14th IMIBIC YOUNG INVESTIGATORS MEETING

BOOK OF ABSTRACTS

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INDEX

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Acknowledgements

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PROGRAMME

Day 1 (16th OCT)

08:30 – 09:00 – Registration and Poster display

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

09:30 – 10:45 – SESSION I. Cancer I (IMIBIC Assembly Hall)

Chairs: **Dr. Henning Kirst & Dr. Yolanda Jiménez**

Ia. 09:30 – 09:45 Metabolic shift underlies tumor progression and immune evasion in S-nitrosoglutathione reductase-deficient cancer. **Ana Mantrana Soldado**.

Ib. 09:45 – 10:00 Targeting glycogen synthase kinase 3 as an effective therapeutic strategy against tumor budding and immune evasion in human colorectal cancer. **Carmen Navarrete Sirvent.**

Ic. 10:00 – 10:15 B-RAF oncogene regulation by dual-specificity tyrosine-regulated kinase 2. **Miguel Torres Ramos.**

Id. 10:15 – 10:30 The splicing machinery represents a targetable vulnerability in bladder cancer. **Antonio Jesús Montero Hidalgo.**

Ie. 10:30 – 10:45 Memory Universal CAR T cells: A new strategy against B-cell malignancies. **Kristina Pavlovic Pavlovic.**

10:45 – 11:45 – Coffee Break (IMIBIC Cafeteria)

11:45 – 12:45 – SESSION II. Multidisciplinary I (IMIBIC Assembly Hall)

Chairs: **Dr. Mª Carmen Vázquez & Dr. Fernando Leiva**

IIa. 11:45 – 12:00 Circadian rhythm disruption in cardiovascular and trauma severe patients admitted to ICU: Influence of environmental conditions. **Luna López Coleto.**

IIb. 12:00 – 12:15 VCE-004.8, a novel PP2A/B55 activator, promoted angiogenesis and arteriogenesis in critical limb ischemia. **María Eugenia Prados González.**

IIc. 12:15 – 12:30 Worsening of Heart Failure with Reduced Ejection Fraction: Impact of the number of previous hospital admissions. **Jorge Perea Armijo.**

IId. 12:30 – 12:45 VCE-009.1, a novel formulation of natural products with positive allosteric modulators for CB1R. **Francisco José Ponce Díaz.**

12:45 – 13:45 – Poster Session I (IMIBIC Meeting & Multipurpose Room)

Chairs: **Dr. Mario Frías Casas, Dr. Marisol Avendaño & Dr. Iván Arias**

PSI.a. Vaccination against SARS-CoV-2 induces FOXP3+HELIOS+ regulatory T cells in severe COVID-19 patients. **Ester Irene Reina Alfonso.**

PSI.b. Enumeration and characterization of circulating tumor cells in patients with hepatocellular carcinoma undergoing transarterial chemoembolization **María Lola Espejo Cruz.**

PSI.c. BioHub, a Python-based bioinformatics framework for analysis of high-throughput microbial genome sequencing on high performance computing systems. **Juan Antonio Marín Sanz.**

PSI.d. The socioeconomic profile of patients with radiographic axial spondyloarthritis is associated with the severity of the disease and with the permanent disability. A cluster analysis in a national Spanish registry. **Desiree Ruiz Vilches.**

PSI.e. Molecular pathways linked to liver complications in psoriatic arthritis: impact of methotrexate cumulative exposure and novel anti-PDE-4 and anti-JAK therapies. **Miriam Ruiz Ponce.**

PSI.f. A possible link between RNA methylation and splicing in lung carcinoids **Daniel Ruiz Palacios.**

PSI.g. Dysregulation of RNA-exosome machinery in hepatocellular carcinoma. **Víctor Jesús Fernández Ramírez.**

PSI.h. bZIP in-frame CEBPA mutation impact assessment as a distinct prognostic entity in AML in 2434 patients. **Esther Prados de la Torre.**

PSI.i. Skin microbiota composition in Alopecia Areata: associations with disease severity and Bacterial Ratio Imbalance. **Jesús Gay Mimbrera.**

PSI.j. Developing a new diagnostic and prognostic method in Pseudomyxoma peritonei based on a mucin isoforms profile. **Melissa Granados Rodríguez.**

PSI.k. Exploring the effects of lifestyle and reproductive factors on postpartum breast cancer. **Alejandra Díaz Chacón.**

PSI.l. Clinical and molecular patterns associated with persistence of inflammation in Spondyloarthritis Patients: unveiling potential biomarkers. **Laura Cuesta López.**

PSI.m Dysregulation of Circulating miRNAs and Implicated Pathways in Severe Forms of Alopecia Areata. **Pedro J. Gómez Arias.**

PSI.n. Development of a food product with probiotic potential and its effect on parameters associated with glucose homeostasis in patients with type 2 diabetes mellitus at the Clinics Hospital of Paraguay. **Eugenia Ruiz Díaz Narváez.**

PSI.o. Exploring the relationship between physical fitness and lifestyle habits in sex-stratified preschool children: the Melipop Study. **Cristina Castro Collado.**

PSI.p. Dysregulation in the machinery controlling the splicing process is associated with clinical features of tumor progression in papillary thyroid cancer. **Isidoro Di Caro.**

PSI.q. Antiproliferative effects induced by an Aqueous Aged Black Garlic Extract on prostate and bladder cancer. **Maria Loreta Libero.**

PSI.r. Integrative meta-analysis reveals molecular signatures and therapeutic implications in Alopecia Areata. **Irene Rivera Ruiz.**

PSI.s. The Role of Positivity in Psychological Distress and Quality of Life among Cardiovascular Disease Patients: A longitudinal study. **Naima Z. Farhane Medina.**

PSI.t. Establishment of a desirable dose using neutral argon plasma to eradicate miliary peritoneal implants: a phase I/II controlled trial. **Alfonso Carlos Pontes García.**

PSI.u. Metabolic adaptations in skeletal muscle of transgenic mice that overexpress cytochrome b5 reductase-3 in male and female mice. **Luz Marina Sánchez Mendoza.**

PSI.v. Immunopathology in aortic stenosis disease. **Pablo Álvarez Heredia.**

PSI.w. Phosphorylation-dependent regulation of MEK1 by DYRK2 promotes oncogenic MAPK/ERK pathway hyperactivation. **Lucía Suanes Cobos.**

PSI.x. Low spinal radiographic progression after a mean of 15 years of follow-up in a cohort of patients with axial spondyloarthritis. **Raquel Granados.**

PSI.y. Transcriptomic Study of Pancreatic and Small Intestine Neuroendocrine Tumors using Oxford Nanopore Technology sequencing. **María Trinidad Moreno Montilla.**

PSI.z. Intestinal microbiota and prediction of cardiovascular disease recurrence. From the CORDIOPREV study. **Javier Arenas Montes.**

PSI.aa. Dietary modulation of advanced glycation end products and kidney function in type 2 diabetes patients with coronary heart disease: from the CORDIOPREV randomized controlled trial. **Alejandro López Moreno.**

PSI.bb. Use of minimally invasive samples from COPD and lung cancer for epigenetic biomarkers identification. **Francisco Rojas Vega.**

PSI.cc. Effects of a spreadable cream containing plant-sterols enriched virgin olive oil in children with hypercholesterolemia: A randomized clinical study. **Antonio Rodríguez Jódar.**

PSI.dd. Molecular characterization of renal and hepatic damage in an experimental model of sickle cell disease by mass-spectrometry. **Lucía Beltrán Camacho.**

PSI.ee. External multicentre validation of Pseudomyxoma Peritonei PSOGI-Ki67 classification. **Ana Martínez López.**

PSI.ff. Severe aortic stenosis treated with surgery and balloon expandable prosthesis. Analysis of a series of cases. **María Teresa Conejero Jurado.**

PSI.gg. Muscle mechanical properties of pelvic floor and paravertebral muscles in women with and without urge incontinence urinary: case-control study. **María Teresa Garzón Alfaro.**

PSI.hh. Autophagy promotes the generation of dormant polyploid giant cancer cells. **María Teresa Sánchez Montero.**

PSI.ii. Forced Expiratory Volume in 1 second (FEV1) and Mortality in Severe Mental Illness: An opportunity for early detection. **David Laguna Muñoz.**

PSI.jj. Deciphering pregnancy-associated breast cancer: distinctive molecular profile and clinical implications. **Regina Peña Enríquez.**

PSI.kk. Prevalence and risk factors associated with chronic kidney disease after heart transplantation. **Isabel López López.**

PSI.ll. Inflammasome machinery is dysregulated in glioblastoma: clinical and translational evidence. **Ignacio Gil Duque.**

PSI.mm. Involvement of EXOSC4 in the progression of hepatocellular carcinoma. **María Isabel Pozo Relaño**.

PSI.nn. Proximity Extension Assay is a novel technology for boosting molecular characterization and personalized clinical management of rheumatic diseases. **Yas Hanaee.**

13:45 – 15:45 – Lunch (IMIBIC Cafeteria)

15:45 – 17:00 – Session III. Nutrition, endocrine and metabolic diseases (IMIBIC Assembly Hall)

Chairs: **Dr. Lourdes Ladehesa & Dr. María Isabel Martínez**

IIIa. 15:45 – 16:00 Analysis of metabolites from the intestinal microbiota and their role as modulators of coronary heart disease as a function of the sex of the patient. **Helena García Fernández.**

IIIb. 16:00 – 16:15 Characterization of a novel molecular mechanism inhibiting the secretory capacity of arcuate Kiss1 neurons in conditions of metabolic stress. **Miguel Ruiz Cruz.**

IIIc. 16:15 – 16:30 Mediterranean diet preserves kidney function in coronary heart disease patients with type 2 diabetes and obesity: An Analysis of the CORDIOPREV Randomized Controlled Trial. **Alicia Podadera Herreros.**

IIId. 16:30 – 16:45 PCSK9 levels and their correlation with the genetic variants present in heterozygous familial hypercholesterolemia. **Alberto Díaz Cáceres.**

IIIe. 16:45 – 17:00 Characterisation of the somatostatin system in chronic liver disease: potential therapeutic role of neuronostatin receptor GPR107. **Antonio García Estrada.**

17:00 – 18:15 – SESSION IV. Multidisciplinary II (IMIBIC Assembly Hall)

Chairs: **Dr. Belén Pastor Villaescusa & Dr. André Sarmento**

IVa. 17:00 – 17:15 Supervised versus home-based programs in kidney transplant recipients: a non-randomized single-center prospective trial. **Anna Crepaldi.**

IVb. 17:15 – 17:30 Beneficial effect of recombinant Klotho administration in acute kidney injury associated with intravascular hemolysis. **Mercedes Vallejo Mudarra.**

IVc. 17:30 – 17:45 Magnesium supplementation reduces the development of renal and cardiac fibrosis present in chronic kidney disease: In vivo and in vitro studies. **Teresa Obrero Sojo.**

IVd. 17:45 – 18:00 Characteristics and outcomes of transcatheter mitral valve edge to edge repair according to mitral etiology. **Luis Carlos Maestre Luque.**

IVe. 18:00 – 18:15 High levels of FGF23 induce experimental hypertension and vascular remodeling. **Raquel María García Sáez.**

Day 2 (17th OCT)

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

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

Chairs: **Dr. Cristian Rodelo Haad & Dr. Silvia León**

Va. 08:30 – 08:45 High-Throughput Sequencing reveals recurrent mutations in RNUs in pancreatic tumors. **Clara González Pérez.**

Vb. 08:45 – 09:00 Prospective feasibility study of localization of lung nodules for sublobar VATS resections by using a novel Computed Tomography (CT) – guided radiopharmaceutical labelling system. **Alba María Fernández González.**

Vc. 09:00 – 09:15 Liquid biopsy-based epigenetic biomarkers for prognosis and monitoring of metastatic pancreatic cancer. **Pablo Francisco Cano Ramírez.**

Vd. 09:15 – 09:30 Clinical, transcriptomic, and functional characterization of telomerase/shelterin system in endocrine intracranial tumors. **Ana S. de la Rosa Herencia.**

Ve. 09:30 – 09:45 Deciphering the mechanisms of somatostatin analogue resistance in pheochromocytomas and paragangliomas. **Víctor García Vioque.**

09:45 – 10:30 – Coffee Break (IMIBIC Cafeteria)

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

Chairs: **Dr. María Soledad Avendaño, Dr. Mario Frías & Dr. Iván Arias**

PSII.a. Dialysis modalities, uraemic toxins and microinflammation, can we do any more?. **Raquel Ojeda López.**

PSII.b. Effects of GLP-1 therapy on male gonadal function in conditions of diabesity: therapeutic implications for diabesity-induced hypogonadism. **Víctor Manuel Serrano López.**

PSII.c. Intratumoral BromAc effects in unresectable Pseudomyxoma peritonei: a single arm phase I/IIA study. **Lidia Rodríguez Ortiz.**

PSII.d. Adults over 40 years diagnosed with one or more chronic pathologies who go to a pharmacy to withdraw medication. **María José Reyes Medina.**

PSII.e. In chronic kidney disease, iron deficiency-induced anemia is associated with higher levels of FGF23 that are not reduced by iron administration. **Karen Valdés Díaz.**

PSII.f. Complete vs. Incomplete percutaneous revascularization in patients with chronic total occlusions. **Lucas Barreiro Mesa.**

PSII.g. Active Rheumatoid Arthritis patients undergo profound alterations in lipid metabolism, which can be successfully reversed through the administration of anti-TNF, anti-IL6R, and JAK inhibitors. **Laura Muñoz Barrera.**

PSII.h. The utilization of high-throughput technologies for molecular profiling in Rheumatoid Arthritis enables the identification of patient subgroups with distinctive disease activity and therapeutic response. **Ismael Sánchez Pareja.**

PSII.i. Molecular and serological survey of rat Hepatitis E virus (Rocahepevirus ratti) in people living with HIV in Spain. **María Casares Jiménez.**

PSII.j. Influence of donor type (donation after brain death vs. donation after cardiac death) on lung transplant outcomes. **Benito Cantador Huertos.**

PSII.k. Functional profile of extracellular vesicles from Salmonella-infected intestinal cells and their ability to elicit immune activation on adjacent cells. **José Manuel Suárez Cárdenas.**

PSII.l. SMG7 as a potential new biomarker in chronic liver disease associated with obesity. **Betsaida Ojeda Pérez.**

PSII.m. Cardiovascular health assessment in vulnerable families from E-ducass program. **Esther Porras Pérez.**

PSII.n. Expression profile of miRNAs involved in aging-related processes in middle-age and older patients with cardiovascular disease: From CORDIOPREV study. **Maite Sánchez Giraldo.**

PSII.o. Identification of biomarkers of visceral adipose tissue weight gain. **Olga García Ruiz.**

PSII.p. DNA damage and repair in glioblastoma cells. **Ariadna Muñoz Fernández.**

PSII.q. A comprehensive bioinformatic approach for splicing analysis and biomarker identification in different cancer subtypes. **Jesús Miguel Pérez Gómez.**

PSII.r. Psychosocial factors on perceived well-being in children and adolescents with type 1 diabetes: a cross-sectional study. **Joaquín Villaécija Rodríguez.**

PSII.s. Application of threshold concepts to teaching in the degree of Medicine. **María José Gálvez Medina.**

PSII.t. Study of lipoprotein subfractions profile in peripheral arterial disease and diabetes: From the CORDIOPREV Study. **María del Pilar Coronado Carvajal.**

PSII.u. Screening of miRNAs targeting the Prader-Willi-related gene Magel2 in the hypothalamus of female rats with obesity-induced precocious puberty. **Álvaro Aranda Torrecillas.**

PSII.v. miR-103/107 as central metabolic regulator of puberty. **Yolanda Guerrero Ruiz.**

PSII.w. Impact of insulin resistance in presence or absence of chronic inflammation in adipose tissue fibrosis. **María González Ruiz.**

PSII.x. Effect of sitagliptin on skin wound healing in D-vitamin deficient diabetic rats. **Victoria Pulido Escribano.**

PSII.y. Effect of calcifediol on skin wound healing in obese and diabetic rats. **Bárbara Torrecillas Baena.**

PSII.z. Metabolic and molecular benefits of two healthy dietary approaches (mediterranean vs. Low fat diet) on the reversion of obesity and diabetes in mice. **Andrea Martínez Vara.**

PSII.aa. A new proteomic workflow to evaluate the presence of microbiome in appendiceal mucinous adenocarcinoma. **Florina Iulia Bura.**

PSII.bb. Relationship between stress and anxiety in healthcare professionals in Primary care during the Covid-19 pandemic. **María Valeriano Sánchez.**

PSII.cc. Aerobic exercise as a pain reliever in fibromyalgia patients. **David Casanova Rodríguez.**

PSII.dd. Impact of calorie restriction and bariatric surgery in human skeletal muscle mitochondria: exploring the effects of two different weight loss protocols through a systematic review with meta-analysis. **Miguel Pérez Rodríguez.**

PSII.ee. Co-sensitization study between Ole e 7 and Pru p 3 nsLTPs. **Paula Álvarez Romero.**

PSII.ff. Relation of the fibrotic process and clinical severity of the mammary periprosthetic capsular contracture. **Juan Cámara Pérez.**

PSII.gg. Mindfulness-based Interventions in Young Population with Type 1 Diabetes Mellitus: A Systematic Review. **Tamara Gutiérrez Domingo.**

PSII.hh. Design and evaluation of the effectiveness of a digital health platform for monitoring the clinical status of home oxygen patients. Randomized clinical trial. **Anisbed Naranjo Rojas.**

PSII.ii. Dyslipidemia and pathological cognitive impairment in people over 65. **María Morales Cabanillas.**

PSII.jj. Analysis of mandatory Mental Health questionnaires in crew members and air traffic controllers. **Juan Manuel Millán López.**

PSII.kk. Pathophysiological relevance of molecular machineries controlling RNA metabolism (Nonsense-mediated decay and RNA-exosome) in craniopharyngiomas. **José Hernández Hernández.**

PSII.ll. Role of DYRK2 as a novel regulator of MEK1 in the MAPK/ERK1/2 signaling pathway. **Alejandra Serrano Yubero.**

11:30 – 12:45 – Session VI. Infectious and immunological diseases (IMIBIC Assembly Hall)

Chairs: **Dr. Ignacio Gómez García & Dr. Antonio Romero**

VIa. 11:30 – 11:45 SARS-CoV-2 accessory proteins induce mitochondrial dysfunction and impair cellular metabolism. **Raúl Fernández Rodríguez.**

VIb. 11:45 – 12:00 Clinical factors and the role of bacterial load in long-term eradication of intestinal colonization by KPC-producing Klebsiella pneumoniae in an endemic nosocomial setting: results from a prospective observational study (KLEBCOM). **Alejandra Méndez Natera.**

VIc. 12:00 – 12:15 Prevalence and Factors Associated with Multimorbidity in Patients with Rheumatoid Arthritis. Data from the Cordobesian Rheumatoid Arthritis Registry. **Santiago Dans Caballero.**

VId. 12:15 – 12:30 Early postoperative complications of lung transplantation. Patricia **Victoria Childers Canduela.**

VIe. 12:30 – 12:45 Genomic epidemiology study of hospital-acquired, community-acquired and healthcare-related KPC-producing Klebsiella pneumoniae infections at Reina Sofia University Hospital reveals clonal dissemination of ST512/KPC-3 high-risk clone over a 10-year period (KLEBMAN study). **Víctor Gálvez Soto.**

13:00 – 14:00 – Plenary Lecture: Towards tailored antitumor T-cell therapies. Dr. Alena Gros Vidal (Vall d'Hebron Research Institute)

14:00 – 14:30 – Awards and Closing ceremony

Description of the review process for selecting oral/poster presentations

Authors submitted their works through the Young Investigators abstract submission website from June 5th to June 23th. 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 108 abstracts were received. The Organizing Committee distributed all abstracts received amongst 33 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 Organization Committee has not evaluated or scored any of the submitted abstracts.

On September 29th, 2023, 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, two sessions for Multidisciplinary, one season for Nutrition, Endocrine and metabolic diseases and one for Infectious and immunological diseases session.

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 4 researchers (1 clinical and 3 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, three chairs will visit the 10 highest scored abstracts according to the

external reviewers. 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. Metabolic shift underlies tumor progression and immune evasion in S-nitrosoglutathione reductase-deficient cancer.

Authors: Ana Mantrana1,2, Rafael Mena-Osuna1, Silvia Guil-Luna1,2,3, María Teresa Sánchez-Montero1, Carmen Navarrete-Sirvent1, Teresa Morales-Ruiz1,4, Aurora Rivas-Crespo1, Marta Toledano-Fonseca1,2, María Victoria García-Ortiz1, Gema García-Jurado1, María Auxiliadora Gómez-España3,5, Rafael González-Fernández1,6, Carlos Villar7, Francisco Javier Medina-Fernández8, José Manuel Villalba9, Enrique Aranda1,2,3,5, Antonio Rodríguez-Ariza1,2,5.
Affiliations: 1. Maimonides Biomedical Research Institute of Córdoba (IMIBIC), Córdoba, Spain. 2. Cancer Network Biomedical Research Centre (CIBERONC), Madrid, Spain. 3. Department of Medicine, Faculty of Medicine, University of Córdoba, Córdoba, Spain 4. Department of Genetics, University of Córdoba, Córdoba, Spain 5. Medical Oncology Department, Reina Sofía University Hospital, Córdoba, Spain. 6. Immunology Department, Reina Sofia University Hospital, Cordoba, Spain. 7. Pathological Anatomy Department, Reina Sofía University Hospital, Córdoba, Spain. 8. General and Digestive Surgery Department, Reina Sofía University Hospital, Córdoba, Spain. 9 .Cell Biology, Immunology and Physiology Department, University of Córdoba, Córdoba, Campus of International Agrifood Excellence ceiA3, Spain.
Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Colorectal cancer, GSNOR, immune evasion, immunotherapy, metabolism, nitric oxide.

Abstract: S-nitrosoglutathione reductase (GSNOR) is a denitrosylase enzyme which has been suggested to play a tumor suppressor role, although the mechanisms responsible are still largely unclear. In this study, we show that GSNOR deficiency in tumors is associated with poor prognostic histopathological features and poor survival in patients with colorectal cancer (CRC). GSNOR-low tumors were characterized by an immunosuppressive microenvironment with exclusion of cytotoxic CD8+ T cells. Notably, GSNOR-low tumors exhibited an immune evasive proteomic signature along with an altered energy metabolism characterized by impaired oxidative phosphorylation (OXPHOS) and energetic dependence on glycolytic activity. CRISPR-Cas9–mediated generation of GSNOR gene knockout (KO) CRC cells confirmed in vitro and in vivo that GSNOR-deficiency conferred higher tumorigenic and tumor-initiating capacities. Moreover, GSNOR-KO cells possessed enhanced immune evasive properties and resistance to immunotherapy, as revealed following xenografting them into humanized mouse models. Importantly, GSNOR-KO cells were characterized by a metabolic shift from OXPHOS to glycolysis to produce energy, as indicated by increased lactate secretion, higher sensitivity to 2-deoxyglucose (2DG) and a fragmented mitochondrial network. Real-time metabolic analysis revealed that GSNOR-KO cells operated close to their maximal glycolytic rate, as a compensation for lower OXPHOS levels, explaining their higher sensitivity to 2DG. Remarkably, this higher susceptibility to glycolysis inhibition with 2DG was validated in patient derived xenografts and organoids from clinical GSNOR-low tumors. In conclusion, our data support that metabolic reprogramming induced by GSNOR deficiency is an important mechanism for tumor progression and immune evasion in CRC and that the metabolic vulnerabilities associated with the deficiency of this denitrosylase can be exploited therapeutically.

Fundings: PID2019-105256RB-I00, P20-00967.

Ib. Targeting glycogen synthase kinase 3 as an effective therapeutic strategy against tumor budding and immune evasion in human colorectal cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: GSK-3, tumor budding, colorectal cancer, immune checkpoint, PDXs.

Abstract: Glycogen synthase kinase 3 (GSK-3) has been proposed as a novel cancer target due to its regulation of both tumor and immune cells. On the other hand, mechanisms of immunoevasion in the tumor microenvironment have been linked with the process of tumor budding (TB), which enables cancer cells to escape the primary tumor site, invade surrounding tissues, and establish metastatic lesions. However, the connection between GSK-3 and immunoevasive contexture, including TB and the expression of immune checkpoint proteins, has not been previously examined. In this study, we explored GSK-3 expression and its potential correlation with the TB grade and the immune checkpoint proteins PD-L1 and PD-1 in tumor samples from 208 colorectal cancer (CRC) patients. Additionally, we analyzed the efficacy of anti-PD1 and GSK-3 inhibition therapies in humanized patient-derived xenograft models (PDXs). Our results showed that high-grade TB was associated with higher expression of GSK-3, PD-L1 and PD-1 in CRC tumors. Moreover, we demonstrated an improved risk stratification of CRC patients by combining GSK-3 and PD-L1 expression with TB grade. Of note, contrary to anti-PD1 treatment, GSK-3 inhibition promoted an effective antitumor response by reducing tumor buds, augmenting necrosis, and increasing activated tumor-infiltrating CD8+ T cells, NK cells, and CD4- CD8- T cells. Altogether, our study demonstrates that the combination of GSK-3 expression with TB grade may greatly improve risk stratification of CRC patients. Moreover, our findings strongly support GSK-3 inhibition as an effective therapy against TB and immunoevasion in CRC.

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Ic. B-RAF oncogene regulation by dual-specificity tyrosine-regulated kinase 2.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: B-RAF, DYRK2, Phosphorylation, Regulation, MAPK/ERK pathway, Cancer.

Abstract: The MAPK/ERK cell signaling pathway is the core of the signaling network which regulates several fundamental cellular processes such as cell growth, division and differentiation. Given its crucial role in cell biology, its aberrant activation due to mutations of its components is associated to the development of many cancer types. One of the components of MAPK/ERK pathway with one of the highest mutation frequencies in cancer is B-RAF. Serine/threonine protein kinase B-RAF is considered one of the most relevant cancer-driver gene with oncogenic function. As a consequence, different B-RAF inhibitors have been developed. However, the efficacy of all of them is limited by the appearance of resistances after several months of treatment.

In this work, we describe for the first time a completely new regulation mechanism of B-RAF mediated by DYRK2 kinase. First, we show that DYRK2 presents the ability to stabilize B-RAF levels through a kinase activity-dependent post-transcriptional mechanism. We demonstrate that both proteins co-localize in the cytoplasm and DYRK2 directly phosphorylates B-RAF on at least 5 residues, being the phosphorylation at Ser-729 residue required in its stabilization. This DYRK2-dependent B-RAF stabilization is dependent of an increase in B-RAF homodimerization and B-RAF-C-RAF heterodimerization. Furthermore, we demonstrate that this new regulatory mechanism has direct functional consequences on the downstream activation of the MAPK/ERK pathway. Finally, functional assays show that DYRK2 inhibition further decreases cell viability in response to Dabrafenib of different colorectal and breast cancer cell lines, which indicates that the combined B-RAF and DYRK2 inhibition may lead to a new therapeutic strategy in the treatment of certain tumor types. In summary, we demonstrate for the first time a new regulatory mechanism with clear functional consequences of B-RAF, one of the most relevant cancer-driver gene.

Id. The splicing machinery represents a targetable vulnerability in bladder cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: bladder cancer, splicing, NOVA1, therapeutic target, biomarker.

Abstract: Bladder cancer (BLCA) is the most common tumor pathology of the urinary tract which holds a high intrinsic tumor heterogeneity that limits the available therapeutic options. Therefore, it is crucial to identify therapeutic alternatives for this tumor pathology. In this sense, alternative splicing has emerged as a common hallmark of different cancer types, acting as a key regulator of tumor plasticity and as a source of diagnostic/prognostic biomarkers and therapeutic targets. Indeed, some studies have demonstrated the discrete alteration of certain spliceosome components (SCs) and splicing factors (SFs) in BLCA. However, the putative general dysregulation of the splicing machinery in this cancer remains unknown. Therefore, we aimed to evaluate the potential dysregulation and pathophysiological implication of the splicing machinery in this tumor pathology. To that end, we explored the levels of 105 splicing machinery components (SCs and SFs) in six independent cohorts of human samples. Furthermore, we carried out functional (e.g., proliferation, colonies/tumorsphere formation, apoptosis) and molecular (e.g., qPCR, Western-Blot) analyses in response to: i) the modulation of selected key factors (e.g., NOVA1), and ii) the pharmacological inhibition of the spliceosome using different non-tumor and BLCA cell-models (i.e., primary cell-cultures and cell-lines). Our results revealed a robust dysregulation of the splicing machinery in BLCA samples compared to non-tumor samples. Additionally, the levels of some of these elements (e.g., NOVA1) were associated with clinical and molecular parameters of tumor aggressiveness (e.g., recurrence, T-stage). Finally, the genetic modulation (overexpression/silencing) of selected factors, and the pharmacological inhibition of the spliceosome (using pladineolide-B) impaired tumor aggressiveness in vitro by altering key signaling pathways in BLCA (e.g., MYC). Altogether, our results demonstrated a profound dysregulation of the splicing machinery in BLCA samples that might be associated with tumor development/aggressiveness. Moreover, the pharmacological inhibition of the spliceosome might represent a novel therapeutic avenue for BLCA patients.

Ie. Memory Universal CAR T cells: A new strategy against B-cell malignancies.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: CAR-T cells.

Abstract: Over the years, manipulation of the immune system has become a promising therapeutical approach. In particular, chimeric antigen receptor expressing T cells (CAR T cells) represent a breakthrough for cancer treatment, having already proved efficacy in B cell malignancies. Current CAR T cell products are based on autologous T cells, which increases the cost and reduces the efficacy of the therapy. Additionally, some of the adversities of this therapy are related with the phenotype of the infused cells.

To improve these aspects, we have generated universal antiCD19 CAR T cells with a defined memory phenotype. By elimination of B2M and TRAC genes in CAR T cells we expect to avoid both graft versus host and host versus graft reactions in the patient, and we have also selected the less differentiated T cells (CD45RA+/CD45RO-) to obtain more stable and persistent universal CAR T cells. Safety analyses were also carried on in order to prove security of our editing strategy.

