12th IMIBIC YOUNG INVESTIGATORS MEETING

BOOK OF ABSTRACTS

IMIBIC
INSTITUTO MAIMÓNIDES DE INVESTIGACIÓN BIOMÉDICA DE CÓRDOBA

Junta de Andalucía

UNIVERSIDAD D CÓRDOBA

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Córdoba, 28-29 oct. 2021

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Acknowledgements

We thank the External Reviewers and the members of the Scientific Committee for their kind collaboration. We greatly acknowledge the *"Colegio Oficial de Médicos de Córdoba"* for its support and commitment to promote research among residents.

PROGRAMME

Day 1 (28th OCT)

08:15 – 08:45
Registration and Poster display

08:45 – 09:00
Opening ceremony (IMIBIC Assembly Hall)

09:00 – 10:45
SESSION I. Cancer (IMIBIC Assembly Hall)
Chairs: **Dr. Rocío Guzmán** & **Dr. Juan Moreno.**

→ **Ia. 09:00 – 09:15**
Application of a biocomputational approach to identify alterations in the spliceosomic landscape in lung carcinoids. **Víctor García Vioque**.

→ **Ib. 09:15 – 09:30**
The metabolic rewiring induced by impaired denitrosylation contributes to tumor progression and immune escape in colorectal cancer. **Rafael Mena Osuna**.

→ **Ic. 09:30 – 09:45**
Unleashing the therapeutic role of somatostatin and cortistatin in prostate cancer. **Francisco Porcel Pastrana**.

→ **Id. 09:45 – 10:00**
Interval carcinomas in a Breast Cancer Screening Program: differences between women studied with digital mammography or tomosynthesis. **Cristina Pulido Carmona.**

→ **Ie. 10:00 – 10:15**
Surgical treatment of malignant pleural mesothelioma.
Multicenter study. **Eloisa Ruiz López**.

→ **If. 10:15 – 10:30**
Splicing machinery landscape in hepatocellular carcinoma: a central role of EIF4A3 in hepatocarcinogenesis. **Natalia Hermán Sánchez**.

→ **Ig. 10:30 – 10:45**
Revealing the pharmacologically regulable CDC25A/DYRK2 axis: a novel master cell cycle and survival modulator. **Alejandro Correa Sáez**.

10:45 – 11:15
Break

11:15 – 13:15
SESSION II. Multidisciplinary (IMIBIC Assembly Hall)
Chairs: **Dr. Almudena Pino** & **Dr. Juan Solivera.**

→ **IIa. 11:15 – 11:30**
Assessment of the liver disease risk in inflammatory arthritis. Molecular mechanisms involved in hepatocyte dysfunction in the context of psoriatic arthritis. **Cristobal Román Rodríguez.**

→ **IIb. 11:30 – 11:45**
Reduction of renal mass interferes with the phosphaturic action of rapamycin. **Azahara Espartero Castro.**
→ **IIc. 11:45 – 12:00**
Kinetics of the intestinal loads of Klebsiella pneumoniae producing KPC carbapenemase following selective digestive decolonization with oral gentamicin: a 1-year, prospective cohort study. **Alejandra Méndez Natera.**
→ **IId. 12:00 – 12:15**
Unsupervised clustering analysis of the circulating inflammatory profile of Rheumatoid Arthritis patients stratify patients according to their cardiovascular risk. **Laura Muñoz Barrera.**
→ **IIe. 12:15 – 12:30**
Fibroblast growth factor 23 down-regulation by chronic metabolic acidosis in rats. **Ángela Vidal Carrascosa.**
→ **IIf. 12:30 – 12:45**
SARS-CoV-2 ORF7a and ORF7b cooperate in multiple membrane-based processes ranging from cell adhesion, olfaction and immune response interference. **Tránsito García García.**
→ **IIg. 12:45 – 13:00**
Association of gut microbiota and enthesis in axial spondyloarthritis. Data from CASTRO Registry. **Ignacio Gómez García.**

13:15 – 15:30
Lunch (IMIBIC Cafeteria)

15:30 – 16:30
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Chairs: **Dr. Maria Victoria García** & **Dr. Carlos Pérez.**

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→ **PSI.b.** Sexual dimorphism in markers of pathways related with the hallmarks of aging in mice overexpressing CYB5R3 and fed a nicotinamide ribosidesupplemented diet. **Luz Marina Sánchez Mendoza**.
→ **PSI.c.** The expression of splicing machinery components is dysregulated in human neuroendocrine lung tumors. **María Teresa Caro Cuenca**.
→ **PSI.d.** TWEAK/Fn14 axis modulates acute kidney injury associated with rhabdomyolysis. **Melania Guerrero-Hue.**
→ **PSI.e.** Mutations in colistin resistance genes in colistin-resistant subpopulations of wild-type Klebsiella pneumoniae of clinical origin.
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→ **PSI.f.** Glycogen syntase kinase-3 as a relevant target for the treatment of colorectal cancer. **Aurora Rivas Crespo.**
→ **PSI.g.** Use of LC/MS for the identification of new allergens involved in olive pollen allergy. **Samanta Lozano de la Haba.**
→ **PSI.h.** Putative pathophysiological roles of miRNAs in the regulation of pituitary expression of GnRH-R, LHß and FSHß, in the context of obesity-induced hypogonadism. **Yolanda Guerrero Ruiz.**
→ **PSI.i.** A Preliminary Study of Circulating Tumour Cells in Patients with Hepatocellular Carcinoma Undergoing Neoadjuvant Transarterial Chemoembolization. **María Lola Espejo Cruz.**

→ **PSI.j.** Social support in times of pandemic. Intervention study.
Elena López Cerdá.
→ **PSI.k.** In vitro evaluation of the effect of exosomes derived from umbilical cord MSCs grown in normoxia and hypoxia on cell types involved in skin regeneration. **Aina Torres Pallares.**
→ **PSI.l.** Improvement of cetuximab-dependent cellular cytotoxic activity of human NK cells against colorectal cancer cells. **Carmen Navarrete Sirvent.**
→ **PSI.m.** Health-Related Quality of Life in Cardiovascular Patients explicated by Positivity and Self-Efficacy. **Tamara Gutiérrez Domingo.**
→ **PSI.n.** Peritonitis predictive factors in incidental patients in peritoneal dialysis. **Cayetana Moyano Peregrin.**
→ **PSI.ñ.** Role of the phosphatase PNKP in temozolomide resistance.
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→ **PSI.q.** Histological changes of major pectoralis muscle fibres after breast prosthesis implantation. **Juan Cámara Pérez.**
→ **PSI.r.** Inhibition of dipeptidyl peptidase 8/9 negatively affects human mesenchymal stem cell differentiation in vitro. **Bárbara Torrecillas Baena.**
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→ **PSI.t.** Evolution of metabolic phenotypes of obesity after 5-year intervention with two healthy diets. Cordioprev study. **Laura Martín Piedra.**
→ **PSI.u.** Role of intestinal microbiota in the sex-dimorphism differences in the cardiovascular diseases. **Helena García Fernández.**
→ **PSI.v.** Role of DNA repair mechanisms in temozolamide resistance.
Inés Grávalos Cano.
→ **PSI.w.** Enhancing subjective well-being in cardiovascular disease patients through a mHealth psychological intervention in emotion regulation.
Naima Z Farhane Medina.
→ **PSI.x.** Medium-term clinical impact of the ejection fraction recovery in patients with severe left ventricule dysfunction. **Jorge Perea Armijo.**
→ **PSI.y.** Healthy habits intervention program. WhatsApp broadcast.
Eva María Sánchez Cañete.
→ **PSI.z.** Severe aortic stenosis survival and mortality analysis, in a series of patients, clinical and economic factors. **María Teresa Conejero Jurado.**
→ **PSI.aa.** Rare indications of lung transplantation in Andalucia.
David Poveda Chávez.
→ **PSI.bb.** Phase I / II single-arm efficacy and safety study of the use of neutral argon plasma in the debulking of miliary implants on the peritoneal surface. **Francisca Valenzuela Molina.**
→ **PSI.cc.** Late complications in patients with Stent-treated coarctation of the aorta: Long-term follow-up. **Cristina Pericet Rodríguez.**
→ **PSI.dd.** Management and knowledge of soft tissue tumors / sarcoma: Update of primary care physicians. **Raquel Gracia Rodríguez.**

