinomas; n=10 normal pituitary (NPs; used as control)]. Furthermore, bioinformatic analyses (using external cohorts) and functional/molecular approaches (using GH3 cells and primary patient-derived tumour cells) were performed. Results revealed a heterogeneous dysregulation in both machineries, highlighting the overexpression of a NMD factor (NF1*) and an RNA-Exosome factor (EF1*), as the most discriminating factors between PTs and NPs. Moreover, samples with the highest expression levels of these selected genes were enriched with key oncogenic pathways. Moreover, its silencing, through specific siRNAs, reduced: 1) functional parameters (i.e., proliferation, colony formation, etc.) in vitro and 2) tumour molecular features (i.e., cell cycle). Finally, the pharmacological inhibition of mRNA metabolism using NMDi (NMD inhibitor) but not isoginkgetin (RNA-Exosome inhibitor) also reduced proliferation rate and other aggressiveness features. Interestingly, NMDi enhanced the antiproliferative effect of a clinically used somatostatin-analogue in GH3 cells. In conclusion, this study provides evidence indicating the drastic alteration of mRNA metabolism machineries, NMD and RNA-Exosome, in PTs which could represent attractive novel sources of diagnostic/prognostic and therapeutic targets in this tumour pathology.

IVe. BIORICA10- A longitudinal metabolic study in young adult with extrauterine growth restriction.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: Nutrition, metabolism, EUGR, insulin resistance, inflammation.

Abstract:

Extrauterine growth restriction (EUGR) refers to preterm infants who, although being born with a weight and length in accordance with gestational age, show very poor growth in the first weeks after birth. Perinatal growth and nutrition have been shown to be determinant in the programming of different tissues, such as adipose tissue, predisposing to metabolic alterations later in life. Moreover, previous studies have documented an increased risk of metabolic disturbances and low-grade inflammation in prepubertal children with a history of EUGR. Therefore, it is essential to understand the changes resulting from impaired growth during early childhood and their impact on young adult health. We present herein a longitudinal, descriptive and analytical study of a cohort with a history of EUGR recruited at prepubertal age and followed up for 10 years until the end of puberty. Changes over time in anthropometric measurements, blood pressure, biochemical parameters related to lipid and carbohydrate metabolism and plasma adipokines and cytokine were evaluated. All analyses were adjusted for sex, age and body mass index. Our study shows that young adults exhibit an increased abdominal circumference percentile compared to the prepubertal stage ($p<0.001$). Moreover, insulin levels and HOMA-IR were higher in adults ($p<0.001$), with a proportion of 25% of adult subjects with insulin resistance versus 3% of prepubertal subjects. In contrast, arterial hypertension was observed in 48% of prepubertal children compared to 20% after puberty. Lipid values remained within normal ranges. Adiponectin and leptin remained at similar levels in adulthood, with a decrease in resistin. As for cytokines, they showed a decrease in adulthood compared to pre-puberty values. All in all, patients with EUGR show an increased risk of presenting certain metabolic alterations in adulthood which emphasizes the importance of clinical follow-up in these patients to prevent the development of further future complications.

SESSION V.

CANCER II.

Va. Targeting metabolism overcomes immune evasion and improves immunotherapy efficacy in GSNOR-deficient colorectal cancer tumors.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Immunotherapy, metabolic reprogramming, GSNOR, immune evasion, 2-deoxyglucose.

Abstract:

Background and aims: S-nitrosoglutathione reductase (GSNOR) is a denitrosylase enzyme with a tumor suppressor role. We previously described that metabolic reprogramming drives tumor progression and immune evasion in GSNOR-deficient colorectal cancer (CRC). The present study was aimed to determine whether the metabolic vulnerabilities associated with this reprogramming can be exploited to reverse immune evasion and improve the efficacy of immunotherapy in these tumors. **Material and Methods**: Clinical samples from 137 CRC patients were classified as GSNOR-high or GSNOR-low based on immunohistochemical (IHC) GSNOR expression and the association with clinicopathological variables and survival was analyzed. Additionally, RNA sequencing analysis was conducted on 34 tumors (19 GSNOR-high and 15 GSNOR-low). Preclinical platforms included CRISPR-Cas9–mediated GSNOR gene knockout (KO) CRC cells, patient-derived organoids (PDOs), and humanized xenograft models. **Results**: GSNOR-low tumors exhibited poor prognostic features, such as high budding grade and lower survival rates. Additionally, RNA-seq data revealed in GSNOR-low tumors the upregulation of immune evasive pathways (IFNα and IFNγ) and the downregulation of metabolism-related pathways (mTORC1, peroxisome, and OXPHOS). IHC analyses confirmed in GSNOR-low tumors an immunosuppressive microenvironment with exclusion of cytotoxic CD8+ T cells, which may also explain their higher budding grade. Accordingly, GSNOR-KO CRC cells displayed higher immunevasive capacities with an increased expression of the immune checkpoint PD-L1. Moreover, the altered expression of metabolic mitochondrial enzymes suggested a higher dependency on glycolysis for bioenergetic demands in GSNOR-low tumors. Notably, the glycolysis disruptor 2-deoxyglucose improved immune activity against GSNOR-KO CRC cells or PDOs from GSNOR-low tumors and overcame their resistance to anti-PD-1 treatment. Importantly, humanized PDXs models further validated in vivo that glycolysis inhibition enhanced the efficacy anti-PD-1 blockade with nivolumab in GSNOR-deficient tumors. **Conclusions**: Glycolysis represents a targetable metabolic vulnerability in GSNOR-deficient CRC, enhancing the potential for immunotherapy in these high-risk tumors.

Fundings: PID2019-105256RB-I00, P20-00967 and PI23/00489.

Vb. Exploring the role of NOP10 in pancreatic ductal adenocarcinoma: Implications for telomere stability and tumor progression.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: NOP10, Shelterin-Telomerase Complex, PDAC.

Abstract:

Pancreatic Ductal Adenocarcinoma (PDAC) is one of the most aggressive cancers, presenting the lowest survival rate among all tumor types. This is primarily due to its rapid progression and late stage detection. Despite recent advances in the molecular understanding of PDAC, its prognosis remains dismal because there are no effective indicators for early diagnosis and therapeutic options. Numerous studies have described an association between cancer development and progression and telomere stability. Telomeres are protective caps at the ends of chromosomes that help to maintain genomic integrity and cell survival. In cancer, the Shelterin Telomerase complex is altered, leading to genomic instability and immortalization —hallmarks of tumorigenesis—. Nevertheless, the role of this system in PDAC remains insufficiently understood. Firstly, we examined the expression at RNA level of the components of this system in a retrospective cohort of 80 patient derived samples and in six accessible in silico cohorts, seeking correlations and associations to relevant clinical parameters. NOP10 was the only Shelterin Telomerase component consistently overexpressed in all the cohorts studied. Its expression was also related to reduced overall survival, KRAS and TP53 mutations and SMAD4 expression among other poor prognosis parameters, suggesting a possible role in tumor development and progression. Then, based on these results, we studied the functional role of NOP10, modifying its expression in two different PDAC cell lines: Capan 2 and MiaPaca 2. NOP10 silencing decreased cell proliferation, tumorspheres, and colony formation; while its overexpression exhibited the opposite effect, supporting the importance of this molecule in PDAC behavior in vitro. However, modulation of NOP10 seems to have no direct effect on telomere length, suggesting a possible secondary role of this molecule in PDAC cells. Overall, our findings show a dysregulation in the Shelterin Telomerase complex in PDAC, with a focus on NOP10, which may influence this disease's evolution, opening up new therapeutic avenues.

Vc. Pathophysiological dysregulation of the inflammasome machinery in glioblastoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Glioblastoma; inflammasome; tumor microenvironment; biomarkers; therapeutic target.

Abstract:

Glioblastoma (GBM) stands as the most prevalent and lethal primary brain tumor mainly due to the late-stage diagnosis and the acquisition of resistance to gold-standard therapy, based on neurosurgery followed by radiotherapy and/or chemotherapy. These attributes result in the poor prognosis and low quality of life of patients, with an approximate median survival rate of 8-9 months after diagnosis. Therefore, the identification of novel molecular biomarkers of diagnosis and/or prognosis, as well as therapeutic targets becomes crucial to deal with this devastating pathology. In this context, the inflammasome molecular machinery, the master regulator of cell inflammation, plays a crucial role in the modulation of tumor microenvironment (TME), essential in the initiation, progression and aggressiveness of different tumor pathologies. Therefore, the objective of this study was to comprehensively characterize the expression and putative pathophysiological role of the molecular components of this cellular machinery in GBM, using an internal cohort of samples [GBM (n=63) and non-tumor brain samples (NTB; n=19)] and 5 external cohorts of samples (Validation cohorts; RNA-Seq and microarray data). A profound dysregulation of multiple inflammasome components was observed in glioblastoma vs. NTB. Of note, through bioinformatic analysis, we identified an inflammasome factor (IF1*) strongly associated with relevant clinical parameters (e.g. survival, mesenchymal subtype, etc.) and oncogenic pathways (e.g. angiogenesis, cell proliferation, hypoxia, epithelial-mesenchymal transition, etc.) related with GBM pathophysiology. Additionally, silencing of IF1 expression in GBM cell models resulted in reduced proliferation and migration capacity, as well as apoptosis induction. Taken together, these findings demonstrate a clinically relevant dysregulation of the inflammasome machinery in GBM, which could serve as a source of novel diagnostic/prognostic biomarkers and therapeutic targets to improve the management of GBM, highlighting the putative importance of IF1 in GBM pathophysiology.

Fundings: Junta de Andalucía (P20_00442), MICIIN (FPU21/00857, FPU20/03954, PID2022-1381850B-I00).

Vd. NK cell profiling predicts cetuximab efficacy in metastatic colorectal cancer and highlights TIGIT as a potential therapeutic target.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: metastatic colorectal cancer; natural killer cells; immunophenotype; cetuximab; ADCC; TIGIT.

Abstract:

Background and aims: The anti-EGFR monoclonal antibody cetuximab is the main therapy for wild-type RAS metastatic colorectal cancer (mCRC) patients, but only half of them respond to this treatment. Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) induced by Natural killer (NK) cells is one important mechanism by which cetuximab exerts its anti-tumoral effect. Therefore, molecular characterization of NK cells subpopulations may identify predictive biomarkers of cetuximab efficacy in mCRC patients and would provide novel therapeutic targets to enhance cetuximab-mediated ADCC. Methods: Blood samples from 25 mCRC patients pre-cetuximab treatment were utilized to purify NK cells for immunoprofiling and proteomic analyses. Patients were categorized as non-responders (NR, n=12) if they progressed before 9 months, and as responders (R, n=13) if progression occurred after. NK cells from healthy donors were co-cultured with CRC cell-lines spheroids or patient-derived organoids (PDOs) for in vitro ADCC assays. Results: None of the clinical-pathological variables were associated with the response to cetuximab. However, NK cells from NR patients displayed a higher proportion of CD16bright NK cells and a distinct inhibitory immune profile with lower expression of activation markers (CD25, NKG2C, NKp30 and NKp46) and, remarkably, higher expression of the inhibitory receptor TIGIT, in comparison with R patients. Moreover, unsupervised proteomic analysis efficiently differentiated NR from R patients, revealing altered drug resistance and immune evasion pathways in NK cells from NR patients, confirming mechanisms underlying their lack of response to cetuximab. Finally, in vitro assays revealed enhanced cetuximab-mediated ADCC when combined with the anti-TIGIT antibody tiragolumab. CD16bright NK cells were the main sub-population infiltrating spheroids, suggesting that NR patients might derive significant benefits from the tiragolumab/cetuximab combination therapy. Conclusions: Our findings underscore the potential of molecular profiling of NK cells in predicting cetuximab efficacy in mCRC patients and highlight TIGIT as a promising target for enhancing treatment outcomes.

Fundings: PI20/00997.

Ve. SMG7 as a potential driver of chronic liver disease progression to HCC.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: SMG7, NMD, cellular stress, biomarker, CLD and HCC.

Abstract:

SMG7 nonsense mediated mRNA decay (NMD) factor is a fundamental component of the NMD machinery, which eliminates altered mRNAs where translation is interrupted, such as genes implicated in stress response. In addition, SMG7 promotes the survival of cells after genotoxic stress by inducing the ATR-Chk1 pathway. The continuous exposition of lipotoxic free fatty acids (FFA) in chronic liver disease (CLD) leads to cellular stress and liver damage. Taking into account these functions in stress conditions, this work aimed at studying the implication of SMG7 in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic-dysfunction associated steatohepatitis (MASH) and hepatocarcinoma (HCC). Expression (mRNA) of 22 NMD components was analyzed in a retrospective HCC cohort [n=89 HCC and non-tumor paired adjacent tissues (NTAT)] by microfluidic-based qPCR array and validated in seven external cohorts with healthy, MASLD, MASH, HCC, and/or NTAT samples. Human (THLE2) and mouse (primary) hepatocytes were treated with FFAs (oleate and palmitate). Pharmacological (NMDI14, which blocks SMG7-UPF1 interaction) and genetic modulation of SMG7 were carried out in two HCC-derived cell lines to explore the functional effects on proliferation, migration, and colony formation, and NMD genes target expression (mRNA to pre-mRNA ratio) were measured. SMG7 factor was consistently overexpressed in HCC, MASH, and MASH-derived HCC samples. In addition, SMG7 expression (mRNA) was induced by palmitate and its overexpression in HCC cell lines induces proliferation and colony formation. Using NMDI14 treatment or SMG7/UPF1 co-silencing, the aggressiveness of HCC cell lines decreased. However, NMD target genes expression did not change when SMG7 is modulated, suggesting alternative pathways. These results suggest a role and potential use as biomarker and therapeutic target of SMG7 in CLD and HCC.

Fundings: ISCIII (PI20/01301, FI21/00141, PI23/00652, MV23/00068; co-funded by the European Union), MINECO (FPU20/03957, FPU21/04833), JdA (PEMP-0036-2020, BIO-0139), FSEEN and CIBERobn/CIBERehd.

POSTER SESSION II.

PSII.a. The administration of anti-FGF23 normalizes iron metabolism and erythropoiesis alterations associated with high FGF23 levels with normal kidney function.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: FGF23, iron metabolism, erythropoiesis.