Our in vitro data demonstrate that we are able to generate functional universal CAR T cells. The elimination of TCR and HLA-I from the surface of CAR T cells reduces the bidirectional allogeneic response between cells from different donors, and this edition persists in time, and does not affect neither phenotype of cells nor CAR expression. Universal CAR T cells with a memory phenotype proved to be equally lytic as regular CAR carrying cells.

SESSION II.

MULTIDISCIPLINARY I.

IIa. Circadian rhythm disruption in cardiovascular and trauma severe patients admitted to ICU: Influence of environmental conditions.

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Scientific Program: Active aging and frailty.
Keywords: circadian desynchronization, clock genes, critical care, intensive care unit, melatonin.

Abstract: Patients admitted to the Intensive Care Units (ICU) are exposed to environmental conditions that can affect their patients' sleep-wake patterns and overall well-being. However, there was a lack of knowledge regarding the levels of melatonin and the expression of clock genes in these patients. Thus, the project aimed to prospectively analyze circadian chronodisruption and associated elements in cardiovascular and trauma-severe patients admitted to ICUs.

The study collected information on environmental conditions (sound and light levels), urinary melatonin levels, and clock gene expression in peripheral blood mononuclear cells (PBMC). Urine samples were collected every 2h, and blood samples were drawn every 5h over a period of 48 hours. Clock gene expression was measured using RNA extraction from PBMC and subsequent rtPCR and qPCR techniques. Melatonin levels were measured using the ELISA technique.

The study found statistically significant differences in the expression of the PER2, CRY2, and RORA genes between different time points within each day, in both groups of patients. Patients with cardiac pathology also exhibited differences in the CLOCK and BMAL1 genes. Melatonin levels showed a potential pattern difference between day 1 and day 2, but due to sample variability, statistical significance could not be obtained except when comparing samples taken at 20:00 hours in the group of cardiac patients.

Significant differences were observed in sound levels, light levels, and physiological values. Higher luminosity and sound levels were associated with elevated mean values in physiological variables such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and respiratory frequency (RF) compared to periods with lower sound and light levels. The study suggests that environmental conditions, particularly light and noise in the ICU, could impact circadian disruption in polytrauma patients, which in turn could influence their clinical status.

IIb. VCE-004.8, a novel PP2A/B55α activator, promoted angiogenesis and arteriogenesis in critical limb ischemia.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Peripheral arterial disease, angiogenesis, vascularization, arteriogenesis.

Abstract: Peripheral arterial diseases (PAD) affect more than 200 million people around the world. PAD is usually caused by atherosclerotic obstructions in the large arteries of the leg(s), beginning with vessel occlusion and severe hypoxia, then failing spontaneous revascularization and ending with tissue necrosis that can lead to amputation. Nowadays, experimental vasculogenic therapies with exogenous growth factors and gene therapy have failed in clinical trials. Thus, the development of novel vasculogenic therapies based on hypoxia preconditioning and induction of angiogenesis are needed. We have recently shown that VCE-004.8 is a promising cannabidiol aminoquinone derivative that activates PP2A/B55/HIF pathway, and it is also a dual agonist of PPARα and CB2 receptors.

Herein, we further explored the mechanism of action of VCE-004.8 and evaluated its ability to promote neovascularization and angiogenesis in vitro and in vivo. VCE-004.8 activates HIF through a mechanism that target the protein phosphatase B55α/PP2A, and also targets AMPK and Sirtuin 1 upstream pathways. VCE-004.8 protects vascular endothelial cells against proinflammatory and prooxidant damages and prevents endothelial senescence. In aorta ring assay, sprouting was observed after treatment with VCE-004.8. Matrigel plug assay was used to assess the angiogenic potential of VCE-004.8 in vivo and after 10 days of oral treatment, the formation of functional vessels (CD31+/Ki67+) was identified. Critical limb ischemia mice model was induced by double ligation in the femoral arteria. After 10 and 28 days of oral administration of VCE-004.8, semimembranosus and gastrocnemius muscles were harvested for histological and genes expression studies. VCE-004.8 increases capillary density, enhances endothelial cells proliferation and induces angiogenic gene expression in the affected leg but not in the contralateral leg. In addition, VCE-004.8 improves collateral vessel formation (arteriogenesis) analyzed by microvascular casting assay and micro-CT analysis. Biomarker detection was performed in plasma using proximity extension assay and by laser capture microdissection followed by protein identification by mass spectrophotometry. In Phase IIa clinical trial for Systemic Sclerosis (clinicaltrial.gov: NCT03745001) oral VCE-004.8 has meet the primary endpoints of safety and tolerability, and therefore, a design of a phase II clinical trial for PAD in underway.

IIc. Worsening of Heart Failure with Reduced Ejection Fraction: Impact of the number of previous hospital admissions.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Worsening of heart failure; HFrEF.

Abstract:

Introduction and objectives: Worsening Heart Failure (WFH) includes HF hospitalisation, representing a strong predictor of mortality in patients with Heart Failure with Reduced Eyection Fraction (HFrEF). However, there is little evidence analysing the impact of the number of previous HF admissions. Our main objective was to analyse the clinical profile according to the number of previous admissions for HF and its prognostic impact in the medium and long-term. **Methods:** Retrospective study of a cohort of patients with HFrEF classified according to previous admissions: Group 1 (0-1 previous admission) and Group 2 (≥2 previous admissions). Clinical, echocardiographic and therapeutic variables were analysed, and the medium and long-term impact in terms of hospital readmissions and cardiovascular mortality was assessed. **Results:** A total of 406 patients were analysed. The mean age was 67.3 ± 12.6 years, with male predominance (73.9%). The 88.9% (361 patients) were included in Group 1 and 45 patients (11.1%) in Group 2. Group 2 had a higher proportion of atrial fibrillation (49.9% vs 73.3%;p=0.003), chronic kidney disease (36.3% vs 82.2%; p<0.001) and anaemia (28.8% vs 53.3%;p=0.001). Despite having similar baseline ventricular structural parameters, Group 1 showed better reverse remodelling. Both at baseline and at the end of follow-up, there was a higher proportion of diuretic and ICD-CRT in Group 2, with no difference in drug treatment with prognostic benefit. With a median follow-up of 60 months, Group 1 had longer survival free of hospital readmissions for HF (37.5% vs 92%; p<0.001) and cardiovascular mortality (26.2% vs 71.9%; p<0.001), with differences from the first months. **Conclusion:** Patients with HFrEF and ≥2 previous admissions for HF have a higher proportion of comorbidities. These patients are associated with worse reverse remodelling and worse medium and long-term prognosis from early stages, where early identification is essential for close follow-up and optimal intensive treatment.

IId. VCE-009.1, A NOVEL FORMULATION OF NATURAL PRODUCTS WITH POSITIVE ALLOSTERIC MODULATORS FOR CB1R.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: CB1R, Positive allosteric modulators, Analgesia, Inflammation, Plant extracts.

Abstract: Cannabinoid receptor type I (CB1R) as part of the endocannabinoid system plays a critical role in numerous physiological and pathological conditions. Thus, considerable efforts have been made to develop ligands for CB1R. Orthosteric ligands of CB1R including ?9-tetrahydrocannabinol, the psychotropic compound of Cannabis sativa, show some biomedical benefits, however the side effects greatly limit its clinical implementation. Thus, allosteric modulators without psychoactive activity have arisen as an alternative and more secure way of modulating CB1R.

Since natural products have the potential to modulate cannabinoid receptors, a large collection of plant spices was screened on CB1R and other molecular targets. Among the whole collection, several plant extracts showed a high selective activity as positive allosteric modulators (PAMs) for CB1R enhancing cAMP levels in CB1-CRE-Luc cells, while most of them did not show CB1R orthosteric activity. Using SwissDock docking tool, several components inside each plant extract were selected to assay their CB1R PAM activity, finally identifying trans-anethol and eugenol, two compounds with proven analgesic activity, as the main compounds with CB1R PAM activity. Next, we developed VCE-009.1, a formulation containing three different plants extracts, for further preclinical studies in vitro and in vivo, and by oral and topical delivery. In addition to CB1R PAM activity, VCE-009.1 also showed antioxidant activity by reducing reactive oxygen species and inducing HMOX-1 expression, anti-inflammatory and analgesic activities by activating CB2R and inhibiting TRPV1 receptors.

The development of CB1R allosteric modulators has become an area of immense importance within the cannabinoid field with potential for the treatment of different types of pain, inflammation, neurological disorders and metabolic diseases where other avenues, such as agonists and antagonists, have been unsuccessful or have produced critical side effects.

POSTER SESSION I.

PSI.a. Vaccination against SARS-CoV-2 induces FOXP3+HELIOS+ regulatory T cells in severe COVID-19 patients.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Viral infection, inflammatory disease, immunosenescence.

Abstract:

AIMS: COVID-19, caused by SARS-CoV-2, presents symptoms from mild to severe. An acute reduction of peripheral lymphocytes has been associated with the disease severity. Specifically, studies show that lower levels of regulatory T cells (Tregs), a CD4+ T-cell subset, may be related to the cytokine storm observed in severe patients. However, high levels of Tregs are also associated with over-immunosuppression and poor prognosis. In this context, there is little information about the influence of COVID-19 vaccine on the Tregs-balance. Given that vaccines are known to induce the increment of specific Tregs, we aim to study the frequency of Tregs and Tregs-associated markers in COVID-19 severe patients stratified by vaccination status. **METHODS:** We analyzed, by flow cytometry, the expression of FOXP3, HELIOS and Ki-67 transcription factors within the Tregs cells (CD3+CD4+CD127low) in peripheral blood of hospitalized SARS-CoV-2 infected patients, unvaccinated (57-73 years) and vaccinated (54-60 years), sex/age-matched with healthy donors (HD). **RESULTS:** As expected, a decreased percentage of lymphocytes was observed in severe patients compared to HD ($p<0.0001$ unvaccinated, $p<0.001$ vaccinated). In addition, a reduction in Tregs was observed in hospitalized individuals ($p<0.01$). However, an increased proportion of FOXP3+HELIOS+ Tregs cells ($p<0.001$) was observed only in vaccinated hospitalized patients compared to HD. Ki-97+ Tregs cells proportion increased ($p<0.001$) in both severe groups. **CONCLUSIONS:** Despite the lower levels of general Tregs, the increment of FOXP3+ and Ki-67+ within the Tregs cells suggest a proliferation of SARS-CoV-2 specific Tregs that is happening during the infection. Given that HELIOS indicates high stability of Tregs, the increment of FOXP3+HELIOS+ Tregs also indicates that these proliferative cells are specific clones induced after COVID-19 vaccination, instead of polyclonal CD4+T cell-derived Tregs. These results suggest that the COVID-19 vaccine in severe patients could enhance the Tregs balance during the infection process inducing the expansion of SARS-CoV-2 specific Tregs.

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from Carlos III Spanish National Institute of Health, Spain Government and European Union (to Alexander Batista-Duharte).

PSI.b. Enumeration and Characterization of Circulating Tumor Cells in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Hepatocellular carcinoma, transarterial chemoembolization, circulating tumor cells, liquid biopsy.

Abstract:

Background. Circulating tumor cells (CTCs) and particularly circulating cancer stem cells (cCSCs) are prognostic cancer biomarkers and can be detected by liquid biopsies. The ex-vivo culture of cCSCs could provide useful information about biological aggressiveness of the tumor and allow monitoring adaptive changes acquired by the tumor in real time. In this study, we evaluated the prognostic impact of CTC enumeration on the response of hepatocellular carcinoma (HCC) patients to transarterial chemoembolization (TACE). Additionally, we described different approaches for the isolation and culture of cCSCs. **Methods.** This prospective study included 37 HCC patients, from 2019 to 2022. The enumeration of EpCAM+ CTCs was performed in peripheral blood samples (7ml) by the IsoFlux® system. The radiological response to TACE was assessed by the mRECIST criteria at day 30. Different strategies were applied for the CTC isolation: (1) positive selection of EpCAM+ CTCs (IsoFlux® system) and (2) negative selection of CD45- cells (immunomagnetic separation). Isolated cells were cultured in ultra-low adherence, normoxia (21% O2) and/or hypoxia (1% O2), 37°C and 5% CO2. **Results.** All patients had detectable CTCs at baseline, and 20 patients (54.1%) showed CTC clusters in peripheral blood. The increases in total tumor diameter (p=0.006) and the absence of CTC clusters at baseline (p=0.049) were independent predictors of poor response to TACE. The ex-vivo culture of cCSCs was successfully achieved in five of thirty-three patients, mainly by negative enrichment of CD45- cells. Hypoxia was a stimulus for the growth of cells with stem-like phenotype. **Conclusions.** Patients with large HCC tumors and with no CTC clusters at baseline should not undergo TACE as first line therapy. Adjuvant systemic therapies could be tested in this patient subgroup. The culture of CTCs requires complex protocols that could include negative enrichment strategies. Future research should aim to increase the survival of CTC cultures.

PSI.c. BioHub, a Python-based bioinformatics framework for analysis of high-throughput microbial genome sequencing on high performance computing systems.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Klebsiella pneumoniae carbapenemase, bioinformatics, Python, HPC systems.

Abstract:

Background: Infections by multidrug-resistant bacteria can lead to significant morbidity and mortality. In the last decade, next-generation sequencing (NGS) has led to a paradigm shift in the clinical diagnosis of these infections and has inevitably increased the volume of high-throughput sequencing (HTS) data. The management and analysis of this data requires the use of new and improved bioinformatics tools. To meet this challenge, we have developed BioHub, a flexible Python-based bioinformatics framework for analysis of large microbial genomics datasets on high performance computing (HPC) systems. **Methods:** BioHub was developed as an open-source Python-based bioinformatics framework to facilitate management of files and processes related to bioinformatics analysis of HST data on HPC systems. This framework automatically performs sequence read processing, genome assembly, functional annotation, resistance and virulence gene characterisation, plasmid annotation, MLST and core-genome MLST profiling, phylogenetic analysis, single nucleotide variant (SNV) analysis and other bioinformatic processes,integrating a wide range of open-source tools. **Results:** We evaluated BioHub applying the workflow to a case study involving comparative genomics and phylogenetic analysis of a microbiological collection of 316 clinical isolates of Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae (KPC-KP) obtained from consecutive patients with evidence of extraintestinal infection at Reina Sofía University Hospital over a 10-year period (KLEBMAN study). The validation procedure was developed using 10 computational threads per isolate. Each isolate took 3.5 hours to complete the entire workflow, drastically reducing process and analysis time. **Conclusion:** The key feature of BioHub is the control, reproducibility and optimisation of processes for use in shared and distributed memory HPC systems. The framework is scalable and achieves high-performance, significantly reducing the execution time of high-throughput microbial genome sequencing case studies. This facilitates and accelerates the integration and implementation of complex microbial genomics workflows into routine clinical microbiology diagnosis and epidemiological surveillance.

PSI.d. The socioeconomic status of patients with radiographic axial spondyloarthritis and its association with the severity of the disease and permanent disability: A cluster analysis in REGISPONSER.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Spondyloarthritis, disability, work participation.

Abstract:

Objectives: The objective of this study was to identify clusters of patients according to their socioeconomic characteristics and to evaluate the associations between these clusters and the severity of the disease and permanent disability. **Methods:** This was a cross-sectional and multicentre study including Spanish patients with spondyloarthritis (SpA) according to the ESSG criteria. Patients considered by their treating rheumatologist as suffering from radiographic axSpA (r-axSpA) were included. A cluster analysis was conducted using information on sociodemographic (age, sex, race, marital status, education) and socioeconomic characteristics (employment, profession, housing conditions and social level). The clinical features, burden of the disease and permanent disability were compared between the different clusters using logistic regression adjustied for disease duration. **Results:** A total of 866 patients with r-axSpA were included. Two clusters were found according to the socioeconomic characteristics: Cluster 1 (n=476), with a predominantly low socioeconomic profile, and Cluster 2 (n=479), with a predominantly high socioeconomic profile. After adjusting for disease duration, patients from Cluster 1 showed a longer diagnosis delay (7.8 vs. 6.8 years), higher body mass index (27.6 vs. 25.9) and greater structural damage than those from Cluster 2 (BASRI total (5.7 vs. 4.6) and BASRI cervical (6.9 vs. 5.7)). The access to bDMARDs was similar for both groups. However, patients from Cluster 1 showed a higher prevalence of permanent disability than those from Cluster 2 after adjusting for disease duration and disease activity (30.8% vs. 13.2%, OR 2.58 (95%CI 1.76-3.83), p<0.001). **Conclusions:** This study suggests that the socioeconomic status of patients with r-axSpA may have implications in the severity of the disease and in permanent disability despite a similar use of bDMARDs.

PSI.e. Molecular Pathways Linked to Liver Complications in Psoriatic Arthritis: Impact of Methotrexate Cumulative Exposure and Novel anti-PDE-4 and anti-JAK Therapies.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Psoriatic arthritis; non-alcoholic fatty liver disease; hepatocyte dysfunction; methotrexate; anti-PDE-4; anti-JAK treatments.

Abstract:

Background: the prevalence of hepatic abnormalities in Psoriatic Arthritis (PsA) has gained attention due to the complex factors involved, including inflammation, metabolic complications, and potential hepatotoxicity of therapeutic interventions. **Objectives:** 1) to investigate the influence of PsA and cumulative doses of methotrexate on liver function through comprehensive in vivo and in vitro investigations; 2) to unravel the molecular mechanisms underlying hepatocyte dysfunction in a PsA context and 3) to identify the potential of methotrexate, anti-PDE-4 and anti-JAK treatments to restore hepatocyte functionality. **Methods:** a cross-sectional study analyzed 387 subjects, including 200 PsA patients, 87 patients with non-alcoholic fatty liver disease (NAFLD), and 100 healthy donors (HDs). Clinical and laboratory parameters, as well as liver disease risk indexes, were assessed. In vitro experiments using a hepatocyte cell line (HEPG2) treated with PsA serum alone or combined with methotrexate, anti-PDE4, or anti-JAKs were conducted. Inflammatory, fibrotic, and apoptotic pathways were explored using RT-PCR and Olink PEA technology (Inflammatory proteome, Cobiomic Bioscience). **Results:** In our cohort of PsA patients, there was an increased risk of liver disease linked to systemic inflammation and concurrent cardiometabolic comorbidities. Treatment with PsA serum on hepatocytes induced inflammatory, fibrotic, cell stress, and apoptotic processes, indicating potential liver injury in PsA. In vivo and in vitro studies showed that cumulative doses of methotrexate did not affect liver function. Interestingly, anti-PDE-4 and anti-JAK therapies restored hepatocyte dysfunction caused by PsA serum by reducing the inflammatory proteome profile. **Conclusions:** this study highlights the presence of altered hepatocyte function in PsA patients, attributed to inflammation and metabolic status. Cumulative Methotrexate administration did not influence negatively liver function. Encouragingly, our preclinical investigations demonstrated the therapeutic potential of anti-PDE-4 and anti-JAK treatments in reducing PsA-induced hepatocyte activation. These findings provide a foundation for further research into managing liver complications in patients with PsA.

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PSI.f. A possible link between RNA methylation and splicing in lung carcinoids.

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

Abstract: Lung carcinoids are slow-proliferating neuroendocrine neoplasms that show high heterogeneity and difficult clinical management. Despite valuable advances in their molecular characterization, some aspects remain still unknown. Recent studies have shown that alternative splicing is severely dysregulated in lung carcinoids and may be promoting tumoral features. However, the implication of other RNA processing mechanisms has been poorly explored in these tumors. An example is the regulation of RNA methylation (N6-methyladenosine or m6A), the most usual internal RNA modification, which is largely understudied in this pathology despite its relevance in RNA metabolism. We hypothesized that m6A processing machinery may be altered in lung carcinoids 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 carcinoid development and aggressiveness. To this end, we have carried out a pilot analysis on 16 atypical carcinoids, and, through biocomputational analyses, we have assessed the expression of 13 m6A regulators, exploring their putative associations with clinical features and splicing alterations. Remarkably, we observed a clear relationship between the expression levels of several m6A readers and patient survival, highlighting the relevance of these factors. Interestingly, we found a strong link between abnormal m6A-related gene expression and cellular functions and pathways associated with carcinoids tumorigenesis, development, and aggressiveness features. Among them, the more remarkable ones were related to key metabolic pathways, including cellular adhesion, ionic transport, and tumor-related features, such as proliferation, differentiation, and increased sensitivity to growth factors. Altogether, our preliminary results suggest that lung carcinoids also possess another level of RNA processing dysregulation involving m6A alteration, which would be linked to tumor development and aggressiveness and may be useful in the future to improve the clinical management of this disease.

PSI.g. Dysregulation of RNA-exosome machinery in hepatocellular carcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Hepatocellular carcinoma; RNA-Exosome; Gene silencing; Biomarker; Therapeutic target.

Abstract: Hepatocellular carcinoma (HCC) is the most common liver cancer, and its incidence is increasing in recent decades. HCC is characterized by its aggressive behavior, poor prognosis, and great capacity to develop metastasis. Previous studies have revealed a significant alteration of the mechanisms controlling RNA processing and metabolism in HCC. However, the implication of the RNA-Exosome machinery, which is crucial for RNA processing, degradation, and quality control, is still to be fully defined.

This work aims to elucidate the alteration of the RNA – Exosome components in HCC and its correlation with clinical parameter, in order to identify early biomarkers and new therapeutic opportunities. Therefore, we analyzed the mRNA and/or protein levels of n=26 RNA-exosome components in tumor and non-tumor tissue samples, in 9 different cohorts: two retrospective cohorts (n=94 and n=62 respectively), five in silico cohorts (Zhou, Roessler 2, Mas, Wurmbach and TGCA) and two cohorts that include patients with Non-Alcoholic Steatohepatitis (NASH) derived-HCC (Arendt and Pinyol). Additional bioinformatics approaches (MetaboAnalyst or GSEA enrichment analysis) were performed.

Our results revealed a heterogeneous pattern of dysregulation in gene and protein expression of the 26 RNA-Exosome components analyzed, with percentages of altered RNA-exosome elements ranging from 7,70% (one of our retrospective cohorts) to 76,72% (Zhou cohort). Remarkably, EXOSC4, EXOSC9, and EXOSC10 were the most consistently altered factors (up-regulated) in all HCC cohorts, whereas EXOSC8 and PABPN1 were the most dysregulated genes in NASH-derived HCC patients. Some of these alterations were associated with key clinical parameters and with the enrichment in oncogenic traits (such as DNA repair pathway), suggesting important clinical implications.

In conclusion, analysis of gene expression dysregulation patterns in RNA-exosome elements reveal a strong dysregulation in HCC samples, which were associated with clinical parameters and with the dysregulation of oncogenic pathways.

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PSI.h. bZIP in-frame CEBPA mutation impact assessment as a distinct prognostic entity in AML in 2434 patients.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: AML, prognosis, NGS, CEBPA, Overall Survival, co-mutation.

Abstract: In-frame bZIP mutations of the CEBPA gene have been defined as a new favorable prognostic and diagnostic entity for patients with Acute Myeloblastic Leukemia(AML). Using Next-Generation Sequencing(NGS), we evaluated CEBPA mutations(in-frame bZIP and other types) incidence and the impact they may have in AML patients, as well as to elucidate co-mutation patterns and their possible effect on patient prognosis.

We included 2434 AML patients studied in PLATAFO-LMA-PETHEMA, since October-2017. Genomic-DNA extracted from bone marrow(or peripheral blood) of each patient at the time of diagnosis was analyzed at reference hospitals. NGS was performed with commercial panels using IonTorrent or Illumina platforms, using MyeloidSolution panels(SOPHIAGenetics), or OncomineMyeloid Research Assay(Thermo Fisher Scientific). Statistical analysis was performed with R version-4.3.0(https://www.r-project.org/).

We reported 153 patients with CEBPA mutation(6.28%), 78 had mutation in bZIP-domain and 62 of them had in-frame mutation. We found that CEBPA-bZIP-inf patients showed significantly more frequent de-novo AML(P=0.017), presented normal karyotype in 70% of cases and they were significantly younger than those with CEBPA-other-mut and CEBPAwt(58.6 years vs. 67.2, P=0.008). Intensively treated CEBPA-bZIP-inf patients had a 4-year survival of 97.50%(92.8-100) significantly better than CEBPA-other-mut(80.6%(69.3-93.7),P=0.029) and CEBPAwt(67.48%(63.8-71.4),P=0.001). We identified significantly higher percentage of mutations in WT1, GATA2 y C-KIT in CEBPA-bZIP-inf patients compared to CEBPA-other-mut(17.7%vs.3,3%, 14.5%vs.4.4% and 8%vs.0%, respectively). CEBPA-other-mut patients harbored significantly higher mutation percentage in IDH2 and NPM1 than CEBPA-bZIP-inf(18.7%vs.6.4 and 29.7%vs.4.8%, respectively). We highlighted that TET2 mutations conferred significant worse outcomes to CEBPA-bZIP-inf and CEBPA-other-mut and co-mutation in ASXL1 gen negatively impact on OS in CEBPA-bZIP-inf patients.

In summary, CEBPA-bZIP-inf as a newly defined entity presents with low incidence and favorable OS, compared to CEBPA-other-mut, is restricted to intensively treated patients. The narrow definition of in-frame may not be clinically relevant and all bZIP mutations could be included in the entity. Presence of co-mutations in TET2 and other chromosome/DNA modifier genes has a negative impact on OS.

PSI.i. Skin Microbiota Composition in Alopecia Areata: Associations with Disease Severity and Bacterial Ratio Imbalance.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: microbiotic skin; alopecia areata; SALT disease severity; inflammatory Response.

Abstract:

Background: The skin microbiome is a complex microbiological system with multiple interactions that can lead to both local and distant changes in homeostasis. **Objective:** This study aimed to investigate the relationship between skin microbiota composition and disease severity in patients with alopecia areata (AA). **Methods:** Swab samples were collected from lesional scalp areas of 20 treatmentnaïve AA patients (8 severe, 12 mild) and 4 healthy controls. The 16S rRNA gene was analyzed using an Ion Torrent S5 sequencer. Disease severity was classified as mild/moderate (<50% involvement and <1 year duration) or severe (≥1 year, ≥50% SALT, AT, or AU). Linear discriminant analysis (LDA) effect size scores were used to identify the bacterial taxa that best distinguished between the groups. **Results:** Alpha diversity did not differ among the samples. However, beta diversity (Jaccard) showed significant differences in mild AA ($p = 0.002$) and severe AA ($p = 0.005$) compared to controls. The healthy scalp was predominantly populated by four bacterial phyla: Actinobacteriota (56.1%), Firmicutes (27.2%), Bacteroidota (8.5%), and Proteobacteria (7%), representing a total of 18 different groups. There were noticeable shifts in dominance associated with AA severity, with a decrease in Actinobacteriota (56.1% control; 48.4% mild; 37.9% severe) and an increase in Proteobacteria (7% control; 6.1% mild; 17.4% severe) groups. Several bacterial species, including Brevibacillus, Anaeroplasma, Jeotgalicoccus, Asteroleplasma, Paraprevotella, Helicobacter, Turicibacter, Ruminococcaceae, Victivallis, and Thermicanus, showed significant differences ($LDA > 2$, $p < 0.05$) between control and AA groups. **Conclusions:** The quantity of scalp microbiota does not vary between healthy individuals and AA patients. However, changes in the relative abundance of bacteria are associated with disease severity, with a positive correlation between the proinflammatory (Proteobacteria) and anti-inflammatory (Actinobacteriota) bacteria ratio. Further research is needed to determine whether these changes are a cause or consequence of AA.

PSI.j. Developing a new diagnostic and prognostic method in Pseudomyxoma peritonei based on a mucin isoforms profile.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pseudomyxoma peritonei, cancer, molecular characterization, proteomic analysis, mucins.

Abstract: Pseudomyxoma peritonei (PMP) is a rare malignant disease characterized by progressive accumulation of mucin and secreting tumour cells within the abdomen and pelvis. As a result, patients suffer cachexia and malnutrition leading to a fatal ending. The diagnosis of PMP is challenging because it is a silent disease, and it must be confirmed by histological analysis, always after surgery. The current treatment option for this disease is based on complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). Unfortunately, a considerable percentage of patients suffer tumoral relapse without effective treatment.
In this context, molecular characterization is necessary to classify the tumour, improve the prognosis, and develop effective therapeutic strategies. However, there are no functional studies (based on proteins) on this rare disease, mainly due to the rarity and high concentration of glycoprotein (mucin), which protects the tumoral cells. In this sense, our research group has developed the first protocol to isolate the protein fraction and carry out high-throughput approaches. Recent bioinformatic analyses implemented with these data have revealed an isoform mucin fingerprint which could characterize the tumour. These mucin isoforms are MUC: 2, 4, 5AC, 5B, 6, 12, 13, 16, 17, 18, and 19. Our preliminary results show that the mucin profile is sadistically different between PMP subtypes and control. This work describes the first molecular method, not based on histology analysis, to detect and classify de tumour. We are improving and validating the predictive power of this new tool.

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PSI.k. Exploring the effects of lifestyle and reproductive factors on postpartum breast cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Postpartum breast cancer; pregnancy; prognosis; lactancy; reproductive factors.

Abstract: Postpartum breast cancer (PPBC) that occurs in young women up to 5 to 10 years´postpartum, is associated with an increased risk for metastasis and death compared with breast cancer diagnosed in young non-pregnant women. Although it is an increasing health concern, the impact of reproductive and lifestyle factors are poorly understood for this challenging entity. This study aimed to examine the association between lifestyle habits and reproductive factors on PPBC risk.

An observational, analytical, and retrospective study including 2039 women, aged under 45 years old and mothers, was carried out. Information on family history of cancer, lifestyle factors and reproductive factors were collected through an online questionnaire (https://.cancerdemamaposparto.es). Conditional logistic regression models were used to estimate 95% confidence intervals for categorical variables.