16:30 – 18:15
Session III. Nutrition, Endocrine and metabolic diseases
(IMIBIC Assembly Hall)
Chairs: **Dr. Alejandra Pera** & **Dr. André M. Sarmento.**

→ **IIIa. 16:30 – 16:45**
Long-term consumption of a Mediterranean diet or a low-fat diet on kidney function in coronary heart disease patients: an analysis of the CORDIOPREV randomized controlled trial. **Alicia Podadera Herreros.**

→ **IIIb. 16:45 – 17:00**
Molecular Diagnosis of Polycystic Ovary Syndrome in Obese and Non-Obese Women by Targeted Plasma miRNA Profiling. **Cecilia Perdices López.**

→ **IIIc. 17:00 – 17:15**
Evaluation of the effect of COVID-19 on body composition and the development of obesity in Spanish preschool children: Coral Study. **Laura Velarde Morales.**

→ **IIId. 17:15 – 17:30**
Microvascular endothelial function, long-term dietary intervention and cardiovascular risk of recurrence: from the cordioprev study. **Marta Millán Orge.**

→ **IIIe. 17:30 – 17:45**
Hypothalamic lipid sensing: a new player in the metabolic control of puberty. **Elvira Rodríguez Vázquez.**

→ **IIIf. 17:45 – 18:00**
Relationship between Physical Activity, Oxidative Stress, and Total Plasma Antioxidant Capacity in Spanish Children from the
GENOBOX Study. **Francisco Javier Aguilar Gómez-Cárdenas.**

→ **IIIg. 18:00 – 18:15**
Circulating miRNA profile in childhood early obesity and metabolic syndrome. **Miguel Ruiz Cruz.**

Day 2 (29th OCT)

08:30 – 09:00
Registration and Poster display

09:00 – 10:45
Session IV. Cancer II (IMIBIC Assembly Hall)
Chairs: **Dr. Oriol Rangel** & **Dr. Rafael Pineda.**

→ **IVa. 09:00 – 09:15**
GSK-3 inhibition as an immunotherapeutic approach in colorectal cancer. **Ana Mantrana Soldado.**

→ **IVb. 09:15 – 09:30**
SF3B1 inhibition disrupts malignancy and prolongs survival in glioblastoma patients through the imbalance of BCL2L1-splicing and mTOR/ßcatenin-pathways. **Antonio Carlos Fuentes Fayos.**

→ **IVc. 09:30 – 09:45**
The emerging role of the dual-specifity tyrosineregulated kinase 2 (DYRK2) regulating FBXW7 tumor suppressor in cancer development and progression. **Rafael Manuel Jiménez Izquierdo.**

→ IVd. 09:45 – 10:00
Dysregulation of the splicing machinery in rare tumors: The splicing process is altered in Pseudomyxoma Peritonei.
María Trinidad Moreno Montilla.
→ IVe. 10:00 – 10:15
The Combination of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio with Liquid Biopsy Biomarkers Improves Prognosis Prediction in Metastatic Pancreatic Cancer. **Marta Toledano Fonseca.**
→ IVf. 10:15 – 10:30
Spliceosome dysregulation accompanies diet-induced chronic liver disease progression towards hepatocellular carcinoma in mouse models. **Antonio García Estrada.**
→ IVg. 10:30 – 10:45
Incidence of cancer in the native lung after single lung transplantation. **Alba María Fernández González.**

10:45 – 11:15
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11:15 – 12:15
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Chairs: **Dr. Maria Victoria García** & **Dr. Clementina López.**

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→ PSII.b. Pharmacological inhibition of Nox4 protects against acute kidney injury associated to massive intravascular hemolysis. **Cristina García Caballero.**
→ PSII.c. Autophagy and mitochondrial alterations by anti-aging interventions with NAD+ boosters and CYB5R3 overexpression are sex dependent in mice kidney. **Miguel Pérez Rodríguez.**
→ PSII.d. Utility of copy number variation analysis detected by next generation sequencing in acute myeloid leukemia patients. **Kamila Janusz.**
→ PSII.e. SARS-CoV-2 and CMV chronic infection. **Pablo Álvarez Heredia.**
→ PSII.f. Circadian biorhythm and cardiometabolic risk among patients with coronary heart disease. **Juan Luis Romero Cabrera.**
→ PSII.g. The Yin-Yang of Adipose Tissue Fibrosis. **Carmen Tercero Alcázar.**
→ PSII.h. Improvement of "off-the-shelf" allogeneic CAR-T cells.**Kristina Pavlovic Pavlovic.**
→ PSII.i. Alterations of mitocondrial ultrastructure due to aging and CYB5R3 overexpression. **Sara López Bellón.**
→ PSII.j. Influence of low back pain, sequenced movement, short-term rest, and age on lumbar muscle mechanical properties. **Sandra Alcaraz Clarina.**
→ PSII.k. Low fat diet modulates oxidative stress through FOXO1A genetic variant in coronary heart disease patients with type 2 diabetes. **Cristina Hidalgo Moyano.**
→ PSII.l. Sensitisation Profile of Patients Allergic To Apis Mellifera. **Ana Belén Carmona Casado.**
→ PSII.m. Impact of the use of diuretics after the onset of hemodialysis. **Victoria Eugenia García Montemayor.**
→ PSII.n. Preliminary results on the establishment of an animal model of pseudomyxoma peritonei with human xenograft. **Blanca Rufián Andújar.**

→ **PSII.ñ.** Additive antitumor effect of metformin and simvastatin combination in glioblastoma: evidence for a potential drug repurposing. **Miguel Eduardo García García.**
→ **PSII.o.** Impact of the number of comorbidities on the outcome measures and on the retention rate of the first anti-TNF in patients with Ankylosing Spondylitis. Two-year follow-up REGISPONSER-AS. **María Ángeles Puche Larrubia.**
→ **PSII.p.** Outcomes in patients with anti-gbm glomerulonephritis in a multicentric spanish cohort. **Marina Sánchez-Agesta Martínez.**
→ **PSII.q.** Lipoprotein subclasses, particle sizes and standard lipid panel and their relationship with peripheral artery disease in coronary heart disease patients: from the CORDIOPREV study. **María del Pilar Coronado Carvajal.**
→ **PSII.r.** Evaluation of Sedentary Behavior and Physical Activity Levels using Different Accelerometry Protocols in Children from the GENOBOX study. **José Manuel Jurado Castro.**
→ **PSII.s.** Pediatrics eating disorders during the sars-cov19 pandemic in reina sofia university hospital. **María Jordano González.**
→ **PSII.t.** A proposal for modification of PSOGI classification according to Ki-67 proliferation index in pseudomyxoma peritonei. **Ana Martínez López.**
→ **PSII.u.** Rab34 or how to turn lipid storage on and off. **Jaime David López Alcalá.**
→ **PSII.v.** Prevalence and Associated Factors of Low Bone Mineral Density in the Femoral Neck and Total Hip in Axial Spondyloarthritis: Data from the CASTRO Cohort. **Laura Bautista Aguilar.**
→ **PSII.w.** Relationships between Body Mass Index and Psychosocial variables to predict the well-being of children and adolescents: a preliminary study. **Joaquín Villaécija Rodríguez.**
→ **PSII.x.** Construccion of a predictive test for postpartum depression.
Irene Cabedo Olaya.
→ **PSII.y.** Intratumoral Bromelain and Acetylcysteine for Recurrent and Unresectable Pseudomyxoma Peritonei. A Phase I/II, unicentric study.
Lidia Rodríguez Ortiz.
→ **PSII.z.** Aortic valve infiltrating pro-inflammatory cells in aortic stenosis patients. **José Joaquín Domínguez del Castillo.**
→ **PSII.aa.** Ventilatory therapies and Intensive Care admissions for patients with COVID-19: a systematic review. **María del Rocío Valverde León.**
→ **PSII.bb.** Analyzing the Role of Autophagy in the Control of Puberty and Reproductive Function. **Manuel Jiménez Puyer.**
→ **PSII.cc.** Relation between Helicobacter spp. isolated in bile and biliary tract malignancies. **Beatriz Gros Alcalde.**

12:15 – 12:30
Presentation of the UCAIBs

12:30 – 13:30
Plenary Lecture: Pluripotency for organ regeneration.
Dr. Núria Monserrat, ICREA Research Professor. Institute for Bioengineering of Catalonia (IBEC).