Abstract:

Iron deficiency correlates with elevated FGF23. Recent evidence suggests that high FGF23 levels may also influence iron metabolism and erythropoiesis. We aim to investigate the bidirectional interaction between FGF23 and iron deficiency with normal kidney function. Normal Wistar rats were distributed into the following experimental groups: control, FGF23 (15 µg/day) and anti-FGF23 (1 mg/kg every two days). Hematological and mineral metabolism parameters were determined after 28 days. Rats treated with FGF23 had alterations in hematological parameters, with a tendency toward decreased hematocrit and hemoglobin, significantly low serum iron levels that correlated with hepcidin, and a significant increase in circulating HIF1alpha. Ferritin was normal and positive Prussian Blue staining was observed in bone marrow smears. Regarding erythropoietic activity, there was a significant decrease in reticulocyte count and a slight reduction in erythroid precursors in bone marrow. In the group receiving anti-FGF23, hepcidin levels tended to decrease, and iron deficiency was corrected. Additionally, there was an increase in erythropoietic activity, evidenced by a significant increase in reticulocyte count and erythroid hyperplasia in the bone marrow. In the absence of renal damage, high levels of FGF23 correlate with alterations in iron metabolism and decreased erythropoietic activity. Administration of anti-FGF23 reverses these effects, suggesting therapeutic potential.

PSII.b. Role of regulatory T cells in the cellular immune response to influenza vaccine in older adults.

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Scientific Program: Infectious and immunological diseases. Organ transplantation.
Keywords: Lymphocytes, T Cells, Regulatory T cells, Vaccines.

Abstract:

Influenza significantly affects the health of older adults, associated with a decrease in the effectiveness of the vaccine. Previous studies have noted increased regulatory T cells (Tregs) potentially limiting vaccine efficacy.However, conclusive evidence remains lacking. Herein, we evaluate the effect of the Treg response in young and old before and after vaccination and its effects on the Th1 and CD8 T response. Flow cytometry was employed to assess the frequency of Tregs (CD4+CD25+Foxp3), including their proliferative (Ki67) and suppressive activity (CD39), stability (Helios) and their impact on T-helper and CD8+ T cell responses. This analysis involved individuals vaccinated during the 2023/2024 campaign. After vaccination, older individuals displayed a heightened response of central memory Tregs, indicated by increased frequency in peripheral blood. Both age groups exhibited augmented suppressive activity of Tregs (CD39+) post-vaccination, while older individuals showed reduced response of Helios+ Tregs, suggesting a reduced stability and peripheral induction origin. Conversely, older individuals showed baseline activation profile (Ki67+) in CD8 T cells that was slightly reduced post-vaccination implying a response to antigens other than the vaccine. Furthermore, an inverse correlation was observed between effector memory Tregs and the post-vaccination Th1 and CD8 TemRA cell response, mainly in older adults. These results highlight a potential adverse influence of Tregs on the vaccine-triggered response of TCD8 and Th1 lymphocytes. Considering the importance of these cell populations in the anti-influenza response, this suggests a detrimental effect of Tregs on the effectiveness of influenza vaccines. Further research is underway to explore additional effects of Tregs on these groups, including specific antibody, cytokine responses, and functional studies.

PSII.c. Assessing the Effects of a Basketball Program on Children's Physical Fitness and Cardiometabolic Health: The BIPIC Study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: sedentary lifestyle, boys, training.

Abstract:

Background: Sedentary behavior plays a role in the development of obesity and related health issues from an early age. To counteract sedentary lifestyles in children, it is important to implement strategies that encourage physical activity (PA), particularly through sports as extracurricular activities. **Objective**: To assess anthropometric measurements, cardiometabolic parameters, and fitness levels after a year of regular basketball training in school-aged boys. **Methods**: A basketball training program, the training started with an initial 4-week training period, followed by a 32-week intervention as an extracurricular sport. Baseline measurements were taken for both the intervention group and a control group of children. The program focused on basketball training and included matches. Participants were assessed at baseline, at two intermediate points (6 and 9 months), and again one year later. **Results**: In total, 17 subjects completed the intervention. Initially, they had comparable physical fitness levels to the control group. However, by the conclusion of the intervention, the children exhibited superior results compared to the control group in fitness assessments conducted one year later. There was an observed increase in lean mass across most body segments, while BMI remained within normal range throughout the intervention period. **Conclusion**: A 32-week basketball training program for prepubertal boys, conducted three days a week with a weekend match at moderate to vigorous intensity, enhances physical fitness and body composition, thereby improving overall health status.

PSII.d. Age-dependent modulatory role of diet on the expression of miRNAs involved in aging-associated processes in patients with coronary heart disease: From CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: diet; aging; miRNAs; oxidative stress; inflammation; CORDIOPREV study.

Abstract:

Introduction and Objective: According to the latest WHO reports, mortality from age-related diseases such as T2DM, obesity, cardiovascular disease, has been increasing in the last decade. MicroARNs are epigenetic mechanisms that are involved in biological processes disease-related. In addition, the effect of components of diets on the expression of miRNAs has been demonstrated. The aim of the present study was to analyze the ability of diet, as a function of age, to modulate miRNAs related to aging-associated processes (such as oxidative stress and inflammation) in patients with coronary heart disease. Material and Methods: Within the framework of the CORDIOPREV study (n=1002), the population was divided by age tertiles, <56 years (Tertile 1) and >66 years (Tertile 3). Thus, 120 subjects per tertile were selected (60 follow the Mediterranean diet and 60 follow the low-fat diet). Using RT-PCR the expression profile of 28 miRNAs from PBMC were analysed. The levels of oxidative stress parameters and inflammatory cytokines were determined too. Results: Baseline levels of miR-1, -145, and -150 were higher in < 56 years patients than > 66 years patients (all $p<0.05$). In addition, miR-1 and miR-145 expression increased in patients <56 years who consumed a Mediterranean Diet after 5 years of follow-up ($p<0,034$ and $p<0,026$, respectively). On the other hand, a correlation was found between the increase in these two miRNAs and the decrease in GPx levels at year 5. Finally, for patients with elevated miR-1 levels, the CRP levels remained constant during follow-up. Conclusion: Diet, according to the age, can modulate epigenetic mechanisms (miRNAs) that in turn regulate biological processes associated with aging (oxidative stress and inflammation) in patients with coronary heart disease.

PSII.e. Linking Synovial Protein Signatures to Inflammation and Early Treatment Response in Rheumatoid Arthritis patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Rheumatoid Arthritis, Synovitis, Biomarkers, Bioinformatics.

Abstract:

Objectives: 1. Characterize proteins secreted by synovial tissue in rheumatoid arthritis (RA) patients that contribute to serum inflammatory profiles based on immune cell infiltration. 2. Identify RA patient subsets with distinctive serum levels of these proteins, their correlation with disease activity, and early response to conventional DMARDs. **Methods**: Synovial explants from 17 early RA patients were examined for histomorphological features including lining thickness, inflammation, fibrosis, and immune cell infiltration (identified using anti-CD3, anti-CD20, anti-CD138, and anti-CD68 antibodies for T and B lymphocytes, plasma cells, and macrophages). These tissues were cultured in vitro for 24 hours, and secreted proteins were profiled using proximity extension assay (PEA) technology (Olink) for 92 inflammation-related proteins. Serum samples from the same subjects underwent parallel proteomic profiling and correlation studies were performed. An independent cohort of 83 early-stage RA patients was used to test relevant signatures and evaluate their association with DMARD response. **Results**: Histopathological analysis revealed lymphohistiocytic inflammation in RA synovium with abundant CD3+ and CD68+ cells, associated with increased lining thickness, inflammation, and fibrosis. Ten synovial-secreted proteins (CDCP1, CXCL1, IL10RA, IL10RB, IL10, IL15RA, PDL1, CCL28, IFN-gamma, FGF19) exhibited significant correlations with serum levels in RA patients. Higher levels were observed in patients with active disease (DAS28 > 3.2), elevated acute phase reactants, and anti-citrullinated-peptide antibodies (ACPAs) positivity. Elevated synovial CD3+ T-lymphocyte infiltration was strongly linked to the source of these proteins. In an independent cohort of 83 early-stage RA patients, unsupervised clustering based on the ten-protein signature identified two distinct patient groups. The group with higher inflammatory profiles demonstrated increased disease activity and a better response to DMARDs after three months. **Conclusions**: We identified a ten-protein signature secreted by synovial tissue that contributes to the circulating inflammatory profile in RA patients. This signature correlates with immune cells infiltration, clinical features, and early DMARD response. The study underscores the potential for personalized RA treatment using biomarkers reflecting the molecular characteristics of synovial tissue.

PSII.f. Metastatic prostate cancer prediction model based on telomeres.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Prostate Cancer, telomere, PSA, Digital Rectal Examination.

Abstract:

Currently, prostate cancer (PCa) is considered one of the cancers with the highest incidence globally. It is the second most common cancer among men, with approximately 1,276,106 new cases per year worldwide. With the advent of PSA, most patients are now diagnosed at very early stages of the disease. However, between 5-10% of patients are diagnosed with metastatic disease at the initial diagnosis, depending on the series. The diagnosis of metastatic disease is relevant due to the different treatment options that can be offered to these patients based on the stage of the disease. Telomeres are nucleoprotein structures that have proven useful as tools in the diagnosis of PCa. A prospective study was conducted on patients at risk of PCa, measuring telomere length in lymphocytes from peripheral blood. Clinical variables were evaluated in those patients diagnosed with PCa, including those with metastasis at diagnosis. Regarding telomeric variables, the mean telomere length was shorter in patients diagnosed with metastasis, 10,163 PB in non-metastatic cases compared to 9,221 PB in metastatic cases ($p < 0.01$). The mean PSA level in metastatic patients was 30 ng/mL, and the digital rectal exam was suspicious in 73% of cases. A regression model was generated including the variables: PSA, suspicious digital rectal exam, and mean telomere length. The model reached an accuracy of AUC of 0.91 with a 95% CI: 0.87-0.96. These data show the putative role of telomeres markers in complementing the prognosis information of clinical variables for patients with metastatic disease; however, studies with a larger number of patients are necessary to validate these findings.

PSII.g. Phenotypic and Functional Analysis of Cytokine-Induced Memory-Like Natural Killer Cells.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Immunotherapy, Memory, Cytokines, Cancer Immunology, NK/NKT Cells.

Abstract:

Natural Killer (NK) cells play a crucial role in innate immunity against virus-infected and tumor cells. Interleukin-12/15/18 exposure in vitro induces a memory-like phenotype in NK cells, termed cytokine-induced memory-like (CIML) NK cells, characterized by heightened cytotoxicity and prolonged survival. This study focuses on exploring the expression patterns of activating and inhibitory receptors in CIML NK cells and evaluate its cytotoxic capacity against target cell lines, that is crucial for understanding their therapeutic potential. To obtain human CIML cells, peripheral blood NK cells were isolated and preactivated with IL-12/15/18 overnight and expanded during 7 days with IL-15. Multiparametric flow cytometry analysis to assess phenotypic profiles was performed on day 0 (before stimulation), at 16 hours and at 7 days of incubation. Functional assays, including CD107a degranulation and IFN-γ and TNF-α production, were conducted to evaluate CIML NK cell cytotoxicity against target cells K562 and 721.221. CIML NK cells exhibited increased expression of NKG2A, NKG2D, NKp30, NKp46, CD25, and CD69 compared to control NK cells stimulated with IL-15, highlighting the potency of IL-12/15/18 in stimulating a functionally enhanced phenotype. Additionally, preactivation with IL-12/15/18 significantly increased CD107a expression in CIML NK cells after stimulation with target cells compared to control NK cells, indicating higher cytotoxicity against tumor cells. Moreover, CIML NK cells demonstrated elevated intracellular IFN-γ and TNF-α production when stimulated with IL-12/15/18, underscoring their enhanced antitumor functionality. This study underscores the potential use of CIML NK cells in cancer immunotherapy. Enhanced expression of activating receptors and increased functional capacities, including degranulation and cytokine production, suggest CIML NK cells as promising candidates as antitumor agents. Further investigations into refining CIML NK cell expansion protocols and understanding their mechanisms of action are needed to advance their clinical translation and improve cancer treatment outcomes.

PSII.h. Nox4 modulates erythropoiesis in response to massive intravascular hemolysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: hemolysis, AKI, Nox4, erythropoiesis, bone marrow, red blood cells.

Abstract:

Intravascular hemolysis is a common characteristic of several pathologies. The reduction in red blood cells due to intravascular hemolysis leads to the activation of erythropoiesis in the bone marrow. NADPH oxidase 4 (Nox4) is an enzyme present in hematopoietic progenitor cells that regulates the production of reactive oxygen species (ROS). Since oxidative stress regulates erythropoiesis, the aim of our study was to elucidate whether Nox4 modulates erythropoiesis during hemolysis. We performed an experimental model of intravascular hemolysis in wild-type (Nox4+/+) and Nox4 knockout (Nox4-/-) mice by injection of phenylhydrazine (200 mg/kg, i.p.). In this experimental model we also evaluated whether pharmacologic inhibition of Nox4 with GKT137831 (10 mg/kg/day) modulated erythropoiesis. Mice were sacrificed at different time-points to analyze erythroid populations in bone marrow and peripheral blood. In experiments on human K562 cells and PBMCs from healthy volunteers were evaluated whether treatment with GKT137831 affected hemin-mediated expression of GATA-1 transcription factor and the number of erythroid colonies. Hemolysis reduced the number of erythrocytes, whilst increased reticulocytes in peripheral blood. Hemolysis also promoted mobilization of hematopoietic progenitor populations in the bone marrow, as demonstrated by elevated levels of CFUs, BFUs, pro-erythroblasts (CD71+/Ter119-), and erythroblasts (CD71+/Ter119+). Hemolysis also increased expression of GATA-1 in bone marrow as well as and augmented synthesis of erythropoietin in the kidney. All these effects were greater in Nox4-/- mice and GKT137831 pre-treated mice. In hemin-stimulated K562 cells, treatment with GKT137831 also accelerated erythroid differentiation, evidenced by a decrease in GATA-1 expression. Similarly, we observed that Nox4 inhibition increased the number of erythroid colonies in differentiation assays using PBMCs. In conclusion, our results indicate that the enzyme Nox4 plays a deleterious role on both production and differentiation of erythrocytes in response to massive intravascular hemolysis.

PSII.i. Impact of treatment of anemia on the quality of life in patients with chronic kidney disease.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Chronic Kidney Disease, Anemia, Quality of Live, Iron, Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors.