A total of 117 women were diagnosed as PPBC, 46 were non-PPBC and 1876 were healthy women (control group). In relation to lifestyle habits, alcohol consumption was significantly higher in PPBC women than in healthy women (71.1% vs 57.9%, p=0.024). In addition, the percentage of women with previous gynecological pathology was higher in those with PPBC compared to healthy women (35% vs. 25.7%, p=0.026) as well as in women with previous breast pathology (40.2% vs. 21.6%, p<0.001). Significant differences were also found in relation to breastfeeding. Thus, the mean breastfeeding duration in PPBC women was shorter (10.7 months) than in healthy women (13.57 months) (p=0.05). Interestingly, the percentage of women with PPBC who abruptly interrupted breastfeeding was significantly higher (30.4%) compared to healthy women (12.6%) (p<0.001).

The results of this study confirm the potential impact of reproductive factors and, in particular, the effect of breastfeeding for PPBC risk demonstrating the importance and the need of a larger, multicenter study from a more experimental perspective.

Fundings: PI22/00969.

PSI.I. Clinical and molecular patterns associated with persistence of inflammation in Spondyloarthritis Patients: unveiling potential biomarkers.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: spondyloarthritis, cardiovascular disease, persistent inflammation, biomarkers.

Abstract:

Background: Chronic inflammation present in diseases such as Spondyloarthritis (SpA) is closely associated with an increased risk of cardiovascular diseases (CVD). The aim of this study was to characterize SpA patients with persistent inflammation, to identify potential plasma protein biomarkers for easy identification, and to study its connection to CVD. **Methods:** Clinical and laboratory parameters, as well as CVD risk factors from 136 SpA patients, were recorded. A patient was classified as having persistent inflammation if increased CRP levels were detected in 100% of the measurements taken during the preceding 5-year timeframe. The plasma levels of 92 proteins related to CVD were analyzed using Olink PEA technology (Target 96 CVD III panel, Cobiomic Biosciences). **Results:** 36% of SpA patients had persistence of inflammation. These patients showed higher levels of disease activity (ASDAS), peripheral forms, structural damage (mSASSS), acute phase reactants, altered metabolic profile, and higher rates of cardiometabolic comorbidities compared to non-persistent SpA patients. 16 CVD-related plasma proteins were significantly associated with the presence of persistence of inflammation: MMP-9, RETN, PGLYRP-1, UPAR, PRTN-3, TR, RARRES-2, AZU-1, GP-6, TNF-R1, MPO, GDF-15, CCL-16, IL-2RA, PI3, and PDGF. Enrichment analysis showed that these proteins exhibit specific biological functions such as neutrophil degranulation, immune response, leukocyte migration, and apoptosis. The most contributing proteins to differentiate groups of SpA patients were MMP-9, RETN, PGLYRP-1, and UPAR. The combination of these proteins could predict the presence of constant persistent inflammation with an AUC=0.865. **Conclusions:** 1)persistent inflammation over five years was associated with peripheral forms, increased disease activity, and radiographical damage in SpA patients. 2)SpA patients with persistent inflammation display a pronounced alteration in their plasma CVD protein profile, indicating a connection between subclinical CVD risk and chronic inflammation. 3)novel biomarkers that have the potential to differentiate SpA patients with persistent inflammation have been identified, offering valuable insights for therapeutic approaches.

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PSI.m. Dysregulation of Circulating miRNAs and Implicated Pathways in Severe Forms of Alopecia Areata.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: alopecia areata; Circulating miRNAs; immune pathways; metabolic pathways; drug repositioning.

Abstract:

Background: Alopecia areata (AA) is the most common type of non-scarring inflammatory alopecia. **Objectives:** To determine which immune and metabolic pathways are dysregulated by circulating miRNAs in patients with alopecia areata (AA). **Methods:** Disease status was classified as mild/moderate (<50% involvement and <1 year duration) and severe (≥1 year, ≥50% SALT, AT, or AU). We interrogated 754 miRNAs in 26 treatment-naïve patients and 5 controls using OpenArray RT-PCR technology. Pathway enrichment analysis and drug repositioning were performed using GeneCodis and CMaps LINCS, respectively. **Results:** We identified 19 downregulated miRNAs in patients with severe AA compared to mild/moderate AA and controls, showing enrichment of pathways related to the immune system (antigen processing and presentation, cytokines, TCR regulation, Th1/Th2, IL-1, IL-4, IL-13), cell cycle, DNA damage repair, cellular stress response, and post-translational protein modification. Some of the specific overrepresented pathways were p53, GFR, NOTCH1, PIP3/AKT, FGFR1, and PDGFR. Finally, 39 drugs were predicted to potentially reverse this dysregulation state, with JAK kinase inhibitors being the most important group, followed by antioxidants, antimicrobials, and inhibitors of mTOR, FGFR1, VEGF, Raf, and endoplasmic reticulum stress response proteins. **Conclusions:** Prospective studies should be conducted to determine the value of these circulating miRNA expression profiles in severe forms of AA and their potential as prognostic markers in clinical practice.

PSI.n. Development of a food product with probiotic potential and its effect on parameters associated with glucose homeostasis in patients with type 2 diabetes mellitus at the Clinics Hospital of Paraguay.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Diabetes, intestinal dysbiosis, probiotics.

Abstract: Type 2 diabetes mellitus (T2DM) is one of the major health problems in the world, with high morbidity and mortality rates. Studies link metabolic diseases to intestinal dysbiosis, suggesting that certain bacterial strains could play a beneficial role on metabolic parameters. Our aim was to develop a food product containing strains with probiotic potential and to study the effect of its consumption on parameters associated with glucose homeostasis. Forty-six subjects with T2DM from the Endocrinology Department of the Hospital de Clínicas (Paraguay) were randomised into three intervention groups. The first group received 300 g/d of a fermented milk product containing a strain of the Bifidobacterium genus (PPY), developed exclusively for this study. The second group received 300 g/d of a conventional fermented dairy (CY), and the third group received none (NON). All three groups followed American Diabetes Association (ADA) nutritional recommendations for 12 weeks. Biochemical parameters related to lipid profile and glucose homeostasis were determined at baseline and after the follow-up period. Repeated measures and Pearson correlation analyses of the biochemical parameters included in the study were performed. The results showed a decrease in HbA1c levels of 13% in patients taking PPY compared to the NON group (p= 0.009). Furthermore, at baseline, a positive correlation between blood glucose and CRP (p=0.025, r2=0.576) and HbA1c and hs-CRP (p=0.003, r2= 0.707) was observed in patients who had consumed PPY. However, these correlations lost significance after the intervention period. Consumption of the product with probiotic potential could be used as a tool in clinical practice, as it could improve glucose homeostasis in patients with diagnosed T2DM.

PSI.o. EXPLORING THE RELATIONSHIP BETWEEN PHYSICAL FITNESS AND LIFESTYLE HABITS IN SEX-STRATIFIED PRESCHOOL CHILDREN: THE MELIPOP STUDY.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Physical activity, Mediterranean diet, physical condition, childhood.

Abstract:

Introduction: Obesity is a health issue that affects individuals from the early stages of life. It is widely recognized that physical activity (PA) and the Mediterranean diet (MD) play crucial roles in enhancing long-term health outcomes. However, the association between these habits and physical fitness as well as health outcomes among preschool children remains poorly understood. **Aim:** To assess the adherence to PA and the MD, and explore their relationship with physical fitness and metabolic markers in Spanish children aged 3 to 6, with a stratification by sex. **Methods:** A total of 172 children (84 girls; 92 boys) at risk of obesity were selected. Body composition was assessed using bioimpedance and anthropometric measurements conducted following the ISAK protocols. Physical (standing long jump and upper body isometric strength tests) and cardiometabolic (20-m shuttle run by Course-Navette test) fitness were assessed. Adherence to PA and the MD was evaluated using questionnaires for childhood population. **Results:** A low adherence to the MD was observed, although girls tended to have better dietary habits (High adherence to MD: 21.4% vs. 11.1%, P=0.064). No sex differences were found regarding adherence to PA (P=0.632). Both girls and boys displayed similar levels of PA, with approximately 40% engaging in an active lifestyle. There were no significant differences in fat-free mass index, although boys showed a tend to have higher values (P=0.079). Boys exhibited a higher strength in left-hand (P=0.018) and tend to jump longer (P=0.055), although the differences disappeared after adjusting for fat-free mass (P=0.475, P=0.086, respectively). No sex differences were observed in right-hand strength. Boys and girls demonstrated comparable levels of cardiometabolic fitness (P=0.501). Nevertheless, we observed that insulin and triglyceride levels are higher in girls and glucose and cholesterol levels are higher in boys. All analyses were adjusted

for age. Neither boys nor girls showed any correlation between levels of PA, adherence to the MD, and both physical fitness and metabolic markers. **Conclusions:** Our preliminary findings suggest that preschool children have a low adherence to healthy dietary habits, while exhibiting a higher level of PA. Metabolic status in early childhood may be influenced by sex differences.

PSI.p. Dysregulation in the machinery controlling the splicing process is associated with clinical features of tumor progression in papillary thyroid cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Thyroid cancer; Splicing, SF3B1.

Abstract: Different evidences indicate that the cellular machinery that controls the splicing process, named spliceosome, is altered in several tumors types, originating oncogenic splicing variants associated with characteristics of tumor progression and aggressiveness. However, to date, the alterations and implications of the spliceosome in papillary thyroid cancer (PTC) have not been studied in detail. Therefore, the main objective of the present work was to explore the dysregulation of the expression of spliceosome components and splicing factors in clinically well-characterized PTC samples compared to non-tumorous tissue and then, to analyze whether these possible alterations could be associated with relevant clinical parameters. Our results showed a clear dysregulation of several components of the splicing-machinery in PTC samples compared to its adjacent non-tumoral tissue, wherein the expression of specific components was associated with key clinical parameters such us body mass index, tumor size, etc. We next explored different functional (proliferation, migration, colonies and tumorospheres formation) and mechanistic (gene expression/signalling pathways) assays in human thyroid cancer cell models (TPC-1 and Cal-62) in response to the inhibition of the splicing machinery activity [using the splicing-factor-3B-subunit-1 (SF3B1; a core component of this machinery) inhibitor pladienolide B]. These in vitro studies revealed that pladienolide-B significantly decreased aggressiveness features in thyroid cancer cells. Likewise, the same methods were performed in response to SF3B1 silencing, obtaining similar results to those obtained with pladienolide-B administration. Taken together, our data demonstrate a drastic dysregulation of multiple components of the splicing machinery in PTC that could be associated with tumor progression, and that could be used as a source of diagnostic/prognostic biomarkers in PTC. In particular, the pharmacological inhibition of SF3B1 may represent a promising and novel therapeutic strategy worth to be explored through randomized controlled trials that could improves the outcome of patients affected by clinically aggressive thyroid cancer.

Fundings: Grupo Español de Tumores Neuroendocrinos/ Spanish Group of Neuroendocrine Tumors (GETNE G211).

PSI.q. Antiproliferative effects induced by an Aqueous Aged Black Garlic Extract on prostate and bladder cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: prostate, bladder cancer, aged black garlic, phytotherapy.

Abstract: Prostate (PCa) and bladder (BC) cancers are the most common genitourinary tumors and a major cause of cancer-related death in developed countries. The available therapies for these tumor pathologies are certainly limited, especially in their most aggressive phenotype, thus revealing the need of identifying novel therapeutic strategies. In this scenario, recent studies from our group have demonstrated a therapeutic benefit of phenolic bioactive compounds (e.g., hydroxytyrosol) in PCa, indicating a putative protective effect of nature-derived products in this tumor pathology. Therefore, in this study, an aqueous aged black garlic extract (ABGE) was tested based on its chemical composition and biological properties (anti-inflammatory, antioxidant, and cardioprotective effects). Specially, ABGE was obtained from fresh garlic fermented at high temperature and humidity for a certain period of time. The phytochemical analysis of ABGE by HPLC-DAD-MS revealed that this extract was rich in polyphenolic compounds, being gallic acid and catechin the prominent phytochemicals. Then, we investigated the putative beneficial effects of ABGE on PCa and BCa models by performing functional assays (e.g., proliferation, migration, tumorsphere- and colony-formation) on normal-like (e.g., PNT2, SV-HUC-1), PCa- (e.g., LNCaP, PC-3), and BCa-derived (e.g., SW780) cell lines at different stages of cancer progression. Our results indicated that ABGE was able to alter functional parameters of tumor aggressiveness in BCa-derived but, especially, in PCa-derived cell lines in a dose-dependent manner. Additionally, ABGE treatment also altered critical signaling pathways related with tumor development/progression (e.g., AKT, ERK, JNK). Therefore, our data suggest that ABGE might represent a natural source of antiproliferative compounds to treat PCa and BCa, most likely due to its bioactive contents such as phenolic acids. Moreover, ABGE might be exploited for different clinical applications as a diet-supplement for health promotion and disease prevention.

PSI.r. Integrative Meta-analysis Reveals Molecular Signatures and Therapeutic Implications in Alopecia Areata.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: alopecia areata; gene expression microarray; molecular signature; chemokines; keratins.

Abstract:

Aim: The objective of this study was to identify a molecular signature of scalp lesions in alopecia areata (AA) through meta-analysis of gene expression microarray datasets. **Materials and Methods:** We employed a meta-analytic approach to integrate the gene expression profiles from five independent datasets available in the Gene Expression Omnibus (GEO) database (GSE68801, GSE45512, GSE80342, GSE58573, GSE74761), involving 82 AA patients and 50 controls. Meta-analysis was conducted using a random-effects model, and enrichment analysis of biological pathways was performed using imaGEO and GeneCodis or GSEA. **Results:** We identified 1,366 differentially expressed genes (494 upregulated, 872 downregulated), with CXCL9, CCL18, CXCL10, CD8A, and GZMB being the most consistent across all studies (all FDR < 0.05). The transcriptome exhibited a high representation of chemokines (CCL13, CXCL9, CXCL10, CCL18, CCL13, CCR1, XCL1) and markers of cytotoxic T lymphocytes (GZMA, GZMB, GZMH, GZMK) and NK cells (NKG2A, NKG2D). We also found significant downregulated genes encoding the majority of type I keratins (KRT31-35, KRT38) and type II keratins (KRT81-86), as well as proteins associated with keratin and other proteins regulating the structural conformation (PADI3, GPRC5D, DSG4) or functionality (FGF18) of the hair follicle. Furthermore, we discovered previously unreported associations as molecular signatures of "contact dermatitis" with/without associated atopic dermatitis, "house dust mite hypersensitivity," and "delayed sensitivity" to black rubber, fragrances, and nickel (all p < 0.01). **Conclusions:** Our study presents an integrative transcriptome of AA scalp lesions derived from independent microarray-based gene expression studies. The use of chemokine-blocking agents may represent a promising therapeutic strategy for these patients.

PSI.s. The Role of Positivity in Psychological Distress and Quality of Life among Cardiovascular Disease Patients: A longitudinal study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Cardiovascular disease; positivity; psychological distress; health-related quality of life.

Abstract: Cardiovascular disease patients frequently exhibit heightened levels of psychological distress, leading to potential repercussions on a multitude of health-related outcomes, including lower adherence to treatment, poorer quality of life, and non-health-promoting behaviors. The increasing prevalence of chronic and cardiovascular diseases necessitates an adaptation and update of interventions proposed in cardiac rehabilitation and general clinical care, as they face new challenges. This requires a thorough exploration of the variables that can serve as a bulwark against psychological distress, enabling the acceptance of the disease, effective management, better adherence to treatment and an improved quality of life in those patients. Research indicates that a positive orientation has a beneficial effect on the health and well-being of these patients, but further investigation in this aspect is necessary. Therefore, the aim of this study was to evaluate the role of positivity in psychological distress (anxiety and depression) and quality of life among cardiovascular patients. A total of 593 cardiac patients (M = 64.75, SD = 9.07; 85.7% men) completed the Positivity Scale, the Hospital Anxiety and Depression Scale, and the Short Form-12 Health Survey at baseline and 9 months later (n = 323). Correlation coefficients and structural equation modeling were employed to explore the relationships between these variables both cross-sectionally and longitudinally. Positivity was found to have a negative correlation with anxiety and depression, and a positive correlation with health-related quality of life. In the path analysis, it was observed that positivity at baseline was negatively associated with anxiety and depression levels. Longitudinally, positivity yielded similar outcomes for psychological distress and showed a positive association with health-related quality of life. These findings suggest that emphasizing positivity may be crucial in reducing psychological distress among patients receiving cardiac care, supporting the necessity of psychological interventions for these patients, and highlighting the importance of considering psychological variables in cardiac rehabilitation programs.

PSI.t. Establishment of a desirable dose using neutral argon plasma to eradicate miliary peritoneal implants: a phase I/II controlled trial.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Peritoneal carcinomatosis, Cytoreductive surgery, Neutral argon plasma, Suggested doses.

Abstract:

Introduction: Neutral argon plasma (NAP) system could meet the requirements to achieve oncological cytoreduction of peritoneal carcinomatosis with miliary lesions, minimizing the associated morbidity. This phase I/II trial aims to establish the desirable dose that is safe and effective in eliminating tumor cells with lower penetration. **Methods:** Patients diagnosed with different origins for peritoneal carcinomatosis and miliary implants were selected for the study. The safe and potentially effective dose (desirability) of NAP was evaluated according to three factors: distance (mm), application time (s) and power (%), to evaluate the response variables such as the presence of tumor cells (Y/N) and the depth of penetration. **Results:** Ten patients and 120 samples were evaluated and treated with NAP. There was no vascular or organ injury intraoperative using a pre-established dose of 100% (coagulation mode) at a distance of 2-3 cm. The distance was found to be correlated with the presence of the tumor cells in ex-vivo analysis, with an OR of 15.4 (4.0-111.4). The time and energy used were protective factors to eliminate tumor cells with an OR of 0.4 (0.1-0.9) and 0.8 (0.8-0.9), respectively. The safest and most effective desirability results were as follows i) energy 80% during 2-4 seconds with a distance of 2 cm (0.89), and ii) energy 100% during 2-4 seconds with a distance of 3 cm (0.90). **Conclusions:** The use of NAP during a CRS and HIPEC is safe and effective for eradicating tumor cells on the peritoneal surface at suggested doses of energy, distance and duration.

PSI.u. Metabolic adaptations in skeletal muscle of transgenic mice that overexpress cytochrome b5 reductase-3 in male and female mice.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: CYB5R3, Mitochondria, Sexual dimorphism, Skeletal muscle.

Abstract: NADH-cytochrome b5 reductase-3 is a flavoprotein that oxidizes NADH to NAD+. Previous studies developed in our group have set the basis to consider NADH-cytochrome b5 reductase-3 (CYB5R3) as a new pro-longevity gene. CYB5R3 contributes to maintain respiratory metabolism, protects cells and tissues against oxidative stress, and prevents cellular senescence in male transgenic mice overexpressing this reductase (TG mice). However, no data are yet available about the outcome of CYB5R3 overexpression in female mice. The main objective of our work was to study the impact of sex on metabolic adaptations elicited by CYB5R3 overexpression, and on key markers related with mitochondrial function in skeletal muscle in comparison with their WT littermates. Studies were carried out in skeletal muscle from 3-mo old CYB5R3-TG and control mice (males and females) in a C57BL/6 background. CYB5R3 and the levels of key protein markers of the mitochondrial electron transport chain, mitochondrial fusion and fission, biogenesis and mitophagy, and SIRT3 and SIRT1 were measured by Western blot. NAD+ and NADH levels were measured by a bioluminescent assay. Metabolic rates were assessed in metabolic chambers. The rate of oxygen consumption by skeletal muscle mitochondria was measured following a Seahorse respirometry assay. Ultrastructural analysis was carried out by transmission electron microscopy. We show here that CYB5R3 is markedly overexpressed in skeletal muscle of TG mice regardless of sex. NAD+ and NADH levels exhibited sexual dimorphism and were modulated by CYB5R3 overexpression. While young TG mice did not exhibit adaptations in carbon metabolism, CYB5R3 overexpression upregulated markers consistent with enhanced mitochondrial biogenesis and function, and increased mitochondrial abundance in skeletal muscle, producing most of these potentially beneficial actions in females.

PSI.v. IMMUNOPATHOLOGY IN AORTIC STENOSIS DISEASE.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: aortic stenosis, immunopathology, cardiovascular disease, inflammation.

Abstract:

Aims: Aortic stenosis is a cardiovascular condition characterized by the narrowing of the aortic valve, which obstructs blood flow. While aortic stenosis has been primarily attributed to degenerative changes associated with aging, emerging research suggests that the immune system may also play a role in its development. The immune response triggered by chronic inflammation and autoimmune processes can contribute to the progressive calcification and fibrosis of the aortic valve, leading to stenosis. We have developed a novel protocol for the study and characterization of infiltrating populations in valve tissue, aiming to achieve a higher level of precision in their characterization. The results obtained from this study will contribute to describing and providing new insights into the etiology and pathophysiology of aortic stenosis. **Methods:** We performed a detailed phenotypical and functional characterization of both peripheral and valvular T cells from AS patients (49-80 years), and sex/age-matched healthy volunteers (HD) by multiparametric flow cytometry. **Results:** Significant correlations were observed between the increase of certain immune populations in peripheral blood and their presence in the inflammatory infiltrate of the valve tissue. Furthermore, significant associations were identified between disease severity and distribution (increase/decrease) of certain immune populations present in the valve infiltrate. **Conclusions:** These findings provide a valuable opportunity not only to identify potential peripheral blood biomarkers for disease risk or progression, but also to gain precise insights into the characteristics of aortic valve infiltrating immune populations at different stages of the disease.

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PSI.w. Phosphorylation-dependent regulation of MEK1 by DYRK2 promotes oncogenic MAPK/ERK pathway hyperactivation.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: MEK1, DYRK2, MAPK, targeted-therapy, phosphorylation, cancer.

Abstract: The MAPK/ERK signaling pathway is one of the key cellular pathways in cell growth control, division and differentiation. Specifically, this pathway consists of the cascade activation of RAF-MEK-ERK kinases. Since this pathway is hyper-activated in 85% of all human tumors, the scientific community has tried to develop specific inhibitors of these kinases. However, these therapies have been insufficient due to the emergence of resistance mechanisms, mostly unknown. As a result, the need arises to discover new members of the signaling pathway that serve as treatment targets. Here we describe for the first time the Dual specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2) as a new component and potential treatment target of the MAPK/ERK pathway. We demonstrate that DYRK2 colocalizes in the cytoplasm with MEK1 performing MEK1 phosphorylation at the residues Thr292 and Ser298. We show that the regulation of MEK1 by DYRK2 promotes the hyperactivation of the pathway, which can be reduced by using DYRK2-specific inhibitors. In addition, we show that exposure to clinically used classical MAPK/ERK pathway inhibitors cause DYRK2 accumulation suggesting DYRK2 as a possible novel unknown resistance mechanism responsible of patient recurrence. Finally, we show that DYRK2 inhibition in breast, colon, and lung cancer cells with the MAPK/ERK pathway hyperactivated has a more potent antitumor action than the clinically used RAF inhibitor Dabrafenib, being even more potent the combination of both treatments in cell lines where RAS or RAF is mutated. Overall, these relevant results show DYRK2 a new key member of the pathway and a potential therapeutic target for patients with MAPK/ERK pathway hyperactivated.

PSI.x. Low Spinal Radiographic Progression After a Mean of 15 Years of Follow-up In a Cohort of Patients With Axial Spondyloarthritis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Spondyloarthritis, Radiografic progression.

Abstract:

Background/Purpose: Axial spondyloarthritis (axSpA) is characterized by progressive structural damage on the sacroiliac joints and/or the spine. Conventional radiology allows to assess radiology through available scales such as the mSASSS (modified Stoke Ankylosing Spondylitis Spinal Score) in the spine. However, scarce is the data on long-term radiographic progression and factors associated with such progression. The aim of this study was to evaluate the radiographic progression in the spine in patients with axSpA after a mean of 15 years of follow-up as well as the factors associated with such progression. **Methods:** Patients with axSpA pertaining to the Reina Sofia University Hospital and included in the multicentre Spanish registry REGISPONSER between 2006-2007 were re-evaluated in 2021-2022. Spine (cervical and lumbar) radiographs were obtained with the aim to be compared with those obtained in 2007. Two trained blinded readers scored the mSASSS in radiographs from both visits (baseline and current). First, intraclass correlation coefficients (ICC) were obtained to evaluate the agreement between both readers in mSASSS. Mean mSASSS of both readers in both timepoints were calculated and the absolute progression (ΔmSASSS) was evaluated. In addition, it was evaluated the mean and median progression per year dividing the ΔmSASSS by the years of follow-up in each patient. Then, the median progression per year was used to divide patients in “low progressors” and “high progressors”. Baseline characteristics between these two groups were compared using univariate analysis. **Results:** A total of 77 axSpA patients with both baseline and current radiographs were included. A total of 53 (68.8%) were male and the mean disease duration was 10.15 (SD 9.2) years. All of them were naïve to bDMARD at baseline and 38% had radiographic sacroiliitis. The mean years of follow-up (i.e, mean time separating the radiographs) was 15 years (SD 3.3) (Figure 1). ICC between the two readers was moderate for mSASSS at baseline (0.73, 95%CI 0.26-0.88) and at the 15 years visit (0.65, 95%CI 0.11-0.84) (Figure 2). After a mean of 15y of follow-up, the mean progression was 0.54 (SD 0.55) points in mSASSS per year and the median progression was 0.38 points per year. A total of 37 (48%) patients were considered “low progressors” (i.e., median progression <0.38 points per year) and 40 (52%) were considered as “high progressors” (i.e., median progression ≥0.38 points per year). The only significant variable associated with “high progression” was low back pain before the diagnosis (82.5% vs. 48.6%, p-value 0.003). Neither sex, smoking, disease duration, HLAB27 or c-reactive protein were associated with the “high

progression" group (Table 1). **Conclusion:** In this stablished axSpA population, the mean and median progression were 0.54 and 0.38 points in mSASSS per year respectively, which is lower than what has been reported in similar cohorts (i.e., change in 2 points in mSASSS). Only low back pain was found as predictor of spinal radiographic progression.

References: 1. Aouad K, Ziade N, Baraliakos X. Structural progression in axial spondyloarthritis. Joint Bone Spine. 2020;87(2):131-136. doi:10.1016/j.jbspin.2019.04.006.

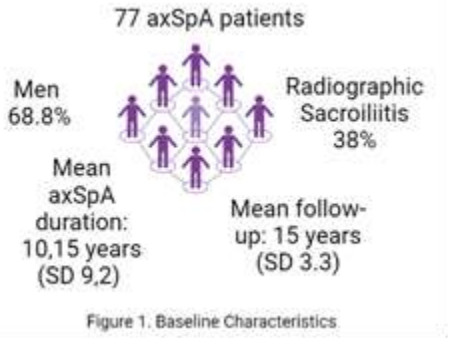

Figure 1. Baseline Characteristics

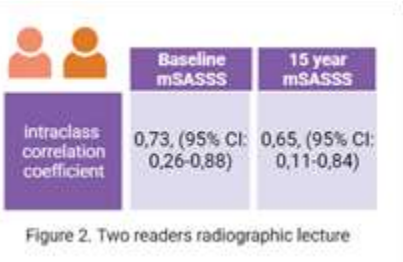

Figure 2. Two readers radiographic lecture

		15 year progression according to mSASSS/year		
Baseline Variables		Low progressors 37 (48%) (<0,38 points mSASSS/year)	High progressors 40 (52%) (≥0,38 points mSASSS/year)	P-value
Sex	Male	25 (67.6)	28 (70.0)	1.000
	Female	12 (32,4)	12 (30.0)	
Age at diagnosis (mean, SD)		31.1 (9.5)	34.7 (8.1)	0.08
Smoking		1 (2.7)	3 (7.5)	1.000
HLAB27 +		32 (86.5)	34 (85.0)	0.670
Inflamatory low back pain		18 (48.6)	33 (82.5)	**0.003**
Entesitis now or preview		10 (27.0)	8 (20.0)	0.600
Dactilitis now or preview		0 (0.0)	4 (10.0)	0.120
BASDAI median (SD)		4.38 (2.3)	4.3 (2.3)	0.890
BASFI median (SD)		3.8 (2.6)	3.6 (2.4)	0.630
High PCR (mg/L)		18 (48.6)	21 (52.5)	0.450
High VSG (mm/h)		8 (21.6)	14 (35.0)	0.330
NSAID now or preview		34 (91.9)	36 (90.0)	1.000

Table 1. Baseline population characteristics observed by two readers

PSI.y. Transcriptomic Study of Pancreatic and Small Intestine Neuroendocrine Tumors using Oxford Nanopore Technology sequencing.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Neuroendocrine Tumors; Oxford Nanopore Technology Sequencing; Transcriptomic; Splicing Variants.

Abstract: Neuroendocrine tumors (NETs) are rare and heterogeneous neoplasms with limited molecular understanding. While the genetic landscape of some NETs types has been reported, their transcriptomic knowledge remains clearly insufficient. Increasing evidence indicates that, in cancer, pathogenic transcriptomic changes often derive from alterations in the splicing process, which can generate abnormal isoforms with oncogenic potential. This information in NETs is lacking. Accordingly, the purpose of our study was to attain a detailed characterization of Pancreatic (PanNETs) and Small Intestine NETs (SiNETs) at the transcriptomic level using new sequencing methods that can enhance our understanding of their molecular landscape and, ultimately, help to identify novel markers and actionable targets. Long-read Oxford Nanopore Technology (ONT) has emerged as the greatest sequencing tool to deeply study transcriptomics due to the length of the sequences obtained. Thus, we used ONT to sequence cDNA obtained from RNA extracted from a set of 8 PanNETs and 3 SiNETs samples. After a quality check of the output, performed using pycoQC v2.5.2, we used the software EPI2ME to preprocess, identify full-length reads, trimming and correct the orientation (pychopper). Then, we mapped the sequences to the human reference genome (minimap2); assembled the sequences (stringtie); compared to the reference annotation (gffcompare) and detected fusion genes (JAFFA). We observed that the quality of the sequencing was tightly dependent on quality of the RNA, and thus cDNA, of each sample, and determined the performance of the subsequent analyses. The high quality for the samples studied enable us to identify multitude of annotated and, more interestingly, novel transcripts, splicing isoforms and fusion genes that may be relevant in NETs Overall, our results indicate that long-read sequencing with ONT leverages the precision and depth of transcriptomic knowledge extracted from NETs, which can help to better understand their molecular architecture and, ultimately, explain their clinical behavior.