13:30 – 14:00
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 24th to July 19th. 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 **89 abstracts** were received. On July 28th, the Organizing Committee distributed all abstracts received amongst **31 external reviewers** in a completely anonymized manner. All reviewers were selected based on their leadership position in their fields. The full list of the external reviewers can be found at the beginning of this book. Abstracts were **peer-reviewed** by the external reviewers from August 1st to September 15th, 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 17th and 20th, the Organizing Committee held two new meetings 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 4 sessions (7-8 communications/each), while poster presentations were distributed in 2 sessions (7-8 presentations were selected in each session to be presented in front of the chairs). Considering the number and scores of oral presentations submitted for each category, the Organizing Committee decided to establish two sessions for Cancer, one session for Nutrition, Endocrine and Metabolic diseases, and one Multidisciplinary session, which mostly include communications about Chronic, Inflammatory, Immunological and Infectious diseases.

Description of the review process for award selection

In order to motivate and boost high-quality presentations, IMIBIC establishes awards to the best oral communication within each of the 4 sessions. These awards will be selected based on the scores derived from the (i) Scientific Committee, which includes 1 translational researcher and coordinator and 3 researchers (1 clinical and 2 translational), (ii) all the chairs of the sessions (10 researchers), and (iii) the external reviewers (31 researchers). The full list of members of the Scientific Committee, chairs and external reviewers 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, and also the score provided by the external reviewers. The four highest scored oral communications will compete for the Best Presentation Award of the Meeting. The best oral communication presented by a Resident Medical Intern will be also awarded by the "*Colegio Oficial de Médicos de Córdoba*".

To assess the poster presentations, two chairs will visit the 15 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

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Abstracts

SESSION I. **Cancer I**

Ia. Application of a biocomputational approach to identify alterations in the spliceosomic landscape in lung carcinoids.

Authors: Víctor García-Vioque(1,2,3,4), Ricardo Blázquez-Encinas(1,2,3,4), M. Teresa Caro(1,5), Trinidad Moreno-Montilla(1,2,3,4), Antonio Agraz-Doblas(1,2,3,4), Ángel Salvatierra(1,6), Aura D. Herrera-Martínez(1,7), Matthieu Foll(8), Raúl M. Luque(1,2,3,4), Lynnette Fernández-Cuesta(8), Alejandro Ibáñez-Costa(1,2,3,4), Justo P. Castaño(1,2,3,4).

Affiliations: 1.-Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), 14004 Cordoba, Spain. 2.-Department of Cell Biology, Physiology and Immunology, University of Cordoba, 14004 Cordoba, Spain. 3.-Reina Sofia University Hospital, 14004 Cordoba, Spain. 4.-CIBER Physiopathology of Obesity and Nutrition (CIBERobn). 5.-Anatomical Pathology Service, Reina Sofia University Hospital, 14004 Cordoba, Spain. 6.-Thoracic Surgery Service, Reina Sofia University Hospital, 14004 Cordoba, Spain. 7.-Endocrinology & Nutrition Service, Reina Sofia University Hospital, 14004 Cordoba, Spain. 8.-International Agency for Research on Cancer, 69008 Lyon, France.

Scientific Program: Cancer I.

Keywords: Lung carcinoids, splicing, splicing factors, biocomputational analysis.

→ **Abstract:** Lung carcinoids (LC) account for approximately 2% of all lung cancers, and their incidence has increased in recent decades. LC are characterized by a late diagnosis, which complicates their treatment. Thus, it is necessary to find new biomarkers to improve their diagnosis and management. The alteration of alternative splicing is emerging as a transversal hallmark of cancer that pervades all the cancer hallmarks and provides attractive therapeutic opportunities. The main objective of this work is to explore the consequences of the dysregulation of the splicing machinery in LC. To this end, we first used a qPCR array to measure the expression of a panel of selected splicing factors in samples of tumor tissue and adjacent non-tumor tissue from 26 patients with LC. Correlations with relevant clinical parameters were assessed, which identified a set of splicing factors relevantly altered in LC. We then applied a biocomputational approach, using SUPPA2, to analyze expression data from a RNA-seq of 20 LC and interrogate the potential influence of the dysregulation of the selected factors on global splicing patterns. This revealed a marked change in the type of predominant events observed when comparing samples with high and low expression of these factors. Specifically, the number of events of each type that occurs differentially between the two groups is considerable, with alternative first exon and exon skipping events being most prominently distinct. The transcripts resulting from this altered splicing pattern also differed between the two groups; in many cases the expression in both groups was clearly divergent. Finally, we performed functional enrichment analysis with different databases, which uncovered the possible involvement of unexpected processes in the changes observed. In conclusion, this work demonstrates the suitability of this biocomputational approach for the identification of splicing-related molecular targets that hold potential for diagnostic and/or therapeutic purposes in LC.

Ib. The metabolic rewiring induced by impaired denitrosylation contributes to tumor progression and immune escape in colorectal cancer.

Authors: Rafael Mena-Osuna1, Ana Mantrana1, Carmen Navarrete-Sirvent1, Marta Toledano-Fonseca1,2, Ana Calero1, F. Javier Medina3, Carlos Villar4, Teresa Morales-Ruiz1, Gema García1, Enrique Aranda1,2,5,6, Silvia Guil-Luna1,2 and Antonio Rodríguez-Ariza1,2,5.

Affiliations: 1.-Maimónides Institute of Biomedical Research of Córdoba (IMIBIC). 2.-CIBERONC, Madrid, Spain. 3.-General Surgery and Digestive System Department, Reina Sofía University Hospital, Córdoba, Spain. 4.-Pathological Anatomy Department, Reina Sofía University Hospital, Córdoba, Spain. 5.-Medical Oncology Department, Reina Sofía University Hospital, Córdoba, Spain. 6.-Department of Medicine, Faculty of Medicine, University of Córdoba, Córdoba, Spain.

Scientific Program: Cancer I.

Keywords: colorectal cancer, immune evasion, metabolism, mitochondria, S-nitrosylation.

Abstract: S-nitrosoglutathione reductase (GSNOR) is a highly evolutionarily conserved denitrosylase enzyme, which is coded by ADH5 gene in humans. We previously reported that impaired GSNOR/ADH5 levels are associated with poor response to treatment and survival in HER-2 aggressive type of breast cancer. Therefore, the present study was aimed to investigate the significance of GSNOR/ADH5 in colorectal cancer (CRC).

Immunohistochemical and gene expression analysis showed that low GSNOR/ADH5 expression was associated with CMS4 aggressive CRC type, worse prognosis and poor survival in CRC patients. Besides, analysis of T cell gene expression signature revealed an immune suppressed microenvironment in GSNOR/ADH5-low tumors. CRISPR-Cas9–mediated ADH5 gene knockout (KO) in CRC cells confirmed that GSNOR/ADH5 deficiency confers higher tumorigenic capacity. Thus, in comparison with parental cells, ADH5-KO cells possessed greater ability to generate tumorospheres and tumor spheroids, and initiated tumors with higher efficiency in immunodeficient mice. Moreover, ADH5-KO cells had a lower expression of the intestinal differentiation marker CDX2 and a higher expression of the immune checkpoint protein PD-L1, indicating enhanced immunoevasive capacity.

Importantly, the higher tumorigenic potential of ADH5-KO cells was associated to a metabolic switch from oxidative phosphorylation to aerobic glycolysis, as indicated by increased lactate production, decreased ATP content and higher 2-deoxyglucose sensitivity. Moreover, confocal microscopy analyses revealed that ADH5-KO cells were characterized by a fragmented mitochondrial network, which is consistent with a higher rate of mitochondrial fission, impaired oxidative phosphorylation and increased aerobic glycolysis. Accordingly, a proteomic approach confirmed that clinical tumors with low GSNOR/ADH5 expression exhibit an altered energy metabolism, with impaired oxidative phosphorylation and increased aerobic glycolytic activity, along with an immune suppressive proteomic signature.

In conclusion, our results support that metabolic reprogramming induced by impaired denitrosylation constitutes an important novel mechanism contributing to the acquisition of aggressive and immune evasive phenotypes in CRC.

Fundings: Funded by PID2019-105256RB-I00.

Ic. Unleashing the therapeutic role of somatostatin and cortistatin in prostate cancer.

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Scientific Program: Cancer I.

Keywords: Somatostatin system, Somatostatin, Cortistatin, Prostate Cancer, Therapeutic Tool.