Abstract:

Introduction. Anemia is a highly prevalent comorbidity in advanced chronic kidney disease (CKD), presenting a multifactorial etiology. This comorbidity significantly deteriorates the quality of life, making proper treatment crucial. Despite conventional treatments, some patients present refractory anemia, in which a new group of drugs, known as prolyl hydroxylase inhibitors (HIF-PHI) may be effective. The main objective of this project is to study whether the correction of anemia in CKD patients with current treatments improves their quality of life. **Material and Methods**. A prospective descriptive study was conducted, including 20 patients diagnosed with stage IV-V CKD, non-dialysis, with Hemoglobin (Hb) <10.5 g/dl, and without diseases that contraindicate their inclusion. Two quality of life questionnaires (CKD-AQ and KDQOL-36) were requested before and after anemia correction. Demographic, clinical, and laboratory data were also analyzed. **Results**. A statistically significant improvement in the quality of life of patients was observed with anemia correction, with improvements in symptoms such as fatigue, lack of energy, or tiredness. Significant improvements were found in glomerular filtration rate ($p<0.001$) and Hb ($p<0.001$), with no significant changes in iron metabolism parameters. **Conclusion**. The correction of anemia leads to an improvement in the quality of life for patients with CKD. Despite the availability of effective treatments, some patients experience persistent anemia, for which HIF-PHIs could be key. Given the multifactorial origin of this condition, an individualized approach is necessary.

PSII.j. Optimization of adipose tissue fibrosis model based on 3D cell culture platforms.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Obesity, extracellular matrix, fibrosis, 3D cultures, spheroid.

Abstract:

Obesity is a complex disease with increasing prevalence, characterized by an excessive and/or abnormal accumulation of adipose tissue. One the hallmarks of the adipose tissue in obesity is fibrosis, caused by an imbalance between the synthesis and the degradation of extracellular matrix components. Currently, there is no available therapy for the treatment of fibrosis in this tissue, in part due to the lack of in vitro models which include the extracellular environment. Therefore, the aim was to optimize a three- dimensional (3D) culture model for the study of adipose tissue fibrosis. Thus, 3D models based on spheroids of preadipocytes and mature adipocytes were optimized using the 3T3-L1 cell line and primary human adipocytes. Morphology, cell viability and gene expression studies were carried out to check optimal spheroid culture conditions. In additional experiments, spheroids were exposed to obesogenic conditions to assess extracellular matrix components. Our studies demonstrate the capacity of both preadipocytes and adipocytes to generate spheroids. Moreover, non-differentiated preadipocytes remain viable until day 7 of culture though optimal conditions (morphology and viability) were observed at day 4 of culture. Adipocyte differentiation occurred normally when preadipocyte spheroids were exposed to adipogenic signals, containing fully differentiated adipocytes by day 10 of differentiation. A comparison of housekeeping genes in 2D cultures vs. spheroids during differentiation was carried out, with RPL32 being considered by RefFinder the most stable housekeeping gene at any time point tested. These studies showed that genes associated with adipocyte differentiation, such as PPARγ, showed similar expression levels regardless of the culture model used, 2D or 3D. Exposure of preadipocyte spheroids to conditions of hyperglycemia/hyperinsulinemia increased while TNFα decreased the production of extracellular matrix components. In conclusion, the 3D adipocyte model based on spheroids represents a useful tool for understanding the pathophysiological changes related with fibrosis in the adipose tissue in obesity.

PSII.k. Proteogenomic approaches reveal novel pathogenic splicing variants in hepatocellular carcinoma: the RBM22-PNKD axis.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: hepatocellular carcinoma; proteogenomics; splicing variants; PNKD; RBM22.

Abstract:

Splicing is profoundly dysregulated in hepatocellular carcinoma (HCC), the most prevalent hepatic tumor. However, the identification of functionally and clinically relevant splicing variants remains challenging. In this work we implemented a proteogenomic approach to identify and characterize novel splicing variants in HCC. Non-targeted quantitative proteomics was performed on cytosolic and nuclear fractions of liver tissue from 41 HCC patients [HCC vs. non-tumor adjacent tissues (NTAT)]. Variant-specific peptides were identified by proteogenomics and used to estimate the abundance of splicing variants. The effects of the overexpression/silencing of splicing factors and variants (proliferation, migration, colonies/tumorspheres formation) were assessed in liver cancer-derived cell lines (HepG2, Hep3B, SNU-387). eCLIP/RNAseq data from the ENCODE database was analyzed. With this approach, 8 and 53 differentially expressed splicing variants were identified in cytosolic and nuclear fractions, respectively. These results were corroborated in external mRNA cohorts. A short variant of PNKD (PNKD-202) was consistently overexpressed in tumors and associated to worse prognosis while the canonical variant (PNKD-203) remained unchanged. The overexpression of PNKD-202 in vitro lead to increased aggressiveness (proliferation, colonies/tumorspheres formation). Analysis of eCLIP data revealed a set of 62 PNKD-mRNA binding proteins in HepG2 cells, including the splicing factor RBM22, whose silencing reduced the expression of PNKD-202 without affecting PNKD-203 (RNAseq data). Remarkably, RBM22 was overexpressed in HCC tissues and its silencing in vitro reduced cell aggressiveness, which was partially recovered by the overexpression of PNKD-202. These alterations were accompanied by a dysregulation of mitochondrial markers, consistently with the role of PNKD-202 as chaperone of the electron transport chain. This study reveals the utility of a proteogenomic approach for the identification of functionally and clinically relevant splicing variants in HCC, as the mitochondria-associated short variant of PNKD.

Fundings: ISCIII (PI20/01301, PI23/00652; co-funded by the European Union), MINECO (FPU20/03957), JdA (PEMP-0036-2020, BIO-0139), FSEEN and CIBERobn/ehd.

PSII.I. DYRK2 protein kinase as an unknown main member of MAPK pathway and its implications in cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: DYRK2, MAPK, B-RAF, MEK1, cancer, treatment.

Abstract:

The MAPK/ERK cell signalling pathway, hyperactivated in the 85% of all human cancers, is considered key in the control of a variety of biological processes such as cell growth, division and differentiation. This pathway consists in the cascade activation of RAS-RAF-MEK-ERK, which promotes the activation of relevant transcription factors. Therefore, its hyperactivation is related to proliferation, migration, or metastasis. Despite its relevance, current knowledge of the pathway is insufficient to explain the resistance mechanisms that arise to current targeted treatments. In this context, it is essential to increase knowledge of the pathway to search for new potential treatment targets. Here we describe for the first time the Dual specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2) as a new main member of MAPK/ERK pathway, positively regulating the activation through the phosphorylation of its components. DYRK2 phosphorylates B-RAF on at least 14 residues, promoting its stabilization and improving its ability to phosphorylate and activate MEK1. Moreover, DYRK2 also directly phosphorylates MEK1 at residues T292 and S298, favoring the interaction, activation and translocation of ERK2 in the nucleus. Consequently, DYRK2 contribute with these two independent-mechanisms to the activation of ERK2 and proliferation-related transcription factors. Furthermore, this activation is reversed using chemical inhibitors of DYRK2. Functional assays demonstrate that DYRK2 is necessary for the proliferation and survival of melanoma, breast, colorrectal and lung cancer cell lines with MAPK/ERK pathway hyperactivated (A375, MDA-MB-468, HT-29, A549, etc.). In the same sense, MAPK/ERK pathway inactivation leads to DYRK2 stabilization. Overall, these relevant results show DYRK2 as a new main member of MAPK/ERK pathway and point it as a potential therapeutic target for patients with drug-resistant melanoma, breast, colorectal and lung cancer.

PSII.m. VIRADS, is the new RADS really useful?

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Bladder cancer, Magnetic Resonance (MR), VIRADS.

Abstract:

Recently, a group of experts has proposed a standardized bladder study system (VI-RADS) in which they establish a score in the different sequences of the magnetic resonance imaging (MRI) protocol to define the risk of muscle invasion in bladder cancer. bladder (MIBC). Our objective was to evaluate the capacity of MRI in predicting muscle invasion of the bladder cancer. MATERIAL AND METHODS: 66 consecutive patients, over 18, were recruited from June 2021 to January 2023 with a suspected diagnosis of bladder cancer (BC) by some diagnostic technique (ultrasound, CT, MRI or cystoscopy), who underwent pre-TUR MRI in RM 3T after signing informed consent. Exclusion criteria: patient refusal to participate in the study, contraindication for MRI, concomitant pelvic tumor and pregnant women, or TUR due to bladder cancer 6 months prior. The studies were analyzed by two radiologists with 10 years of experience in abdominal radiology. RESULTS: 66 patients (53 men and 13 women), of which 46 (69.7%) were NMI and 16 (24.3%) MI. 17 patients (27.8%) had multiple injuries. The pathological anatomy was urothelial carcinoma in all cases except in 4 patients where non-malignant lesions were found. In two cases, prostate lesions were incidentally diagnosed (PIRADS 5). We divided the results by the VI-RADS system considering probability of NMI bladder cancer at values 1-3 and probability of MI at 4-5. Of the sample, 44 were classified as VI-RADS ≤3, with category 2 being the most frequent. The VI-RADS system obtained a sensitivity (S) of 87%, specificity (E) of 82.6%, positive predictive value (PPV) of 63.6% and a negative predictive value (NPV) of 95% to detect MIBC. CONCLUSION: Our initial experience highlights the promise of this new VI-RADs classification system to help determine the risk of MIBC and improve healthcare protocols.

PSII.n. Lack of peroxiredoxin 6 in colon cancer cell line HCT116 alters cell proliferation, migration and invasion.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Peroxiredoxin 6; Colorectal Cancer; Cell Cycle; Migration; Invasiveness.

Abstract:

PRDX6 is an atypical member of the peroxiredoxin family. Apart from canonical peroxidase activity, which is exert by other peroxiredoxin family members, it exhibits two additional enzymatic activities, phospholipase A2 and lysophosphatidylcholine acyl transferase, and has been found to act repairing peroxidized cell membranes. PRDX6, through its activities, plays a role in cellular proliferation, migration and invasiveness as has been demonstrated in different tumoral cell lines, including colorectal cancer cells. However, its deprivation in these cells has never been studied. Here, we constructed a PRDX6 knockout colon cancer cell line HCT116 using CRISPR/Cas9 technology to examine whether the role of this enzyme on proliferation, migration and invasiveness observed in other cell lines also applies in these tumor cells. To this end, we compared wildtype and PRDX6 knockout cell lines using growth curves, survival assays, BrdU flow cytometry, western blotting, zymogram, wound healing and transwell invasion assays. The PRDX6 knockout cell line showed decreased proliferation rates and lower metabolic status but no changes in survival. The decreased proliferation is consistent with the altered cell cycle in PRDX6-deficient cells, indicating cell cycle arrest in S and G2/M phases. Furthermore, reduced migration and invasiveness capacities were detected in PRDX6 knockout HCT116 cells, consistent with lower expression of N-cadherin and reduced activity of pro-invasive enzymes like metalloproteinases. The mechanisms underlying the effects of PRDX6 elimination may vary between different cell lines, as the results obtained in HCT116 differ slightly from those previously obtained in hepatocarcinoma HepG2 cells. This underlines the importance of assessing the role of PRDX6 in the development of different tumors. Considering all the above-mentioned, our results point to this protein as a promising therapeutic target also for colorectal cancer.

PSII.ñ. Characterization of the rna-exosome machinery component exosc4 in the development and progression of hepatocellular carcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: RNA-Exosome, EXOSC4, silencing, overexpression, hepatocellular carcinoma.

Abstract:

Introduction: Liver pathologies has become one of the main health problems worldwide. Particularly, hepatocellular carcinoma (HCC) is the most common primary liver cancer with an increasing overall incidence, aggressive behavior, poor prognosis, and limited treatment options. However, its pathophysiology and the underlying molecular causes involved in its development are still to be fully defined. Previous studies have suggested a putative involvement of certain cellular machineries related to the processing and quality control of RNA, such as RNA-Exosome, in HCC. However, the role of the components of this machinery has not yet been explored in HCC. **Objective**: To characterize the dysregulation and putative role of the RNA-Exosome machinery component EXOSC4 in the development and progression of HCC. **Methodology**: EXOSC4 expression levels and correlations with key clinical parameters were analyzed in HCC and control samples (normal or adjacent) in two retrospective cohorts and eleven in silico cohorts. The role of EXOSC4 was characterized in vitro (proliferation, migration, clonogenic and tumorsphere assay) by modulating its expression (silencing/overexpressing) in two HCC lines (Hep3B and SNU-387), and in vivo through a preclinical model of Hep3B-induced xenograft tumors. Results: EXOSC4 was consistently overexpressed in most of the cohorts analyzed, where it is associated with poorer survival and with higher capacity for invasion and recurrence, and with the enrichment of certain oncogenic pathways related to DNA damage. Furthermore, in vitro assays showed that EXOSC4 silencing reduces tumor aggressiveness parameters, while its overexpression increases them in the two cell lines. In addition, in vivo studies confirmed the pro-tumorigenic potential of EXOSC4 by inducing tumor growth in murine models. **Conclusions**: EXOSC4 could be a potential diagnostic/prognostic biomarker and/or therapeutic target due to its possible involvement in the development and progression of HCC.

Fundings: ISCIII (PI20/01301, DTS22/00057, PI23/00652; co-funded by the European Union), MINECO (FPU20/03957), JdA(PEMP-0036-2020, BIO-0139), FSEEN y CIBERobn/ehd.

PSII.o. Association between mortality and serum phosphorus in incident dialysis older patients.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: chronic kidney disease, dialysis, mortality.

Abstract:

Background: Hyperphosphatemia is a major cause of morbility and mortality in patients with chronic kidney disease (CKD). To effectively manege hyperphosphatemia in dialysis patients, we have several options. The main control mechanisms are dietary restrictions, the use of phosphorus blinders and its clearance though dialysis. Many factors affect the nutrition in older patients, such as dental problems. In these patients, dietary restrictions may not be advisable. The objective of this study in to evaluate whether age or serum albumin modify the association between serum phosphorus and mortality. **Methods**: We included 200 incident subjects on dialysis. We used the latent class linear mixed models method to identify longitudinal trends in serum phosphorus for samples drawn at time 0,6,12 months from the start of dialysis. The lean tissue index (LTI) and overhydration were determinated by bioimpedance. Survival analysis was performed using kaplan-Meier method and cox regression. The R stadistical package was used for analysis. **Results**: Three different trajectories os serum phosphorus were identified throughout the first year on dialysis: normal phosphorus (n=162), lowered phosphorus (n=16) and high phosphorus. Subjects with a downward trajectory were older (66 vs. 76 vs 69 years) and showed lower albumin levels (3,63 vs. 3,6 vs 3,67 g/dl, respectively) and lower LTI at baseline (12,1 vs. 9,5, vs 12,1; p=0,025). Subjects with a downward trajectory showed a higher risk of mortality compared to the normal trajectory (HR 3,36, 95% CI 1,43-11,2; P=0,008). Age, albumin andl LTI attenuated the effect of the downward trajectory on mortality. **Conclusions**: The decrease in phosphorus after the start of dialysis in associated with a higher risk of mortality. This could suggest underlying nutritional alterations. For this reason, phosphorus control should be individualized in elderly people on dialysis.