PSI.z. Intestinal microbiota and prediction of cardiovascular disease recurrence. From the CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine, and Metabolic diseases.
Keywords: Intestinal microbiota, diabetes mellitus type 2, Clinical Application, Cordioprev Study.

Abstract: Identification of biomarkers for risk of developing cardiovascular events is especially important in patients undergoing secondary prevention. On the other hand, the relationship between the intestinal microbiota and the development of cardiovascular disease (CVD) is known. Our objective was to identify an intestinal microbiota profile associated with the development of cardiovascular events by analyzing the stools of patients with established CVD, as well as to develop a score that would allow the risk of CVD recurrence to be calculated according to the microbiota profile.

This study was carried out in 679 patients from whom we had stool samples of the 1002 included in the CORDIOPREV study, a randomized clinical trial in which the Mediterranean diet and the low-fat diet were compared in secondary prevention of cardiovascular events. Using 16S metagenomics and sequence analysis, intestinal microbiota of the patients was determined. Using Random Survival Forest, an intestinal microbiota profile associated with CVD recurrence was identified. We performed a random classification of patients into two different datasets: a Training Set 70% of the total and a Validation Set, with 30% of the patients. Subsequently, a cardiovascular risk score was constructed based on the bacterial taxa included in this profile, whose association with the risk of recurrence was analyzed using COX analysis.

The Random Survival Forest identified 16 taxa with which the model with the lowest predictive error was built. These bacterial taxa were combined in a cardiovascular risk score and showed an association with the development of new cardiovascular events, with an area under the curve of 63.7% with a confidence interval of 57.4-70.0 and Hazard Ratio (HR) 2.56 (CI 1.55-4.25) in the validation set and HR 4.70 (CI 1.93-11.47) in the validation set.

Our results suggest that there is a microbiota pattern associated with the recurrence of cardiovascular events. The clinical utility of these results lies in the fact that the intestinal microbiota, combined with clinical parameters, could be used to identify cardiovascular patients at high risk of recurrence.

PSI.aa. Dietary modulation of advanced glycation end products and kidney function in type 2 diabetes patients with coronary heart disease: from the CORDIOPREV randomized controlled trial.

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Scientific Program: Nutrition, endocrine, and metabolic diseases.
Keywords: kidney disease; Mediterranean diet; advanced glycation end products.

Abstract: Advanced glycation end products (AGEs) are involved in kidney disease pathogenesis in type 2 diabetes. However, to date, no previous controlled clinical trials have evaluated the long-term effect of specific dietary patterns as a therapeutic strategy to modulate AGE metabolism and its impact on kidney function in secondary cardiovascular prevention. We aimed to evaluate whether the reduction of AGE levels and the consequent modulation of AGE metabolism, after dietary intervention, delay the impairment of kidney function in patients with coronary heart disease (CHD) and type 2 diabetes (T2D).

T2D patients (540 out of 1002 patients with CHD, from de CORDIOPREV study), with estimated glomerular filtration rates (eGFR) ≥60 mL/min/1.73 m2, were classified according to eGFR at baseline: normal eGFR (≥90 mL/min/1.73m2), mildly-impaired eGFR (60-<90 mL/min/1.73m2) and severely-impaired eGFR (<60 mL/min/1.73m2). Serum AGE levels (methylglyoxal-MG) and N-carboximethyllysine-CML) and gene expression related to AGE metabolism (AGER1, RAGE, and GloxI mRNA) were measured before and after 5-years of dietary intervention [Mediterranean diet (35% fat, 22% MUFA, <50% carbohydrates) or a low-fat diet (28% fat, 12% MUFA, >55% carbohydrates)]. Mediterranean diet produced a lower decline of eGFR compared to the low-fat diet, both in total population and in mildly-impaired eGFR patients ($p = 0.035$). Moreover, Mediterranean diet was able to decrease MG levels and increase GloxI expression in normal and mildly-impaired eGFR patients (all $p<0.05$). An increment of a SD of MG levels, after dietary intervention, determined 5.5-fold (95% CI 0.053–0.633) more the probability of declining eGFR. These findings reinforce the clinical benefits of the Mediterranean diet in the context of secondary cardiovascular disease prevention providing a dietary strategy for the reduction of AGEs that could reduce CKD complications.

PSI.bb. USE OF MINIMALLY INVASIVE SAMPLES FROM COPD AND LUNG CANCER FOR EPIGENETIC BIOMARKERS IDENTIFICATION.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Lung cancer, COPD, epigenetics, DNA methylation, early diagnosis, minimally invasive samples.

Abstract: Lung cancer (LuCa) is the most common cause of cancer-related death worldwide due to its asymptomatic nature during the early stages. It also shares many symptoms with chronic obstructive pulmonary disease (COPD), which is recognized as a risk factor for LuCa development, along with tobacco use. The diagnostic process for both LuCa and COPD is complicated by sampling intricacies and the lack of specific biomarkers available for accurate detection.

DNA methylation is an epigenetic mark that leads to gene silencing. Alterations of DNA methylation patterns are frequently observed in many diseases, including cancer. For example, tumour cells show hypermethylation at tumour-suppressor gene promoters and hypomethylation in repetitive sequences. We aim to establish a highly sensitive methodology for early diagnosis of COPD and LuCa by using minimally invasive samples such us blood plasma or exhaled breath condensate, based on the detection of DNA methylation.

For this purpose, samples were classified into four groups: 1- healthy: control group without risk factor; 2-smokers: smokers risk factor group; 3-COPD: chronic obstructive pulmonary disease with risk factor; 4- LuCa: lung cancer group. The workflow was as follows: DNA extraction, bisulfite-modification, and quantitative methylation specific PCR (qMSP). Thus, we studied the methylation patterns for a group of genes associated with COPD or LuCa (p16, RASSF1, SHOX2 and PTGER4).

To date, blood plasma samples (n=60) have been analysed and preliminary data showed RASSF1 methylation in 38.46% of LuCa, 5.88% of COPD, 5.56% of smokers and 8.33% of healthy subjects. On SHOX2, methylation was observed in 23.08% of LuCa and 5.88% of COPD patients. On p16, methylation was observed in 7.69% of LuCa and 5.88% of COPD subjects. No methylation was observed at pTGER4 in any patient. Our results suggest that epigenetic analysis of minimally invasive samples may be a useful approach for diagnosis of COPD and lung cancer.

PSI.cc. Effects of a spreadable cream containing plant-sterols enriched virgin olive oil in children with hypercholesterolemia: A randomized clinical study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: olive oil; cardiovascular disease; metabolic syndrome; sterol; mediterranean diet; hypercholesterolemia.

Abstract:

Background: Children with hypercholesterolemia (HC), characterized by elevated serum low density lipoprotein (LDL) levels from birth, are at risk of suffering premature cardiovascular diseases at early age. Statins are the primary approach for familial HC, but their use is not recommended for children. Hence, dietary modifications are considered as the main factor to regulate LDL levels. Plant-sterols are steroids with a chemical structure similar to cholesterol which exhibit significant hypocholesterolemic effects. Therefore, plant sterols supplementations can be an effective strategy to enhance the lipid profile of children with HC. **Aims:** To evaluate whether the intake of a spreadable cream (SC) containing virgin olive oil enriched with plant-sterols, compared to a control group, might have a cardio-protective and a positive effect in the lipid profile in children with HC. **Methods:** A randomized clinical study based on a nutritional intervention was conducted on 56 children with HC aged from 8 to 18 years. Participants underwent a crossover design with two-month periods and one-month washout periods. A SC containing virgin olive oil (90%) enriched at 8% with beta-sitosterol, beta-sitostanol, campesterol, campestanol, stigmasterol and brassicasterol was consumed by the intervention group (n= 28) (containing 1.2 - 2.4 g/d of plant-sterols depending on body weight), and a non-plant-sterol enriched virgin oil SC by the control group (n= 28). Anthropometric measurement, fasting glucose, fasting insulin, lipid and hepatic markers were recorded before and after the two-months periods. **Results:** Glucose levels significantly decreased in the intervention group (delta values: control SC: 3.0 ± 6.13 mg/dL vs. enriched SC: -2.1 ± 7.51 mg/dL, p=0.041). A tend for a reduction in total cholesterol (delta values: control SC: 11.2 ± 23.25 mg/dL vs. enriched SC: -2.89 ± 22.86 mg/dL, p=0.086) and a slight decrease in the elevation of glutamate-pyruvate transaminase (delta values: control SC: 10.21 ± 14.29 mg/dL vs. enriched SC: 3.22 ± 7.92 mg/dL, p=0.088) were also detected in comparison to controls. **Conclusion:** The findings show the extra virgin olive oil supplemented with plant-sterols might exert a positive effect on cardio-metabolic risk factors.

PSI.dd. Molecular characterization of renal and hepatic damage in an experimental model of sickle cell disease by mass-spectrometry.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: sickle cell disease; kidney and renal damage; proteomic characterization.

Abstract: Sickle cell disease (SCD) is characterized by an abnormal hemoglobin (Hb) expression (HbS instead of healthy HbA), resulting in distortion of red blood cells (RBCs). These patients show early RBCs destruction, leading to altered blood flow, vasoconstriction and ischemia, and ultimately tissue damage, mainly kidney and liver injury. The HbSS Townes mice resemble clinical features reported in patients with SCD. This experimental model of SCD was developed by replacing the endogenous mouse Hb by the altered human HbS (knock-in). We performed an experimental model in 6 months male HbSS Townes and HbAA Townes mice. Blood samples and dissected kidneys and livers were collected for hematological, histochemical and proteomic analysis. To this end, organs were lysated and then prepared for a label free quantitative (LFQ) approach by protein aggregation capture (PAC) digestion with trypsin and lys-C. Analysis was made by TIMS-TOF Pro instrument operated in data independent acquisition mode. As expected, HbSS Townes mice showed decreased hematocrit and erythrocyte number as well as iron deposits in kidney and liver in comparation with HbAA Townes mice. LFQ approach revealed 2075 and 1388 proteins identified in kidneys and livers, respectively, which allowed differential expression patterns (up- and down-regulated proteins) in SCD vs Healthy comparison. According to functional analysis, molecular changes were associated with reduced kidney function and liver inflammation. Proteins differentially expressed correlated with anemia, oxidative stress response and iron metabolism disorders, among others. In addition, hemoproteins such as ferritin or transferrin confirmed the alteration of processes associated to SCD. In conclusion, we reported a number of proteins differentially expressed in HbSS mice, thus identifying new pathogenic mechanisms involved in renal damage and hepatic injury in an experimental model of SCD.

PSI.ee. External Multicentre Validation of Pseudomyxoma Peritonei PSOGI-Ki67 Classification.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pseudomyxoma peritonei, diagnostic, classification, mucinous adenocarcinoma, appendix.

Abstract:

Background: Pseudomyxoma peritonei (PMP) is a rare cancer defined by the accumulation of mucus in the peritoneal cavity, where the patients have a poor survival rate. The PMP tumour's diagnosis is considered a challenge because is limited to a histological analysis after surgery. The most successful protocol has been established by PSOGI (The Peritoneal Surface Oncology Group International)1. This classification has been validated by our group2. Moreover, we have described two subcategories inside the high-grade (HG-PMP) depending on the Ki67 % proliferation index (≤15% and >15%) with significant differences in terms of overall survival (OS) and disease-free survival (DFS)3. The present study is an external and multicentre validation of this new proposed classification4. **Method:** We implemented a prospective analysis from a historical and international cohort of patients. A representative area with higher cellular density was used to determine the Ki67%. The Ki67 proliferation index (%) was determined in all the HG-PMP patients. A COX proportional hazard models and multivariable COX models were used. The Kaplan–Meier method and the two-tailed log-rank test were used to analyse the effect of different PSOGI-Ki67 categories on OS and DFS. Its predictive accuracy was analysed using Harrel's C-index and the ROC curve. The calibration was performed using the calibration plots matching. **Results:** After exclusions, 349 patients were available for analysis. The 5-years OS were 86% for LG-PMP, 59% for HG-PMP≤15, 38% for HG-PMP>15 and 42% for SRC-PMP (p = 0.0001). The 5-years DFS were 49% for LG-PMP, 35% for HG-PMP≤15, 16% for HG-PMP>15 and 18% SRC-PMP (p = 0.0001). The discrimination capability of PSOGI-Ki67 was validated. **Conclusion:** The PSOGI-Ki67 classification discriminates and predicts the OS and DFS in patients with PMP dividing the HG-PMP category into two well-defined sub-categories. The Ki67 proliferation index should be incorporated routinely in the pathology report for these patients.

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PSI.ff. Severe aortic stenosis treated with surgery and balloon expandable prosthesis. Analysis of a series of cases.

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Scientific Program: Active aging and frailty.
Keywords: TAVI; Surgery; Survival.

Abstract:

INTRODUCTION: Severe aortic stenosis (SAS) has a high prevalence in developed countries. Both standard surgery and percutaneous procedures are used to treat SAS. Here we present a series of cases, treated with TAVI (CoreValve) or conventional surgery. We evaluated survival, major complications, and other factors associated with mortality. **METHODS:** 92 patients (after applying the propensity score matching test, on 137 patients), aged 70 years or older, that were treated between 1 January 2010 and 31 December 2011, and were followed up to December 2022. The mean global age was 78.34 ±3.79 years. 56 (60.9%) patients were in NYHA functional class III. The mean log euroSCORE was 11.80% ± 7.18%. **RESULTS:** The mean survival time was 96.219 ± 5.31 months, 94.42 ± 8.03 months (CI 95%: 78.67-110.17) for the surgery group and 97.95 ± 6.92 months, (CI 95%: 84.38-111.52) for the TAVI group, Log Rank (Mantel-Cox), p =0.846. At the end, 31 patients (67.4%) in the TAVI group and 32 patients (69.6%) in the surgery group died (p=0.822). There was no difference in in-hospital mortality, p=0.485, nor in the development of periprocedural stroke, p=1. The TAVI group required more definitive endocavitary pacemaker, p<0.059. **CONCLUSIONS:** Long-term differences with respect to survival are not significant. The treatment of aortic valve pathology has expanded. It would be desirable to be able to individualize each case in order to optimize both the economic resources of each health system and the success of the selected procedure.

PSI.gg. Muscle mechanical properties of pelvic floor and paravertebral muscles in women with and without urge incontinence urinary: case-control study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: pelvic floor dysfunctions; urine leakage; manual tonometry.

Abstract: Urge urinary incontinence (UUI) is a condition with big social and psychological repercussions, its causes are not well understood and it remains difficult to treat. Although no single factor completely explains the etiology of UUI, the main focus relies on the condition of lumbopelvic region. Muscle mechanical properties (MMPs) are relevant to understand the physiopathology of lumbopelvic dysfunctions. Nevertheless, relationships between UUI, pelvic floor muscles (PFMs) and lumbar paravertebral musculature (LP) have not been fully elucidate. The objective was to identify potential differences in the MMPs of the PFMs and LP between women with and without UUI, and evaluate the relationship with sociodemographic and clinical variables, as well as lumbopelvic MMPs.

The participants of this case-control study comprised 34 women with UUI (UUI group) and 34 continent women (control group). Sociodemographic and pelvic floor clinical state were obtained. The MMP, that is, frequency (tone), stiffness, decrement (inverse of elasticity) and viscoelastic properties (PV) such as relaxation and creep, of PFM and LP were assessed with a hand-held tonometer device called MyotonPRO. Between-groups differences and intra-group correlations were identified.

The IUU group had higher frequency and stiffness, as well as shorter relaxation time in the PFM, while the LP had lower tone and stiffness, and higher PV, compared to the control group ($p<0.05$). The IUU group showed a pattern of moderate correlations ($|0.403|<r<|0.600|$), where all MMP of LP correlated with some MMP of PFM, which did not appear in the control group.

In conclusion, the existence of IUU can affect the lumbopelvic MMPs, increasing the tone and rigidity of the PFM but reducing them and increasing their PVs in the LPs. Futhermore, the IUU could generate associations between the MMP status of PFMs and LPs.

PSI.hh. Autophagy promotes the generation of dormant polyploid giant cancer cells.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Polyploid giant cancer cells; autophagy; colorectal cancer; therapy resistance.

Abstract:

Background and aims: Polyploid giant cancer cells (PGCCs) are a distinct subpopulation of cancer cells that possess unique mechanisms for survival. These cells exhibit remarkable resilience against diverse stresses within the tumor microenvironment, enabling them to evade treatments and persist within the tumor. Notably, PGCCs have the capacity to repopulate tumors through asymmetric daughter cell budding. The objective of this study was to explore the role of autophagy, which is a cellular process involved in degradation and recycling, in the formation of PGCCs. **Material and Methods:** To induce the formation of PGCCs HCT-116 colorectal cancer (CRC) cells were treated with CoCl2, a hypoxia mimetic. Hoescht staining was employed to evaluate nuclear size, whereas PGCCs budding division and tumor cell culture recovery/repopulation was assesed by time-lapse imaging (IncuCyte® ZOOM). Stabilization of HIF-1α, and the expression of autophagy-associated proteins, such as mTOR, LC3 and p62 were evaluated by western blotting. **Results:** Treatment with CoCl2 resulted in the significant stabilization of HIF-1α and the formation of PGCCs exhibiting nuclei that were 3–10 times larger than those of regular cells. Interestingly, exposure to CoCl2 led to the selective elimination of almost all regular-sized cells, while PGCCs demonstrated remarkable survival. Subsequently, PGCCs underwent asymmetric cell division, giving rise to daughter cells through budding. These daughter cells exhibited rapid proliferation, ultimately facilitating the repopulation and recovery of tumor cell cultures. Notably, the emergence of PGCCs in HCT-116 CRC cells was accompanied by the induction of autophagy, evident from mTOR activation, an increase in the LC3-II/I ratio, and a decrease in p62 expression levels. **Conclusions:** The formation of dormant PGCCs in CRC is associated with autophagy induction. Suppression of autophagy before standard treatments may constitute a valuable approach for preventing dormant PGCC formation, which contributes to treatment resistance and cancer recurrence. Funding: PDI2019-105256-RB-100.

PSI.ii. Forced Expiratory Volume in 1 second (FEV1) and Mortality in Severe Mental Illness: An opportunity for early detection.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Mortality, Forced Expiratory Volume, Severe Mental Illness.

Abstract:

Background: People with severe mental illness (SMI), including schizophrenia or bipolar disorder, has a life expectancy reduced to 20 years compared with general population. This premature mortality is due, between others, to respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD). Spirometry is the Gold Standard in its diagnosis and quantification of severity. Indeed, it is known the association between a worse result in FEV1 and premature mortality. **Material and Methods:** This is a cross-sectional sub-analysis, belonging to a multicenter, randomized, open, controlled clinical trial, with a 12 month follow-up. Patients with schizophrenia or bipolar disorder who attended their scheduled check-up appointment in the Mental Health Team were recruited. They had mental stability, over 40 years and without a previous diagnosis of respiratory disease. FEV1 was evaluated by spirometry. **Results:** The study sample consisted of 92 patients (74.2% schizophrenia). Of the total, 8 of them died (8.2%), with a mean age of 52.6 years. In the case of survivors, the mean age was 49.9 years. In relation to FEV1, the deceased patients had lower levels compared to the survivors, both in absolute terms (2137.5 mL vs 2741.1 mL) and in % (65.1% vs 82.2%), with differences statistically significant. The same differences were also detected after bronchodilation, presenting a global mean lung age of 81.2 years (around 30 years of difference respect to chronological age) compared to 62.4 years of the survivors (around 12 years of difference) (p: 0.002). **Conclusions:** The measurement of FEV1 levels is an easy and important tool for the early detection of those SMI patients with a high risk of premature mortality, favoring a longer and better life expectancy.

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

PSI.jj. Deciphering pregnancy-associated breast cancer: distinctive molecular profile and clinical implications.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pregnancy-associated breast cancer; gene expression; tumor signatures; molecular profile; DNA damage repair.

Abstract: Pregnancy-Associated Breast Cancer (PABC) is defined as breast cancer diagnosed during pregnancy, breastfeeding, or within the first-year post-partum. This challenging entity occurred in younger women (≤45 years old) and has worse prognosis compared to non-PABC patients. Identification of specific molecular pathways is crucial to explain its aggressive biological characteristics and potential relation with pregnancy as well as may have important clinical implications. This study assessed the gene expression profile of an age-matched cohort of patients diagnosed with PABC (n=46) and non-PABC (n=49). RNA isolation from tumor tissue samples was used to analyze the expression of 776 genes involved in 23 key breast cancer pathways, using the nCounter Breast Cancer 360 Panel (NanoString Technologies). Additionally, intrinsic molecular subtypes as classified by the expression-based PAM50 assay were also available. Associations between gene expression profiles and the clinicoepidemiological features were also explored. PABC patients showed a higher incidence of breast/ovarian cancer family history compared to non-PABC patients (52.17% vs 26.53%) ($p=0.0124$). Moreover, a distinct molecular profile in PABC patients was also found. The cell proliferation and p53 signature were significantly associated (adj $p<0.05$) with PABC tumors as well as a significant increase in BRCAness and HDR signatures (adj $p<0.05$) both related to the breakdown of damage repair. Interestingly, most of the significantly upregulated genes (CCNA2, DEPDC1, FAM83D, etc…) in PABC patients were involved in cell cycle regulation and DNA damage repair. Our study shows that PABC is a molecular different breast cancer entity characterized by the activation of specific oncogenic pathways related to cell proliferation, DNA damage repair, and p53 mutations that may contribute to its more aggressive phenotype. These findings open new avenues for PABC patients who may benefit from personalized therapies targeting DNA repair or cell-cycle checkpoints, such as PARP inhibitors.

Fundings: PI22/00969.

PSI.kk. PREVALENCE AND RISK FACTORS ASSOCIATED WITH CHRONIC KIDNEY DISEASE AFTER HEART TRANSPLANTATION.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Heart Transplantation, Chronic Kidney Disease, risk factors.

Abstract:

Background: Chronic kidney disease (CKD) is one of the main long-term complications after heart transplantation (HT). The development of CKD makes it difficult to manage other complications that may appear in these patients. The incidence of CKD in HT ranges between 10-80%. This variation depends on the time of follow-up of the patients and the method of measurement of renal function over time. We conducted this study to find out the prevalence of CKD in heart transplantation in our center. **Methods**: We analyzed sociodemographic and laboratory variables, comorbidity, and renal function of 165 HT recipients between 1986 and 2021 and currently under follow-up in our hospital. Patients who had received a combined transplant, recipients of a second heart graff and patients who had received a HT in the pediatric age were excluded. **Results**: We found that 127 of the patients had a CKD-EPI estimated glomerular filtration rate (eGFR) of less than 90 ml/min/1.72m2: 56 patients (33.9%) with CKD stage 2 (eGFR 90-60 ml/min1.72m2), 59 (35 .8%) with CKD stage 3 (eGFR 59-30 ml/min1.72m2) and 16 (9.7%) with GFR less than 30 ml/min/1.72m2 (CKD stage 4-5). Patients with CKD stage 3 were older with a mean age of 60.1±13.9 years (p=0.005), and there was a non-significant trend towards a higher proportion of diabetes mellitus (42.4%, p=0.059) and a higher prevalence of hyperuricemia (37.3%, p=0.008) with respect to CKD stage 2 group. We found no differences between groups in terms of the prevalence of hypertension, immunosuppressive treatment, or the time elapsed since the transplant. **Conclusions**: In conclusion, in the analysis of our population of patients with a HT, three out of four have impaired kidney function and more than half have moderate-advanced CKD. Classic risk factors are not different between CKD stage 2 and CKD stage 3 patients.

PSI.II. Inflammasome machinery is dysregulated in glioblastoma: clinical and translational evidence.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Inflammasome; Glioblastoma; MYD88; Anakinra; Metformin.

Abstract: Glioblastoma (GBM) is the most lethal brain tumor, which, in addition to the late-stage diagnosis and the lack of effective novel therapies, results in the poor prognosis and quality of life of patients. Accordingly, the identification of novel molecular biomarkers of diagnosis and/or prognosis, and therapeutic targets becomes crucial to combat this devastating disease. In this context, the inflammasome machinery, the master regulator of cell inflammation, could be critical in the modulation of the tumor microenvironment, which is essential in the initiation, progression, and aggressiveness of different cancer types. In this study, we characterize for the first time the inflammasome machinery in GBMs at the genomic, transcriptomic, and proteomic levels, showing a profound dysregulation in comparison to non-tumor brain samples. Interestingly, the presence of mutations in the inflammasome machinery, as well as the alteration in the expression of key components such as MYD88, NLRP2, and RBP4, was found to be associated with relevant clinical parameters of prognosis such as survival rate, recurrence, and MGMT methylation status. Of note, an overall upregulation of the effectors of the inflammasome was observed, suggesting a possible activation of this machinery in GBMs. Moreover, we demonstrated that the inhibition of the activity of the inflammasome (using the inhibitor anakinra) failed to alter the proliferation of GBM cells, but that the treatment with metformin was able to successfully reverse the dysregulation in the expression pattern of the inflammasome previously observed in GBMs. Taken together, our results demonstrate a dysregulation of the inflammasome machinery in GBMs, which could serve as a source of new diagnostic/prognostic biomarkers and therapeutic targets to combat this devastating pathology.

Fundings: AECC.

PSI.mm. INVOLVEMENT OF EXOSC4 IN THE PROGRESSION OF HEPATOCELLULAR CARCINOMA.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: ARN-exosome, EXOSC4, silencing, hepatocellular carcinoma.

Abstract: Liver cancer represents one of the main health problems and the fourth leading cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) is the most common primary liver cancer (90% of cases) and exhibits a highly aggressive phenotype and an increasing incidence. Different cancer types, including HCC, are associated with a severe dysregulation of the molecular machineries responsible for RNA processing and metabolism. One of these machineries is the RNA-exosome, a ribonuclease complex that cooperates with multiple cofactors in the processing, quality control and degradation of RNAs. However, the implication of this machinery in HCC development and/or progression has not yet been explored. In this study we aimed to characterize the dysregulation and putative role of the RNA-Exosome machinery component EXOSC4 in HCC, as it could be useful to discover new diagnostic or prognostic biomarkers, as well as possible therapeutic targets in this disease. The expression levels of RNA-Exosome components were analyzed in HCC samples and non-tumor adjacent tissues from two retrospective cohorts (n=94 and n=62 respectively) and seven in silico cohorts (Zhou, Roessler 2, Mas, Wurmbach, Arendt, Pinyol and TGCA) and their relationship with key clinical parameters in the pathology was analyzed. In addition, functional assays were performed on HCC cell lines Hep3B and SNU-387 in response to EXOSC4 silencing by siRNAs. Our result show a consistent overexpression (at the RNA and protein level) of EXOSC4 in HCC samples, where its levels were associated with certain key clinical parameters such as survival, recurrence, or invasion capacity. Consistently, the modulation (silencing) of its expression by two different siRNAs in vitro reduced tumor aggressiveness parameters such as proliferative capacity, migration or colony formation. Our results indicate that EXOSC4 could be a potential novel biomarker and/or therapeutic target capable of reducing the lethality of this pathology and/or improving patients quality of life.

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PSI.nn. Proximity Extension Assay is a novel technology for boosting molecular characterization and personalized clinical management of rheumatic diseases.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, spondyloarthritis, biomarkers, clustering.

Abstract:

Background: Rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and spondyloarthritis (SpA) are characterized by complex clinical and molecular heterogeneity. Novel and disruptive technologies might shed light on their pathogenesis and clinical management. The aim of this study was to evaluate the potential of the innovative proteomic technology "proximity extension assay" (PEA) to identify useful biomarkers, subgroups of patients, and novel insight into rheumatic diseases. **Methods:** 363 consecutive patients with rheumatic diseases (141 SLE, 50 RA, 72 SSc, and 100 axialSpA) and 50 healthy donors (HDs) were included in the study where serum samples and clinical data were obtained. A signature of 460 proteins divided into 5 panels of 92 biomarkers associated with Inflammation (SLE and HDs), Organ Damage (SLE, SSc, and HDs), cardiovascular disease (RA, SpA, and HDs), and cardiometabolism (RA and HDs) was analysed by using PEA technology from Olink (Cobiomic Bioscience SL). Data analysis included t-test, unsupervised clustering analysis, ROC curves, and PCA among others. **Results:** In SLE patients, the unsupervised cluster analysis using the circulating proteome identified 2 clusters with distinctive clinical features mainly differentiating disease activity and the presence of renal damage. Similarly, in SSc, a panel of proteins related to organ damage identified a subgroup of patients characterized by multiple organ involvement including lung and skin fibrosis and oesophageal dysmotility, along with a preponderance of anti-scl70 antibodies positivity. In axialSpA patients, the levels of several proteins related to cardiovascular disease were altered compared with HDs and associated with key clinical features. A specific signature of several proteins associated with CVD and metabolism was identified as a potential biomarker of RA diagnosis. Likewise, a combination of various plasma proteins before therapy identified non-responders RA patients to Methotrexate or anti-JAK, pointing out its role as a predictor of therapy response. **Conclusions:** PEA technology might boost the future of precision medicine in rheumatic diseases through the identification of novel biomarkers of disease and therapy response and the stratification of patients with key clinical and molecular features.

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SESSION III.

NUTRITION, ENDOCRINE AND METABOLIC DISEASES I.

IIIa. Analysis of metabolites from the intestinal microbiota and their role as modulators of coronary heart disease as a function of the sex of the patient.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: N-trimethylamine Oxide, intestinal microbiota, sexual dimorphism.