Abstract: Somatostatin (SST), cortistatin (CORT), neuronostatin (NST) and their receptors (sst1-5/sst5TMD4-TMD5/GPR107) comprise a hormonal pleiotropic system involved in the regulation of multiple pathophysiological functions. Certain components of this system are dysregulated in different endocrine-related cancers (ERC), including prostate cancer (PCa), wherein they play a critical role in the development and progression of this disease. However, a comparative, parallel study of the presence and therapeutic role of SST and CORT in PCa has not been reported hitherto. Thus, functional (proliferation/migration/colonies-formation) and mechanistic (Western-blot/qPCR) assays were performed in response to SST and CORT (10-7M) in different PCa-derived cell lines [androgen-dependent (AD): LNCaP; and androgen-independent (AI): 22Rv1 and PC-3; models of hormone-sensitive and Castration-Resistant PCa (CRPCa), respectively], and in the normal prostate cell-line RWPE-1. SST/CORT-treatment inhibited proliferation and migration rate only in AI-PCa cells. Additionally, SST-treatment also reduced the colonies formed. The antitumor capacity of SST/CORT peptides was associated with the modulation of important oncogenic pathways (PTEN/AKT/JNK). Interestingly, among all SST/CORT receptors, only sst5 was significantly overexpressed in AI-PCa cells vs. normal cells, suggesting that the antitumor actions of SST/CORT might be potentially mediated through sst5. Remarkably, CORT was highly expressed in all prostate cell-lines analysed, suggesting that endogenous CORT could exert antitumor actions in PCa-cells through an autocrine/paracrine mechanism. Consistently, siRNA-induced CORT-silencing drastically modulated key functional aggressiveness parameter (e.g. enhanced proliferation rate) of AI-PCa cells. Most importantly, CORT-silencing also blunted the antitumor activity of octreotide and pasireotide, two SST/CORT-analogues commonly used as medical therapy for tumor control in different ERC. Finally, we found that CORT was overexpressed and correlated with key clinical parameters (Gleason-Score/metastasis) in PCa samples from two in silico cohorts of patients (Grasso/Taylor). Altogether, our results indicated that SST/CORT could represent a potential new therapeutic alternative for PCa, especially for CRPCa.

Fundings: MINECO (PID2019-105564RB-I00/FPU18/06009/FPU17-00263/PRE2020-094225), Junta de Andalucía (BIO-0139) and CIBERobn.

Id. Interval carcinomas in a Breast Cancer Screening Program: differences between women studied with digital mammography or tomosynthesis.

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Scientific Program: Cancer I.
Keywords: Breast cancer, Cancer screening, Digital breast tomosynthesis, Interval cancer, Mammography.

Abstract: Objectives. To compare the rate of interval carcinoma in patients participating in a round of screening divided into two groups: some screened with mammography (group 2D) and others screened with mammography + tomosynthesis (group 2D + 3D). Also compare the sensitivity of the program and the characteristics of the interval carcinomas between the two groups and, on the other hand, the characteristics of the interval carcinomas with those of the screening carcinomas.
Methods. Retrospectively, the histories of the women participating in a round of the Screening Program between January 2015 and December 2016 were reviewed. An exhaustive search was carried out for the screening carcinomas detected in that round and the interval carcinomas diagnosed in that group of women. After collecting different variables, the planned comparisons were carried out.
Results. 43,256 women were reviewed, 16,870 were in the 2D + 3D group and 26,386 in the 2D group. 309 cancers were diagnosed in that sample, 247 were screening cancers (100 in the 2D + 3D group and 147 in the 2D group) and 62 were interval carcinomas (14 in the 2D + 3D group and 48 in the 2D group). The interval carcinoma rate was lower in the 2D + 3D group (0.82 / 1000 screened women vs. 1.81 / 1000 screened women in the 2D group, p = .006). The sensitivity of the program was higher in the 2D + 3D group (87% vs. 75% in the 2D group, p = RU.008). Interval carcinomas are larger in group 2D and tend to be diagnosed in more advanced stages in this group. Interval carcinomas present characteristics of worse prognosis than those detected on screening.
Conclusion. The rate of interval carcinomas is lower in the group screened with 2D + 3D compared to women screened only with 2D.

Ie. Surgical treatment of malignant pleural mesothelioma. Multicenter study.

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Scientific Program: Cancer I.

Keywords: Malignant Pleural Mesothelioma, surgical treatment, hyperthermic intrathoracic chemotherapy.

Abstract: Objective: To analyze the results of Malignant Pleural Mesothelioma (MPM) surgical treatment at two centers of national experience during the last 10 years.

Material and methods: Retrospective descriptive study of patients whith MPM underwent surgical treatment between January 2011 and December 2020. Variables recorded: patient demographics, surgical treatment, hyperthermic intrathoracic chemotherapy (HITHOC), cancer staging, complications, mortality and overall survival. Results were compared by histology (epitelial/non-epitelial) and surgical technique (extrapleural pneumonectomy (EPP)/ pleurectomy-decortication (P-D)).

Results: 25 consecutive patients were analyzed, 17 male and 8 female, mean age was 54±11 years. EPP was performed at 16 patients (64%) and P-D at 9 (36%). Histology: 76% epitelial, 8% sarcomatoid, 16% mixed.

Induced chemotherapy was administered in 32% of patients. HITHOC was used in 28%.

Postoperatory complications occurred in 14 patients (56%). Overall mortality was 84% (21 patients) with a disease-free interval median of 12.6 months.

Overall survival at 6 months, 1, 3 and 5 years was, respectively: 84%, 68%, 34%, 21%. (median: 24,8 months, CI-95%: 12-37 months).

Survival by histology (6 months, 1, 3 and 5 years); Epithelial: 84%, 73%, 40%, 28% (median: 30 months, CI-95%: 18-42 months); Sarcomatoid: 0% < 6 months; and mixed: 75%, 75%, 25%, 0% (median: 25 months, CI-95%: 0-51 months) (p=0.002).

Survival by surgical treatment (EPP vs. P/D) (6 months, 1, 3 y 5 years): 75%, 50%, 21%, 14% (median: 10 months, CI-95%: 0-27 months) vs. 89%, 89%, 55%, 33% (median: 38 months CI-95%: 27-48 months) respectively (p=0.03).

Conclusions: MPM is a high mortality neoplasm, even with an aggresive treatment including neo-adyuvant chemoterapy and HITHOC.

In our study, epitelial type has better survival. Initial stages underwent a P/D presenting better survival tan EPP, that was performed in more advanced stages. The use of HITHOC haven't improved survival rates and it's associated with worse postoperative complications.

If. Splicing machinery landscape in hepatocellular carcinoma: a central role of EIF4A3 in hepatocarcinogenesis.

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Scientific Program: Cancer I.

Keywords: hepatocellular carcinoma; splicing machinery; EIF4A3; FGF19.

Abstract: Hepatocellular carcinoma (HCC) is associated with the expression of oncogenic splicing variants, which might be linked to a dysregulation of the cellular machinery that controls the splicing process (spliceosome). Here, we explored the dysregulation and pathophysiological role of key spliceosome components in HCC.

Expression (mRNA/protein) of key (n=72) spliceosome components and clinical implications were assessed in HCC patients from two retrospective (n=154, n=172) and six in silico [TCGA (n=369), Wurmbach (n=45), Roessler (n=43), Roessler-2 (n=445), Chen (n=179), Mas (n=57)] cohorts. Gene Set Enrichment Analysis (GSEA) and mutational landscape were analysed in TCGA. Functional/molecular consequences of siRNA-mediated EIF4A3-silencing were evaluated in liver-derived cell lines (HepG2, Hep3B, SNU-387) and Hep3B-induced xenograft tumours. RNAseq from EIF4A3-silenced HepG2 cells was analysed.

A consistent, profound dysregulation (mRNA/protein) of many spliceosome components was found in HCC vs. control-tissues, specially EIF4A3, RBM3, ESRP2 and SRPK1, whose expression was associated with clinical (survival, recurrence) and/or molecular parameters of aggressiveness. Particularly, EIF4A3 was overexpressed in all HCC cohorts and associated with alterations in cancer-related pathways (e.g., cell cycle) and relevant mutations (CTNNB1, TP53). EIF4A3-silencing reduced proliferation, migration and tumorsphere/colony formation in vitro and tumoral growth in vivo, and modulated liver-derived cell lines sensitivity to clinical treatments (e.g., Lenvatinib). RNAseq showed that EIF4A3-silencing altered the expression and splicing of genes involved in RNA splicing, translation and metabolic processes, including key hepatocarcinogenesis-associated genes (e.g., FGFR4). Indeed, in vitro assays demonstrated that EIF4A3 modulates FGFR4 splicing and the pro-oncogenic signalling of the FGF19/FGFR4 axis.