PSII.p. Optimization of a Rabbit Severe Corneal Disease Model for Pre-Clinical Studies.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Animal model, corneal disease, alkali burn.

Abstract:

Severe corneal disease (SCD) is characterized by persistent epithelial defect, opacity, and corneal vascularization that causes vision impairment and blindness. The most used treatment in these patients is corneal transplant; however, 12.7 million people around the world are waiting a transplant due to the shortage of donor corneas. Furthermore, 1/3 transplanted corneas ultimately lead to rejection because of significant complications. Nowadays, multiple research studies are being carried out to develop new therapeutic approaches for this disease. Notwithstanding, to evaluate these new therapeutics, there is a growing demand for translatable preclinical animal models that replicate the complexity of human SCD. Corneal alkali burn is one of the most used chemical procedures to generate SCD. However, only 50% of animals develop the complete disease. Herein, our aimed was the optimization of a rabbit alkali burn model for preclinical studies. Our ex vivo dose/time-response curves demonstrated that 1M NaOH administered with gauze in the corneal region for 30s promoted opacity and epithelial damage in both porcine and rabbit eyes. Next, we proceeded to generate the in vivo SCD model in 8 two-month-old New Zealand rabbits using 1M NaOH for 30s. The ophthalmological evaluation of anterior segment was performed at pre-intervention, and after 3, 7 and 14 days post-intervention by slit lamp and AS-OCT. After intervention, all animals displayed epithelial defect, corneal opacity and conjunctival hyperemia until the end of follow-up. A qualitative measurement of these parameters demonstrated that the 12.5% and 87,5% of animals displayed grade 2 and 3 corneal neovascularization, respectively. Moreover, the 100% of them exhibited grade 3 epithelial defect, whereas the 12.5%, 63.5% and 25% of rabbits showed grade 2-3, 3, and 4 corneal opacity, respectively. Overall, our results indicate that rabbit SCD model developed in the present study could be an adequate model for preclinical studies of this disease.

PSII.q. Human Leukocyte Antigen class II susceptibility for non-specific Lipid Transfer Proteins allergy.

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Scientific Program: Infectious and Immunological diseases.
Keywords: HLA, nsLTP, allergy, epitopes.

Abstract:

Introduction: Type I hypersensitivity involves the production of specific immunoglobulin E (sIgE) by B cells and peptide presentation to T cells mediated by Human Leukocyte Antigen (HLA) class II molecules, expressed in dendritic cells. The purpose of this study was to elucidate the role of HLA-class II peptide presentation in the development of allergy to non-specific Lipid Transfer Proteins (nsLTPs), specifically to Pru p 3 and Ole e 7, the peach and olive pollen nsLTP, respectively. **Methods**: Allergic patients to Ole e 7 and/or Pru p 3 were selected at Reina Sofía University Hospital (Córdoba, Spain) according to sIgE levels and classified into three groups: MONOLE (Ole e 7-monosensitised; n=14), MONPRU (Pru p 3-monosensitised; n=15) or BI (bisensitised; n=13). DNA extraction was performed using MagCore® Genomic DNA whole blood kit and HLA class II alleles (HLA-DRB1, -DQB1, -DPB1) were sequenced using Luminex® xMAP® technology. Prediction of T-cell epitopes was conducted by Immune Epitope Database Analysis Resource, using Uniprot code Q9LED1 for Pru p 3 and Ole e 7 sequence from literature. **Results**: HLA-class II frequency analysis showed the predominance of HLA-DRB1*04, –DQB1*03, including serologic DQ7, DQ8 and DQ9, and DPB1*04 (23.8%, 42.9%, and 50%, respectively). Statistical analysis revealed significant differences in DR11-DQ7 frequency between the three groups (MONOLE=0/14; MONPRU=10/15; BI=4/13; for DR11 and MONOLE=1/14; MONPRU=12/15; BI=4/13; for DQ7; $p<0.05$) and a tendency for DR4 (MONOLE=10/14; MONPRU=5/15; BI=4/13; $p=0.054$). Furthermore, T-cell epitope analysis predicted a high binding capacity between Pru p 3 epitopes and DR11, and also between Ole e 7 epitopes and DR4. DQ3 epitope binding showed good scores with both nsLTPs. **Conclusion**: Certain HLA class II alleles could promote presentation of specific nsLTPs epitopes to T-cells. The difference in the binding ability among epitopes and HLA molecules could underlie the predisposition of some individuals to nsLTPs allergy.

PSII.r. Effect of re-exposure to repeated mismatches in kidney retrasplant.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Kidney Transplantation, Rejection, HLA antibodies.

Abstract:

Background: There is no consensus on the impact of re-exposure to repeated mismatches (RRM) between the first and second donors on kidney graft survival in retransplantation. Some studies suggest a higher risk of graft loss in certain patients with class II RRM and elevated PRA. Others find no significant effect. The heterogeneous results could be explained by differences in the study population, the type of immunosuppression used and the HLA determination techniques. In our center, RRM do not determine retransplantation, but they do suggest intensifying immunosuppression. Avoiding RRM may prolong the time on the waiting list and, on the other hand, intensifying immunosuppression to mitigate alloimmune damage associated with RRM could increase non-immune complications. Therefore, the objective of our work was to analyze the influence of RRM on the survival of retransplanted patients, without preformed HLA antibodies. **Methods**: We performed a retrospective analysis of a total of 128 patients with 0% PRA who received at least a second kidney graft between 1988 and 2024. We studied the effect of RRM on all-cause graft loss and death-censored graft loss. **Results**: A total of 128 patients were identified, 37 of whom presented RRM and 91 without re-exposure to HLA antigens from previous grafts. There were a total of 36 (28.1%) graft losses and 30 deaths (23.4%). The median follow-up of the kidney graft was 5.05 years (25th-75th percentile: 2.43 - 9.53 years). No significant differences were found in the age or sex of the recipient, age of the donor, cold ischemia time, or time on the waiting list. Kaplan-Meier survival curves were performed for recipients grouped by RRM. There was no association between RRM and graft loss (p=0.18), as well as in death-censored graft loss (p=0.12) and similarly, in patient survival (p=0.26). **Conclusions**: In our series we did not find evidence to support that re-exposure of mismatches increases the risk of graft loss due to any cause in renal retransplantation in patients with 0% PRA. Therefore, the presence of RRM in retransplantation in patients with low immunological risk seems safe. However, these findings cannot be extrapolated to patients with higher PRA and more studies are necessary to evaluate the safety of patients in these conditions.

PSII.s. How affect caloric restriction and nutritional supplementation in diabetic rat wound healing?

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

Abstract:

Diabetes is associated with aging, and it is associated with a high risk for the development of chronic skin ulcers. Nutrition is very important for diabetes control. The aim of this study is to evaluate how a period of caloric restriction following by a basal diet or a high protein diet influence in diabetic rats wound healing. For that, streptozotocin-induced diabetic rats were divided into two groups: (C) unrestricted diet, (RC) 50% diet. After two weeks, two wounds were made on the dorsum of the rats and the group 50% diet was divided into three subgroups: (RC50) continued with 50% diet, (RC100) unrestricted diet was added, (RC100pr) unrestricted protein-rich diet was added. Wound closure was studied by photographic analysis. After 7 days, circulating endothelial progenitor cells (EPC) were quantified by flow cytometry and after 14 days the animals were sacrificed for histological study of the wounds. In the calorie-restricted rats, blood glucose values decreased, and weight was like the C group. However, in 60% of the rats in the RC100 and RC100pr groups, an increase in weight, a decrease in blood glucose and a lower food intake were observed. Wound closure was faster in the RC100 group at 3 and 7 days compared to the other groups. In addition, the RC100 group had a smaller wound width at 14 days and a higher number of circulating EPCs at 7 days. In conclusion, caloric restriction in diabetes can help to regulate glucose levels and may improve the body's regenerative capacity, promoting an increase in circulating EPCs and skin wound healing, when a full diet is restored. Extra protein supplementation of the diet after calorie restriction does not produce these effects. This suggests in our model a greater effectiveness of a macronutrient-balanced diet.

PSII.t. The dual role of SNW1 in splicing and transcription as an approach to explore pancreatic neuroendocrine tumors progression.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: pancreas, neuroendocrine tumors, progression, SNW1, splicing.

Abstract:

Pancreatic neuroendocrine tumors (PanNETs) are low-grade neoplasms categorized into functional grades (G1-G3) based on proliferative capacity. Higher grades exhibit increased cellular dedifferentiation and metastatic potential. However, the cellular and molecular mechanisms underlying PanNETs progression remain poorly understood. In this context, our group has demonstrated that splicing is linked to tumor characteristics of PanNETs, potentially contributing to their progression and offering new therapeutic possibilities. Specifically, SNW1, a multifunctional regulator of splicing and transcription, involved in cell growth, homeostasis, apoptosis, and cell cycle regulation, appears overexpressed in tumor tissue and associated to grade and relapse. Thus, we hypothesize that SNW1 is involved in PanNET progression through its dual role in transcription and splicing. RNA-seq analysis on 174 PanNETs revealed that SNW1 is upregulated in G2 and G3 tumors, suggesting a relationship with tumor progression. GSEA analysis showed that SNW1 expression correlates with target genes of the MYC, E2F, and MTORC1 pathways, together with cell cycle related genes, DNA repair, basal transcription factors, and the spliceosome. Additionally, it correlated with Notch target genes SOX2 and INSM1, essential for cell differentiation and proliferation, and CCNE1/CCNE2 cyclins, responsible for the G1-S transition. In contrast, inverse correlation with Notch-inhibitor NCOR2 was found. Moreover, after tumor classification according to SNW1 expression, changes in splicing events related to G-protein signaling and retinoic acid response stood out, both related to pancreatic differentiation. Ongoing experiments are aimed to define SNW1 molecular function and therapeutic potential in PanNET progression, using novel cellular models that better resemble the disease. Using RNAi, we are silencing SNW1 and conducting functional experiments to assess its impact on cell cycle, pluripotency, and differentiation. Concurrently, immunoprecipitation and proteomics are being used to identify direct protein interactions with SNW1. Altogether, these studies will enhance our understanding of SNW1 role in PanNETs formation and its potential as a therapeutic target.

PSII.u. Exploring the Relationship Between Hormonal Contraceptive Use And Ulcerative Colitis Flares: A Longitudinal Analysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Pituitary tumour; RNA metabolism; Nonsense-Mediated Decay; RNA-Exosome; biomarkers; therapy.

Abstract:

Background: Numerous studies have implicated hormonal contraceptive therapy (HCT) as a potential trigger for IBD onset. However, data regarding disease flares in hormonal contraceptive users are limited in ulcerative colitis (UC). This study aims to explore this association. **Methods**: Female patients who were diagnosed with UC after 1st January 2014, and born between 1966-2008 were included. The Andersen-Gill extension of the Cox proportional hazards model was used to account for recurrent events within the same subjects. Two models were employed: M1: the first included each patient corresponding to only one cohort, while in the second M2: one those who initiated HCT after diagnosis, were included twice, one from diagnosis to HCT as non-exposed and as exposed thereafter. **Results**: Among 2359 patients in our local database, 545 were women with UC, of whom 131 met the inclusion criteria for analysis. The majority had UC proctitis 57 (43.2%) with 24 (18.2%) were smokers. The median age was 32.5 (23.3-42) years. Of the cohort, 52 (39.1%) women exposed HCT, with a median exposure duration of 1.5 (0.5-5.0) years. Of these, 33 (25%) were exposed to HCT during follow-up. Over 518 person-years of follow up, 173 flares and 196 courses of steroids were observed with 54 admissions, differences were observed among the hospitalization rates between groups Table 1. Additionally, there were 24 pregnancies documented in our cohort. No differences in time to first flare (log-rank test p=0.83). However, the Cox proportional hazard model showed that HCT was associated with higher cumulative risk of flares in both models (M1: aHR 1.53, 95%CI 1.05-2.22, p=0.029) and (M2: aHR 1.47, 95%CI 1.019-2.11, p=0.039), Figure 1A and 1B. No adverse events associated to HCT occurred during follow-up. **Conclusions**: Our study suggests that HCT is associated with an increased cumulative risk of flares, steroid prescription and hospitalization rates in ulcerative colitis patients. Furthermore, no safety signals were observed with the use of HTC in this cohort.

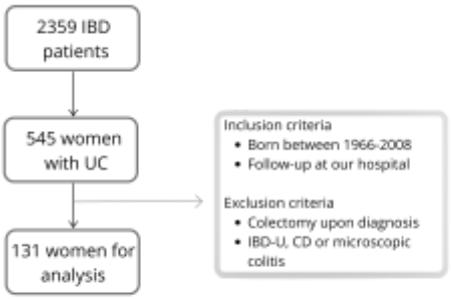


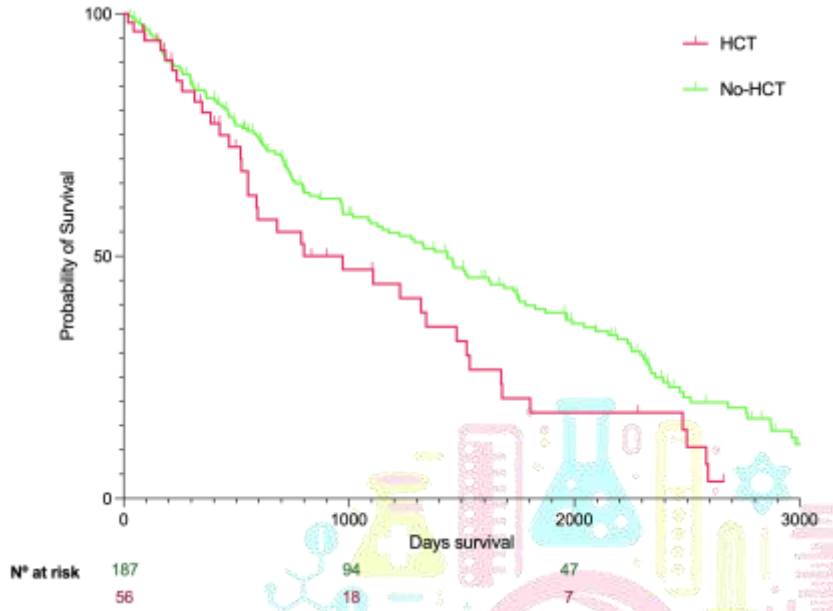
Table 1.