Abstract: The incidence of cardiovascular disease (CVD) is influenced by sex, being more frequent in men than in women. Trimethylamine (TMA), a microbial metabolite, is oxidized to trimethylamine N-oxide (TMAO) which is closely linked to the etiology of CVD. Our aim was to study differences in plasma levels of TMAO and TMA in men and women with CVD. For this purpose, we used patients from the CORDIOPREV study, who represent the sexual dimorphism in the incidence of CVD, and a control population without CVD. TMA and TMAO plasma levels were quantified by HPLC coupled to QQQ-MS/MS. Higher levels of both metabolites were observed in the presence of CVD. TMAO levels were higher in men, whereas no differences were found in TMA levels. In the population without CVD, no differences in TMA or TMAO levels were observed according to sex. Greater intima-media thickness and a great number of atherosclerotic plaques were observed in men than in women with CVD. Our study showed higher levels of TMAO in men than in women with CVD and found no sex differences in TMA.

IIIb. Characterization of a novel molecular mechanism inhibiting the secretory capacity of arcuate Kiss1 neurons in conditions of metabolic stress.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Reproduction, kisspeptin, metabolism, fasting, secretory pathway.

Abstract: Reproduction is an energy-demanding function that is influenced by the metabolic state, being inactivated in situations of energy deficit. Kiss1 neurons of the arcuate nucleus (Kiss1ARC), which produce kisspeptin and participate in the regulation of pulsatile luteinizing hormone (LH) secretion, act as transducers of this metabolic information to the brain centers governing reproduction. Although special attention has been paid to transcriptional mechanisms participating in the metabolic control of Kiss1ARC, the characterization of other non-transcriptional mechanisms regulating Kiss1ARC remains elusive. Here, we report the identification of a novel molecular mechanism inhibiting the secretory capacity of Kiss1ARC neurons in response to 24-hour fasting, as a model of negative energy balance seen in clinically relevant conditions, such as anorexia or cachexia. To this end, we implemented chemo-/opto-genetic and in vivo calcium imaging fiber photometry approaches to functionally evaluate the secretory capacity of Kiss1ARC after 24-hour fasting. Our results showed that LH response to the chemo- and opto-genetic activation of Kiss1ARC neurons is reduced after 24-hour fasting, even though (i) kisspeptin content in these neurons is augmented; and (ii) the LH response to the central injection of kisspeptin is enhanced in this condition. We confirmed that this regulatory mechanism also operates during endogenous LH pulses, which were affected by 24h-hour fasting despite unaltered calcium dynamics during Kiss1ARC neuron activation episodes. Subsequently, transcriptomic profiling of FACS (Fluorescent-Activated Cell Sorting)-isolated Kiss1ARC neurons from 24-hour fasted and control-fed mice allowed us to identify a panel of eleven deregulated genes that participate in the secretory pathway, nine of which were confirmed by qPCR using an independent set of samples. Thus, our results are the first to characterize a molecular mechanism inhibiting the secretory capacity of Kiss1ARC neurons, which likely contributes to the impairment of reproductive function in conditions of energy deficiency.

IIIc. Mediterranean diet preserves kidney function in coronary heart disease patients with type 2 diabetes and obesity: An Analysis of the CORDIOPREV Randomized Controlled Trial.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: obesity; diabetes; kidney; Mediterranean diet.

Abstract: Type 2 diabetes mellitus (T2DM) is considered an independent risk factor for chronic kidney disease (CKD). The specific contribution and differential response to dietary strategies for reducing kidney dysfunction, depending on the presence of obesity together with T2DM or not, have not been fully elucidated. We aimed to establish a more accurate understanding of the contribution of obesity to T2DM on kidney function in patients with coronary heart disease (CHD) in order to determine the most appropriate dietary strategy for preserving kidney function. 1002 CHD patients (CORDIOPREV study) were classified into four groups according to the presence or absence of T2DM and/or obesity: Non-Obese/Non-T2DM, Obese/Non-T2DM, Non-Obese/T2DM and Obese/T2DM. Kidney function was assessed by the estimated glomerular filtration rate (eGFR) at baseline and after 5-years of dietary intervention [Mediterranean diet (35% fat, 22% MUFA, <50% carbohydrates) or a low-fat diet (28% fat, 12% MUFA, >55% carbohydrates)]. The urinary albumin-to- creatinine ratio (uACR) was also evaluated. Among all groups, obese/T2DM patients showed the lowest eGFR and the highest uACR (all $p<0.05$). Moreover, these patients had lower eGFR compared to their counterparts without T2DM (all $p<0.05$). After dietary intervention, the Mediterranean diet reduced eGFR decline only in patients with concomitant T2DM and obesity, compared to a low-fat diet ($p=0.014$). The Mediterranean diet also reduced uACR (-1.62±12.98mg/g), compared to the low-fat diet (18.51±12.65 mg/g; $p=0.024$) only in obese/T2DM patients. The presence of obesity had an additive effect to T2DM leading a greater impairment of kidney function in patients with CHD. However, those with T2DM and obesity, with more metabolic complications, appeared to be more susceptible to beneficial effects of the consumption of the Mediterranean diet compared to a low-fat diet in preserving kidney function. These findings provide valuable insights into defining potential responsiveness to lifestyle modifications, allowing for a better understanding of personalized health in the context of secondary cardiovascular disease prevention.

IIId. PCSK9 LEVELS AND THEIR CORRELATION WITH THE GENETIC VARIANTS PRESENT IN HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: Genetic variants; familial hypercholesterolemia; PCSK9.

Abstract: Heterozygous Familial Hypercholesterolemia (HF) is a common genetic disorder worldwide. It is caused by mutations in the LDLR, ApoB, ApoE and PCSK9 genes. The importance of HF as a health problem lies in the high incidence of premature coronary disease. It is necessary to search biomarkers that allow us to individualize the cardiovascular (CV) risk of these patients. Our main objective is to study the relationship between PCSK9 levels and the different genetic mutations present in individuals with HF, in order to individualize their CV risk.

This is a transversal descriptive study of a prospective cohort of 403 patients with HF (SAFEHEART cohort). It included patients >18 years of age with HF and their families. It also included anthropometric, biochemical and clinical data, as well as their genetic diagnosis. PCSK9 levels were determined by ELISA. Subsequently, the relationship between PCSK9 levels and the different mutations present in patients with HF was analyzed, as well as the correlation with biochemical and lipid parameters.

Individuals with mutation in the LDLR gene showed higher levels of PCSK9 than those who did not carry it. Patients with mutation in the ApoB gene showed lower levels of PCSK9 than those who did not carry it. In addition, PCSK9 levels were positively correlated to LDL, total cholesterol, blood glucose, and serum ApoB levels.

Knowledge of the relationship between the different genetic mutations and the behavior of molecules associated with the development of CV disease (PCSK9) would be useful to determine CV risk individually in patients with HF, allowing us to optimize their pharmacological treatment.

IIIe. Characterisation of the somatostatin system in chronic liver disease: potential therapeutic role of neuronostatin receptor GPR107.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: somatostatin, neuronostatin, GPR107, neuroendocrinology, metabolic-associated fatty liver disease, hepatocellular carcinoma.

Abstract: With a 5-year survival rate of ~20%, hepatocellular carcinoma (HCC) is the third most incident and sixth most lethal cancer worldwide. Tumoral endocrine environment and signalling play a pivotal role in several cancer types (e.g., neuroendocrine tumours). However, little is known about (neuro) endocrine influence in HCC and one of its underlying aetiologies, metabolic-associated fatty liver disease (MAFLD). Here, we aimed at describing the expression and function of a key neuroendocrine system, the somatostatin (SST) system, in the MAFLD to HCC progression.

We evaluated the expression of SST and cortistatin (CST) receptors (SSTR1-5) and neuronostatin (NST) receptor GPR107 in 2 internal retrospective cohorts [cohort 1: HCC vs. adjacent tissue (n=93); cohort 2: HCC vs. adjacent tissue (n=58), cirrhotic (n=39) and healthy liver (n=5)], 13 external validation cohorts (7 MAFLD, 6 HCC) and 2 HCC cell lines (Hep3B, SNU-387). Functional assays (proliferation, wound-healing, colony and hepatosphere formation) were implemented to assess the impact of SST system ligands, both natural (SST, CST, NST) and synthetic (octreotide, lanreotide, pasireotide, BIM-23926, BIM-23120) and GPR107 expression modulation (silencing, overexpression).

MAFLD samples were characterised by SSTR expression alteration (mostly, downregulation) and GPR107 overexpression, a profile that was reproduced and exacerbated in HCC samples. Hep3B showed higher SSTR and GPR107 expression than SNU-387 and, consequently, higher antitumoral effects were observed for BIM-23926, octreotide and NST in Hep3B. GPR107 silencing (alone or in combination with NST treatment) reduced tumoral establishment and growth, while GPR107 overexpression alone boosted it and GPR107 overexpression with NST treatment offered neutral effects.

Altogether, these results demonstrate a profound alteration of the SST system in chronic liver disease, highlighting the potential diagnostic, prognostic and therapeutic value of GPR107 for the clinical management of the MAFLD-HCC progression.

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SESSION IV.

MULTIDISCIPLINARY II.

IVa. Supervised versus home-based programs in kidney transplant recipients: a non-randomized single-center prospective trial.

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Scientific Program: Active ageing and fragility.
Keywords: kidney transplantation; supervised exercise; home-based exercise; outcomes.

Abstract: Physical inactivity and poor physical fitness are important targets to address in order to improve clinical outcomes after kidney transplantation. In this study, we aim to compare adherence and outcomes after an exercise program prescribed and conducted in supervision in a selected gym class with qualified professionals or at home. Twenty-one kidney transplant recipients (KTr) were contacted for possible inclusion. Patients underwent baseline testing sessions including a Balke-Ware treadmill test for peak oxygen consumption estimation (VO2peak), a 6-minute walking test (6MWT), and a 5-time sit-to-stand test (5STS). Thereafter, patients could decide to perform exercise under supervision in a specialized physical activity center (SUP) or at home (HB). KTr chose SUP and underwent 3-weekly 60-minute training sessions including aerobic exercise, strength training, and stretching. Those selecting HB performed an inside-home progressively increasing interval walking training (walk-rest ratio 1:1) for 10 minutes per day. At the end of both 6-month programs, the testing session was re-administered.

Seventeen patients (81%) adhered, 8 selecting SUP and 9 HB. At baseline, KTr of the SUP group were younger (55±11 vs 63±2; p=0.04) and presented a greater 6MWT (480±62 vs 356±112 m; p=0.03). After 6 months, 6 subjects of the SUP group (two dropped out for intercurrent disease) and all 9 subjects of the HB group safely completed the programs. Both groups significantly improved all outcomes, with greater variations observed in HB for 6MWT (SUP: +15 vs HB +52m), 5STS (SUP: -1.2 vs HB – 5.0s), and VO2peak (SUP: +1.2 vs HB +3.1 ml/100g/min). The between-group comparison corrected for baseline covariates highlighted a significant difference in favor of HB for 6MWT variations (p=0.046).

Physical activity is effective in improving cardiovascular fitness in KTr when supervised in specialized centers or carried out at home by validated structured programs for subjects unable or unwilling to attend supervised certified gyms.

IVb. Beneficial effect of recombinant Klotho administration in acute kidney injury associated with intravascular hemolysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Acute kidney injury, intravascular hemolysis, Klotho, Nrf2/HO-1 axis.

Abstract:

Introduction: Intravascular hemolysis is associated with massive accumulation of hemoglobin in the kidney, leading to increased oxidative stress, inflammation and renal cell death, promoting the development of acute kidney injury (AKI). Klotho is a protein that is mainly synthesized in the kidney and plays an important role in kidney physiology. However, the role of Klotho in AKI associated with intravascular hemolysis has not been explored. **Materials and methods:** We performed an experimental model of AKI associated with intravascular hemolysis by injection of phenylhydrazine (200mg/kg, i.p.) in C57BL/6J mice. One group of mice was treated with recombinant Klotho (rKl) (0.1 mg/kg) 30 min before induction of the damage. Mice were sacrificed 24h after induction of hemolysis to collect blood, urine and kidney samples. In addition, murine tubular cells (MCTs) were stimulated with hemoglobin and its hemoderivatives to study Klotho levels and the possible beneficial effect of rKl administration in vitro. **Results:** Intravascular hemolysis increased serum creatinine and BUN levels, and increased renal expression of inflammatory mediators (TNFα, IL-6) and cell death (TUNEL). We observed a significant decrease in renal expression and serum levels of Klotho in mice with hemolysis compared to control mice. rKl administration improved renal function and reduced the inflammatory response and cell death in mice with hemolysis. Stimulation with hemoglobin, heme or iron also decreased gene and protein Klotho expression in cultured tubular epithelial cells. Furthermore, administration of rKl reduced oxidative stress and inflammation associated with these hemoproteins in vitro. Finally, we also observed that rKl activated Nrf2/HO-1 axis. **Conclusion:** Renal Klotho expression decreases in AKI associated with intravascular hemolysis. Furthermore, administration of recombinant Klotho could be a possible therapeutic approach to decrease the severity of renal damage associated with pathological accumulation of hemoglobin and its hemoderivates.

IVc. Magnesium supplementation reduces the development of renal and cardiac fibrosis present in chronic kidney disease: In vivo and in vitro studies.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Renal fibrosis; Cardiac fibrosis; Magnesium; Phosphorous; TGFβ; Langendorff.

Abstract: High serum phosphate levels in chronic kidney disease (CKD) contribute to cardiorenal syndrome type 4 (CRS4), characterized by renal tissue fibrosis, oxidative stress, inflammation, and subsequent heart damage. We conducted a study to explore the potential of dietary magnesium (Mg) supplementation in reducing CRS4.

In vivo experiments used 5/6Nx rats on a high (0.9%) phosphate diet with dietary interventions to modulate Mg levels. The study aimed to evaluate: 1) The effects of dietary Mg supplementation (0.3%) on oxidative stress, inflammation, cardiac and renal fibrosis. 2) The role of hypomagnesemia in CRS4 progression in Nx and control rats. 3) Whether dietary Mg supplementation could reduce renal and cardiac fibrosis in Nx rats with established CRS4. In vitro experiments assessed the impact of Mg (Mg2Cl) on mesangial and renal tubular cells exposed to high TGF-β levels.

Dietary Mg supplementation improved renal function, reduced oxidative stress, FGF23 levels, hypertension, renal and cardiac fibrosis. It restored renal expression of Klotho, decreased ANP and BNP levels (markers of cardiac hypertrophy and ventricular fibrosis), and showed a positive correlation between BNP and cardiac damage in Langendorf studies. Conversely, a low Mg diet increased FGF23 and renal fibrosis. In Nx+0.9%P rats with hypomagnesemia, dietary Mg supplementation did not significantly improve CRS4 parameters but did reduce renal fibrosis. Moreover, in the established renal and cardiac fibrosis model after 8 weeks of Nx+0.9%P, an additional 8 weeks of dietary Mg supplementation did not modify renal and cardiac fibrosis.
In HK2 and rat mesangial cells treated with TGF-β (100 ng/ml), high Mg levels (2.6 mM) reduced pro-fibrotic protein presence (α-smooth muscle actin, fibronectin, renin), restored Klotho expression, and decreased Smad3 phosphorylation.

In conclusion, dietary Mg supplementation is a valuable approach to improve renal function and prevent CRS4 by reducing renal and cardiac fibrosis progression.

IVd. Characteristics and outcomes of transcatheter mitral valve edge to edge repair according to mitral etiology.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Mitral regurgitation, Transcatheter edge to edge repair.

Abstract:

Background: Transcatheter edge-to-edge repair (TEER) has been increasingly used for selected patients with mitral regurgitation (MR), but limited data are available regarding clinical outcomes in patients with varied etiology of MR. Studies usually identify 2 types of MR: degenerative mitral regurgitation (DMR) and functional mitral regurgitation (FMR). However, patients with mixed etiology (MMR) are excluded from studies. **Objective:** We aimed to evaluate and compare the baseline clinical and echocardiographic characteristics and outcomes after TEER among patients with FMR, DMR, and MMR. **Material and Methods:** Patients (n=151) who had severe MR and underwent TEER between November 2011 and June 2022 were included in the study. 89 patients with structurally normal mitral valves were classified as FMR, while 38 patients with valvular abnormalities were classified as having DMR. 24 patients with both structural and functional deformation were classified as having MMR. **Results:** Baseline echocardiographic and clinical characteristics are summarized in Table 1. Median (p25-75) follow-up of patients was 16 (6-44) months. Time-to-event curves of the composite endpoint of all-cause mortality and heart failure hospitalization and all-cause mortality according to severe MR for patients with FMR, DMR, MMR are shown in Figure 1. **Conclusions:** The baseline characteristics of patients with FMR, DMR and MMR treated with TEER are different. Despite this, the prognosis after treatment is similar in the three groups of patients.

IVe. High levels of FGF23 induce experimental hypertension and vascular remodeling.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: FGF23; Hypertension; Artery; Chronic Kidney Disease; Calcium channel; Phosphate.

Abstract:

Introduction: Fibroblast growth factor-23 (FGF23) levels increase parallelly to the progression of chronic kidney disease (CKD). Our group has previously demonstrated that high FGF23 levels increase arterial stiffness. High FGF23 levels have been related with hypertension, but it is unclear its role on hypertension in the context of CKD. **Methods:** We have performed different animal's models to demonstrate the direct effect of FGF23 on hypertension. Firstly, we used nephrectomized rats (Nx) with low (0,2%) or high phosphate (1,2%) in the diet. After 4 weeks, phosphate content in the diet was interchanged for 4 additional weeks. Additional groups, administrating anti-FGF23 to Nx+1,2%P or healthy rat for 4 weeks were included. The effects of high levels of FGF23 were also evaluated in rats through recombinant FGF23 infusion for 4 weeks (FGF23, 15µg/day) and HYP mice from 5 months-old. Changes in blood pressure (BP) and vascular remodeling were evaluated. **Results:** In the model of Nx with different content of P in the diet it was observed a concomitant increase of P, FGF23 and BP. The blockage of anti-FGF23 decreased BP in Nx rats demonstrating a direct effect of FGF23 on BP. Similarly, in healthy rats, FGF23 blockage led to a significant hypotension. Anti-FGF23 administration significantly reduced the expression of Orai1 in thoracic aorta. Direct infusion of recombinant FGF23 or HYP mice (which have high levels of FGF23) also showed an increase of BP and vascular remodeling. **Conclusion:** High levels of FGF23 promote vascular remodeling and hypertension in normal and uremic rats. Blockage of FGF23 led to a vascular change promoting the reduction of blood pressure.

SESSION V.

CANCER II.

Va. High-Throughput Sequencing reveals recurrent mutations in RNUs in pancreatic tumors.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: pancreatic ductal adenocarcinoma; neuroendocrine tumor; splicing; genomics.

Abstract: Small nuclear riboproteins (snRNPs) comprise the core of the spliceosome, the macromolecular complex that carries out the splicing process. These snRNPs contain small nuclear RNAs, encoded by RNU genes. We have previously demonstrated that splicing dysregulation plays a key role in pancreatic tumors, both in pancreatic ductal adenocarcinoma (PDAC), and in pancreatic neuroendocrine tumors (PanNETs). A potential underlying cause of such dysregulation may reside in an incorrect folding of RNUs into secondary structures, resulting in impaired splicing and altered gene expression. Our objective was to achieve a detailed genomic picture of the RNUs in pancreatic tumors. Therefore, we analyzed the genomic DNA from tumor-derived tissue from 27 PDAC and 8 PanNETs patients, peripheral blood mononuclear cells (PBMCs) from these patients, and 29 age/sex matched healthy individuals (controls). Due to the small size of the RNUs and the abundant pseudogenes, we carried out a custom made two-step PCR approach followed by high-throughput sequencing. The output was analyzed using a bioinformatic workflow including quality check, trimming, alignment, variant calling, and detection of germline mutations from somatic DNA in tumors. We obtained an average depth of ≈ 5,400 reads from sequencing 21 amplicon/sample, and we identified 31 unique mutations. Interestingly, recurrent mutations were found in PDAC, but not in PanNETs. We found somatic mutations in the coding region of RNU5A-1 and RNU5D-1, particularly in internal loops which may be crucial for recruiting RNU5 into emerging transcripts; and in the promoter region of RNU5B-1 and RNU5D-1. Further, we performed high-throughput sequencing on PBMCs from cancer patients and healthy individuals to determine the presence of potential germline mutations. Ongoing studies are aimed at experimentally testing the relevance of the above findings, by introducing wild-type or mutant RNUs to cell lines and assess if these mutations disrupt snRNPs folding, impair splicing, and contribute to pancreatic tumor progression.

Vb. Prospective feasibility study of localization of lung nodules for sublobar VATS resections by using a novel Computed Tomography (CT) – guided radiopharmaceutical labelling system.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: pulmonary nodule, lung cancer, minimally invasive surgery, VATS, ROLL, 99mTc-MAA.

Abstract:

OBJECTIVE: Lung cancer screening programs make necessary to implement techniques aimed at localizing accurately the pulmonary nodules for surgical planning. We present our preliminary experience with the use of a CT-guided radiotracer labelling for pulmonary nodules requiring sublobar VATS resections, based on Radio-guided Occult Lesion Localization (ROLL). **METHODS:** Preliminary analysis of 10 patients with pulmonary nodules identified in a preoperative CT scan. An injection of 0.1-1 mCi human albumin macroaggregates labelled with 99mTc (99mTc-MAA) was performed preoperatively. Post-marking scintigraphy and SPECT-CT scan confirmed the intraparenchymal location of the radiotracer and facilitated the accurate positioning of the thoracoscopic ports. Patients were transferred to the OR for radio-guided VATS with gammagraphic probe which localized the nodule in the area of greatest uptake. A sublobar resection was completed without need of lung palpation. After the specimen was excised, the probe was used to examine the resection margins and the lack of activity in the remaining lung parenchyma. **RESULTS:** There were 7 males and 3 females 72±4 years old with lung cancer in 6, metastases in 3, and benign nodule in 1 case. Size and depth of nodules were 9.4±6.2 [4-21] mm, and 23±9 [8-36] mm respectively, with mean SUVmax of 14±22 [1-56]. All nodules were accessible for fine needle labelling and excised by radio-guided VATS. Preoperative SPECT-CT and gamma-detector probe showed focal intrapulmonary uptake in all patients. Free resection margins were achieved in all cases. Length of surgery and hospital stay were 51±32 [20-120] min, and 2±1 [1-7] days respectively. Only 1 case of post-puncture pneumothorax was observed, which resolved spontaneously. **CONCLUSION:** CT-guided radiotracer labelling is a safe technique for accurate localization and resection of deep small pulmonary nodules, compensating the lack of lung palpation and avoiding the need for a thoracotomy.

Vc. Liquid biopsy-based epigenetic biomarkers for prognosis and monitoring of metastatic pancreatic cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pancreatic cancer, liquid biopsy, methylation DNA, ddPCR, NPTX2.

Abstract:

Background and aims: Pancreatic cancer is one of the most lethal tumors worldwide. Given the late diagnosis and the limited survival benefit offered by current available treatments, it becomes imperative to optimize the diagnosis and the monitoring of disease to improve treatment options. CA19-9 levels and computed-tomography (CT) imaging are the main standard criteria for assessment of disease evolution and treatment response. In this study we explored the utility of liquid biopsy-based epigenetic biomarkers for prognosis and monitoring disease in metastatic pancreatic ductal adenocarcinoma (mPDAC) patients. **Material and Methods:** Plasma samples were collected from 44 mPDAC patients at the time of diagnosis, and in 15 of them, additional samples were obtained during follow-up of the disease. Plasma cell-free DNA (cfDNA) levels were determined, and circulating levels of methylated NPTX2, SPARC, BMP3, SFRP1 and TFPI2 genes in cfDNA were measured using digital droplet PCR. BEAMing technique was performed for quantitation of RAS mutated allele fraction in cfDNA and tumor marker CA19-9 was measured using standard techniques. **Results:** NPTX2 was the most highly and frequently methylated gene in cfDNA samples from mPDAC patients. Higher circulating NPTX2 methylation levels at diagnosis were associated with poor prognosis and efficiently stratified patients for prediction of overall survival (6.06% cut-off, p= 0.0067). Dynamics of circulating NPTX2 methylation levels correlated with disease progression and response to therapy and predicted better than CA19-9 the evolution of disease. Remarkably in many cases, therapy failure and progress of disease was anticipated through the increase of circulating NPTX2 methylation levels, preceding the confirmation of disease progression by CT scans. **Conclusions:** Circulating methylation levels of NPTX2 gene hold potential as a valuable clinical tool for non-invasive prognosis, disease monitoring, and assessment of treatment response in mPDAC patients. Furthermore, monitoring circulating NPTX2 methylation could provide clinicians with a broader window of opportunity to make necessary modifications of treatment regimens.

Fundings: Junta de Andalucía (PIP 0044-2020 and ProyExcel_00734).

Vd. Clinical, transcriptomic, and functional characterization of telomerase/shelterin system in endocrine intracranial tumors.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Intracranial Tumors, Shelterin-telomerase, Telomere length, biomarkers.

Abstract: Intracranial tumors (ITs) comprise a highly heterogeneous endocrine-metabolic neoplasias associated with neurological disorders and severe comorbidities [such as pituitary tumors (PTs), craniopharyngiomas (CPs), and glioblastomas (GBMs)], characterized by difficult diagnosis based on MRI, challenging predictors, and lack of effective therapeutic approaches. making it tough to find common and effective strategies to handle these pathologies. In this context, it has been shown that some components of the shelterin-telomerase (SHEL-TEL) system, in charge of telomere maintenance, appear to play a key role in different endocrine-tumor pathologies. However, the clinical and functional relevance of this system in ITs has been poorly explored.

Therefore our aim was to extensively analyze the expression of 17 components of the SHEL-TEL machinery in ITs [10 normal pituitaries vs. 83 non-functioning PTs (NFPTs), 50 growth hormone-secreting adenomas (GHomas), 19 adrenocorticotropic hormone-secreting adenomas (ACTHomas), and 6 prolactinomas (PRLomas); 7 healthy brains vs. 69 GBMs and 60 CPs] using a microfluidics-based qPCR array and to analyze the antitumor effect of pharmacological modulation of this machinery in ITs using etoposide and/or BIBR1532 (two telomerase activity and telomere length modulators) in cellular models of ITs.

Our results demonstrate a drastic alteration in the expression of this machinery in ITs. Specifically, TERF2, TREF2IP, and TINF2 show common alterations among PTs, allowing the differentiation of 2 subtypes of NFPTs and GHomas based on the molecular profile of the SHEL-TEL system. In GBMs, the downregulation of TREF2IP and 4 TERT splicing variants showed diagnostic and prognostic potential. TERF2IP stood out as a biomarker in CPs. Furthermore, we observed an antiproliferative effect associated with the use of inhibitors depending on the tumor type.

Altogether, this study revealed that the SHEL-TEL system is dysregulated in ITs, and some of its components may have clinical and/or functional relevance to improve the management of these devastating pathologies.

Ve. Deciphering the mechanisms of somatostatin analogue resistance in pheochromocytomas and paragangliomas.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: pheochromocytomas; paragangliomas; somatostatin analogues; resistance.

Abstract: Phaeochromocytomas and paragangliomas (PPGLs) are infrequent neuroendocrine tumours (NETs). Surgery is the mainstay of treatment for localized PPGLs; however, up to 20 % of cases are metastatic and systemic therapy is considered. While somatostatin receptors (SSTs) are appreciably expressed in PPGLs, their response to somatostatin analogues (SSAs) is less pronounced or null compared to other NETs. Thus, our objective is to unveil the molecular underpinnings of the resistance of PPGLs to SSAs with the ultimate goal of restoring the functionality of this system for therapeutic purposes. To this end, we performed a systematic study of SSTs expression (RNA-seq and qPCR) in 4 cohorts of human samples (366 samples) and in 3 cell models, including one with knockdown in SDHB, the most frequently mutated gene in PPGL. We observed a particular SST profile for PPGLs, with a predominant expression of SST2 and SST1. Of note, SST2 expression was associated with a more aggressive behaviour. Analysis of the downstream pathways of SSTs in PPGL revealed clear differences from NETs that typically respond to SSAs, such as the GH-secreting pituitary somatotropinomas. Functional in vitro assays were performed to assess proliferation, colony formation, migration, and free cytosolic calcium dynamics assays in response to SSAs, which revealed the consistent lack of response of PPGLs to these molecules. The same assays were subsequently reproduced using selective agonists for individual receptors, and, in this instance, SSAs caused antitumour effects in SDHB knockdown cell model. This led us to perform a specific phosphoarray for the main cell proliferation and survival pathways in response to the SSA octreotide and the SST2 agonist BIM-23120. Interestingly, the SST2 agonist, but not octreotide, inhibited key pathways in SDHB knockdown cells. Ongoing studies are aimed at dissecting individual elements of SST2 downstream pathway to identify the mechanism that can restore its therapeutic potential.

POSTER SESSION II.

PSII.a. Dialysis modalities, uraemic toxins and microinflammation, can we do any more?

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: dialysis, inflammation, uremic toxins.

Abstract:

Introduction: Patients on hemodialysis (HD) have a high morbimortality from cardiovascular disease (CVD). Despite advances in HD -medium cut-off membranes (MCO) or techniques that combine diffusion+convection+adsorption such as hemofiltration with ultrafiltrate regeneration-(HFR)-, only online hemodiafiltration (OL-HDF) has been shown to improve survival. Aim: To study whether different HD membrane-techniques improve the clearance of uremic toxins and/or parameters associated with the microinflammation present in these patients. **Method:** 12 stable patients on HD were included, with a minimum time on HD of 3 months. Each patient underwent 4 random HD sessions in which only the dialysis membrane and/or the modality were changed. They underwent an HD session with a high-flux polyphenylene membrane, another session with this same filter in OL-HDF, another with MCO membrane, and another with HFR-H. All sessions were held in a short period. In all of them, pre- and post-dialysis blood samples were taken to assess the clearance of both conventional uremic toxins and protein-bound toxins (indoxyl-sultate and p-cresol), as well as molecules associated with the microinflammation process (proinflammatory monocytes: CD14+/CD16++ and proinflammatory cytokines). **Results:** When evaluating the effect of the different HD techniques on the percentage of proinflammatory monocytes, a relevant, although not significant, decrease was observed in the OL-HDF and HFR-H techniques. Likewise, when evaluating the profile of markers of inflammatory activity, such as IL-12B, IL-17C, CD8A or TNFRSF9, a significant decrease was observed after the dialysis session in HFR-H compared to the rest of the techniques. **Conclusion:** After analyzing the results of our study, HFR-H, is the only one that has shown significantly greater clearance of proinflammatory cytokines, as well as a greater elimination of activated monocytes and protein-bound toxins, although without reaching statistical significance. These results, although preliminary, are promising and open up a new line of research to improve CVD in HD patients.