Therefore, this study demonstrates that splicing machinery is profoundly dysregulated in HCC, wherein it may represent a promising source of diagnostic, prognostic or therapeutic targets.

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Ig. Revealing the pharmacologically regulable CDC25A/DYRK2 axis: a novel master cell cycle and survival modulator.

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Scientific Program: Cancer I.

Keywords: DYRK2, CDC25A, Degradation, Kinase, Phosphatase, Phosphorylation, Cell cycle, Cancer.

Abstract: The Cell division cycle 25A (CDC25A) phosphatase is a key regulator of cell cycle progression that acts on the phosphorylation status of Cyclin-Cyclin dependent kinase complexes, with an emergent role in the DNA damage response and cell survival control. The regulation of CDC25A activity and its protein level is essential to control cell cycle and to maintain genomic integrity. Here we describe for the first time a novel ubiquitin/proteasome-mediated pathway negatively regulating CDC25A stability, dependent on its phosphorylation by the serine/threonine kinase DYRK2 with relevant implications. First, DYRK2 phosphorylates CDC25A on at least 7 residues, resulting in its degradation independent of the known CDC25A E3 ubiquitin ligases. Second, CDC25A in turn is able to control the phosphorylation of DYRK2 at several residues outside from its activation loop, thus affecting DYRK2 localization and activity. Third, we demonstrate the DYRK2's ability to autophosphorylate outside its activation loop which results in changes in its activity. An inverse correlation between DYRK2 and CDC25A protein amounts was observed during cell cycle progression and in response to DNA damage, with CDC25A accumulation responding to the manipulation of DYRK2 levels or activity in either physiological scenario. Functional data show that the pro-survival activity of CDC25A and the pro-apoptotic activity of DYRK2 could be partly explained by the mutual regulation between both proteins. Moreover, we prove that DYRK2 pharmacologically modulation modifies CDC25A expression and/or activity. This evidence highlights DYRK2 as a suitable target in the cell cycle modulation of cancer patients. All together, we provide evidence suggesting that DYRK2 and CDC25A mutually control their activity and stability by a feed-back regulatory loop, with a relevant effect on the genotoxic stress pathway, apoptosis and cell cycle regulation.

SESSION II. **Multidisciplinary**

IIa. Assessment of the liver disease risk in inflammatory arthritis. Molecular mechanisms involved in hepatocyte dysfunction in the context of psoriatic arthritis.

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Scientific Program: Inflammatory, Infectius and Immunological diseases.

Keywords: inflammatory arthritis, psoriatic arthritis, liver, hepatocytes, inflammation, NALFD and fibrosis.

Abstract: Background: Chronic inflammation, prolonged treatments and the cardiovascular (CV) comorbidities suggest the need of monitoring NALFD (non-alcoholic fatty liver disease) in inflammatory arthritis.

Objectives: To analyze the risk of NALFD in inflammatory arthritis, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA); 2) To evaluate clinical and subclinical signs of CV Disease and its relation with the development of NALFD in PsA patients and 3) To describe the mechanisms involved in hepatocyte dysfunction in a PsA context.

Methods: 1) Cross-sectional study in 180 healthy donors (HDs) and 635 patients (280 RA, 170 PsA and 185 axSpA). Specific clinical and analytical variables of each disease were evaluated. The risk of NAFLD was assessed using the Fibrosis-4 (FIB-4) and triglycerides/glucose (TyG) indexes. Plasma levels of 92 CVD proteins in PsA patients and HDs were analyzed. In vitro studies on a human hepatocyte cell line (HepG2) treated with PsA serum were performed.

Results: NALFD risk was significantly increased in PsA patients compared to the rest of inflammatory arthropathies and HDs. Clinical and analytical variables such as disease activity, ESR, CRP, and surface area affected by psoriasis correlated with markers of NALFD. PsA patients showed an altered clinical and molecular profile associated with CVD related to markers of NALFD. Glucocorticoids, methotrexate and NSAIDs did not significantly change the markers of liver disease. PsA serum promoted an alteration in the expression of genes and proteins related to liver dysfunction on hepatocytes.

Conclusion: 1) PsA is the inflammatory arthritis with a greater risk of developing NAFLD compared to others autoinflammatory diseases and HDs; 2) The subclinical hepatic alterations are strongly associated with the CV risk, insulin resistant and the intrinsic characteristics of PsA such as inflammation and activity. 3) Inflammatory and CV mediators in PsA could promote hepatocyte dysfunction activating pathways involved in NALFD.

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IIb. Reduction of renal mass interferes with the phosphaturic action of rapamycin.

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Scientific Program: Inflammatory, Infectius and Immunological diseases.

Keywords: rapamycin, phosphaturia, kidney disease, P intake.

Abstract: Rapamycin has been shown to offer some protection for renal disease and recent data demonstrating a role of mTOR activation in the aetiopathogenesis of diabetic nephropathy strength the therapeutic potential of rapamycin in kidney disease. In addition, rapamycin has been shown to potentiate phosphaturia in rodents with normal renal function fed standard diets. The aim of this study was to investigate whether the phosphaturic action of rapamycin would be modulated by high P intake and by reduction of renal mass.

To this purpose, the following groups of rats (n=16) were studied: control rats fed normal 0.6% P (NP), rats fed high 1.2% P (HP), rats subjected to 5/6 nephrectomy (5/6Nx) fed NP, and 5/6Nx rats fed HP. In each group half the rats received placebo and the other half were treated with rapamycin, administered orally at a dose of 1.3 mg/kg for 17 days. Blood and urine samples were obtained at the end of the experiment.

No changes in plasma P were observed after treatment with rapamycin. Daily urinary excretion of P (mg/day) was recorded and corrected by daily P intake (mg/day). Urinary excretion of P was increased in rats fed HP and in 5/6Nx rats. The ratio P urine/P intake was increased after rapamycin treatment both in controls (0.37±0.03 vs 0.27±0.01, p=0.005) and in rats fed HP (0.49±0.03 vs 0.41±0.01, p=0.025). However, rapamycin did not increase urinary excretion of P neither in 5/6Nx rats fed NP (0.42±0.02 vs 0.42± 0.04) nor in 5/6Nx rats fed HP (0.46±0.02 vs 0.48±0.03).

In conclusion, a phosphaturic effect of rapamycin was observed in rats with normal renal function fed both normal and high P diets. However, in rats with reduced renal function rapamycin did not increase phosphaturia, neither when fed normal or high P.

IIc. Kinetics of the intestinal loads of Klebsiella pneumoniae producing KPC carbapenemase following selective digestive decolonization with oral gentamicin: a 1-year, prospective cohort study.

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Scientific Program: Inflammatory, Infectius and Immunological diseases.

Keywords: KPC-producing Klebsiella pneumoniae, selective digestive decolonization, intestinal colonization, relative bacterial load.

Abstract: Objectives: To monitor the kinetics of intestinal loads of Klebsiella pneumoniae producing KPC carbapenemase (KPC-Kp) in patients receiving selective digestive decolonization (SDD) with oral gentamicin.

Methods: One-year prospective cohort study. We used quantitative real-time PCR (qPCR) to determine the relative load of blaKPC (RLKPC) in patient´s rectal swabs as compared to a pure KPC-Kp strain (set as 100%). We applied the delta-delta threshold cycle (ΔΔCt) algorithm, using 16SrRNA as normalizer gene. qPCR diagnostic accuracy was assessed using a quantitative, culture-based method as gold-standard. Primary endpoints: RLKPC at baseline, 14 and 30 days. Secondary endpoints: decolonization at 14 and 30 days, persistent decolonization, detection of gentamicin-resistant KPC-Kp.

Results: We collected 111 rectal swab samples from 15 patients. The median (range) RLKPC was 0.68% (0.001%-9.83%) at baseline, <0.001% (0.00%-0.06,p=0.173) at 14-days, and 0.01% (<0.001%-2.71%,p=0.071) at 30-days. The median RLKPC was significantly reduced at 30-days in the subgroup of patients with higher baseline-RLKPC (7/15,p=0.043). At 14-days and 30-days, decolonization was observed in 5/15(33.3%) and 2/15(13.3%), respectively. Persistent decolonization at 1, 3, 6 and 12 months was 2/15(13.3%), 3/15(20.0%), 4/15(26.6%) and 6/15(40%), respectively. Four patients (26.6%) developed transient gentamicin-resistant KPC-Kp. The rates of infections (57.1% versus 12.5%,p=0.119) and deaths (71.4% versus 0%,p=0.007) were higher among patients with higher baseline-RLKPC.