N=131	All N=131	No OCP n=98	HCT n=33	Incidence rate difference (95%CI)	p
Age at diagnosis, median (IQR)	33 (24-42)	36 (27-45)	25 (20.5-32)		0.0001
Age at diagnosis or HCT initiation, median (IQR)	32.5 (23.3-42)	36 (27-45)	27.8 (22.8-33.8)		0.001
UC extent, n (%) - E1 - E2 - E3	 56 (42.7) 38 (29) 37 (28.2)	 39 (39.8) 32 (32.7) 27 (27.6)	 17 (51.5) 6 (18.2) 10 (30.3)		0.38
Mayo endoscopic score at diagnosis, n (%) - Mayo 1 - Mayo 2 - Mayo 3 *Missing data: 7	 32 (25.8) 65 (52.4)	 28 (30.1) 47 (50.5)	 4 (12.9) 18 (58.1)		

	27 (21.8)	18 (19.4)	9 (29)		
Tobacco, n (%) - Smoker - Not smoker - Ex-smoker *Missing data 1	 24 (18.5) 105 (80.8) 1 (0.8)	 17 (17.3) 79 (80.6) 1 (1)	 7 (21.2) 26 (78.8) 0		0.79
Time to 1st flare	493 (182-1187)	493 (185-968)	522 (184-1226)		0.83
Person-year follow-up	568	461	107		N/A
Flare rate (nºevent/person-year follow-up)	173/568=0.31	136/461=0.29	37/107=0.35	0.05 (-0.06-0.17)	0.39
Hospitalization rate	54/568=0.10	37/461=0.09	17/107=0.16	0.08 (0.01-0.14)	0.018
Steroid courses rate	196/568=0.35	156/461=0.33	40/107=0.38	0.04 (-0.09-0.16)	0.57

U-Mann Whitney test was used to compare continuous variables. Chi-square or Fisher test were used to compare dicotomic variables. Time to first flare was compared by log-rank test. Incidence rate comparison was done with the exact Poisson method using 95% Confidence interval.

A)


100
50
0
Probability of Survival
HCT
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0
1000
2000
3000
Days survival
N° at risk
187
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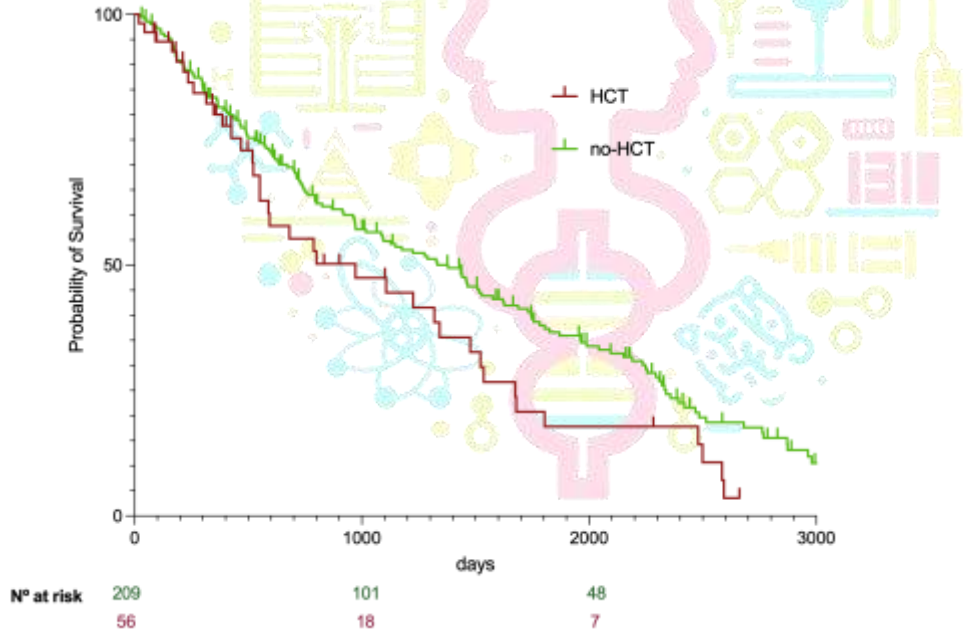
7

B)


100
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Probability of Survival
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days
N° at risk
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101
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7

N=131	All N=131	No OCP n=98	HCT n=33	Incidence rate ratio (95%CI)	p
Age at diagnosis, median (IQR)	32.5 (23.3-42)	36 (27-45)	25 (20.5-32)		0.0001
UC extent, n (%) - E1 - E2 - E3	 57 (43.2) 40 (30.3) 35 (26.5)	 40 (40.4) 33 (33.3) 26.3 (26.3)	 17 (51.5) 7 (21.2) 9 (27.3)		0.38
Time to 1st flare	493 (182-1187)	481 (177-1210)	522 (184-1226)		0.83
Person-year follow-up	517	458	56		N/A
Flare rate (nºevent/person-year follow-up)	167/518=0.34	132/458=0.29	35/56=0.63	0.46 (0.32-0.69)	<0.0001
Hospitalization rate	56/518=0.11	39/458=0.09	17/56=0.3	0.28 (0.16-0.53)	<0.0001
Surgery rate	1/518=0.002	1/458=0.002	0	0.002 (-0.01-0.01)	0.73
Steroid courses rate	198/518=0.38	158/458=0.35	40/56=0.72	0.48 (0.34-0.70)	<0.001

PSII.v. Use of proton pump inhibitors in chronic patients: evaluation of quality of life.

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Scientific Program: Active aging and frailty.
Keywords: proton pump inhibitors, health-related quality of life.

Abstract:

Introduction. Proton pump inhibitors (PPIs) constitute a widely used pharmacological group indicated to suppress acid secretion. In recent years its consumption has increased, although its use and/or duration of treatment is not always justified. Despite being well tolerated drugs, prolonged administration (more than 8 weeks) is associated with adverse effects of clinical relevance, such as cognitive impairment, chronic kidney disease, enteric infections and bone fractures, among others. **Objective**. To determine the relationship between PPI consumption and health-related quality of life (HRQoL) in patients with chronic pathologies. Materials and methods. Descriptive cross-sectional study carried out in June 2023 in the Community Pharmacies of Espejo (Córdoba). 347 patients over 40 years of age diagnosed with chronic pathologies were included. Sociodemographic, clinical and pharmacological variables were collected by interviewing patients and reviewing their clinical records. HRQoL was measured using the EQ-5D-5L index. Statistical analysis of the data was performed using univariate and bivariate analysis. **Results**. Of the 347 subjects that made up the sample, 46.11% (n= 160) were being treated with PPIs, although only 13.83% (n= 48) complied with the indications for use, according to Saiz Ladera, GM, et al. A significant relationship has been observed between PPI consumption and the EQ-5D-5L index, with patients treated with these drugs showing a worse quality of life ($p<0.001$). In fact, PPI consumption is associated with greater problems in the development of daily activities mobility and pain/discomfort ($p<0.05$). **Conclusion**. Chronic PPI treatment is associated with a lower quality of life. Furthermore, a high prevalence of prescriptions without a justified indication is detected. Therefore, we consider that PPI therapy should be reevaluated with the aim of improving therapeutic adequacy and reducing possible adverse effects, ultimately maintaining the quality of life of patients.

PSII.w. Efficacy an Safety of Intraoperative Hyperthermic Intraperitoneal Chemotherapy for Locally Advanced Colon Cancer. A Phase 3 Randomized Clinical Trial.

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Scientific Program: Cancer (Oncology and Oncohemtology).
Keywords: colon cancer, HIPEC, clinical trial.

Abstract:

Peritoneal metastasis in patients with locally advanced colon cancer (T4 stage) is stimated to recur at a rate of approximately 25% at 3 years from surgical resection. It´s associated with poor prognosis. The use of HIPEC (hypertermic intraperitoneal chemotehrapy) is controversy in these patients. Our Clinical trial principal aim is to assess the efficacy and safety of HIPEC in patients with locally advanced colon cancer. This clinical trial was conducted in 17 Spanish centers. Includes patients with locally advanced primary colon cancer diagnosed preoperatively (cT4N02M0) with ages included 18 to 75. Patients were randomly (intention-to-treat) assigned 1:1 to receive cytoreduction plus HIPEC with mitomycin C or cytoreduction alone, both followed by systemic adjuvant chemotherapy. The primary outcome was 3-years locoregional control rate (proportion of patients without peritoneal disease recurrence analyzed by intention to treat). Secondary end points were disease-free survival, overal urvival, morbidity an rate of toxic effects. A total of 184 patients were recruited and randomized (investigational group N89; comparation group,n:95). The 3-year LC rate was higher in the investigational group (97.6%) than the comparation group (87,6-%) (long-rank P=.03;Hazard ratio (HR) 0.21;95% CI). No differences were observed in disease-free survival (investigational 81.2% ;comparator 78%; long-rank P.22;HR, 0.71;95% CI, 0,41-1,222) or overall survival (investigational 91.7%; comparator92,9%; long-rank P=.68; HR 0.79;95%CI (0.26-2.37). Subgrup with pT4siease showed a pronounced Benefit in 3-year LC rate after investigational treatment (investigational :98.3%; comparator 82.1%; long rank P=.003; HR,0.09; 95% CI, 0.01-0.70). No differences in morbidity or toxic effects between groups were observed. In this randomized clinical trial, the addition of HIPEC to complete surgical resection for locally advanced colon cancer improved the 3-year LC rate compared with surgey alone. This approach should be considered for patients with locally advenced colorectal cancer.

PSII.x. Validation of diagnostic nomograms based on mass spectrometry-based urinary biomarkers to distinguish clinically significant prostate cancer: complementing MRI pathway.

Authors: * Ana Cristina Morillo1 ,*Maria Frantzi2, Guillermo Lendinez3, Ana Blanca-Pedregosa1, Daniel Lopez Ruiz4, Jose Parada5, Isabel Heidegger6, Zoran Culig6, Antonio Lopez Beltran 7, Marina Mora-Ortiz 8 Julia Carrasco-Valiente1, Rafael A Medina3, Harald Mischak1,9, Enrique Gomez-Gomez1 *Equally contributors.

Affiliations: 1 Reina Sofia University Hospital, Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), University of Cordoba (UCO), Department of Urology, Cordoba, Spain. 2 Mosaiques diagnostics GmbH, Department of Biomarker Research, Hannover, Germany. 3 Virgen del Rocio University Hospital, IBIS, Department of Urology, Seville Spain. 4 Reina Sofia University Hospital, Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), University of Cordoba (UCO), Department of Radiology, Cordoba, Spain. 5 Virgen del Rocio University Hospital, IBIS, Department of Radiology, Seville Spain. 6 Medical University of Innsbruck, Department of Urology, Innsbruck, Austria. 7 University of Cordoba, Department of Pathology, Cordoba, Spain. 8 Reina Sofia University Hospital, Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), University of Cordoba (UCO), Cordoba, Spain. 9 University of Glasgow, Institute of Cardiovascular and Medical Science, Glasgow, United Kingdom.

Scientific Program: Cancer (Oncology and Oncohemtology).

Keywords: Biomarkers, Mass Spectrometry, mpMRI, Proteomics, Prostate cancer, Urine.

Abstract:

Prostate cancer (PCa) is the most frequently diagnosed cancer among men. A major clinical need is to accurately predict clinically significant PCa (csPCa). A proteomics-based 19-biomarker model (19-BM) was previously developed using capillary electrophoresis-mass spectrometry (CE-MS) and validated in 1000 patients at risk for PCa. Here, our objective was to validate the 19-BM pattern in a multicentre prospective cohort including multiparametric magnetic resonance imaging (mpMRI) in the diagnostic process. Urine samples from 101 PCa patients were collected before prostate biopsy and analysed through CE-MS. All patients underwent mpMRI using a 3-T whole-body system. The 19-BM score was estimated via a support vector machine-based software (MosaCluster; version 1.7.0), employing the previously established cut-off criterion of -0.07. Previously developed diagnostic nomograms including PSA, PSA density, and the risk calculator from the European Randomized Study of Screening (ERSPC) were calculated along with mpMRI. CsPCa was defined as ISUP ≥ 2. The independent validation of the 19-BM yielded a sensitivity of 77% and a specificity of 85% (AUC=0.81). This performance surpasses that of PSA (AUC=0.56), and PSA density (AUC=0.69). For PIRADS ≤3 patients, the 19-BM showed a sensitivity of 86% and a specificity of 88%. The added value of integrating the 19-BM with mpMRI was demonstrated, resulting in significantly better accuracy (AUC=0.90) compared to the individual investigations alone. Examining the decision curve analysis, the 19-BM with mpMRI exhibited enhanced effectiveness in the clinical pathway and surpassed other approaches for the prevailing risk interval of 20-60%. 19-BM exhibited favorable reproducibility for the prediction of csPCa. In patients with PI-RADS≤3, 19-BM correctly classified 88% of the patients with insignificant PCa at the cost of one missed csPCa patient. Utilizing the 19-BM test could prove valuable in complementing MRI and reducing the need for unnecessary biopsies.

PSII.y. Effectiveness of two different Exergaming Systems in addition to Conventional Treatment for Physical Therapy in Patients with Multiple Sclerosis: A Study Protocol for a Multicenter, Assessor-Blind, 24-Weeks, Randomized Controlled Trial.

Authors: Alvaro Alba-Rueda1,2, David Lucena-Anton1,3, Amaranta De-Miguel-Rubio2.
Affiliations: 1 Universidad de Cádiz, Nursing and Physiotherapy. 2 Universidad de Córdoba, Nursing, Pharmacology and Physiotherapy. 3 Biomedical Research and Innovation Institute of Cadiz (INiBICA).
Scientific Program: Chronic and Inflammatory diseases.
Keywords: multiple sclerosis; exergaming; exercise; physical therapy; neurological rehabilitation.

Abstract:

Introduction: Multiple sclerosis is a chronic inflammatory neurodegenerative disease of autoimmune nature and variable course, which produces demyelination and axonal damage in the brain and spinal cord. Currently, there is no cure for this diagnosis, so rehabilitation focuses on long-term symptoms' management and exacerbation prevention. Recently developed neurorehabilitation therapies such as nonimmersive virtual reality exergaming have already been used as an alternative treatment to achieve a high level of functional independence and motor control throughout motivation, multimodal tasks and continuous feedback with a virtual environment. **Objectives**: The main aim is to evaluate and compare the effectiveness of two specific exergaming systems in addition with conventional treatment on improving physical functional capacity, balance, muscle strength, spasticity in lower limbs, and quality of life in patients with multiple sclerosis. The secondary aim is to compare the effectiveness of each exergaming system to isolated conventional treatment. Design: A multicenter, assessor-blind, 24-weeks, randomized controlled trial. **Methods**: 39 patients diagnosed with multiple sclerosis will be allocated to three groups. A control group will perform a conventional treatment based on daily routine activities and/or a combined training, whereas the experimental groups will be randomly divided to develop an active videogame-based exercise program through Nintendo Ring Fit Adventure© or Nintendo Wii Fit©, in addition to the conventional treatment. Study outcomes will be assessed at baseline and at 12 and 24 weeks. One-way ANOVA or Kruskal–Wallis tests will be used to analyze differences between groups at baseline and mixed ANOVA for differences between-within groups over time. **Discussion**: The findings from this evidence-based trial, which includes both Nintendo© active videogames, could potentially establish exergame training as a valuable and reliable therapeutic tool for neurorehabilitation. It is essential to consider the customization, specifically in our case, on each multiple sclerosis condition, and ensure patients' adherence to the treatment.