PSII.b. Effects of GLP-1 therapy on male gonadal function in conditions of diabesity: Therapeutic implications for diabesity-induced hypogonadism.

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Scientific Program: Endocrine and metabolic diseases.
Keywords: Obesity; Type 2 diabetes; Male hypogonadism; Testosterone; GLP-1.

Abstract: Obesity and type 2 diabetes (T2D) are highly prevalent, often co-existing pathologies; the term "Diabesity" was coined to define the combined detrimental effects of obesity and T2D. In addition to increased risk of cardiovascular disease, males with diabesity frequently experience central hypogonadism, characterized by low gonadotropins and testosterone levels. In men, testosterone carries out beneficial effects on metabolic function. Hence, the decrease in circulating androgens may not only affect sexual function, but also contribute to aggravate the metabolic profile of these patients. Yet, current therapies for the integral treatment of metabolic and gonadal dysfunction in obese/diabetic and hypogonadal men are not sufficiently effective. Glucagon-like peptide-1 (GLP-1) analogs have emerged as novel anti-diabetic and anti-obesity drugs. Fragmentary evidence suggests that treatment with GLP-1 analogs may also have beneficial effects on the gonadal function in certain conditions. However, the potential impact of GLP-1 therapy on gonadal function in male diabesity-induced hypogonadism has yet to be explored. In our study, we used two well-validated rodent models of diabesity-induced hypogonadism in males, which were fed with diets of different fat content. Animals were treated with several doses of a GLP-1 analog for 28-days, and an array of metabolic, gonadal and hormonal parameters were analyzed. As expected, treatment with GLP-1, at all doses tested, improved body weight, fat mass, glucose tolerance and other metabolic parameters in both diabesity models, regardless of dietary fat content. In contrast, GLP-1 therapy failed to induce detectable effects on gonadal function, at any dose tested, with changes in circulating androgen and LH levels, as well as on mRNA levels of key testicular steroidogenic enzymes and hypothalamic Kiss1. In sum, our results document that therapeutic intervention with GLP-1 analogs can markedly improve the metabolic profile in rodent models of diabesity, but does not ameliorate markers of gonadal function, therefore suggesting its limited efficacy as optimal pharmacological tool for the integral management of gonadal derangements associated to diabesity-induced hypogonadism in males.

PSII.c. Intratumoral BromAc effects in unresectable Pseudomyxoma peritonei: a single arm phase I/IIA study.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pseudomyxoma Peritonei, Bromelain, N-Acetylcysteine, mutations KRAS, GNAS.

Abstract:

Introduction: Pseudomyxoma peritonei (PMP) is a rare malignant disease for which the only standard treatment is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. However, 20-30% of patients experience recurrences, and supportive care becomes the sole option due to the high morbidity risk. Bromelain and N-Acetylcysteine have shown antineoplastic effects when combined (BromAc). KRAS and GNAS have been reported to be highly mutated in PMP patients. **Objectives:** To evaluate the efficacy and safety of BromAc in reducing tumor burden as a compassionate therapy for patients with inoperable PMP. **Methods:** BromAc was administered to patients through a percutaneous catheter into the masses for 3 consecutive days. Doses were adjusted to the tumor volume. Also, we explored KRAS and GNAS mutations in blood and mucinous samples using ddPCR as an indicator of therapy effectiveness. **Results:** Nine patients and eleven masses were treated. One month after treatment, 7/11 masses had volume reductions ranging from 18.5% to 81.4%. After one year of follow-up, 5/9 patients had a radiological reduction (ranging from 87% to 62%). Tumor progression occurred in 2/11 of the masses. Adverse events occurred in 4/9 patients, including infection, fever, vomiting and an accidental colon perforation. None of them required invasive treatment for resolution. Regarding quality of life, all patients reported a significant improvement in their initial symptoms, which lasted at least 3 months. Moreover, we observed a KRAS and GNAS mutant allele frequency reduction in mucin aspirated after three days of treatment in almost all patients. These results could point to a decrease in tumor burden because of BromAc's efficacy. Interestingly, we did not find mutations in circulating cell-free DNA. **Conclusions:** BromAc reduces tumor volume, relieving symptoms and offering a safe profile without life-threatening complications.

PSII.d. Follow-up from the community pharmacy of chronic pathologies in adults over 40 years of age: protocol study.

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Scientific Program: Active aging and frailty.
Keywords: community pharmacy, multidisciplinary teams.

Abstract:

Introduction: Community pharmacy has proven to be an integral part of the Health System due to its close and constant relationship with the patient, as being of special relevance its inclusion as an active agent in the care of the person with chronic pathologies. Furthermore, data from the National Statistics Institute (INE) for the year 2022 show a new peak in ageing, which also implies a marked increase in the prevalence of elderly people with multimorbidity. **Objective:** To determine quality of life of adults and elderly people who come to the pharmacy with chronic pathologies, as well as the degree of satisfaction with the individualised and complementary follow-up provided by the community pharmacist. **Material and methods:** A prospective cohort study with a total follow-up of 9 months will be carried out on patients aged 40 years or over, diagnosed with one or more chronic pathologies who come to the pharmacy for withdrawal and who sign the corresponding informed consent form. In the pharmacies involved in the present study, the data reflected in the XXI file will be collected, as well as the quality of life, satisfaction, and adherence to treatment. On the other hand, medical history and treatment will be collected at the health center. This project has the favorable report of the Andalusian Ethics Committee. **Results and discussion:** The results obtained are intended to monitor and assess the patient's state of health. In this way, the proposal aims to improve the quality of life of patients who go to the pharmacy to collect their medication. Therefore, the future of community pharmacist is directed towards the implementation of professional services with multidisciplinary teams that include the pharmacy, involving more active participation in the health processes of each patient.

PSII.e. In chronic kidney disease, iron deficiency-induced anemia is associated with higher levels of FGF23 that are not reduced by iron administration.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: chronic kidney disease, anemia, iron deficiency, FGF23.

Abstract: Iron (Fe) deficiency contributes to anemia in chronic kidney disease (CKD). High FGF23 levels are common in CKD. Under normal conditions, there is an association between Fe deficiency and FGF23 but it is unknown whether Fe deficiency might also contribute to the excessive FGF23 in CKD. This study was intended to evaluate the interplay between Fe deficiency, CKD, and FGF23. Normal Wistar rats received either a standard or an Fe-deficient diets for 6 weeks. Then, animals were switched to an adenine-enriched diet to promote renal damage. Anemic and uremic animals were treated with ferric citrate (FC), ferrous sulfate (FS), or ferric carboxymaltose (FCx) for 5 weeks. Hematological and mineral metabolism parameters were determined at sacrifice. CKD per se was associated with derangements in hematological parameters. Iron deficiency-induced anemia further decreased these parameters. In peripheral blood smears a morphological pattern of microcytosis-hypochromia and poikilocytosis was observed. Iron therapy improved hematocrit, hemoglobin, and Fe levels. In uremic rats with Fe deficiency-induced anemia, the reticulocyte count was significantly decreased in correspondence with a hyporregenerative bone marrow. Increased reticulocyte counts, Fe repletion and erythropoietic activity in bone marrow were observed after ferrotherapy. As expected, CKD rats exhibited disturbances in mineral metabolism. Interestingly, uremic and anemic rats showed higher intact and c-terminal FGF23 levels when compared with the CKD animals. Despite normalization of serum Fe, intact FGF23 further increased following administration of FS, and same trend was observed with all the compounds. C-terminal FGF23 levels remained unchanged in all the Fe-treated groups. In experimental CKD, Fe deficiency-induced anemia is associated with increased FGF23 that did not decrease after Fe administration. These results strongly suggests that other factors modulate FGF23 in this setting. Therefore, there is a need for investigating the mechanisms underlying the relationship Fe-FGF23 to optimize the management of CKD-associated anemia.

PSII.f. COMPLETE VS. INCOMPLETE PERCUTANEOUS REVASCULARIZATION IN PATIENTS WITH CHRONIC TOTAL OCCLUSIONS.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Cardiology, Cardiovascular disease, Ischemic Heart Disease, Chronic total oclussion, MACE.

Abstract:

Introduction: There is no solid evidence to support the prognostic benefit of percutaneous coronary intervention (PCI) of chronic coronary artery total occlusions (CTO). The aim of this study was to compare the incidence of major adverse cardiovascular events (MACE) in patients with CTO and complete revascularization (CR) versus incomplete revascularization (IR). **Methods:** Retrospective observational study that included patients diagnosed with CTO at the Hospital Universitario Reina Sofía (HURS) during 2018 and 2019. They were divided into two groups according to treatment: CR (revascularization of the totality of the CTO) and RI (at least one CTO not revascularized). The primary endpoint was a composite of all-cause death, nonfatal infarction, nonfatal stroke, or unplanned revascularization. Mid-term clinical events were compared adjusting for prognostic variables by inverse probability of treatment weighting (IPTW). **Results:** Of the 359 included patients (age 67.7±11.6 years, 18% women), 167 (46.5%) received complete revascularization. The clinical characteristics of the patients are shown in Table 1. After a median follow-up of 42 (46-50) months, the primary combined endpoint occurred in 23.4% of patients in the CR group and in 39.1% in the IR group (HR 0.50, 95% CI 0.34-0.74, p< 0.001) (Figure 1). In the Cox model adjusted by IPTW, this association was still significant (HRaj 0.61, 95% CI 0.61-0.74, p<0.001) (Figure 1).Differences in the primary endpoint were mainly determined by death from any cause (14.4% vs. 32.3% p< 0.001) and non-fatal infarction (4.8% vs 10.9%, p = 0.033). Patients in the CR group had less frequent worsening of heart failure (14% vs 26%, p = 0.006). **Conclusions:** Patients with CTO and complete revascularization presented a lower incidence of MACE in the medium term compared to those treated incompletely (optimal medical treatment).

Table 1. Baseline characteristics

	Incomplete revascularization (n = 192)	Complete revascularization (n = 167)	p
Age (years) [a]	70.0 (61.0-79.2)	66.0 (59.0-74.0)	<0.001
Female sex [b]	35.0 (18.2%)	31.0 (18.6%)	0.935
Weight (Kg) [a]	79.0 (70.0-89.0)	82.0 (72.5-90.0)	0.148
Height (cm) [a]	167.0 (160.0-172.0)	168.0 (161.0-173.0)	0.609
Body mass index (Kg/m^2) [a]	28.1 (26.0-31.9)	29.4 (26.0-32.2)	0.459
Glomerular filtration rate (mL/min/1.73 m^2) [a]	88.8 (56.4-117.1)	95.9 (70.9-121.5)	0.036
Hemoglobin (g/dL) [a]	13.7 (12.4-15.0)	14.0 (12.6-15.3)	0.268
Creatinin (mg/dL) [a]	1.1 (0.9-1.4)	0.9 (0.8-1.2)	<0.001
Platelets (x10^9/L) [a]	207.0 (171.2, 251.0)	213.0 (178.5, 254.0)	0.445

Table 1. Baseline characteristics

	Incomplete revascularization (n = 192)	Complete revascularization (n = 167)	p
Previous stroke [b]	14.0 (7.5%)	12.0 (7.3%)	0.940
Hypertension [b]	147.0 (77.8%)	121.0 (72.5%)	0.245
Diabetes mellitus [b]	94.0 (49.7%)	75.0 (44.9%)	0.363
Dislipemia [b]	113.0 (59.8%)	92.0 (55.1%)	0.371
Smoker [b]	41.0 (21.8%)	49.0 (29.5%)	0.096
Chronic obstructive pulmonar disease [b]	20.0 (10.6%)	22.0 (13.2%)	0.449
Atrial fibrilation [b]	30.0 (16.0%)	18.0 (11.0%)	0.168
Previous ischemic heart disease [b]	68.0 (36.0%)	78.0 (46.7%)	0.040
Previous PCI [b]	43.0 (35.8%)	67.0 (52.8%)	0.007
Previous CABG [b]	10.0 (8.4%)	2.0 (1.7%)	0.016

Table 1. Baseline characteristics

	Incomplete revascularization (n = 192)	Complete revascularization (n = 167)	p
Peripheral arteriopathy [b]	28.0 (15.1%)	22.0 (13.3%)	0.629
Family history of ischemic heart disease[b]	3.0 (1.6%)	8.0 (4.8%)	0.088
Obesity [b]	63.0 (38.7%)	76.0 (47.2%)	0.120
Chronic kidney disease [b]	45.0 (26.8%)	26.0 (16.2%)	0.021
LVEF	53.8 ± 14.9	57.1 ± 12.4	0.082
LVEF < 40%	33.0 (23.6%)	19.0 (17.9%)	0.283
Indication for chest pain [b]	145.0 (78.4%)	135.0 (81.8%)	0.422
Indication for heart failure [b]	45.0 (25.0%)	29.0 (17.7%)	0.099
Indication for evidence of ischemia [b]	45.0 (24.7%)	74.0 (44.8%)	<0.001

[a] Data is presented as Median (IC)

[b] Data is presented as n (%)

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft

Tabla 2. Datos angiográficos

	Incomplete revascularization [a] (n = 192)	**Complete revascularization** [a] (n = 167)	**p**
Cx CTO	**73 (38.0%)**	**30 (18.0%)**	<0.001
Medical treatment	48.0 (25.0%)	0.0 (0.0%)	
Failed PCI	17.0 (8.9%)	0.0 (0.0%)	
Successful PCI	8.0 (4.2%)	30.0 (18.0%)	
RC CTO	**120 (62.5%)**	**91 (54.5%)**	0.124
Medical treatment	83.0 (43.2%)	0.0 (0.0%)	
Failed PCI	25.0 (13.0%)	0.0 (0.0%)	
Successful PCI	12.0 (6.2%)	91.0 (54.5%)	
LAD CTO	**41 (21.4%)**	**52 (31.1%)**	0.035
Medical treatment	25.0 (13.0%)	0.0 (0.0%)	
Failed PCI	6.0 (3.1%)	0.0 (0.0%)	
Successful PCI	10.0 (5.2%)	52.0 (31.1%)	

RMA CTO	**3 (1.6%)**	**1 (0.6%)**	0.627
Medical treatment	3.0 (1.6%)	0.0 (0.0%)	
Failed PCI	0.0 (0.0%)	0.0 (0.0%)	
Successful PCI	0.0 (0.0%)	1.0 (0.6%)	
Multivessel disease [b]	128.0 (66.7%)	75.0 (44.9%)	<0.001

[a] n (%)

[b] Including other no CTO lessions

CTO: Chronic total oclussion; Cx: Circumflex coronary artery; LAD: Left anterior descending artery PCI: Percutaneous coronary intervention ; RC: Right coronary ; RM: Right marginal artery

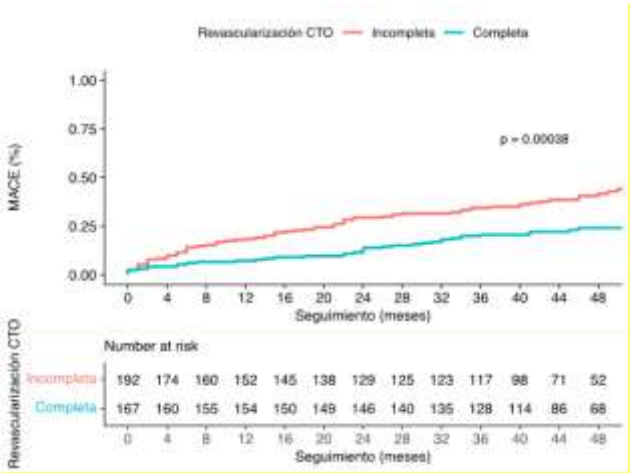

Figure 1. Incidence of primary endpoint in the group of patients treated with complete versus incomplete revascularization.

PSII.g. Active Rheumatoid Arthritis patients undergo profound alterations in lipid metabolism, which can be successfully reversed through the administration of anti-TNF, anti-IL6R, and JAK inhibitors.

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

Abstract:

Lipid metabolism influences immune cell plasticity, governing activation, differentiation, and function. Thus, comprehensive analysis of lipidomic profiles in chronic inflammatory diseases like Rheumatoid Arthritis (RA) using high-throughput metabolomic techniques could aid in better understanding disease pathogenesis. **Objectives:** To analyse the lipidomic profile in RA patients' serum, its association with disease activity and its modulation by biological and targeted synthetic therapies. **Methods:** Serum samples and clinical data from 250 consecutive RA patients were collected. Lipidomic profiling was analyzed by nuclear magnetic resonance spectroscopy (NMR, Nightingale) including over 200 lipid markers. Additionally, active patients from this cohort received biologic therapy [anti-TNF (n=50), anti-IL6R (n=15)], and JAK inhibitors (n=20) and were followed up after 6 months. Serum samples were taken pre- and post-therapy to assess lipid and clinical profile changes. In vitro studies explored mechanisms of lipid accumulation in HepG2 liver cells treated with serum from RA patients with varying disease activity. **Results:** Patients were stratified based on high (68), moderate (117), and low (65) disease activity. Around 100 lipid markers showed alterations across the groups. Notably, the patient subgroup with high disease activity exhibited reduced levels of several lipid markers, including apolipoproteins, cholesterol, fatty acids, triglycerides, cholines, phospholipids, and lipoproteins. Multiple correlations were observed between these lipid markers and inflammatory and autoimmune parameters such as anti-citrullinated protein antibodies and rheumatoid factor. After 6 months of therapy, alongside clinical-analytical improvement, significant lipid marker upregulation occurred, encompassing

common and distinct molecules influenced by each drug. In vitro studies revealed lipid accumulation in HepG2 liver cells treated with serum from RA patients with high disease activity, indicating potential contribution of inflammation-induced hepatocyte metabolism alterations to reduced circulating lipid profiles. **Conclusion:** The lipidomic profile in active RA patients is significantly reduced and correlated with disease activity and the inflammatory-autoimmune profile. Biological therapies and JAK inhibitors restore the abnormal lipid metabolism, leading to clinical improvement. Ongoing studies aim to elucidate the underlying mechanisms.

Fundings: ISCIII (PI21/0591, CD21/00187, RD21/0002/0033), RYC2021-033828-I, J. Andalucía (P20_01367) co-financed by European Union; Fundacion Andaluza de Reumatología.

PSII.h. The utilization of high-throughput technologies for molecular profiling in Rheumatoid Arthritis enables the identification of patient subgroups with distinctive disease activity and therapeutic response.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Rheumatoid Arthritis, Treatment, Multi-omics.

Abstract:

Purpose: To characterize the molecular landscape of RA patients using a multi-omic approach involving transcriptomics and proteomics and its association with disease status and clinical response. **Methods:** PBMCs from 123 RA patients were profiled by RNAseq. The RA cohort included 49 patients taking conventional DMARDs and 74 biologics-naïve patients before receiving biologic (TNFi) or targeted-synthetic DMARDs (JAKinibs). Clinical outcomes were evaluated after 6 months of treatment following EULAR criteria. A consensus cluster approach was used to identify patients' subgroups based on their transcriptomic profile. Simultaneously, 92 inflammatory mediators were analyzed in RA serum by PEA (Olink). **Results:** Unsupervised hierarchical clustering revealed 3 subgroups of RA patients displaying differential expression of 7 gene-modules defining distinctive biological pathways. Cluster 1 showed high expression in myeloid and inflammation genes-modules, while C2 showed low expression levels across all gene-modules. Cluster 3 exhibited high expression of B-cell gene-modules. Serum proteome analysis among these clusters identified 34 proteins showing differential expression levels, including chemokines, interleukins, and growth factors increased in C1 compared with C2 and C3.
Clinically, C1 grouped RA patients with more severe disease activity, higher number of circulating monocytes and neutrophils, and longer disease evolution compared with C2 (with the lowest disease severity and shortest disease duration) and C3 (similar disease activity to C2 but higher number of circulating lymphocytes). Regarding treatment response, C1 patients had the highest response rate to TNFi. The clinical response to JAKinibs was independent of clusters allocation. This suggests that clinical response to each drug might be associated with the deregulated expression of specific gene-modules and inflammatory proteins at baseline. Correlation studies among DAS28 variation at 6 months and baseline levels of different gene-modules and proteins showed drug-specific associations. **Conclusion:** 1. RA patients conform distinctive subgroups

based on altered molecular profiles, directly linked to their clinical status. 2. Clinical effectiveness of TNFi and JAKinibs is associated with specific molecular profiles before initiating these therapies.

Fundings: The EU/EFPIA-IMI Joint Undertaking 3TR, ISCIII (PI21/0591, CD21/00187 and RICOR-21/0002/0033), RYC2021-033828-I, and JA (P20_01367); co-financed by FEDER.

PSII.i. Molecular and serological survey of rat Hepatitis E virus (Rocahepevirus ratti) in people living with HIV in Spain.

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Scientific Program: Infectious and Inmunological diseases.
Keywords: Hepatitis E; rat Hepatitis E virus; acute hepatitis; HIV; zoonoses; public health.

Abstract: Rat hepatitis E virus (ratHEV; species Rocahepevirus ratti) is considered a newly emerging cause of acute hepatitis of zoonotic origin. ratHEV infection of people living with HIV (PLWH) might portend a worse, as with hepatitis E virus (HEV; species Paslahepevirus balayani), and consequently this group may constitute a high-risk population. We aimed to evaluate the prevalence and incidence of ratHEV by measuring viral RNA and specific IgG antibodies in a large Spanish cohort of PLWH. Longitudinal retrospective multicenter study conducted in Spain evaluating the prevalence and incidence of ratHEV infection in PLWHIV included in the AIDS Research Network (CoRIS). Patients were evaluated for ratHEV infection using PCR at baseline and after one year of follow-up. Samples from anti-HEV IgG seropositive patients were investigated by dot blot analyses to evaluate exposure to ratHEV strains. 1,690 samples belonging to 845 individuals were tested. At baseline, one sample was positive for ratHEV RNA (Prevalence of infection: 0.12%; 95% CI: 0.1%-0.58%). ratHEV RNA was not detected in any patients at the end of the study. Of the 101 samples positive for HEV IgG by ELISA at baseline, 7 individuals showed ratHEV IgG specific antibodies (6.9%). Among the 42 individuals who seroconverted during the follow-up, 1 exhibited specific IgG antibodies against ratHEV (2.3%). Altogether, of the 143 individuals with HEV-reactive IgG antibodies identified in the study, eight (5.5%) exhibited specific

antibodies for ratHEV. We concluded that ratHEV is geographical broadly distributed in Spain, representing a potential zoonotic threat.

PSII.j. Influence of donor type (donation after brain death vs. donation after cardiac death) on lung transplant outcomes.

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

Abstract:

INTRODUCTION: Lack of viable lung donors remains the primary limiting factor in increasing the number of lung transplants performed. Recently, controlled donation after cardiac death (DCD) has emerged as a potential source of lung grafts that could potentially expand the pool of lung donors. **OBJECTIVES:** To analyze the influence of lung donor type (brain death-BD vs. controlled donation after cardiac death-DCD) on lung graft viability and compare short-term outcomes of lung transplantation using grafts from BD and DCD donors. **PATIENTS AND METHODS:** Retrospective study of the lung donor population and lung transplants performed at the Reina Sofía University Hospital between January 2020 and December 2022. Demographic characteristics of the donors, donation type (BD vs. DCD), and geographic location of donation (Andalucia vs. others) were evaluated. Lung graft viability rate and immediate post-transplant outcomes were analyzed. **RESULTS:** There were a total of 203 donors for the Reina Sofía Hospital during the study period, of which 149 (73%) were viable. 64 donors were from outside Andalucia (31.5%). Regarding the donation type, there were 176 brain-dead donors (BD, 87%) vs. 27 controlled donation donors (DCD, 13%), with viability rates of 75.5% and 59.2%, respectively. There were 81 offers for single lung transplants (40%) and 122 for double lung transplants (60%). Donor lung evaluation included graft inspection in the majority of cases (N=177, 87%), while bronchoscopy alone was used in 26 donors (13%). Thirty-day post-transplant mortality did not differ between the two donor types (BD vs. DCD): 28 (21%) vs. 3 (18%); p=0.55.

PSII.k. Functional profile of extracellular vesicles from Salmonella-infected intestinal cells and their ability to elicit immune activation on adjacent cells.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Extracellular vesicles (EVs); Salmonella infection; immune response; intercellular communication.

Abstract:

Salmonellosis is a foodborne infectious disease caused by Salmonella Typhimurium (S. Typhimurium). This bacterial infection affects many pathways in the host organism, mainly related to immune response. Extracellular vesicles (EVs) are membrane-derived vesicles released by host cells into extracellular space. They carry a variety of molecules (proteins, lipids and nucleic acids) and play an important role in facilitating intercellular communication in diverse cellular processes. The objectives of this work were to characterize EVs secreted by intestinal cells during Salmonella infection, and to analyze their function on adjacent cells, with the aim of developing new therapeutic strategies. To achieve that objective, HT29-E12 cells were infected with S. Typhimurium and EVs were isolated from the culture media using the ultracentrifugation method. EVs were characterized using specific markers (CD81, CD9, Tsg101), electron microscopy and size quantification, and protein was extracted to perform label-free quantitative analysis. Infected cells produced more EVs than control, and proteomic analysis identified a total of 2073 proteins in EVs, from which 403 were differentially expressed in infected EVs. Fifty of these proteins belonged to Salmonella, being 22 of them virulence factors such as fliC, pgtE, pagC and ompA, among others. Upregulated host proteins in infected EVs included ICAM1, MAPK1 and HK2, involved in activation of integrin, IL-8 and HIF1 signaling. To evaluate the effect of infected EVs on neighbor epithelial cells, we performed an EV uptake assay using control and infected EVs to treat HT29-E12 cells. Uptake of infected EVs induced overexpression of inflammatory genes such as IL8 (FC=4,1), TNFα (FC=12,7), CCL2 (FC=7,5) and ICAM1 (FC=17,2). Based on the results obtained, cells infected by S. Typhimurium secrete higher number of EVs and with a different cargo than non-infected cells, mainly immune response molecules. Also, when in contact with other epithelial cells, these EVs can activate the immune response cascade.

PSII.I. SMG7 as a potential new biomarker in chronic liver disease associated with obesity.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: NMD, Hepatocarcinoma, chronic liver disease, SMG7, treatment, inhibition.

Abstract:

Non-sense mediated decay (NMD) plays a role in controlling gene expression, by eliminating aberrantly produced and/or incorrectly spliced mRNAs and it is known to be altered in cancer. However, it is unknown its implication in chronic liver disease (CLD), including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and hepatocarcinoma (HCC). Indeed, the hepatic lipid accumulation in NAFLD leads to cellular stress and liver damage, resulting in CLD. Taking into account that NMD regulates the cellular response in stress conditions, this work aimed at studying NMD alterations in HCC and NAFLD, as well as the effect of NMD inhibition in HCC cell lines. Expression (mRNA) of 22 NMD components was analyzed in two retrospective HCC cohorts: 1 [n=89 HCC and non-tumor paired adjacent tissues (NTAT)] and 2 [n=58 HCC and n=50 NTAT] by microfluidic-based qPCR array and validated in five in silico cohorts with healthy, NASH, HCC, and/or NTAT samples (TCGA, Roessler 2, Zhou liver, Wurmbach, and GSE164760). Inhibition of NMD through NMDI14 treatment was carried out in two HCC-derived cell lines to explore the effects on proliferation, migration, and colony formation, and stress response genes (GADD45A, B, and ATF3) mRNA expression were measured. The expression of at least 45% of NMD components was altered in HCC samples. Remarkably, SMG7 was consistently overexpressed in all HCC cohorts (top-10 VIP scores) and exhibited higher expression in NASH and NASH-derived HCC samples compared to healthy livers or NTAT. SMG7 expression modulation and pharmacological blockade had a significant impact on proliferation, migration, and colony formation in HCC cell lines. In addition, the expression of the stress response genes GADD45B and ATF3 were elevated in Hep3B cells treated with NMDI14. In conclusion, our results suggest that SMG7 could be a potential biomarker and therapeutic target in CLD.

PSII.m. Cardiovascular health assessment in vulnerable families from E-ducass program.

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

Abstract: Food insecurity, defined as the lack of regular availability to nutritious food that allows for adequate growth and an active and healthy life, is related to the incidence of cardiovascular disease due to low adherence to healthy diets and physical inactivity, mainly in vulnerable populations. Therefore, the aim was assessing cardiovascular health (CVH) in a vulnerable population at risk of food insecurity.

E-ducass program (Clinicaltrials.gov NCT05379842) is based on a healthy lifestyle education program which promotes health literacy to improve the long-term health status and mitigate food insecurity. CVH from E-ducass program's participants (n=460) was assessed baseline using the Life's Simple 7 (LS7) and the new Life's Essential 8 (LE8) scores from the American Heart Association. The LS7 was used to calculate ideal CVH and the LE8 was used to classify CVH into low CVH (0-49 points), moderate (50-79 points) and high (80-100 points).

According to LS7, the CVH was 8.4 points out of 14, with only 0.2% of the population having ideal CVH. When analyzing each item, body mass index (BMI) and adherence to a healthy diet (Mediterranean diet) were the items for which a higher percentage of the population did not meet the ideal criteria (43.0% and 64.5%, respectively). According to LE8, the CVH was 65 points out of 100, with 13.7% of the population at high CVH, 72.9% at moderate and 13.3% at low CVH. The worst scores were found in healthy diet (43.6%), tobacco exposure (49.1%), physical activity (52.8%) and BMI (59.1%) metrics.