Conclusions: Oral antibiotic treatment with nonabsorbable drugs to which KPC-Kp is susceptible appears to be effective for reducing intestinal KPC-Kp loads, however persistent decolonization reaches only 20% within 3 months. Pre-SDD intestinal KPC-Kp loads may be higher in patients at higher risk of death.

IId. Unsupervised clustering analysis of the circulating inflammatory profile of Rheumatoid Arthritis patients stratify patients according to their cardiovascular risk.

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Scientific Program: Inflammatory, Infectius and Immunological diseases.

Keywords: Rheumatoid arthritis, Cardiovascular risk factors, Inflammation, Personalized Medicine.

Abstract: This study aimed to: 1) Analyze the circulating inflammatory profile of Rheumatoid Arthritis (RA) patients, in order to recognize distinctive clinical phenotypes; 2) Evaluate modulatory effects of TNF inhibitors (TNFi); 3) Characterize underlying molecular mechanisms involved.

Two hundred and eight RA patients and 45 healthy donors (HD) were recruited. Serum inflammatory profile was assessed by analyzing 27 cytokines/chemokines -Luminex assays-, and biomolecules related to NETosis and oxidative stress -by base-plate kits-. Parallel extensive clinical analyses were performed. TNFi effects were evaluated in 60 RA patients after 6 months. Lastly, mechanistic in vitro studies were developed.

Unsupervised-clustering identified 3 clusters representing specific molecular profiles. Clinically, even in the presence of similar disease score (DAS28) and positivity for autoantibodies, cluster 1 (C1) identified RA-patients expressing high inflammatory mediators' levels, the highest CV-risk score, and a preponderance of atheroma plaques. Conversely, RA-patients conforming C3 showed the lowest inflammatory profile and the lowest CV-risk score. Lastly, C2 characterized an intermediate phenotype. Comparative analyses with a cohort of 98 RA patients presenting previous CV events, demonstrated that their inflammatory profile mimicked that found in C1, supporting the association of this altered shape with the CV status. In vivo, TNFi-therapy reduced DAS28-score and re-established normal levels of altered biomolecules, reflecting a key role in the CV-risk control.

In vitro, RA patients' serum promoted in purified HD-leukocytes increased pro-inflammatory/prothrombotic mediators' expression, further reversed by the serum of those patients after TNFi therapy.

Conclusions: 1. The systemic inflammatory profile of RA characterizes patients' subgroups with enhanced CV-risk, not associated with their disease activity status. 2. TNFi re-establishes normal levels of circulating inflammatory biomolecules, reducing the CV-risk in RA.

Thus, the analysis of the RA patients circulating inflammatory profile, along with the standard DAS28-score assessment, might contribute to improve the personalized clinical management of these patients and their comorbidities.

Fundings: JA (PI-0285-2017) and ISCIII (PI18/00837 and RIER RD16/0012/0015 co-funded with FEDER).

IIe. Fibroblast growth factor 23 down-regulation by chronic metabolic acidosis in rats.

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Scientific Program: Inflammatory, Infectius and Immunological diseases.
Keywords: metabolic acidosis, FGF23, chronic kidney disease.

Abstract: Metabolic acidosis is a common complication in chronic kidney disease(1) and is associated with its progression(2). Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone that usually increases during renal failure(3). Both, metabolic acidosis and increased FGF23, are risk factors of mortality; however, their relationship remains unclear. To investigate the effect of metabolic acidosis on FGF23, rats with normal (intact) and impaired renal function induced by graded nephrectomy (Nx), 1/2Nx and 5/6Nx, received either water (controls) or were treated with oral NH4Cl for 30 days to induce acidosis. Ingestion of NH4Cl resulted in mild metabolic acidosis with a slight decrease in plasma bicarbonate in intact and 1/2Nx rats (24.7±0.7 vs 25.9±0.5 mmol/l and 23.7±0.6 vs 24.9±0.6 mmol/l, respectively) and severe metabolic acidosis with marked reduction in bicarbonate in 5/6 Nx rats, 12.6±2.9 vs 24.2±1.1 mmol/l. Plasma FGF23 increased with renal deterioration but decreased in all acidotic groups when compared with their non-acidotic control: 239±14 vs 295±16 pg/ml (intact), 346±20 vs 523±29 pg/ml (1/2Nx) and 988±126 vs 2,549±470 pg/ml (5/6Nx). Acidosis resulted in increases in plasma ionized calcium that were significant both in intact and in 5/6 Nx rats. Acidosis also decreased plasma parathyroid hormone (PTH) in all study groups, 95±22 vs 107±19 pg/ml (intact), 113±17 vs 185±22 pg/ml (1/2Nx), and 504±75 vs 1,255±181 pg/ml (5/6Nx). Moreover, a strong direct correlation ($r=0.877$, $p<0.0001$) was observed between plasma FGF23 and plasma PTH concentrations. In conclusion, chronic metabolic acidosis consistently decreased plasma FGF23, both in rats with intact and impaired renal function and this effect seems to be related to the decrease in plasma PTH levels.

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IIf. SARS-CoV-2 ORF7a and ORF7b cooperate in multiple membrane-based processes ranging from cell adhesion, olfaction and immune response interference.

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Scientific Program: Inflammatory, Infectius and Immunological diseases.

Keywords: SARS-CoV-2, accessory proteins, ORF7a, ORF7b, transcriptomic, immune response, COVID-19

Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic that is a serious global health problem. Currently, there is an urgent need to better understand the molecular mechanisms governing SARS-CoV-2 pathogenesis, as this will have implications for the design of better treatments and vaccines. Although much of the research on this virus is focused on the Spike protein, recent reports demonstrate that accessory proteins of SARS-CoV-2 might be involved in COVID-19 pathogenesis by modulating antiviral host responses. SARS-CoV-2 encodes 11 accessory proteins that differ significantly within coronaviruses. Among these proteins, the functions of the accessory protein ORF7a and ORF7b remain to be elucidated, making it less studied than other SARS-CoV-2 proteins. ORF7a is a type-I transmembrane protein of 121 amino acid residues which possess an Ig-like ectodomain containing an integrin binding site. ORF7b is 43 amino acid long and contains a transmembrane segment able to multimerize through a leucine zipper. Here, we characterized the transcriptional response of epithelial cells expressing individually these accessory proteins in order to identify its functions. Using transcriptomic combined with bioinformatic analysis and functional assays we showed that individually expressed ORF7a and ORF7b are sufficient to alter cellular networks in a manner that resembles full SARS-CoV-2 virus infection. Our work demonstrated that ORF7a and ORF7b cooperate in multiple host pathways deregulations, such as immune response, extracellular matrix organization, cell adhesion, metabolism pathways and olfaction. For the first time, this study highlights the involvement of the accessory proteins in aberrant cell adhesion and anosmia symptom of COVID-19.

IIg. Association of Gut Microbiota and Enthesis in Axial Spondyloarthritis. Data from CASTRO Registry.

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Scientific Program: Inflammatory, Infectius and Immunological diseases.

Keywords: Axial spondyloarthritis, gut microbiome, enthesis.

Abstract: Background/Purpose: The etiopathogenesis of axial spondyloarthritis (AxSpA) is multifactorial. Besides environmental and genetic factors, the possible role of the gut microbiota has been recently suggested. However, the association of the gut microbiota and clinical features is still unknown, such as the enthesis involvement. To evaluate the changes in the gut microbiota in AxSpA patients with enthesis involvement.

Methods: Cross-sectional study of 33 patients with AxSpA (according to ASAS criteria) was studied. Enthesis involvement was measured by ultrasonography MASEI index (Madrid Sonographic Enthesis Index), values >17 as pathological and ≤17 as non-pathological. Gut microbiota was evaluated using the Ion Torrent S5 platform and the sequences were processed using the QIIME2 analysis platform. The differential abundance analysis was performed through a linear discriminant analysis effect size (LEFSE) with the web-tool MicrobiomeAnalyst (www.microbiomeanalyst.ca). Significant differences were considered $p<0.05$.