PSII.z. Gender differences in the initiation and persistence of the first bDMARD in Spondyloarthritis: An 18-year follow-up study.

Authors: Diana Maria Margareta Moldovan1,2, María Ángeles Puche-Larrubia1,3,4, María Lourdes Ladehesa-Pineda1,3,4, Mari Carmen Ábalos-Aguilera1,3, Desireé Ruiz-Vilchez 1,3, Eduardo Collantes-Estévez1,3, Clementina López-Medina1,3,4.
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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Spondyloarthritis, biologic DMARDs, gender differences.

Abstract:

Introduction. Spondyloarthritis (SpA) is a family of chronic inflammatory disease that affects both men and women, but gender differences in treatment initiation and response are still unclear. This study aims to evaluate the delay in the initiation and retention rate of biologic disease-modifying antirheumatic drugs (bDMARDs) in men versus women with SpA, over an 18-year of follow-up period. **Methods**. A cohort of patients diagnosed with SpA, initially assessed during a baseline visit in 2004-2007 as part of the REGISPONSER registry, was reassessed 18 years later in a single follow-up visit as part of the REGISPON-3 study. Kaplan-Meier analysis compared the time to bDMARDs initiation from the first symptom or sign and from the diagnosis between male and female. Cox regression assessed factors influencing bDMARDs initiation. **Results**. The cohort consisted in 271 men and 140 women. No significant differences were found between genders in terms of age of diagnosis, age at disease onset or diagnosis delay. However, men had a significantly longer evolution time since first sign/symptom and longer duration of illness since diagnosis. A total of 53% men and 51.1% women initiated bDMARDs during the follow-up. Kaplan-Meier analysis showed no significant difference in median time to bDMARDs initiation from first symptom or diagnosis (Figure 1). Men persisted longer on the first bDMARD (72 vs 65 months, p=0.038). Cox regression identified ASDAS-CRP, BASDAI, and HLA-B27 as significant predictors for the initiation of bDMARDs following diagnosis (Table 1). **Conclusions**. The findings suggests that while gender may not influence biological treatment initiation, it may affect its persistence. Further research is needed to explore additional predictors and their impact on treatment outcomes.

Fundings: The Assessment of Spondylarthritis International Society (ASAS) supported Diana Maria Margareta Moldovan with a research fellowship.

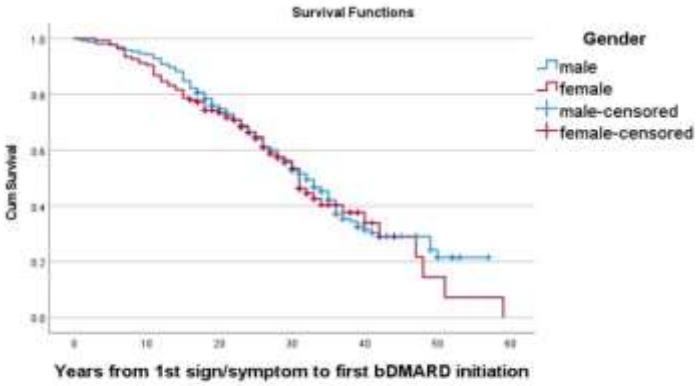
Table 1: Cox regression analysis showing predictive factors of bDMARDs initiation from diagnosis

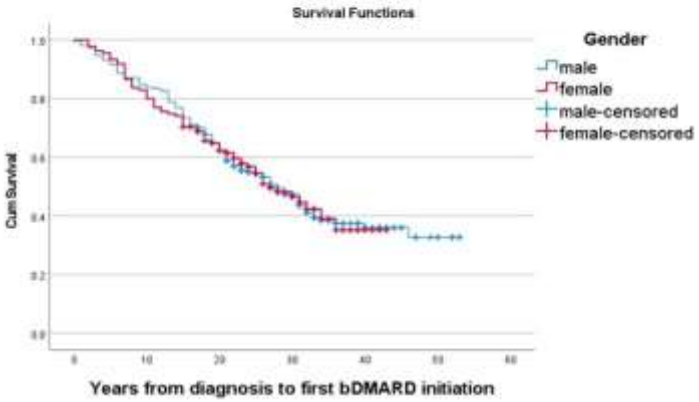
Covariates	Hazard ration	95% CI	p-value

ASDAS-CRP	1.75	1.36 - 2.24	< 0.001
BASDAI	0.84	0.75 - 0.94	0.003
HLA-B27	0.57	0.38 - 0.84	0.005
Gender	1.13	0.80 - 1.60	0.47
Overall model significance	-	-	< 0.001

1. **ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein**
2. **BASDAI: Bath Ankylosing Spondylitis Disease Activity Index**
3. **HLA-B27: Human Leukocyte Antigen B27**

Figure 1: Kaplan-Meier analysis





PSII.aa. Metabolic Gateways to Puberty: Unraveling the Role of Hypothalamic Lipid-Sensing Mechanisms.

Authors: Elvira Rodríguez-Vázquez1-2, María López Sancho1-2, Manuel Jiménez-Puyer1-2, Álvaro Aranda-Torrecillas1-2, Juan Manuel Castellano1-2, Manuel Tena-Sempere1-2.
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Scientific Program: Nutrition, Endocrine, and Metabolic diseases.
Keywords: Puberty; lipid sensing; hypothalamus.

Abstract:

Childhood obesity is often associated with early puberty, especially in girls, and increased risk of diseases later in life; alterations in critical neuronal circuits governing energy balance are though to play a crucial role in this phenomenon. Lipid signaling molecules and hypothalamic lipid/fatty acid (FA)-sensing pathways, including Free FA Receptors (FFARs), the nuclear receptor, peroxisome proliferator-activated receptor-γ (PPARγ), and the bile acid receptor, TGR5, have gained attention as key metabolic mediators. However, its role in regulating puberty and its contribution to obesity-induced precocious puberty remain unknown. Here, we report significant changes in specific lipid species during the juvenile-pubertal transition in the hypothalamus of lean and early-overfed female rats with precocious puberty. Similarly, alterations in hypothalamic expression of specific lipid and FA receptors were also observed. A significant increase in the mRNA levels of the FFARs, Gpr43 and Gpr84, in early-overfed female rats with precocious puberty, and a gradual rise in the hypothalamic content of Gpr84, Ppar-γ, and Tgr5 mRNAs in lean female rats from the neonatal to prepubertal period, were detected. Expression analyses in puberty-stimulatory Kiss1 neurons, isolated from lean and early-overfed female Kiss1Cre/-::tdTomatoloxP/- mice during the juvenile-pubertal transition demonstrated specific expression of Tgr5 and Gpr84 in these neurons. Functional studies involving central manipulation of GPR84, PPARγ, or TGR5-signaling in lean and early-overfed female rats showed specific changes in pubertal timing. In lean female rats, central blocking of PPARγ or GPR84 delayed puberty onset, although the effects were modest with the latter. In early-overfed female rats, central stimulation of TGR5-signaling or blocking of GPR84 partially prevented precocious puberty, with the latter being less effective. These results support the specific contribution of certain lipid/FA-sensing pathways in the hypothalamic control of puberty depending on the maturational and metabolic status, stressing the variable relevance of central PPARγ- and TGR5-signaling under specific nutritional conditions.

PSII.bb. Validation of a CRISPR-Cas9 system for genetic manipulation of multi-drug resistant Klebsiella pneumoniae.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Multi-drug resistant (MDR) Klebsiella pneumoniae, genetic manipulation, CRISPR-Cas9 gene editing, colistin resistance.

Abstract:

Among gram-negative bacteria, Klebsiella pneumoniae (KP) is one of the most common causes of healthcare-related infection. The resistance to colistin and carbapenems in Klebsiella pneumoniae infections have been associated with increased morbidity and mortality worldwide. In a previous report (1), we identified several mutations in genes commonly implicated in colistin resistance, including in three two-component systems—CrrA/B, PmrA/B, and PhoP/Q—and the negative regulator MgrB. In this work, we present the validation of a CRISPR-Cas9/lambda recombineering system utilizing a zeocin resistance cassette as a genetic manipulation system for multidrug-resistant (MDR) KP. We aim to generate isogenic mutants in colistin-resistant (ColR, Sequence type ST512) and colistin-susceptible (ColS, ATCC1705). We describe primer design, cloning genetic manipulation and mutant confirmation for selected novel mutations previously identified by our group in MgrB (L19R), PmrB (G207D and T157P, the latter as a proof-of-concept, since it has already been proven to be a cause of colistin resistance), PhoP (L12Q), PhoQ (V24G and L105Q) and CrrB (G183V). The availability of a highly efficient gene editing in multidrug-resistant KP isolates will allow us to examine how these diverse genetic backgrounds impact colistin MICs and growth and virulence. Irene Sánchez-León, Elena Pérez-Nadales, Juan Antonio Marín-Sanz, Teresa García-Martínez, Luis Martínez-Martínez. Heteroresistance to colistin in wild-type Klebsiella pneumoniae isolates from clinical origin 2023; 12;11(6):e0223823. doi: 10.1128/spectrum.02238-23. Epub 2023 Nov 14.

PSII.cc. Analysis of SHOX2 and LINE-1 methylation and expression profiles in non-small cell lung cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: SHOX2, LINE-1, DNA methylation, Transcriptional expression, Cell lines, Lung cancer.

Abstract:

Lung cancer is the leading cause of cancer deaths worldwide. In recent years, the characterisation of molecular markers that allow early diagnosis and the development of new therapeutic strategies has been carried out. Specifically, aberrant DNA methylation marker patterns have been associated with the activation or silencing of key genes involved in the acquisition of tumour characteristics. In lung cancer, hypermethylation has been described in promoters of tumour suppressor genes such as the gene coding for the short stature Homeobox 2 protein (SHOX2), as well as global hypomethylation reflected in highly repetitive sequences such as Long interspersed element 1 (LINE-1). The aim of this study was to evaluate the methylation and transcriptional expression profiles of the single sequence gene SHOX2 and the repetitive element LINE-1 in non-small cell lung cancer NSCLC cell lines. Five lung cancer-derived cell lines (A549, H23, H292, H727 and PC9) and a control non-tumour bronchial epithelial cell line (BEAS-2B) were analysed. The methodology for methylation analysis included genomic DNA extraction, sodium bisulphite conversion and quantitative methylation-specific PCR (qMSP). Total RNA extraction, cDNA synthesis and qPCR analysis were used to determine expression levels. The methylation levels of the CpG sites assessed in SHOX2 and LINE-1 were found to be associated with gene expression at the mRNA level in each of the cell lines. Specifically, hypermethylation of the SHOX2 single sequence gene was observed in the H292, PC9 and H23 cell lines; as well as their respective decrease in transcriptional expression. On the other hand, hypomethylation of the LINE-1 repetitive element was evident in A549 and H292 cell lines with a significant increase in the expression of ORF1 and ORF2 transcripts. These results contribute to the knowledge of this epigenetic mark and its biological impact in lung cancer.

PSII.dd. Interaction of extracorporeal circulation with the degradation of the endothelial glycocalyx.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: extracorporeal circulation, endothelial glycocalyx, syndecan-1, heparan sulfate.

Abstract:

The endothelial glycocalyx is a structure that covers the vascular endothelium and is composed of polysaccharides, proteoglycans, membrane glycoproteins, and plasma proteins. This layer performs vital functions such as maintaining vascular permeability, regulating inflammatory responses, and reducing leukocyte adhesion and platelet count. The degradation of the glycocalyx is associated with inflammation/sepsis, hyperglycemia, and ischemia/reperfusion injury. Extracorporeal circulation (ECC), used in cardiac surgery to divert blood from the heart and lungs, can induce a systemic inflammatory response. Contact of the blood with the artificial surface of the ECC circuit activates coagulation, complement, proinflammatory cytokines, and causes endothelial cell death. After ECC, the degradation of the glycocalyx is especially sensitive to high levels of inflammatory mediators and oxidative stress, reflected by increased levels of syndecan-1 and heparan sulfate. A prospective observational study was conducted on patients over 15 years old undergoing cardiac surgery with extracorporeal circulation between November 2023 and February 2024 at a tertiary hospital. Clinical variables of the patients, type of cardiac surgery, and extracorporeal circulation were analyzed and related to biomarkers of glycocalyx degradation (heparan sulfate and syndecan-1). A total of 22 patients were included, analyzing the concentrations of syndecan-1 and heparan sulfate in 19 of them. It was observed that patients undergoing cardiac surgery with extracorporeal circulation showed elevated plasma levels of syndecan-1 and heparan sulfate, especially 6 hours after extracorporeal circulation. Extracorporeal circulation appears to accelerate the degradation of the endothelial glycocalyx, as evidenced by changes in plasma concentrations of syndecan-1 and heparan sulfate.

PSII.ee. Aerobic Exercise Prescription for Pain Reduction in Fibromyalgia: A Systematic Review and Meta-Analysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Fibromyalgia; Chronic pain; Exercise therapy; Endurance training; Pain intensity.

Abstract:

Background: Fibromyalgia is a condition characterized by disabling levels of pain intensity. In this regard, aerobic exercise may play a role in the reduction of pain in these patients. Objective: To assest the dose of aerobic exercise needed, following the frequency, intensity, type, time, volume and progression (FITT-VP) model; to obtain clinically relevant reduction in pain. **Methods**: A systematic review and meta-analysis of randomized clinical trials was conducted with the search between July and October of 2023. Methodological quality was assessed with PEDro scale and risk of bias with the Cochrane assessment tool ROB 2. Mean different (MD) and 95% confidence intervals were calculated using a random effect model and minimally clinically relevant difference (MCID) was used to assess the dose of exercise. **Results**: Seventeen studies were included. The quality of the included studies was generally good, with a mean PEDro score of 6.6. The risk of bias varied, with six studies showing low risk, five with some concerns, and six with high risk. Aerobic exercise interventions were analyzed using the FITT-VP model. Frequency ranged from 1 to 10 times per week, intensity varied from light to vigorous, types of exercise included aerobic, interval training, pool-based, stationary cycling, swimming, and walking. Intervention durations ranged from 3 to 24 weeks, with session lengths from 10 to 45 minutes. Most studies showed significant differences favoring aerobic exercise, 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.ff. Diabetes produces changes in serum composition that compromise the differentiation and viability of mesenchymal stem cells to osteoblasts. Possible effect of sitagliptin treatment.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: diabetic, sitagliptin, MSC, osteoblast, adipocyte, cell differentiation.