Low adherence to healthy lifestyle habits and their impact on BMI are key factors contributing to low CVH in vulnerable populations. However, a healthy lifestyle education program that improves health literacy could be a suitable tool to improve modifiable behavioral factors and prevent cardiometabolic diseases in the long term.

PSII.n. Expression profile of miRNAs involved in aging-related processes in middle-age and older patients with cardiovascular disease: From CORDIOPREV study

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: epigenetic markers; aging; oxidative stress; cardiovascular disease; miRNAs; CORDIOPREV study.

Abstract:

Introduction and Objective: Recent studies indicate that the mortality rate from diseases (such as cardiovascular disease, obesity and T2DM) related with aging is increasing. Our objective was to study the relationship between epigenetic markers (miRNAs) and aging-related processes (telomere shortening, oxidative stress and inflammation) in middle-aged patients (<56 years) and older adults (>66 years) participating in the CORDIOPREV study, to know the role of epigenetic mechanisms in the aging process. **Material and Methods**: Within the framework of the CORDIOPREV study (n=1002), the population was divided by age tertiles, from tertiles 1 (<56 years) and 3 (>66 years) 75 subjects per tertile were selected. Using RT-PCR the expression profile of 28 miRNAs from peripheral blood mononuclear cells were analysed. The levels of oxidative stress parameters (GSH, GSSH, LPO, carbonylated proteins), telomere length and inflammatory cytokines were determined. **Results:** Baseline levels of miR-1, -126, -143, -145, -221, -30, -429, and -92 were higher in older patients than middle-age patients (all $p<0.05$). Additionally, an increase in total glutathione and reduced glutathione, as well as a decrease in LPO were observed in subjects showing high levels of miR-126 after 4 years of follow-up. **Conclusion**: miRNAs regulate biological processes associated with aging, such as oxidative stress, and miR-126 emerges as a therapeutic target to take efficient actions focused on slowing down the aging process in patients with cardiovascular disease.

PSII.ñ. Identification of biomarkers of visceral adipose tissue weight gain.

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Scientific Program: Endocrine and metabolic diseases.
Keywords: obesity; adipose tissue; extracellular matrix; proteomic analysis.

Abstract:

Weight gain, including over-weight and obesity, is a global health problem characterized by an abnormal accumulation of body fat. It is commonly associated with many diseases such as insulin resistance and type 2 diabetes, which are related with visceral adipose tissue (VAT) disfunction. During obesity, adipocytes accumulate excessive amounts of lipids, increasing their size (hypertrophy) and number (hyperplasia), as well as immune cells infiltrate the tissue and the extracellular matrix (ECM) undergoes extensible remodeling to allow proper tissue expansion. To elucidate the precise mechanisms underlying the pathogenic processes associated with weight gain, we carried out a comparative proteomic analysis of VAT samples from lean (NW) individuals, and with over-weight (OW), obesity (OB) and severe obesity (OM), with either normoglycemia (NG) or pre-diabetes (PD), using LC-MS coupled with diaPASEF. Further cellular and molecular analyses of selected proteins were also carried out. These studies identified a total of 2526 differentially expressed proteins. Then, the ECM proteome (matrisome) was analysed, which enabled the identification of Leucin-rich glycoprotein-1 (LRG1), an ECM glycoprotein, as a potential weight gain biomarker. Further analysis of the matrisome based on insulin resistance development, identified Cystatin-A (CYTA), an ECM regulator, as a potential insulin resistance biomarker. Characterization of LRG1 and CYTA in pre-adipocytes, adipocytes and macrophages support a role for these proteins in obesity-associated adipose tissue fibrosis.

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PSII.o. DNA damage and repair in glioblastoma cells.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Temozolomide, glioblastoma, DNA damage, DNA repair.

Abstract: Temozolomide (TMZ) is a DNA alkylating agent used in combination with radiotherapy as first-line treatment after surgery. The resistance to therapy is due in great part to the induction of DNA repair mechanisms that repair the damage caused by an antitumor agent. TMZ adds methyl groups to adenine and guanine in DNA, resulting in the modified bases N7-meG (70%), N3-meA (10%) and O6-meG (7%). Such TMZ-induced lesions are mainly repaired through direct repair and Base Excision Repair (BER). On the other hand, single-strand breaks are generated as cytotoxic DNA intermediates during BER. Such single breaks may generate double-strand DNA breaks in a replication-dependent manner, channelling the repair through alternative, BER-independent routes. Since DNA repair mechanisms contribute to TMZ resistance, tumour-specific DNA repair signatures in GBM may be used as predictive biomarkers of patient response to treatment. In this study, we have used sensitive and resistant GBM cells to analyse the expression of different repair genes involved in direct repair, BER and single-strand break repair, including O6-meG DNA methyltransferase (MGMT), N-methylpurine DNA glycosylase (MPG), Apurinic/apyrimidinic endonuclease 1 (APE1), PARP1 (poly-(ADP-ribose) polymerase 1) and XRCC1 (X-ray repair cross complementing 1). Moreover, we have studied the TMZ-dependent DNA damage response and repair capacity in sensitive and resistant GBM cells using alkaline comet assays and PARylation immunofluorescence. Our goal is to generate new knowledge on the DNA repair mechanisms used by GBM cells to repair the DNA damage caused by antitumoral treatment. In doing so, our results may help to identify novel predictive biomarkers and/or therapeutic targets to treat this aggressive tumour.

PSII.p. A Comprehensive Bioinformatic Approach for Splicing Analysis and Biomarker Identification in different cancer subtypes.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Cancer; Splicing; Splicing-variants; Biomarkers; Stratification; Personalized Medicine.

Abstract: Splicing is the process by which introns are removed and exons are joined together during RNA maturation and plays a crucial role in gene expression regulation and protein diversity. Aberrant splicing events have been implicated in various diseases, including cancer. In fact, dysregulation of the splicing process is connected, at different levels, to all classical hallmarks of cancer. Moreover, cancer-specific splicing events have been identified in different tumor types/subtypes, providing valuable insights into tumor heterogeneity and potential biomarkers for diagnosis, prognosis, and therapeutic targeting. In this scenario, the integration of bioinformatic tools and high-throughput sequencing data has revolutionized splicing analysis, enabling comprehensive investigations of splicing alterations in cancer. In this work, we use a pipeline of computational tools that are developed under a framework specifically focused on the study of splicing variants. Specifically, we used gene expression RNA-Seq datasets belonging to different cohorts (open access) and the set of tools belonging to the Vertebrate Alternative Splicing and Transcription Tools - VAST-TOOLS (https://github.com/vastgroup/vast-tools) package. Our results showed 636 significantly different splicing events between control and tumor samples, the most abundant being Exon-Skipping and Intron-Retention. Subsequently, networking analysis showed that these splicing variants were mostly related to an alteration in cellular metabolism, specifically related to small molecules and carboxylic acids pathways. Additionally, an unsupervised clustering analysis allowed the subclassification of the samples into 4 groups with clearly differentiated splicing variant expression patterns between them. Finally, a combined analysis with differentially expressed genes and variants pointed to GLUL, which encodes the enzyme Glutamate-Ammonia Ligase which has been widely shown to have an oncogenic role in different tumor types. Altogether, we conclude that by elucidating the intricate interplay between splicing and cancer, we can enhance our understanding of tumor biology, identify specific subtype signatures, and develop novel therapeutic strategies for personalized cancer management.

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PSII.q. Psychosocial factors on perceived well-being in children and adolescents with type 1 diabetes: a cross-sectional study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: type 1 diabetes; perceived well-being; children and adolescents; psychosocial factors.

Abstract:

Diabetes mellitus type 1 (T1D) is a chronic disease in which the beta cells responsible for insulin production lose their capacity due to an attack by the immune system. The fact that it is mostly diagnosed in early childhood means that these patients must live with this disease for a large part of their lives. From a psychosocial perspective, studying contextual situations that affect disease management and the well-being of these patients is of utmost importance. The main objective of this study was to explore the potential relationship between different psychosocial variables and the perceived well-being of children and adolescents with T1D. The study was conducted at the Pediatric and Adult Endocrinology Units of Hospital Universitario Reina Sofia in Cordoba (HURS). A total of 180 patients participated (mean age = 13.10, SD = 3.50; 42.2% girls). After obtaining informed consent, patients whose families agreed to participate completed a self-reported questionnaire. In addition to collecting sociodemographic variables, the questionnaire assessed perceived social support, positive expectations regarding disease management, self-efficacy for T1D management, and perceived well-being. Descriptive analysis were conducted, followed by tests to examine correlations and regressions between variables. All included variables correlated positively with perceived well-being ($p < 0.001$). Regression analysis further showed that all these variables could act as predictors of well-being in these patients. Based on these results, we can conclude that psychoeducational interventions can play a significant role in improving patients' beliefs and expectations regarding disease management and, therefore, their well-being. It is also important to raise awareness among families about the crucial role they play as the primary social agents during childhood and early adolescence, as their support can contribute to the perceived well-being of their children.

PSII.r. Application of threshold concepts to teaching in the degree of Medicine.

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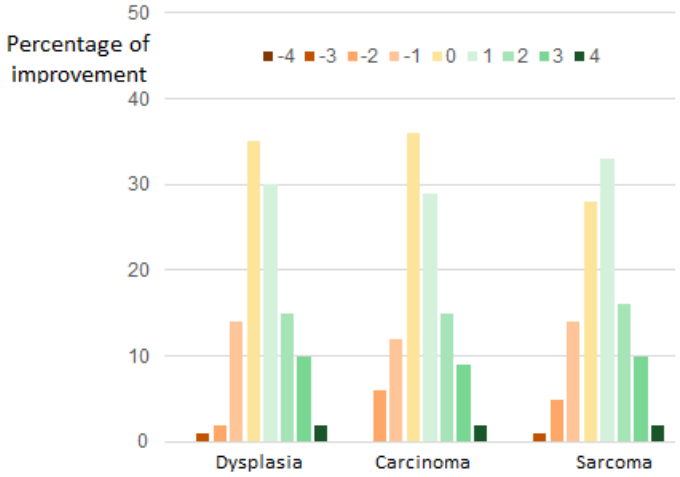
Keywords: threshold concepts; teaching; degree of Medicine.

Abstract:

Background & objectives: Teaching based on threshold concepts is a pedagogical methodology used in various fields of knowledge at the university level. Its application in the field of Medicine could be useful to improve student learning. **Methods:** 109 medical students participated in the study. They filled out two surveys, at the beginning and at the end of the Pathological Anatomy course, which were intended to assess the degree of acquisition of threshold concepts using a Likert-type scale (1-5). A statistical analysis was performed comparing the differences between different sections. **Results:** 71.56% of the participants were women. The majority (97.25%) were enrolled in the third year of Medicine and had a mean age of 20.54 years. At least half of the students improved their level of knowledge in the concepts of dysplasia, carcinoma and sarcoma (52%, 50% and 56% respectively). Graph 1.



Graph 1. Variation in the score before-after the classes (Likert-type scale).

Conclusions: Threshold concepts can be useful to improve the knowledge of Medicine degree students. Receiving feedback through this type of survey allows teachers to reinforce some concepts that have not been adequately integrated.

PSII.s. Study of lipoprotein subfractions profile in peripheral arterial disease and diabetes: From the CORDIOPREV Study.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: Peripheral arterial disease, type 2 diabetes mellitus, lipoprotein particles, cardiovascular risk factors.

Abstract: Peripheral arterial disease (PAD) is an atherosclerotic disease that affects the arteries supplying blood to the lower extremities. One way to diagnose it is by measuring the ankle-brachial index (ABI), with an ABI ≤ 0.9 used as a criterion to identify patients with PAD. PAD is associated with an increased risk of cardiovascular morbidity and mortality. Type 2 diabetes mellitus (T2DM) is also associated with an increased vascular risk, caused by chronic exposure to hyperglycemia, as well as other risks factors such as hypertension and dyslipidemia, which are also risk factors shared with PAD. The objective of this study was to assess lipoprotein subfractions profile in individuals with or without PAD and T2DM in a population of coronary heart disease patients from the CORDIOPREV study. For this purpose, patients were classified according to the presence or absence of PAD and the presence or absence of T2DM. The determination of lipoprotein subfractions was performed using high-resolution nuclear magnetic resonance (NMR). Patients with T2DM showed worse extra-large, large, and medium HDL particles profile, with lower particle number than non-T2DM patients, regardless PAD status. In terms of HDL cholesterol content, patients without PAD and without T2DM displayed the highest concentration of cholesterol being transported compared to the rest of groups under study, with the remaining groups showing similar cholesterol levels among themselves. Upon closer examination, it was observed that almost two-thirds of cholesterol was being transported by large and buoyant HDL2 particles. NMR is a comprehensive analysis technique that offers valuable insights into lipid metabolism by providing a detailed analysis of lipoprotein concentration and composition. By specifically analyzing lipoprotein subfractions, particularly HDL subfractions, NMR will enable a deeper understanding of the pathophysiology of PAD and T2DM that will aid in the study of cardiovascular disorders.

PSII.t. Screening of miRNAs targeting the Prader Willi related gene Magel2 in the hypothalamus of female rats with obesity induced precocious puberty.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: puberty; hypothalamus; Prader Willi; Magel2; microRNA; sequencing.

Abstract: Puberty is a complex developmental phase that culminates in attaining reproductive capacity. This process is mainly controlled by hypothalamic regulatory networks and is highly sensitive to metabolic and nutritional cues. Indeed, obesity is frequently linked to advanced puberty, especially in females. Magel2 is a Prader Willi related gene highly expressed in the hypothalamus that has been associated with alterations in the timing of puberty. However, the molecular underpinnings of its pubertal actions remain unknown. MicroRNAs (miRNAs) have recently emerged as relevant regulatory factors of pubertal timing. Nevertheless, their potential involvement in regulating Magel2 and their contribution to obesity induced precocious puberty remain elusive. To address this question, we initially analyzed the expression of Magel2 mRNA in the mediobasal hypothalamus (MBH) of early overfed female rats with precocious puberty and their control animals, lean female rats with normal pubertal development. Then, we screened direct miRNAs Magel2 mRNA interactions in the MBH of these animals. To this end, we employed a novel technology termed miR eCLIP, which can detect the formation of miRNA mRNA chimeras throughout the transcriptome by employing: (i) immunoprecipitation of the AGO2 protein; (ii) RNA RNA ligation; and (iii) and high throughput sequencing. To analyze direct miRNAs Magel2 mRNA interactions, we subjected all samples to enrichment for this gene. We found that the hypothalamic Magel2 mRNA levels significantly decreased in obese animals with precocious puberty. Moreover, we identified the interaction of 22 miRNAs with Magel2 in the MBH of early overfed female rats with precocious puberty and their control animals. Specifically, we observed that the interaction of three miRNAs, miR 320 3p, miR 149 5p, and miR 143 3p, was significantly upregulated in obese animals, suggesting their potential modulatory role on Magel2 expression. Collectively, our findings support that hypothalamic alterations in the interactions among specific miRNAs and Magel2 might contribute to obesity induced precocious puberty. However, further studies are needed to validate these preliminary data.

PSII.u. miR-103/107 as central metabolic regulator of puberty.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: puberty; microRNA; metabolism.

Abstract: In mammals, reproductive capacity is acquired after pubertal activation of the hypothalamus-pituitary-gonad axis. The timing of puberty onset is critical, especially in girls, as alterations (either advance or a delay) in the age ranges of puberty may increase the risk of multiple pathologies later in life. Among the main factors responsible of perturbations of the tempo of puberty, metabolic alterations stand out. Hence, identification of putative mechanisms connecting metabolic unbalance and pubertal timing remains as an unmet need. In this study, we evaluated the potential role of the microRNA, miR-103/107, with known functions in metabolic homeostasis, in the central control of puberty and its modulation by metabolic cues. Hypothalamic expression of miR-103/107 progressively increased during postnatal maturation in female rats. Yet, in models of delayed puberty, due to postnatal undernutrition or manipulation of sex steroid milieu during the critical neonatal period, the postnatal elevation of hypothalamic miR-103/107 levels was notably enhanced. Repeated central administration of mimic miR-103/107 induced a decrease in basal glucose levels, together with an increase in lean mass, and an overt delay in the age of puberty, manifested by deferred vaginal opening and fist estrus, as well as low levels of LH and reduced ovary weight. Bioinformatic and bibliographic analysis pointed out kisspeptin, Dicer and PTEN, as potential miR-103/107 targets. This regulatory role was confirmed by a decrease in the levels of these factors following central mimic miR103/107 administration. Our results disclose a previously unknown role of miR-103/107 microRNA at the hypothalamic level in the integrated control of metabolism and puberty in the female rat, presumably through the repressive regulation of molecular targets that include kisspeptin, Dicer and PTEN. Our results may illuminate novel therapeutic targets for intervention in conditions of metabolic unbalance and pubertal alterations.

PSII.v. Impact of insulin resistance in presence or absence of chronic inflammation in adipose tissue fibrosis.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: adipose tissue, rheumatoid arthritis, macrophages, insulin resistance, fibrosis.

Abstract: Currently, there is a high increase in metabolic comorbidities such as insulin resistance in patients with chronic diseases such as inflammatory arthritis, including rheumatoid arthritis and psoriatic arthritis, and obesity. Previous studies have shown adipose tissue dysfunction in both pathologies, highlighting the relevance of adipose tissue in metabolic comorbidities. Adipose tissue dysfunction is also related with fibrosis in obesity, however, less is known about fibrosis and arthritis independently of obesity. Therefore, the aim of this work was to analyse adipose tissue function under circulating microenvironment of arthritic patients analysing the function of main cell types (adipocytes, preadipocytes and macrophages). Furthermore, we studied the extracellular matrix component production and the reorganisation by adipose tissue cells and macrophage plasticity. Results revealed a dysregulation in ECM components by adipose tissue cell types between insulin-sensitive and insulin -resistance subjects in presence or absence of chronic inflammation. Moreover, insulin resistance promotes an M2 macrophage phenotype (anti-inflammatory or profibrotic). In conclusion, our findings advance knowledge of the molecular mechanisms underlying metabolic comorbidities, which may serve as potential targets for the development of novel therapies.

PSII.w. Effect of sitagliptin on skin wound healing in D-vitamin deficient diabetic rats.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: diabetes; sitagliptin: wound healing; calcifediol.

Abstract:

Background: The dipeptidyl peptidase (DPP) 4 family includes four enzymes, DPP4, DPP8, DPP9 and fibroblast activation protein (FAP). DPP4 is a ubiquitous exopeptidase that cleaves chemokines, neuropeptides, and peptide hormones, regulating various physiological processes. Increased plasma DPP4 is associated with diabetes and osteoporosis. The incretins GLP-1 and GIP are substrates of DPP4, so inhibition of DPP4 by gliptins, such as sitagliptin, is used for the treatment of patients with type 2 diabetes. They increase GLP-1 and GIP levels, increasing insulin secretion, inhibiting glucagon release, and reducing blood glucose levels. In addition, 88% of the population has low vitamin D levels. Chronic diabetic wounds are a complication of diabetes and a major clinical problem with a high socioeconomic burden. In addition, the prolongation of the inflammatory phase and the increase in oxidative stress produce an unfavorable microenvironment for tissue regeneration. In view of the above, we have studied the effect of sitagliptin on cutaneous wound healing in vitamin D-deficient diabetics. **Methods:** Dorsal skin wounds were performed in vitamin D-deficient diabetic rats treated with sitagliptin, calcifediol and sitagliptin plus calcifediol. The speed of healing was studied by photographs at different times. At the last time they were sacrificed, and wound samples were taken for histological and gene expression analysis. **Results:** Sitagliptin treatment did not improve wound healing. However, treatment with calcifediol increased the speed of wound closure and decreased inflammation, with values like those of healthy rats. Despite this, treatment with sitagliptin counteracted the positive effect of calcifediol. **Conclusion:** Sitagliptin treatment does not improve skin wound regeneration capacity in vitamin D-deficient diabetic rats.

PSII.x. Effect of calcifediol on skin wound healing in obese and diabetic rats.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: diabetes, obesity, calcifediol, wound healing, vitamin D.

Abstract:

Background: Diabetic chronic wounds are a complication of diabetes and a major clinical problem with a high socioeconomic burden. Obesity constitutes a health risk, with associated comorbidities such as type 2 diabetes. Diabetic chronic wounds are a complication of diabetes and a major clinical problem with a high socioeconomic burden. In addition, 88% of the population has low vitamin D levels. Obesity and diabetes are associated with a state of chronic inflammation. The prolongation of the inflammatory phase and the increase in oxidative stress produce an unfavorable microenvironment for tissue regeneration. Calcifediol or 25(OH)D, is a prohormone produced in the liver by hydroxylation of vitamin D3 that in the kidneys will give rise to calcitriol (1,25-(OH)2D3), the active form of vitamin D. Immune cells, such as B cells, T cells and antigen-presenting cells, express the vitamin D receptor, through which vitamin D can modulate the inflammatory response and affect regenerative capacity. Thus, the aim of this study was to evaluate the effect of calcifediol supplementation on a model of wound healing in vitamin D-deficient obese and diabetic rats. **Methods:** Excisional skin wounds were performed in the different groups: control, obese vitamin D deficient, obese vitamin D deficient treated with calcifediol, diabetic, diabetic vitamin D deficient and diabetic vitamin D deficient treated with calcifediol. The speed of healing was quantified by analysis of images taken at different times. At 14 days the animals were sacrificed and the wounds were sectioned for histological and gene expression analysis. **Results:** With respect to control rats, wound healing in obese and diabetic rats deficient in vitamin D was slower. Treatment with calcifediol increased the speed of wound closure and decreased inflammation, with values similar to those of healthy rats. **Conclusion:** Normalization of vitamin D levels recovers regenerative capacity in obese and diabetic vitamin D-deficient rats.

PSII.y. Metabolic and molecular benefits of two healthy dietary approaches (mediterranean vs. Low fat diet) on the reversion of obesity and diabetes in mice.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Obesity, Insulin resistance, Mediterranean Diet, metabolic-status reversion, Inflammasome.

Abstract: Obesity (OB), characterized by a low inflammatory grade, and type-2 diabetes (T2D)/insulin-resistance (IR) are chronic endocrine-metabolic diseases that represent capital health problems. Fortunately, both pathologies are, at least, partially reversible by dietary interventions (DI), but the metabolic/molecular/cellular factors/mechanisms that might be involved in the total/partial OB/T2D/IR reversion by DI are poorly known. Thus, we aimed to evaluate the impact of Mediterranean-diet (MedD) and a low-fat-diet (LFD) on the reversion of OB/IR/T2D at systemic and tissue-specific levels [i.e. visceral adipose tissue (VAT) and liver]. To achieve this objective, 8-weeks old littermate-mice were fed a high-fat diet [HFD; 60% lard (Kcal)] to develop OB/IR, or a control-diet [CD, 17.4% vegetable fat (Kcal), n=12] for 14-weeks. Then, HFD were divided into 3 groups with different DI for additional 13-weeks: i) maintained with the same HFD (n=12); ii) shifted to MedD [35% (Kcal): 21.7% extra virgin olive-oil (EVOO), 4.9% corn-oil, 1% fish-oil, 6.9% butter); n=18]; or, iii) shifted to LFD [30.1% Kcal from fat: 12.7% EVOO, 5.7% corn-oil, 1.1% fish-oil), 9.7% butter; n=18], while the CD group continued with the same diet for a total of 27 weeks. Before and/or after DI, we analyzed body weight and composition, glucose homeostasis, indirect calorimetry, plasma levels of insulin/leptin/ghrelin/ALT, liver triglycerides (TG), and expression of liver and VAT inflammasome-related genes. As result, both MedD/LFD DIs significantly reversed the OB/IR/metabolic-status induced by HFD (i.e. decreased body/tissue weights, body fat-mass and liver TG, improved glucose/insulin tolerance, reestablished respiratory exchange ratio, energy expenditure and activity, recovered plasma insulin/leptin/ghrelin/ALT levels), close to CD group levels. Moreover, MedD/LFD reduced inflammasome-related genes expression vs. HFD group in VAT; however, in liver, only MedD reverted the inflammatory profile vs. HFD-group. Altogether, MedD and LFD intervention successfully reverted OB/T2D/IR, but the molecular fingerprints associated to these beneficial effects in VAT and liver are distinct.

Fundings: CIBERobn (Proyecto Intramural: OBN20PI02/2020).

PSII.z. A new proteomic workflow to evaluate the presence of microbiome in appendiceal mucinous adenocarcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Cancer, appendiceal mucinous adenocarcinoma, proteomic, bioinformatic analysis, bacteria, fungi.

Abstract: Appendiceal mucinous adenocarcinoma is a rare malignant disease characterized by the continuous accumulation of mucus-secreting cells and glycoprotein-rich mucus in the abdominal cavity. The current treatment option for this disease is based on complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). However, patients have a poor survival rate, and recurrence with subsequent progression and death are common. Understanding the pathophysiological mechanisms underlying this disease is critical to find effective therapeutic options for these patients. Thus, despite the difficulties in processing mucinous samples due to the mucus barrier, our group developed the first methodology to obtain native protein extracts. Then, these extracts were analysed by nanoHPLC-MS/MS to determine the proteome profile as well as its possible alterations. Interestingly, our results revealed that, in addition to human proteins differentially expressed, proteins derived from microorganisms, specifically bacteria and fungi, are also present. This is consistent with the literature, in which different genus of bacteria and fungi have been identified using genomic approaches in several types of cancer, including mucinous tumours. In this sense, one of the most important questions when a kind of cancer is studied, is to know unequivocally whether there are microorganisms inside the tumour. In this work, we have developed a new proteomic approach based on a bioinformatic analysis to identify the explicit presence of microbiota (bacteria and fungi) in mucinous tumoral tissue. This advance will require further research to determine its role in mucinous tumour pathogenesis, to understand the oncogenesis mechanisms, and to design better therapeutic strategies for these patients.

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PSII.aa. Relationship between stress and anxiety in healthcare professionals in Primary care during the Covid-19 pandemic.

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Scientific Program: Active aging and frailty.
Keywords: Primary Health Care, Mental Health, Coronavirus Infections, Psychological Stress, Anxiety.

Abstract:

Introduction: Job directly influences the health workers´ mental health. The COVID-19 pandemic has caused it to be harmed consequence of the increased care burden and the lack of training in the first months of the pandemic, raising levels of anxiety and work stress. **Aims:** To analyse the relationship between stress and anxiety of Primary Care workers and the COVID-19 pandemic. The secondary aim was to determine the techno-anxiety degree derived from the greater use of technologies in Primary Care during the pandemic. **Materials and methods:** Observational, cross-sectional, descriptive study. A total of 150 nursing and medicine Primary Care professionals of Córdoba were studied. An original questionnaire created based on a validated test was used. **Results:** 60% stated they did not have adequate Occupational Health and Safety conditions. These conditions ($p<0,001$) and months of data collection ($p=0,009$) showed significative relation with perceived stress, which led to an analysis of the data collected in the moments before the sixth "wave" of infections and during it. **Conclusion:** Poor working conditions during the months of the pandemic have been one of the main causes of the high levels of perceived stress. In addition, changes in the perception of perceived stress in past waves were seen depending on when the survey was completed.

PSII.bb. Aerobic exercise as a pain reliever in fibromyalgia patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: cardiovascular fitness / chronic pain / fibromyalgia / hypoalgesia.

Abstract: Fibromyalgia is a chronic disorder that severely limits the activities and quality of life of its victims, with pain being one of its most prominent symptoms. While medication is still the first-line treatment for these people, physical activity, particularly aerobic exercise, is being more suggested to assist them improve their symptoms. As a result, the primary goal of this systematic review is to analyze the effects of aerobic exercise on pain in fibromyalgia patients. To that goal, a pairwise systematic review was conducted, with only RCT being considered. The first metanalysis showed no significant differences between aerobic exercise and other interventions (mean difference -0.40; confidence interval -0.94, 0.14; p = 0.15; I2 = 61%). Meanwhile, removing one paper results in results in a favorable outcome for aerobic exercise for pain relief in these patients with significative differences with control and other interventions (mean difference -0.55; confidence interval -1.06, -0.04; p = 0.03; I2 = 50%). In conclusion, aerobic exercise appears to be a beneficial therapy for the management of pain in fibromyalgia patients.

PSII.cc. Impact of calorie restriction and bariatric surgery in human skeletal muscle mitochondria: exploring the effects of two different weight loss protocols through a systematic review with meta-analysis.

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Scientific Program: Nutrition, Endocrine and etabolic diseases.
Keywords: Energy restriction; oxidative phosphorylation; muscle metabolism.

Abstract:

Introduction: Calorie restriction (CR) refers to the intentional reduction in energy intake without causing malnutrition. CR, as dietary intervention, has shown benefits for longevity, healthspan, and metabolic regulation. Studying its effect on human skeletal muscle is crucial as it offers insights into potential strategies for preserving muscle mass and function during aging and various metabolic disorders. Objective We performed a systematic review with meta-analysis to determine the changes induced by calorie restriction and bariatric surgery on human skeletal muscle mitochondria. **Methods:** A systematic search of Medline and Web of Science was conducted. Controlled trials exploring CR (≥14 days) and mitochondrial function and/or content assessment were included. Moreover, studies analyzing weight loss following gastric surgery were included for comparison purposes. Human muscle data from 28 studies assessing CR (520 muscle samples) and from 10 studies assessing bariatric surgery (155 muscle samples) were analyzed. A qualitative study of the included trials was also carried out in order to determine metabolic changes induced by CR. **Results:** We report a decrease in maximal mitochondrial state 3 respiration in response to CR but not in response to surgery. Mitochondrial content reported no change after CR or in response to surgery. Moreover, data from CR subjects showed a reduction in complex IV (CIV) activity but not in CIV content. Results of descriptive analysis shown an improved metabolic effect of subjects submited to CR, such as improved insulin sensitivity and reduced basal glucose, total cholesterol and triglycerides levels. **Conclusion:** The observation of the reduction of the intrinsic activity of the electron transport chain without altering the mitochondrial content, in human skeletal muscle, together with the biochemical results described, suggests that CR mainly modulates the intrinsic mitochondrial function and promotes an enhancement of metabolic health.