Results: AxSpA patients were studied by ultrasonograpgy and 10 patients exhibited pathological MASEI. Alpha-diversity markers, such as observed ASV (amplicon sequence variant) and Chao1 index showed an increase in AxSpA patients with pathological MASEI respect to normal MASEI. The analysis of gut microbiota demonstrated a significant decrease in family Bacteirodaceae in patients with pathological MASEI (p=0,041). At genus level, Slackia (p=0.007), Eubacterium (p=0.033) and Prevotella (p=0.050) were significantly increased, while Oscillospira (p=0.031) and Bacteroides (p=0,041) were decreased in AxSpA patients with pathological MASEI compared to AxSpA patients with non-pathological MASEI. At species level, Prevotella copri (p=0.02) and Eubacterium biforme (p=0.03) showed a significant increase in AxSpA patients with pathological MASEI.

Conclusion: AxSpA patients with pathological MASEI showed a significant alteration in gut microbiota (family Bacteroidaceae; genus Slackia, Eubacterium, Prevotella, Oscillospira and Bacteroides, and species Eubacterium biforme and Prevotella copri).

Fundings: JA PI-0151-2018 an FIS PI19/00701.

POSTER SESSION I

PSI.a. Effect of the consumption of yogurt with Bifidobacterium lactis B420/205 and Lactobacillus acidophilus 207 on the parameters associated with glucose homeostasis in patients with type 2 diabetes mellitus of the Clinics Hospital from Asunción, Paraguay.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: Type 2 diabetes mellitus, probiotics, glucose homeostasis.

Abstract: Background: Type 2 diabetes mellitus (T2DM) is one of the main health problems worldwide with high rates of morbidity and mortality. Previous studies have shown that probiotic intake improves the intestinal microbiota profile which is associated with an improvement glucose homeostasis. Our objective was to study the effect of yogurt consumption with concentrated and lyophilized probiotic cultures of Bifidobacterium lactis B420/205 and Lactobacillus acidophilus 207 on parameters associated with glucose homeostasis.

Materials and Methods: 46 subjects with T2DM were recruited from the Endocrinology service of the Clinics Hospital (Paraguay), and were randomly assigned to three different intervention groups. The first received 300 g/d of yogurt with Lactobacillus acidophilus 207 and Bifidobacterium lactis B420/205 (Yogurt premium). The second received 300 g/d of conventional yogurt and the third did not receive any type of fermented dairy. The intervention period was 12 weeks. Biochemical parameters related to lipid profile and glucose homeostasis were determined at baseline and after the follow-up period.

Results: No significant differences were observed in the baseline characteristics of the subjects included in the study, except for a difference in weight between the subjects with the premium yogurt and the conventional yogurt ($p=0.043$). In addition, the results showed that glycosylated hemoglobin decreased after 12 weeks of premium yogurt intake compared to baseline ($p<0.001$). Finally, an increase in HOMA-IR was observed at 12 weeks of intervention in the group of subjects without fermented dairy products compared to baseline ($p = 0.016$). In contrast, the intake of premium and conventional yogurts did not show significant differences in HOMA-IR after the intervention.

Conclusion: The consumption of yogurt with Bifidobacterium lactis B420/205 and Lactobacillus acidophilus 207 could be a useful nutritional tool in clinical practice to regulate parameters associated with glucose homeostasis such as glycosylated hemoglobin and HOMA-IR in patients with diagnosed T2DM.

PSI.b. Sexual dimorphism in markers of pathways related with the hallmarks of aging in mice overexpressing CYB5R3 and fed a nicotinamide riboside–supplemented diet.

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Scientific Program: Active aging and fragility.

Keywords: CYB5R3, NR, sexual dimorphism, skeletal muscle.

Abstract: CYB5R3 is a NADH-dehydrogenase that plays a key role in the control of mechanisms that promote healthy aging. Transgenic mice overexpressing CYB5R3 (CYB5R3-TG) show improved glucose metabolism and increased survival. Since NAD+ levels decrease with aging, therapies aimed at preserving this molecule are of extreme interest as anti-aging interventions. Several metabolites of the NAD+ biosynthesis salvage pathway as nicotinamide riboside (NR) act as NAD+ boosters that improve metabolic health and may increase longevity. Our objective was to study how CYB5R3 overexpression and NR supplementation interact in the regulation of NAD+ and NADH levels, and of several markers of autophagic signaling and mitochondrial function as two of the main pathways regulating the rate of aging. Moreover, since the outcome of antiaging interventions may be strongly influenced by sex, we focused our research to both females and males. Studies were carried out in skeletal muscle from 7-mo old CYB5R3-TG and control mice in a C57BL/6 background that had been fed for 4 months an AIN93M diet, either supplemented or not with NR. Protein markers were measured by Western blot. NAD+ and NADH were measured by a bioluminescent assay. Both NAD+ and NADH were higher in CYB5R3-TG females and males supplemented with NR, without alteration of the NAD+/NADH ratio. Markers indicative of increased autophagic flux were upregulated in NR-supplemented CYB5R3-TG mice of both sexes. However, for mitochondrial mass markers, there was an increase with NR in male CYB5R3-TG mice, but not in females. Mitofusins exhibited significant differences with respect to sex and NR supplementation. We conclude that CYB5R3 overexpression and NR supplementation exert synergistic effects on skeletal muscle autophagy in mice of both sexes but their effect on some mitochondrial markers exhibit sexual dimorphism.

PSI.c. The expression of splicing machinery components is dysregulated in human neuroendocrine lung tumors.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: Neuroendocrine tumors, lung cancer, splicing.

Abstract: Neuroendocrine tumors of the lung (LungNETs) make up a heterogeneous family of neoplasms ranging from quite indolent lesions with long-term life expectancy to extremely aggressive tumors with very poor prognosis. These tumors represent a broad clinical-pathologic spectrum and have variable morphologic features and biologic behaviors. These family of neoplasms are classified into four histological variants: typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC). Molecular studies are providing new information to refine this classification. In this sense, alternative splicing is dysregulated in several cancers, and one of the causes is the splicing machinery expression alteration. The goal of this study was to understand the dysregulation of the splicing machinery in LungNETs, particularly from an anatomopathological perspective. To this aim, 33 pulmonary carcinoids (TC and AC) samples were collected retrospectively (2005-2014) from Reina Sofia University Hospital, obtained from primary surgery. To determine and analyze the pattern of dysregulation of the components of the spliceosome, a custom-made array was performed to measure gene expression. Then, IHC analyses were carried out to study the location of these proteins in tumor tissue. In vitro assays were performed to unveil the relevance of the dysregulated factors in two lung carcinoid-derived cell lines H-727 and UMC-11. The expression array unveiled a profound dysregulation of the splicing machinery, and subsequent clustering and classification analysis identified five elements particularly dysregulated: NOVA1, SRSF1, SRSF10, SRSF9, PRPF8. A systematic IHC anatomopathological analysis showed a remarkable difference of these factors at protein level when comparing tumor versus non-tumor tissue. Furthermore, pilot functional assays in vitro revealed that NOVA1, PRPF8 and SRSF10 may be involved in key cancer-related processes, such as proliferation and colony formation. In sum, this work provides additional evidence for a role of the splicing machinery dysregulation in LungNETs and points to three specific factors that deserve further study.

PSI.d. TWEAK/Fn14 axis modulates acute kidney injury associated with rhabdomyolysis.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Acute kidney injury, rhabdomyolysis, myoglobin, TWEAK, Fn14.

Abstract: One of the main complications of rhabdomyolysis is acute kidney injury (AKI). TWEAK (TNF-like weak inducer of apoptosis) and its sole receptor Fn14 (fibroblast growth factor-inducible molecule 14) regulate renal inflammation and tubular cell death, pathogenic mechanisms involved in AKI. In this study we analyzed the role of TWEAK/Fn14 axis in AKI associated with rhabdomyolysis and the AKI to chronic kidney disease (CKD) transition.

AKI associated with rhabdomyolysis was induced by intramuscular injection of 50% glycerol (10mg/kg) in wild-type (WT), TWEAK- and Fn14-knockout mice (TWEAK-/- and Fn14-/-, respectively). Blood, urine and kidney samples were taken from 3h to 30 days after rhabdomyolysis induction. In vitro studies with murine tubular cells (MCTs) were also conducted.