Abstract:

Background: The loss of bone mass associated with age or certain pathologies is related to physiological changes that alter the niche of progenitor cells located in the bone marrow. These changes include increased oxidative stress and proinflammatory cytokines, among others, which alter the process of osteoblastogenesis. All these factors have been associated with an increase in bone marrow adiposity because mesenchymal stem cells (MSC), precursors of osteoblasts, under these conditions tend to differentiate into adipocytes instead of osteoblasts. This favors the loss of bone mass and impairs the body's regenerative capacity. In addition, diabetics have a lower mobilization of progenitor cells, reducing their regenerative capacity. The use of antidiabetic drugs such as Sitagliptin could improve these physiological changes and the regenerative capacity of the organism. **Methods**: The animals were divided into 3 groups: control, diabetic control and diabetic treated with sitagliptin. At 14 days after treatment, the animals were sacrificed by exsanguination. Serum was obtained from the extracted blood and used for human bone marrow MSC culture. Viability and apoptosis assays were performed. In addition, MSC were differentiated into adipocytes and osteoblasts, and different stains such as Oil Red and Alizarin Red were performed. Gene expression was also studied. **Results**: MSC grown in the presence of serum from diabetic animals showed less viability and more apoptosis relative to those grown in serum from non-diabetic animals. Sitagliptin did not reverse this effect. However, in osteoblast cultures, ectopic mineralization was formed in presence of diabetic serum, while in adipocyte cultures, no significant changes were seen. **Conclusion**: The results suggest that serum from diabetic animals treated or not with sitagliptin negatively influences on viability of MSC differentiated into osteoblast. This may be related to the increased risk of osteoporosis in diabetics.

PSII.gg. Planning-navegation assisted surgical treatment of orbital fractures.

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Scientific Program: Active ageing and fragility.
Keywords: diabetic, sitagliptin, MSC, osteoblast, adipocyte, cell differentiation.

Abstract:

Introduction and objectives: The anatomical reconstruction of the orbital walls is key in the treatment of orbital fractures to achieve the correct position of the eyeball. The main objective of our research work is to show our experience with virtual planning, testing of a pre-moulded orbital reconstruction mesh (virtual surgery) and intraoperative navigation in orbital fractures. In addition, we want to assess the benefits of planning-navigation in orbital fractures. **Methodology**: We included 34 patients with orbital fractures treated in our department, in whom virtual planning +/- surgical navigation was performed. The virtual planning procedure is as follows: the patient's CT scan is imported into the iPlan virtual planning software of the BrainLab system (preoperative planning). We perform the autosegmentation of the orbits. Using the "mirror" tool, we simulate the healthy orbit on the fractured orbit. We imported a pre-moulded mesh in STL format to perform the virtual surgery and checked its size and shape. **Results**: During surgery we performed anatomical navigation (first navigation) to check the position of the instruments and the adequate detachment of the orbital walls. Once the reconstruction mesh was in place, we performed the check navigation. In all patients the enophthalmos was corrected and the precise anatomical reconstruction of the orbital walls was achieved, verified with postoperative CT scans. **Conclusions**: Virtual planning and subsequent surgical navigation are tools that are increasingly used in our speciality, particularly in facial traumatology. The anatomical peculiarities of the orbit make the reduction of its fractures a surgical challenge. Planning-navigation provides safety and precision in the placement of customised meshes.

PSII.hh. Kisspeptins centrally modulate food intake and locomotor activity in mice independently of gonadal steroids in a sexually dimorphic manner.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Kiss1 neurons, kisspeptins, food intake, energy expenditure, locomotor activity, sex steroids.

Abstract:

Kisspeptins are essential regulators of the reproductive axis, with capacity to potently activate GnRH neurons, acting also as central conduits for the metabolic regulation of fertility. Recent evidence suggests that kisspeptins per se may also modulate several metabolic parameters, including body weight, food intake or energy expenditure, but their actual roles and site(s) of action remain unclear. We present herein a series of studies addressing the metabolic effects of central (1 nmol) and peripheral (3 nmol) administration of Kp-10 for 11 days in mice of both sexes. To assess direct metabolic actions of Kp-10 vs. those derived indirectly from its capacity to modulate gonadal hormone secretion, kisspeptin effects were tested in adult male and female mice gonadectomized and supplemented with physiological doses of testosterone or 17β-estradiol, respectively. Central administration of Kp-10 decreased food intake in male mice, especially during the dark phase, which was accompanied by a reduction in total and nocturnal energy expenditure and locomotor activity, although differences were not detected in body weight at the end of treatment. In contrast, opposite patterns were detected in female mice, with an increase in total and nocturnal locomotor activity, despite no changes in body weight, food intake or energy expenditure. Peripheral administration of Kp-10 failed to alter any of the metabolic parameters analysed, except for a decrease in locomotor activity in male mice and a subtle increase in 24h food intake in female mice, denoting a predominant central role of kisspeptins in the control of energy metabolism. Finally, glucose tolerance and insulin sensitivity were not significantly affected by central or peripheral Kp-10 treatment. In conclusion, our data reveal a potential role of kisspeptins in the control of key metabolic parameters, including food intake, energy expenditure and locomotor activity, with a preferential action at central level, which is sex steroid-independent but sexually-dimorphic.

PSII.ii. Role of hyperandrogenism in the pathogenesis of metabolic dysfunction-associated fatty liver disease (MAFLD) linked to polycystic ovary syndrome.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: PCOS, MAFLD, hyperandrogenism, steatosis, fibrosis.

Abstract:

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder among premenopausal women, whose main clinical manifestation is hyperandrogenism, which drives reproductive abnormalities. Women suffering PCOS often exhibit also metabolic disorders and have four-times higher risk of developing metabolic-dysfunction associated fatty liver disease (MAFLD). MAFLD is considered the most common liver disease worldwide, and its incidence in PCOS women is considerably high (35-70%). MAFLD encompasses an array of hepatic manifestations that begin with fat accumulation (hepatic steatosis) that may progress to non-alcoholic steatohepatitis (NASH); a more severe stage of the disease that may predispose to the development of cirrhosis, liver failure and hepatocellular carcinoma. Cumulative evidence suggests that the higher incidence of MAFLD in PCOS women may be linked to the metabolic derangements associated to this endocrinopathy. However, recent findings suggest that chronic hyperandrogenism might be considered an independent risk factor for the development of MAFLD in PCOS women. In this study, we assessed the effect of chronic androgen excess, alone or in combination with an obesogenic diet, on the metabolic and hepatic profile in a well-validated murine model of PCOS. Our results show that chronic androgen exposure increased body weight, fat mass and caused glucose intolerance and insulin resistance; metabolic parameters that were exacerbated when the animals were fed a high-fat diet (HFD). In addition, the combination of hyperandrogenism and HFD increased serum and hepatic lipid accumulation, a defining feature of MAFLD, and altered liver expression of genes related to lipid metabolism, inflammation, apoptosis and fibrosis, with a variable impact of hyperandrogenism, HFD or their combination. Our results set the basis for understanding the physiopathology of PCOS-bound MAFLD and are part of a large-scale study that aims to evaluate the direct impact of androgens on the liver and the time-course of this hepatic disease in the context of PCOS.

PSII.jj. Exploring the interplay between RNA methylation and splicing dysregulation in neuroendocrine tumors.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: RNA methylation, splicing, neuroendocrine tumors, lung NETs, pan NETs.

Abstract:

Neuroneuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that originate from neuroendocrine cells and are found in several organs of the body, being particularly prevalent in pancreas and lung. Recent research has demonstrated significant dysregulation of alternative splicing in these NETs, which may contribute to their tumorigenic properties. However, the potential implication of other RNA processing mechanisms, such as RNA methylation —being the most usual internal RNA modification the N6-methyladenosine, commonly named m6A—, in the regulation of NET pathobiology is still largely unexplored. We hypothesized that m6A processing machinery may be altered in these NETs and linked to splicing dysregulation, thus RNA metabolism would be severely modified in these tumors. Our main aim was to identify alterations in the m6A process coupled to splicing alterations that may interfere with lung and pancreatic NETs development and aggressiveness. To this end, we have carried out a biocomputational analysis in two cohorts comprising 281 lung and 174 pancreatic NETs, respectively, exploring putative associations between m6A regulators with clinical features and splicing alterations. We observed a clear relationship between the expression levels of several m6A elements with mutations in key genes, metastatic status and differentiation grade. Interestingly, there was a strong link between abnormal m6A-related gene expression and cellular functions and pathways tied to tumorigenesis, development, and aggressiveness. Key affected pathways included metabolic processes, cellular adhesion, ionic transport, and tumor-related features such as proliferation, differentiation, and increased growth factor sensitivity. Altogether, our results suggest that lung and pancreatic NETs also possess another level of RNA processing dysregulation involving m6A alteration. Ongoing studies are investigating these mechanisms using in vitro models to elucidate their precise role. This research may unveil new therapeutic strategies targeting m6A, promising innovative approaches for treating these challenging tumors.

PSII.kk. Potential use of ceftazidime-avibactam in patients with KPC-producing Klebsiella pneumoniae with low-risk of death: ¿when is it indicated?

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Scientific Program: Infectious diseases.
Keywords: KPC-Klebsiella pneumoniae; colonization; infection; risk-scores; management.

Abstract:

Background. It is known that ceftazidime/avibactam decreases mortality in patients with KPC-KP infection and INCREMENT-CPE score > 7 (ICS). **Methods**. Prospective observational study of patients who developed carbapenemase producing Klebsiella pneumoniae (KPC-KP) infection treated with best available therapy (BAT) vs ceftazidime/avibactam. Primary outcome: crude mortality in day 30. Logistic regression was used to identify risk factors related to increased crude mortality, performing a propensity score (PS) to receive treatment with ceftazidime/avibactam. A sensitivity analysis selected a risk group. **Results**. Logistic regression analysis performed to study risk factors for mortality since the availability of ceftazidime/avibactam included 152 patients: 113 (74.3%) treated with BAT and 39 (25.7%) with ceftazidime/avibactam. The variables included in the final model were: PS to receive ceftazidime/avibactam, development of bacteremia (OR 2.96, 95% CI 1.16-7.54), P = 0.02), the McCabe RF index (OR = 2.98, 95% CI 1.16-7.64, P = 0.02) and Pitt score ≥ 2 (OR = 7.52, 95% CI, 2.90-19.52, P = < 0.001). The sensitivity analysis conducted in the global cohort selected Charlson index ≥ 5 as a predictor of high risk of mortality in patients treated with BAT, with 33.6% (36/107) of mortality vs 10.7% (3/28) in the ceftazidime/avibactam group (OR = 4.23, 95% CI 1.20; 14.94). **Conclusion**. Patients who develop KPC-KP infection with ICS < 8 may benefit from empirical treatment with ceftazidime/avibactam when they have a Charlson ≥ 5 index.

PSII.II. Deciphering pulmonary tumor microenvironment through MALDI Imaging Mass Spectrometry: new approaches for tumor expansion inhibition.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Tumor angiogenesis; vessel co-option; ALK1 receptor; Maldi-imaging and biomolecular signatures.

Abstract:

Tumor growth increases the demand for oxygen and nutrients, necessitating the formation of new blood vessels. Tumor angiogenesis, the process of creating new blood vessels from existing ones, is a primary mechanism for tumor vascularization. Despite over 40 years of research and the development of anti-angiogenic strategies, such as targeting vascular endothelial growth factor (VEGF), these therapies have shown limitations. One of these limitations is that cancer cells can use non-angiogenic mechanisms to obtain oxygen and nutrients by using alternative methods like vessel co-option (VCO), where cancer cells hijack existing blood vessels rather than forming new ones. Vessel co-option poses a significant resistance mechanism to anti-angiogenic therapies, presenting a new frontier in cancer research. Since pre-existing blood vessels are generally quiescent (inactive), a new strategy proposes inhibiting this quiescence as a way to counteract VCO. This project investigates whether inhibiting vessel quiescence induced by bone morphogenetic protein 9 (BMP9) through the ALK1 receptor can block VCO, and whether it could enhance the effectiveness of chemotherapies, immunotherapies, or anti-angiogenic drugs. To explore this hypothesis, lung metastases were created by injecting 4T1 breast cancer cells into mice. The animals were then treated with either a placebo or PF-03446962, an antibody targeting the ALK1 receptor, over two weeks. At the study's conclusion, the lungs were analyzed using MALDI Imaging to compare treated and untreated samples. Early results showed distinct biomolecular signatures between tumor regions and nearby blood vessels, suggesting that inhibiting vessel quiescence could impact tumor behavior. Some peptides identified in the study were linked to platelet activation, blood coagulation, fibrin clot formation, and angiogenesis, offering new insights into the mechanisms of VCO in tumors.

PSII.mm. Relationship of glycosylated haemoglobin levels to cognitive impairment in the geriatric population.

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Scientific Program: Biomedicine. Line of research: Neuroplasticity and oxidative stress.
Keywords: Aged; Dementia; Cognitive Impairment; Diabetes Mellitus; Glycated Hemoglobin.

Abstract:

Introduction: Increasing ageing generates an increase in the prevalence of chronic diseases that frequently coexist in older people, including type 2 diabetes mellitus (T2DM) and dementia. Previous literature has linked the two conditions. **Aim:** To examine whether glycosylated haemoglobin (Hb1Ac) levels are associated with the degree of cognitive impairment in the geriatric population. **Methods**: Retrospective longitudinal observational study including patients ≥ 65 years with cognitive impairment [scores ≥ 3 on the Pfeiffer scale (SPMSQ)]. Sociodemographic data, cognitive impairment and analytical parameters were collected (from 2012 to 2022). Data collection was conducted between November 2022 and May 2023. **Results**: Of the 50 patients included, 76% were women. The mean age of the subjects was 85 years. Regarding the relationship of HbA1c levels with cognitive impairment, the data reflect a statistically significant difference (p=0.0027) between the mild (6.7567 ± 0.73), moderate (6.2464 ± 0.56) and severe (7.4100 ± 0.73) cognitive impairment groups. These findings determine that mean serum HbA1c levels over the past 10 years differ significantly in the groups of older people with mild and moderate cognitive impairment compared to those with severe cognitive impairment. **Conclusions:** Given that T2DM is a risk factor for cognitive impairment and that HbA1c is the tool of choice for the management of T2DM, these findings are relevant both from the point of view of the importance of the correct follow-up of T2DM in primary care and the involvement of primary care in the prevention and detection of cognitive impairment.