PSII.dd. Co-sensitization study between Ole e 7 and Pru p 3 nsLTPs.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: LTP, food and pollen allergy, cross-reactivity.

Abstract:

Introduction: Non-specific Lipid Transfer Proteins (nsLTP) are a highly conserved and allergenic protein family, contained in a variety of vegetables, as are the cases of Pru p 3 (Prunus persica, peach) and Ole e 7 (Olea europaea, olive). Pru p 3 is a common primary sensitizer in southern Europe, while Ole e 7, a minor antigen of olive pollen, is a very powerful sensitizer particularly in Andalusian area. The aim of this study was to explore the existence of cross-reactivity between these allergens that could explain the high prevalence of co-sensitization. **Materials and methods:** Allergic patients from Allergy department in Reina Sofía University Hospital were selected according to Ole e 7 and Pru p 3 IgE levels, measured by ImmunoCap 250 (positivity threshold>0.35 kUI/L). Basophil Activation Test (BAT) was performed with increasing concentrations of both allergens. For epitopic mapping, recombinant proteins were digested and further sequenced by Liquid Chromatography-Mass Spectrometry (LC-MS). **Results:** Patients were classified in MONOLE (Ole e 7 monosensitized; n=3), MONPRU (Pru p 3 monosensitized; n=3) or BI groups (bisensitized; n=3). Attending to clinical criteria, all patients described rhinitis, while Oral Allergy Syndrome with Rosaceae fruits were also described in MONPRU and BI groups. As we expected, BAT result was concordant with sensitization profile in BI and MONPRU patients. Remarkably, Ole e 7 monosensitized patients showed positive BAT for both allergens, in spite of negative levels of Pru p 3 sIgE. Epitopic mapping proved MONOLE patients recognize Pru p 3 fragment “ISASTNCATVK”, and, at the same time, Ole e 7 fragment “KSALALVGNKV” was recognized by MONPRU patients, although linear alignment of protein sequences exhibited low identity percentage. **Conclusions:** A possible cross-reactivity between different epitopes from Ole e 7 and Pru p 3 could be the underlying cause of the co-sensitization observed in the south Mediterranea.

PSII.ee. Relation of the fibrotic process and clinical severity of the mammary periprosthetic capsular contracture.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: capsular contracture, fibrosis, augmentation mammoplasty.

Abstract:

Background: Augmentation mammoplasty with prosthesis implantation is one of the most frequent aesthetic and reconstructive surgical procedures. Periprosthetic capsular contracture is the main complication of this surgery which is related to tumescence, pain and deformity. Although the aetiology remains unclear, histological changes are gaining more relevance in understanding this pathology in correlation with the clinical symptomatology. **Objectives:** The aim of this study has been to describe the histological grade of fibrosis in relation to the clinical severity of the capsular contracture. **Methods:** Patients who underwent surgery due to capsular contracture were divided in 4 groups (5 patients per group) depending on the severity of the clinical manifestations according to the Baker's scale. Samples from the periprosthetic capsule were taken and they were processed in order to undertake their histological, histochemical and immunohistochemical study. Histological changes observed were compared between the 4 groups. **Results:** Our results showed that in the follow-up time (mean 4 years) the presence of histological capsular fibrosis was demonstrated in at least 45%, showing an increase in connective tissue. Similarly, in these patients the presence of fewer perifibrotic myofibroblasts was identified, as well as vascular and neural lesions due to the interposition of collagen. Myofibroblasts were found in the outer layer of the capsule and constituted an average 13.5% of the capsule thickness. **Conclusions:** The tensile strength of the mammary capsules was correlated with the degree of capsular contracture. The authors believe that myofibroblasts appear during an active phase of wound contraction and decline when the wound has matured. The histological and, in the future, the molecular study of the fragments of the capsular contracture can help to create predictive models to avoid capsular contractures.

PSII.ff. Mindfulness-based Interventions in Young Population with Type 1 Diabetes Mellitus: A Systematic Review.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Type 1 diabetes mellitus, young population, mindfulness-based interventions, distress diabetes, health related quality of life.

Abstract:

Background: Type 1 diabetes mellitus (T1DM) in young population is one of the main chronic diseases worldwide in this population group and has an incidence rate that is increasing. In addition to the physical symptoms associated with the disease, it can also affect emotionally, affecting their well-being and health related quality of life. Therefore, living with this chronic, long-term disease could be a significant challenge in adolescence, which is associated with the involvement of psychosocial factors. Promoting emotional well-being and self-regulation through psychological interventions based on mindfulness practice could favor a greater perception of HRQoL, which could influence self-management behaviors of T1DM in adolescents. **Objective:** To know the impact of mindfulness-based interventions, as a strategy for regulating emotional well-being and distress diabetes in young patients with type 1 diabetes mellitus. **Method:** A systematic review of trials published in the period 2013- 2023 was carried out through a bibliographic search in electronic databases (Web of Science, MEDLINE, SciELO, Scopus, PsycINFO, and Cochrane Library). **Results:** A total of 344 articles were found, after eliminating the duplicates, a total of 238 articles were submitted to the title and abstract reading. Further, 231 were excluded by title and abstract as they did not fit the article profile based on the established criteria. Finally, 7 were subjected to complete reading and detailed analysis of inclusion criteria. **Discussion and conclusions:** The psychosocial interventions contributing to improve psychosocial factors linked to suffering from chronic diseases, improving health related quality of life. In this sense, mindfulness-based interventions, after reviewing the preliminary results, could be presented as a type of strategy to improve the emotional well-being of young T1DM patients by reducing perceived stress associated.

PSII.gg. Design and evaluation of the effectiveness of a digital health platform for monitoring the clinical status of home oxygen patients. Randomized clinical trial.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Oxygen therapy, COPD, E-Health, Mobile applications, Home healthcare.

Abstract: Chronic Obstructive Pulmonary Disease (COPD), according to the World Health Organization (WHO), is considered the third leading cause of death worldwide. In Colombia, approximately 8% of the population suffers from COPD. One of the main treatments for this disease is oxygen therapy, which promotes the control of dyspnea and increases survival. Some research shows that COPD patients who do not adhere to oxygen therapy experience a significant decrease in their quality of life. On the other hand, mobile health technologies (m-Health), such as mobile applications (apps), have great potential in monitoring patients with chronic diseases. A Cochrane review indicated that symptom self-management through apps in patients with chronic diseases has a beneficial effect on the development of self-care and self-management skills. Therefore, we designed an app for monitoring the clinical status of patients with COPD and oxygen therapy. For the content and screen architecture, we used a user-centered methodology. Through focus groups, we identified the needs and perceptions of patients, caregivers, and healthcare professionals.

Subsequently, we evaluated the app's usability satisfaction through user testing, identifying a high degree of satisfaction. Currently, our objective is to evaluate the effectiveness of the mobile application through a clinical trial. We are randomly recruiting patients to complete a sample of 44 individuals, who will be divided into two groups. The intervention group (22) will receive conventional clinical follow-up and also use the mobile application. On the other hand, the control group (22) will only receive conventional clinical follow-up. Finally, we will assess the perceived usability and ease of use by users using the Technology Acceptance Model (TAM).

PSII.hh. Dyslipidemia and pathological cognitive impairment in people over 65.

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Scientific Program: Biomedicine. Line of research: Neuroplasticity and oxidative stress.
Keywords: Dyslipidemias; Cholesterol, LDL; Cholesterol, HDL; Aged; Dementia; Cognitive impairment.

Abstract:

Introduction: The prevention of dementia, specifically Alzheimer disease (AD), is of utmost importance to tackle the significant increase of this neurodegenerative pathology, which mainly affects elderly people. Therefore, it can be essential to come to know the mechanism of development of dementia as well as the influence of risk factors like dyslipidemia. **Aim:** To examine and synthesize the existing scientific literature to test the relationship between dyslipidemia and the cognitive impairment in people over 65. **Methodology:** It has been carried out a systematic search in Medline, through Pubmed, which included the terms "Dyslipidemias" [Mesh], "Cholesterol, LDL" [Mesh], "Cholesterol, HDL" [Mesh], "Aged" [Mesh], "Dementia" [Mesh] and "Cognitive impairment". The search has been limited to articles published in the last 5 years in both English and Spanish. A theme analysis with the selected articles has been performed. **Results and discussion:** Lastly, a total of 13 articles have been included in the revision. The existing articles indicate that hypercholesterolemia, a frequent disorder in elderly people, increases the risk of AD. It is mainly because of cholesterol on the blood-brain barrier, which can jeopardise its integrity. In addition, experimental studies have proved that hypercholesterolemia is associated with a greater amyloid-β (Aβ) peptide deposit, a higher neurofibrillary tangles (NFT) formation, as well as cognitive impairment, neuroinflammation, cholinergic neurons dysfunction and cerebral microhaemorrhage compatible with AD. **Conclusion:** The systematic revision carried our has concluded that the effect of lipids on cognition is more important before age 65. Consequently, it would be interesting to make early interventions in the lifestyle to slow the onset of dementia. Community nursing plays an important role here.

PSII.ii. Analysis of mandatory Mental Health questionnaires in crew members and air traffic controllers.

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Scientific Program: Occupational Medicine, Occupational Epidemiology and Sustainability.
Keywords: mental health; air crews; incapacitation; air safety.

Abstract: The accident of Germanwings Flight 9525 in 2015 was a turning point in the approach to the mental health of air crews. French and German authorities confirmed the suicide of co-pilot Andreas Lubitz who deliberately crashed the plane in the Alps, killing 149 other people on board. The French air accident investigation commission (BEA) in its final report recommended regular examinations to check the mental health of pilots. Recommended that the European Aviation Safety Agency (EASA) include in the European Aviation Safety Plan a mechanism to establish in the EU analysis to anticipate in-flight incapacitation due to psychological or psychiatric aspects and contribute to the continuous review of the evaluation criteria medical, improve in-flight incapacitation data and validate the effectiveness of these criteria. A working group made up of the State Aviation Safety Agency (AESA) established a mandatory mental health check-up tool in aeronautical examinations based on a questionnaire and a semi-structured interview. A quantitative study of its twenty variables with five levels of response is proposed using analysis of variance (ANOVA) to analyze the variability between four groups and determine if there are significant differences between them that can help the Air Medical Examiners (AMEs) beyond an intuitive assessment. With a sequential sampling of four groups to be compared in the twenty variables of interest and using statistical software we will see the homogeneity of the variances of each group and if the conditions such as the normality of the data and the independence of the groups are met. After the analysis of variance, the significant differences between groups will be shown. These results will be presented in the form of tables, graphs, and descriptive statistics, and will be carefully interpreted to provide a comprehensive, meaningful, and reliable view of the study.

PSII.jj. Pathophysiological relevance of molecular machineries controlling RNA metabolism (Nonsense-mediated decay and RNA-exosome) in craniopharyngiomas.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: RNA-exosome; Nonsense-Mediated Decay; Adamantinomatous Craniopharyngioma; RNA Metabolism; Senescence.

Abstract: Craniopharyngiomas (CPs) are benign tumors but associated with severe neuro-psychiatric, visual, and endocrine symptoms due to their sellar location and increased intracranial pressure. Diagnostic methods, response evaluation to therapies, and current treatments are very limited. Thus, the identification of new diagnostic/prognostic biomarkers and therapeutic strategies is necessary. In this regard, the regulation of RNA metabolism has been revealed as a key process in the pathophysiology of multiple tumor pathologies. Therefore, our aim was to determine the pathophysiological importance of two key molecular machineries controlling gene expression in CPs: Nonsense-Mediated Decay (NMD) and RNA-exosome. For this purpose, we analyzed the gene expression of components from both machineries (using microfluidic qPCR technology) in CP samples as compared with control samples (Healthy Pituitaries: HPs), and we employed different bioinformatic analyses, and an in vitro approach following the pharmacological inhibition of both machineries in primary CP cell cultures. We observed that the expression levels of multiple components belonging to both machineries are dysregulated in CPs compared to HPs, highlighting SEC13 and PABPC1 (from NMD) and EXOSC5 (from RNA-exosome) because of their potential pathophysiological significance. Additionally, we found that PABPC1 expression was overexpressed in the CP-phenotypes with higher senescence. Furthermore, functional enrichment assays revealed the importance/association of these factors with classical pathways in CPs and cancer, such as the cell cycle or the Wnt/β-catenin pathways. Finally, pharmacological inhibition of NMD (with NMDi), but not of the RNA-exosome (with isoginkgetin), reduced the proliferation of primary CP cells. Altogether, this study reveals that certain components of the NMD and RNA-exosome machineries could serve as potential biomarkers and/or therapeutic targets in CPs.

Fundings: AECC.

PSII.kk. Role of DYRK2 as a novel regulator of MEK1 in the MAPK/ERK1/2 signaling pathway.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: DYRK2, MAPK, MEK1, regulation, phosphorylation, cáncer.

Abstract: Mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 (MAPK/ERK1/2) is considered as the most important MAPK signaling pathway implicated in cell proliferation, differentiation and survival across a range of eukaryotic organisms. However, dysregulation of this pathway and subsequent hyperactivation of its components contribute to tumor development. Despite the established significance of dual-specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2) in carcinogenesis and its dual role as both tumor suppressor and oncogene, along with its phylogenetic association with MAPKs, the regulatory interactions between DYRK2 and MAPK/ERK1/2 remain poorly understood. In this work, DYRK2 has been identified as a novel regulator of the MAPK/ERK1/2 signaling pathway, specifically focusing on its interaction with MEK1. Several experimental approaches have provided evidence for a delay on MEK1 electrophoretic mobility through a post-transcriptional mechanism dependent on DYRK2 kinase activity. An in vitro kinase assay (IVK) confirmed the direct phosphorylation of MEK1 by DYRK2, followed by tandem mass spectrometry (MS/MS) analysis. MS/MS analysis identified 10 potential phosphorylated residues of MEK1, which were represented in a 3D model structure. Directed mutagenesis was performed on the most relevant phosphorylated sites, showing the critical role of T292 and S298 residues in DYRK2-mediated phosphorylation on MEK1. Additionally, functional analysis shows the potential efficacy of combining the pharmacological suppression of DYRK2 in response to the commercially approved B-RAF inhibitor Dabrafenib targeting lung cancer cells viability (A549K-Ras(G12V)). These findings highlight that DYRK2 could be considered as a promising therapeutic target for the development of innovative and effective cancer treatments.

PSII.mm. Proximity Extension Assay is a novel technology for boosting molecular characterization and personalized clinical management of rheumatic diseases

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, spondyloarthritis, biomarkers, clustering.

Abstract:

Background: Rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and spondyloarthritis (SpA) are characterized by complex clinical and molecular heterogeneity. Novel and disruptive technologies might shed light on their pathogenesis and clinical management. The aim of this study was to evaluate the potential of the innovative proteomic technology “proximity extension assay” (PEA) to identify useful biomarkers, subgroups of patients, and novel insight into rheumatic diseases. **Methods:** 363 consecutive patients with rheumatic diseases (141 SLE, 50 RA, 72 SSc, and 100 axialSpA) and 50 healthy donors (HDs) were included in the study where serum samples and clinical data were obtained. A signature of 460 proteins divided into 5 panels of 92 biomarkers associated with Inflammation (SLE and HDs), Organ Damage (SLE, SSc, and HDs), cardiovascular disease (RA, SpA, and HDs), and cardiometabolism (RA and HDs) was analysed by using PEA technology from Olink (Cobiomic Bioscience SL). Data analysis included t-test, unsupervised clustering analysis, ROC curves, and PCA among others. **Results:** In SLE patients, the unsupervised cluster analysis using the circulating proteome identified 2 clusters with distinctive clinical features mainly differentiating disease activity and the presence of renal damage. Similarly, in SSc, a panel of proteins related to organ damage identified a subgroup of patients characterized by multiple organ involvement including lung and skin fibrosis and oesophageal dysmotility, along with a preponderance of anti-scl70 antibodies positivity. In axialSpA patients, the levels of several proteins related to cardiovascular disease were altered compared with HDs and associated with key clinical features. A specific signature of several proteins associated with CVD and metabolism was identified as a potential biomarker of RA diagnosis. Likewise, a combination of various plasma proteins before therapy identified non-responders RA patients to Methotrexate or anti-JAK, pointing out its role as a predictor of therapy response. **Conclusions:** PEA technology might boost the future of precision medicine in rheumatic diseases through the identification of novel biomarkers of disease and therapy response and the stratification of patients with key clinical and molecular features.

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SESSION VI.

INFECTIOUS AND INMUNOLOGICAL DISEASES.

VIa. SARS-CoV-2 accessory proteins induce mitochondrial dysfunction and impair cellular metabolism.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: SARS-CoV-2; Accessory protein; Inflammatory response; Mitochondrial dysfunction.

Abstract: SARS-CoV-2, the causative agent of the COVID-19 pandemic, possesses eleven accessory proteins encoded in its genome. While not necessary for virus replication, these proteins play a crucial role in virus-host interactions, immune response suppression, and immune evasion. However, the effect of SARS-CoV-2 accessory proteins on cellular metabolic activity is still unknown. Mitochondria plays an important role in maintaining multiple metabolic functions, such as energy metabolism and generation of reactive oxygen species (ROS). Mitochondria are also known to be essential for an effective innate immune response. Recent studies have suggested the involvement of mitochondria in SARS-CoV-2 infection as a hallmark of COVID-19 pathology. In this study, A549 human bronchoalveolar epithelial cells were transduced to express each of the SARS-CoV-2 accessory proteins. Transcriptomic analysis revealed dysregulation of metabolic and mitochondrial genes in these cells, suggesting that mitochondria metabolism is disrupted by SARS-CoV-2 accessory proteins. We performed metabolic flux analysis using the Seahorse Analyzer to determine the functional role of accessory proteins on mitochondrial performance and glycolytic rate. The results demonstrated that the expression of certain accessory proteins (ORF7a, ORF8, ORF9b and ORF9c) led to alteration in mitochondrial function, resulting in decreased basal and maximal respiration. Glycolysis was also significantly reduced in these cells. This mitochondrial and metabolic dysfunction could be related to an increase in ROS generation. Overall, our findings suggest that the impairment of mitochondrial function by accessory proteins may contribute to COVID-19 pathogenesis.

VIb. Clinical factors and the role of bacterial load in long-term eradication of intestinal colonization by KPC-producing Klebsiella pneumoniae in an endemic nosocomial setting: results from a prospective observational study (KLEBCOM).

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Scientific Program: Infectious and Immunological diseases.
Keywords: Sustained eradication, relative gastrointestinal load, Klebsiella pneumoniae carbapenemase.

Abstract:

Background: The relative gastrointestinal load (RLKPC) of KPC-producing Klebsiella pneumoniae (KPC-KP) has been associated with increased risk of bacteremia and all-cause mortality in colonized patients. We aimed to examine if the RLKPC, in an endemic nosocomial setting, is associated with sustained eradication within 6 months. **Methods:** Patients with a positive KPC-KP rectal surveillance culture were recruited in a tertiary hospital with endemicity by a ST512/KPC-3 K. pneumoniae clone. Rectal swabs were collected at recruitment and monthly thereafter for one year. The RLKPC was estimated by qPCR and defined as the proportion of blaKPC relative to 16S rRNA gene copy number. Sustained eradication was defined as the absence of KPC-KP both by culture and qPCR and no subsequent KPC-KP positive rectal swabs. Factors associated with sustained eradication were evaluated by a Fine-Gray competing risk regression analysis, establishing death as competing risk. **Results:** Among 80 patients recruited, 68 (85.0%) were hospitalized. Carriage of KPC-KP was confirmed in 89.6% (43/48), 71% (27/38), 41.4% (12/29) and 33.3% (7/21) patients with available follow-up samples at 1, 3, 6, and 12 months, respectively. The median RLKPC was 0.28% (range 0.001%-2.70%, minimum <0.001%, maximum 59.39%) at baseline, 0.02% (range <0.001%-0.41%, p-value relative to baseline=0.055] at 1 month and remained below 0.001% (p<0.001) thereafter. Twenty-four (27.5%) patients had at least one negative sample during follow-up, however only 15 (18.8%) showed sustained eradication, within a median time of 90 days (range 75-120). During follow-up, 43 (53.8%) patients died and 33 (41.3%) developed KPC-KP-related infections. In multivariable analysis, Charlson Comorbidity Index (SHR 0.473, 95% CI 0.23-0.97, p=0.041) was independently associated with sustained eradication of KPC-KP. **Conclusion:** The RLKPC is not associated with sustained eradication of KPC-

KP in colonized patients. A high Charlson comorbidity index is associated with lower probability of sustained eradication. This is important to implement adequate preventive measures.

VIc. Early postoperative complications of lung transplantation.

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Scientific Program: Infectious and Immunological diseases. Organ.
Keywords: lung transplantation, surgical complications, mortality, survival.

Abstract:

Objective: To analyze the incidence of surgical complications after lung transplantation (LT) and the influence on early mortality and long-term survival. **Methods:** Retrospective analysis of 769 LT performed at our Center between January 1994 and December 2022. Univariable and multivariable analysis was performed. The overall and stratified survival were analyzed by diagnosis, type of transplant and surgical complications using Kaplan-Meier test. A Cox regression analysis was used to determine predictors of mortality. **Results:** 769 patients were analyzed (533 men and 236 women): single-LT (n=385; 50%), double-LT (n=371; 48%), lobar LT (n=8; 1%), combined lung and liver transplantation (n=5; 0.6%). Indications: Chronic Obstructive Pulmonary Disease (n=300;39%), pulmonary fibrosis (n=171; 22%), cystic fibrosis (n=145; 19%), bronchiectasis (n=24; 3%), pulmonary hypertension (n=8; 1%), retransplantation (n=9; 1%). 249 patients developed surgical complications (32%): bronchial complications (n=61) ; vascular complications (n=55); pneumothorax (n=33); phrenic nerve paralysis (n=22). LT for bronchiectasis (58%), pulmonary hypertension (50%) and retransplants (78%) presented more surgical complications, as well as double- LT (40%), lobar LT (88%) and combined lung and liver transplantation (100%) ($p<0.001$). Patients with complications were younger (49±15 vs. 45±17 years; $p=0.001$), with longer ischemic times (429±67 vs. 450±76 min ($p=0.007$), and needed extracorporeal life support (ECLS) (43% vs. 57%; $p<0.001$). Survival at 1, 5, 10, 15, 20 years (not complicated vs. complicated): 78%, 63%, 52%, 41%, 31% vs. 52%, 42%, 35%, 26%, 22%; $p<0.001$. Predictive factors of mortality: ECMO (OR: 4.14; $p<0.001$), mechanical ventilation (OR: 1.01; $p< 0.001$) and vascular complications (OR: 4.78; $p<0.001$). **Conclusions:** surgical complications following LT are an important source of morbidity and mortality. Patients with bronchiectasis , pulmonary hypertension, retransplantation, combined lung and liver transplantation, or undergoing procedures needing ECLS, have a higher rate of complications. The use of ECMO, prolonged intubation and vascular complications are predictors of post-transplant mortality.

VId. Prevalence and Factors Associated with Multimorbidity in Patients with Rheumatoid Arthritis. Data from the Cordobesian Rheumatoid Arthritis Registry.

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Scientific Program: Infectious and Immunological diseases.
Keywords: Rheumatoid arthritis, multimorbidity, comorbidities.

Abstract:

Background/Purpose: Rheumatoid arthritis (RA) is the most common chronic arthritis, affecting approximately 0,5-1% of the global population. It has long been recognized that RA is associated with an increased risk of several pathologies, such as cardiovascular diseases or osteoporosis. Recent studies, including the notable COMORA study, have focused on researching the impact of comorbidities on this disease and whether they influence response to different treatments. **Methods:** A cross-sectional study was conducted at the Reina Sofia University Hospital, involving patients with RA who were actively monitored and had data recorded in the Cordobesian Rheumatoid Arthritis Registry (CRheAR). Multimorbidity was determined according to the current definition provided by the World Health Organization (WHO), which encompasses patients with two or more chronic diseases in addition to RA. Various comorbidities were documented, including Charlson comorbidity index (adjusted for age), high blood pressure, dyslipidemia, diabetes, osteoporosis, interstitial lung disease (ILD), depression and cardiovascular disease. Additionally, specific disease characteristics were collected, such as diagnosis delay, erosions, nodules, rheumatoid factor (RF) and anti-cyclic citrullinated peptid antibodies (anti-CCP). The data were subjected to descriptive and multivariate statistical analysis to identify association among these attributes and multimorbidity**. Results:** A total of 402 patients with RA were enrolled in this study, with a mean age of 64.3 (±13.4) years. Of the participants, 72.8% were female. Approximately three-quarters of the patients tested positive for RF and anti-CCP. The most prevalent comorbidities were dyslipidemia (45%) and high blood pressure (44%), followed by osteoporosis (27%) and interstitial lung disease (ILD) (14.8%). Table 1 presents the identified differences between patients with and without multimorbidity. Age, disease duration, diagnosis delay, Charlson index, and mortality, among others, were identified as risk factors in the multimorbidity group. Moreover, a multivariate analysis was conducted, revealing that diagnosis delay of RA [OR 1.22; 95% CI (1.06-1.44)], Charlson index adjusted for age [OR 2.87; 95% CI (2.34-3.85)], and current use of bDMARD [OR 2; 95% CI (1.23-4.01)] were identified as independent factors associated with multimorbidity, with adjustment for disease duration. **Conclusion:** In our study population, multimorbidity was observed in a significant proportion of patients with RA;

this finding carries substantial clinical implications for therapeutic decision-making in daily practice. Although we did not observe any differences in various disease activity indexes, there were slight variations in the usage of disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs (bDMARDs).

Attribute	Multimorbidity (n=251)	No multimorbidity (n=138)	p-value
Age (years), mean (SD)	69,23 (11,1)	55,23 (12,1)	**<0.001**
Sex (female), n (%)	175 (69,7)	107 (77,5)	0.12
Smoking anytime, n (%)	98 (41,8)	47 (35,3)	0.26
Disease duration (years), mean (SD)	14,29 (9,9)	10,71 (7,2)	**<0.001**
Diagnosis delay (years), mean (SD)	2,07 (4,07)	0,91(1,21)	**<0.001**
Rheumatoid factor positive, n(%)	196 (78)	108 (78)	1
Rheumatoid factor, (mean)	161,1 (261,1)	119,7 (169,2)	0.08
Anti-CCP positive, n (%)	189 (77)	106 (76,8)	1
Anti-CCP, mean (SD)	224,74 (210,7)	203,87 (210,2)	0.449
Erosions, n(%)	96 (38,5)	50 (36,5)	0.772
Nodules, n(%)	22 (8,9)	15 (10,9)	0.621
DAS28-ESR, mean (SD)	2,64 (1,05)	2,57 (1,2)	0.545
SDAI, mean (SD)	9,67 (7,2)	8,88 (7,7)	0.352
CDAI, mean (SD)	8,66 (6,6)	8,21 (7,3)	0.569
DMARD now, n (%)	189 (77,1)	120 (87)	**<0.001**
DMARD now or previous, n(%)	239 (95,2)	137 (99,3)	0.223
bDMARD now, n (%)	83 (33,7)	48 (34,8)	**<0.001**
bDMARD now or previous, n (%)	94 (39)	55 (41)	**<0.001**
Charlson index, mean (SD)	2,18 (2)	0,99 (0,1)	**<0.001**
Charlson index adjusted for age, mean (SD)	4,59 (2,5)	2,18 (1,1)	**<0.001**

Table 1. Characteristics of the cohort and differences observed according to multimorbidity. Note: SD = standard deviation. p-value indicates the statistical significance of the observed differences between the two groups.

VIe. Genomic epidemiology study of hospital-acquired, community-acquired and healthcare-related KPC-producing Klebsiella pneumoniae infections at Reina Sofia University Hospital reveals clonal dissemination of ST512/KPC-3 high-risk clone over a 10-year period (KLEBMAN study).

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Scientific Program: Infectious and immunological diseases. Organ transplantation.
Keywords: Klebsiella pneumoniae, KPC Carbapenemase, Infection, Community Dissemination, Nosocomial Dissemination.

Abstract:

Introduction: The first outbreak in Spain by a KPC-producing K. pneumoniae clone (ST512/KPC-3) occurred at Reina Sofía University hospital (HURS) in 2012. This study aimed to characterize the genomic epidemiology of KPC-producing Klebsiella pneumoniae (KPC-KP) infections over a 10-year period following the initial outbreak. **Methods:** Whole-genome sequencing (WGS) was applied to KPC-KP clinical isolates collected from diagnostic samples in the KLEBMAN cohort from June 2012 to December 2022. Long-read WGS (PacBio) was used to characterize resistance plasmids in the outbreak index KPC-KP isolate (HURS512_1). Short-read WGS (Illumina) was performed on the first KPC-KP isolate available for each infection episode. Clinical data comparisons, antimicrobial resistance and virulence profile analysis, cgMLST and phylogenetic analysis were performed. **Results:** A total of 467 clinical KPC-KP infection episodes were identified. Among these, 316 had an available clinical specimen at the hospital microbial collection. Of them, 212 (67.1%) were hospital-acquired, 81 (25.6%) were healthcare-related and 23 (7.3%) were community-acquired. Isolates were most prevalent in blood (17.4%), respiratory (21.84%) and urine (37.0%). The outbreak index (HURS512_1) harboured a chromosome of 5,334,700 bp and five plasmids (ranging 20.2 to 218 kb). The blaKPC-3 gene was integrated into the Tn4401a transposon within a 130.9 kb plasmid that showed high similarity with the IncFIIK2-pKpQIL plasmid originally described in the ST258/KPC-3 K. pneumoniae clone isolated in Israel in 2006. All but one isolate (ST280/KPC-3) belonged to clone ST512 and all had a genetically identical Tn4401a transposon. Phylogenetic analysis revealed a close genetic relatedness between isolates of nosocomial and non-nosocomial origin. **Conclusions:** Our results suggest that the spread of blaKPC in our region has occurred mainly through plasmidic (Tn4401a/pKpQIL) and clonal

dissemination of the K. pneumoniae ST512/KPC-3. The considerable spread of blaKPC to the community and healthcare facilities highlights its high potential for transmission and the need to intensify control efforts.