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

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Scientific Program: Infectious and Immunological diseases.

Keywords: KPC-producing Klebsiella pneumoniae; hospital-onset infections; community-onset infections; mortality rates; infection prevention and control intervention (IPC).

Abstract:

We characterized the incidence, clinical and molecular features of non-hospital onset (non-HOI, including healthcare-associated and community-acquired) versus hospital-onset (HOI) infections by KPC carbapenemase-producing K. pneumoniae (KPC-KP) in a prospective (2012-2022), longitudinal, cohort. Overall, patients (N=467, 66.8% HOI, 33.2% non-HOI) presented high Charlson comorbidity indexes (median 5, range 3-7). The incidence of infections was 0.53 cases/1.000 admissions/month (range 0.06-0.90) for HOI and 0.30 (range 0.0-0.60, p=0.39) for non-HOI, and decreased in both groups following an infection prevention and control intervention (IPC), with a 4-month lag cross-correlation coefficient (0.35, 95% CI 0.17-0.53), as assessed by interrupted time series and linear mixed model analyses. Whole Genome Sequencing revealed that most available KPC-KP isolates (315/316) were clonal and belonged to the high-risk clone of sequence type (ST) 512/KPC-3. Multivariable analyses showed no differences in crude mortality, clinical and microbiological response between non-HOI and HOI. In conclusion, non-HOIs are a serious emerging problem. Multifaceted IPC interventions may be instrumental in reducing non-HOI rates.

PSII.ññ. Loss of peroxiredoxin 6 impairs mitochondrial function and biogenesis in the human colon cancer cell line HCT116.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Peroxiredoxin 6, Mitochondria, Lipid Peroxidation, Ferroptosis, Oxidative Stress.

Abstract:

PRDX6 is a unique member within the peroxiredoxin family that presents not only peroxidase but also phospholipase A2 (iPLA2) and lysophosphatidylcholine acyl transferase (LPCAT) activity, acting on phospholipid hydroperoxides. It is also the only peroxiredoxin member that translocates to damaged mitochondrial membranes to regulate mitophagy by suppressing ROS. PRDX6 has been considered a tumor promoter, associated with the proliferation and invasive capacity of different tumor cell lines including colorectal cancer cells, although the effect of its complete deletion in these cells has not been studied. Here, using CRISPR/Cas9 technology, we constructed a colorectal cancer cell line HCT116 knockout for PRDX6 to study the effect of its removal in mitochondrial function and whether it differs from that observed in other tumor cells. The lack of PRDX6 in HCT116 cells induced oxidative stress as indicated by the increase in ROS and lipid peroxidation and a decrease in the antioxidant response regulator NRF2, sensitizing cells to ferroptosis. Furthermore, there is also a severe impairment of mitochondrial function and biogenesis when PRDX6 is deleted as showed by the alteration in mitochondrial morphology and the decrease of mitochondrial complexes I/III activity and respiratory capacity. Therefore, PRDX6, through its membrane turnover functions, can provide a deeper ROS tolerance, avoiding lipid peroxidation, which is essential to maintaining the proper organelle functionality and preventing ferroptosis in the presence of large ROS. This means that PRDX6 downregulation could be considered a good therapeutic strategy together with a ferroptosis inducer because of its capacity to sensitize colorectal cancer cells to ferroptosis cell death.

SESSION VI.

INFECTIOUS AND IMMUNOLOGICAL DISEASES. ORGAN TRANSPLANTATION.

VIa. The role of central pulmonary venous gas measurement in extending donor lungs criteria for transplantation: a multicenter analysis of the European society of thoracic surgeons (ests) lung transplant working group.

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Scientific Program: Infectious and Inmunological Diseases. Organ Transplantation
Keywords: donation, lung transplantation, thoracic surgery.

Abstract:

Objective: Peripheral arterial PaO2/FiO2 ratio (p-P/F ratio) over 300 mmHg remains as the classical cut-point in the acceptance of lung donors for transplantation. In the era of ex-vivo reconditioning, this parameter should be re-assessed. We aimed at analyzing the early outcomes of lung transplantation from donors with p-P/F ratio under 300 mmHg but with central pulmonary venous P/F ratio (c-P/F ratio) above 300 mmHg, to estimate to what extent the donor pool could be increased. **Methods**: Prospective multicenter analysis recruiting 124 consecutive lung donors over a 1-year period. Donors were categorized into two groups: optimal donors (p-P/F ratio >300 mmHg) and extended donors (p-P/F ratio <300 mmHg and c-P/F ratio >300 mmHg). Early post-transplant outcomes and survival were compared between groups. **Results**: We assessed 106 double-lung and 18 single-lung donors. There were 29 extended (23%) and 95 (77%) optimal donors. In the extended group, p-P/F ratio was 234±51 mm Hg and the c-P/F ratio 439±76 mmHg (P/F ratio gap: 205±82 mmHg) (p<0.001). In the control group, p-P/F ratio was 435±8 mm Hg and the c-P/F ratio 487±103 mmHg (P/F ratio gap: 51±80 mmHg) (p=ns). Lung transplants from the extended donor group did not differ from those optimal donors in terms of early graft function and survival. **Conclusion**: 1. Peripheral P/F ratio <300 mmHg should not be considered a major criterion to discard a potential lung donor. 2. Single lung donors should be assessed with central venous gas analysis instead of a standard peripheral arterial blood gas analysis, which may increase the donor pool for lung transplantation in up to 23%. 3. In bilateral lung donors, those with p-P/F ratio >215 mmHg should undergo intraoperative c-P/F ratio deter.

VIb. Metabolic Reprogramming Induced by SARS-CoV-2 Accessory Proteins in Lung Epithelial Cells.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: ORF3a, ORF9b, ORF9c, ORF10, mitochondria, genome-scale metabolic modelling (GSMM).

Abstract:

It has been established that SARS-CoV-2, the causative agent of COVID-19, dysregulates antiviral signaling, the immune response and cell metabolism. However, the role of accessory proteins in this respect has yet to be elucidated. This study demonstrates that SARS-CoV-2 accessory proteins ORF3a, ORF9b, ORF9c and ORF10 induce a significant mitochondrial and metabolic reprogramming in A549 lung epithelial cells. While ORF9b, ORF9c and ORF10 induced largely overlapping transcriptomes, ORF3a induced a distinct transcriptome, including the downregulation of numerous genes with critical roles in mitochondrial function and morphology. On the other hand, all four ORFs altered mitochondrial dynamics and function, but only ORF3a and ORF9c induced a marked alteration in mitochondrial cristae structure. To assess the impact of SARS-CoV-2 accessory proteins on cellular bioenergetics, we analyzed intracellular ROS levels and examined mitochondrial and glycolytic stress using Seahorse technology. Our findings indicate that ORF9b and ORF9c overexpression results in the most significant alteration to mitochondrial function. In this study, based on differentially expressed gene analysis, a genome-scale metabolic model (GSMM) was reconstructed by integrating transcriptome data, identifying metabolic flux reprogramming features that are both shared across all accessory proteins and specific to each individual accessory protein. Notably, a reduction in amino acid metabolism was observed in ORF9b, ORF9c and ORF10, while ORF3a distinctly induced an increase in lipid metabolism. These findings reveal metabolic dependencies and vulnerabilities prompted by SARS-CoV-2 accessory proteins that may be exploited to identify new targets for intervention.

VIc. Refining the QuantiFERON-CMV cut-off: the Quanti-CMV study enhances CMV non-replication prediction in kidney and lung transplant recipients.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: QuantiFERON-CMV, cut-off, CMV, solid organ transplant.

Abstract:

The commercial test QuantiFERON-CMV (QF-CMV) establishes a cut-off value of ≥0.2 IU/mL for having CMV-specific cell-mediated immunity (CMI). We hypothesized that in solid organ transplant (SOT) patients, the predictive capacity for non-replication risk of the QF-CMV test depends on the interferon-gamma (IFN-γ) production of each patient. The objective was to evaluate the best QF-CMV cut-off point for predicting the risk of no significant CMV replication in 30 days after determination. 403 samples from 130 transplant recipients were analyzed retrospectively; 71 kidney transplant (KT) recipients came from the TIMOVAL (Clin Infect Dis. 2022; 74:757-765) and 59 lung transplant (LT) patients from the CYTOCOR (NCT03699254) clinical trials. The best cut-off point was established according to the highest Youden Index (J). We calculated the area under the receiver operating characteristic (AUROC) to predict significant CMV replication using both the manufacturer's recommended cut-off point and the one obtained in our study. We also compare sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the different cut-off points. A multivariable logistic regression was used to establish whether the new cut-off value was an independent risk variable with respect to other clinical variables. Finally, a predictive risk score was calculated using the beta coefficients of logistic regression (Quanti-CMV Score). The proportion of patients, sensitivity, specificity, PPV, NPV, and accuracy values for different breakpoints of the score values were calculated. The best cut-off point for predicting protection against significant CMV replication is 2.20 IU/mL in both kidney and lung transplant recipients, instead of the currently used cut-off point. This cut-off point can be used as part of a predictive score to assist clinical daily practice.

VId. Analysis of surgical indication and time to surgery in infective endocarditis and its relationship with prognosis.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: infective endocarditis, early surgery, timing of surgery, valve diseases, prognosis.

Abstract:

Introduction: Infective endocarditis (IE) is a condition associated with a high in-hospital morbidity and mortality, often requiring early surgery in a significant percentage of patients. Our objective was to analyze the surgical indications and the timing of surgery (emergent, urgent and elective), as well as its impact on prognosis. **Materials and methods** : We analyzed a cohort of 368 patients consecutively diagnosed with IE at our center between January 2000 and April 2021, including cases of IE related to cardiac implatable electronic device (CIED). We examined the indications for surgery, the surgical interventions and the timing according to the criteria established by the 2015 ESC Guidelines (emergent <24 hours, urgent <7 days and elective ≥ 7 days), the reasons for the indications and their relationship with prognosis (all-cause mortality) in the medium-to-long term. **Results**: We analyzed a total of 368 patients, with a median age 62 years [IQR 52-73], 32.1% women, and a predominance of native valve IE (62.8%). Of the total, 282 patients (76.6%) had a surgical indication according to ESC criteria: emergent in 29 cases (10.3%; 100% due to refractory hear failure (HF)), urgent in 151 cases (53.5%; 37.7% due to HF, 41.1% due to uncontrolled infection, 18.5% for embolic event prevention and 2.6% due to CIED-related IE) and elective in 102 cases (36.2%; 24.5% due to HF, 5.9% for embolic event prevention, 16.7% for CIED-related IE and 35.3% for new valve disease requiring surgery). Out of the 282 patients with surgical indication, 226 (80,1%) underwent surgery. In-hospital mortality was 26.4% and 1-year mortality 35.9%. With 1-year follow-up, mortality was lower in patients without a surgical indication (24.4% vs 39.4%; p=0,01). Among patients with a surgical indication, the mortality rate was 71.4% in those who did not undergo surgery and 31.4% in those who did (p<0,001)(figure 1a). The timing of the indication was associated with prognosis, with a 30-days mortality rate 37.9% for emergent indication, 31.1% for urgent indication and 6.9% for elective indication (p<0,001)(figure 1b). **Conclusions**: More than three quarters of patients with IE have an indication for cardiac surgery, and the vast majority of them undergo the procedure. Patients with a surgical indication had a worse prognosis and among these patients, those operated on with emergent and urgent indications had a worse prognosis.

Figure 1a

1-year survival according to surgical intervention in patients with surgical indication.

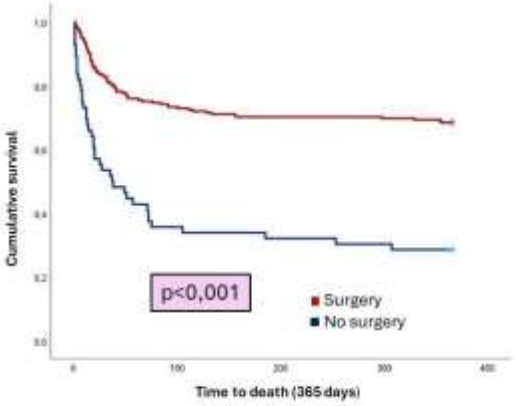
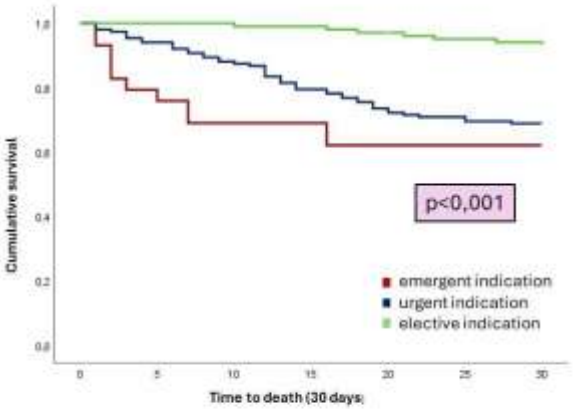


Figure 1b

30-days survival according to indicated timing to surgery in patients with surgical indication.



VIe. Serological and molecular survey of rat hepatitis E virus (Rocahepevirus ratti) in drug users.

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Scientific Program: Infectious and Immunological diseases.

Keywords: rat hepatitis E virus; hepatitis E; zoonoses; people with drug consumption; public health.

Abstract:

Rat hepatitis E virus (ratHEV) is an emerging cause of acute hepatitis of zoonotic origin. Since seroprevalence studies are very scarce, at-risk humans' populations are almost unknown. Because blood-borne infections frequently occur in people with drug consumption, who are particularly vulnerable to infection due to lack of housing and homelessness, this population constitutes a priority in which ratHEV infection should be evaluated. Therefore, the aim of this study was to evaluate the ratHEV seroprevalence and RNA detection rate in drug users as a potential at-risk population. We designed a retrospective study involving individuals attended drug rehabilitation centers. Exposure to ratHEV was assessed by specific antibody detection using ELISA assay and dot blot (DB) assay and the presence of active infection by ratHEV RNA detection using RT-qPCR. Three-hundred and forty-one individuals were included, being the most of them men (67.7%) with an average age of 45 years. A total of 17 individuals showed specific IgG antibodies against ratHEV (4.6%; 95% CI; 3.1% - 7.9%). One case of active ratHEV infection was identified (0.3%; 95% CI: 0.1% - 1.8%). This was a 57-year-old homeless woman with limited financial resources, who had active cocaine and heroin use via parenteral route. In conclusion, we identified a noteworthy exposure to ratHEV among drug users. Targeted studies in drug users with proper control groups are necessary to evaluate high-risk populations and transmission routes more accurately.