Rhabdomyolysis increased renal TWEAK and Fn14 expression in the experimental model, in line with decline of renal function and appearance of kidney damage. In MCTs cells, myoglobin (Mb) stimulation induced Fn14 expression in a time and dose dependent manner. The use of antioxidants such as NAC and inducers of the transcription factor Nrf2 reduced Mb-mediated Fn14 expression in cultured renal cells. Moreover, co-stimulation with Mb and TWEAK produced an increase in the pro-inflammatory cytokines in MCTs. TWEAK and Fn14 deficiencies prevented rhabdomyolysis-related characteristics, resulting in reduced urea and creatinine serum levels, less histological damage, and decreased expression of tubular and endothelial injury markers. TWEAK and Fn14 deletion decreased rhabdomyolysis-associated inflammatory response in the kidney, with reduced macrophage infiltrate, and diminished expression of cytokines and inflammatory regulators. Furthermore, TWEAK-/- and Fn14-/- mice were protected against cell death. Rhabdomyolysis promoted AKI to CKD transition since increased renal fibrosis and inflammatory infiltrate was observed in WT mice sacrificed 30 days after glycerol-injection; however these parameters were reduced in TWEAK-/- and Fn14-/- mice.

Our data suggest that the TWEAK/Fn14 axis is involved in AKI associated with rhabdomyolysis as well as the AKI to CKD transition.

PSI.e. Mutations in genes related to colistin resistance in colistin-resistant subpopulations of wild-type Klebsiella pneumoniae of clinical origin.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.

Keywords: Klebsiella pneumoniae, colistin, mgrB.

Abstract: Background: Heteroresistance (HR) can be defined as the presence of bacterial subpopulations with various susceptibilities to an antibiotic within an isolate, which may result in the selection of stable mutants (stable increment of MIC). The aim of this study was to identify mutations in genes involved in colistin resistance in heteroresistant subpopulations of wild-type Klebsiella pneumoniae of clinical origin.
Materials/methods: Five wild-type clinical isolates cultured from different patients were evaluated. Colistin HR was determined by population-analysis-profiling (PAP), performing bacterial counts on Mueller-Hinton agar plates with increasing concentrations of colistin (up to 64 mg/L), incubating the plates for 48h-5d-7d. Up to 5 colonies of plates with 4xMIC, 16xMIC and maximum concentration with bacterial growth [MAX] were selected from PAP. Bacteria were subcultured twice in antibiotic-free medium and broth microdilution was again performed. The genomic DNA (gDNA) of the isolates (5 parental and 5 colistin-resistant derived from each parental isolates) was extracted from colonies grown on Mueller-Hinton plates, using MagCore automatic extraction and submitted for whole-genome sequencing with Illumina platform. The fastq sequences were assembled and genes related to colistin-resistant pmrABC, phoPQ, crrAB and mgrB were analyzed for the presence of mutations.
Results: The five parental isolates corresponded to 170652 sequence type (ST34), 170943 (ST3478), 171289 (ST3477), 171503 (ST29), 171703 (ST1628). In the resistant subpopulations deletions and substitutions in different amino acids were mainly found in the MgrB protein (ΔV1, K2E, ΔC28, ΔQ22, D31N, L19R). PhoP (K22E, L12Q, M175K) and PhoQ (V24G, K46E) showed amino acid substitutions in different subpopulation. In addition, a 15 amino acid insertion in PhoQ was found in one subpopulation of 171703. PCR of the mgrB gene identified a band of approximately 1400 bp that matched an insertion sequence that inactivated the gene. There was not amplification for the mgrB gene in 2 isolates.
Conclusions: Colistin HR is frequent among wild-type isolates of K. pneumoniae. It is caused by the selection of stable mutants. These mutants usually contain mutations in currently identified colistin resistance genes.

PSI.f. Glycogen syntase kinase–3 as a relevant target for the treatment of colorectal cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Colorectal cancer, CMS4 subtype, GSK-3, SB415286, organoids.

Abstract: One of the current limitations of targeted therapy in colorectal cancer (CRC) is the complex genetic landscape that may harbor distinct molecular subtypes with variable treatment response and prognosis. Therefore, the critical challenge now is to develop new strategies for targeting poor prognosis CRC subtypes, such as CMS4 subtype, which shows highest recurrence rate and the worst clinical outcome. In this regard, glycogen syntase kinase-3 (GSK-3) has been recently shown to affect tumorogenesis and progression of a variety of human cancers, including CRC. However, the precise role of this multi-functional kinase in CRC biology is still unknown. Therefore, the aim of this study was to evaluate GSK-3 expression (by immunohistochemical and qRT-PCR analyses) in 71 CRC clinical samples and to analyze its association with clinicopathological data and with the consensus molecular subtypes (CMS subtypes). In addition, we evaluated GSK-3 expression (isoforms α and β) in HCT116 CRC cells by qRT-PCR and we analyzed the viability of HCT-116 organoids treated with a specific GSK-3 inhibitor (SB415286). Our results showed that an increased GSK-3 expression in clinical tumor samples was associated with adverse clinicopathological factors such as more advanced TNM stages, right sided location, vascular and lymphatic invasion and metastasis presence. Moreover, GSK-3 expression in tumor cells was associated with the poor-prognosis CMS4 subtype. On the other hand, GSK-3 α and β expression was confirmed in HCT116 CRC cells and a clear dose-dependent antitumoral effect of SB415286 GSK-3 inhibitor was observed. Altogether, our findings support that GSK-3 plays an important role in CRC progression and that specific GSK-3 inhibitors could be novel therapeutic agents for the clinical treatment of CRC patients.
Fundings: Funded by PIP-0044-2020.

PSI.g. Use of LC/MS for the identification of new allergens involved in olive pollen allergy.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Allergy, olive, LC/MS, allergens.

Abstract: Introduction: Severity of the symptoms suffered by olive allergic patients depends both on the type and the number of allergens recognized. Currently, only the levels of three of them, Ole e 1, Ole e 7 and Ole e 9, considered to be the main allergens, are measured and the diagnosis is made on the basis of these profiles.
Objective: Knowledge of the complete sensitization profile of each patient will allow us to know the severity of their symptoms and help to the physicians in taking of decision of the best treatment.
Materials and methods: We studied the IgE recognition protein profile of 17 olive allergic patients. SDS-PAGE, Western Blot, ImmunoCap and LC/MS were used in the characterization of the allergens recognized by the patients.
Results: Sensitization profiles of the patients varied widely from 2-allergen profiles to more complex profiles with recognition of up to 6 allergens. In addition, four patients recognized two bands with a molecular size between 50 and 75 kDa, not yet characterized in the literature. These patients were sensitized to at least one of the major allergens and had symptoms compatible with this type of allergy.
Conclusions: It is necessary to carry out more in-depth studies in the characterization and development of allergens from olive pollen, since, as shown in this study, a high number of patients may be sensitized to other allergens that cause a worsening of their symptoms and not a good evolution in the treatment of its symptoms.

PSI.h. Putative pathophysiological roles of miRNAs in the regulation of pituitary expression of GnRH-R, LHβ and FSHβ, in the context of obesity-induced hypogonadism.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: Obesity, hypogonadotropic hypogonadism, miRNAs, metabolism, hypothalamic-pituitary-gonadal axis, reproduction.

Abstract: Obesity has become a pandemic that currently affects >650 million people worldwide. Obesity is a major risk factor that enhances mortality rates, due to its numerous co-morbidities. These include male hypogonadotropic hypogonadism, characterized by a decrease of LH and FSH levels, and consequently of testosterone. This combination of hypogonadism and obesity generates a harmful vicious circle, which promotes the perpetuation of this pathological state, with deleterious impacts on energy balance, metabolic homeostasis and gonadal function.

While the mechanisms whereby obesity elicits central hypogonadism remain unfolded, this is mainly a condition of central origin; namely, defined by a primary alteration of the upper components of the hypothalamic-pituitary-gonadal (HPG) axis. Therefore, characterization of new factors regulating these central elements may help to reveal the pathophysiological mechanisms of obesity-induced hypogonadism (OIH). In this context, we report herein our initial efforts to identify miRNAs that may participate in the regulation of key pituitary elements of the HPG axis, namely GnRH-R, as receptor for the gonadotropin-releasing hormone, and the gonadotropin subunits, LHβ and FSHβ.

Bioinformatic and bibliographic analyses pointed out that miR-129-3p, rno-miR-325-3p and miR-205-5p are potential regulators of the expression of GnRH-R, LHβ and FSHβ, respectively. Using a preclinical model of OIH in male rats, which phenocopy the cardiometabolic and reproductive alterations, we have documented that the levels of theses miRNAs in the pituitary are increased in OIH, while the levels of their targets, GnRH, LHβ and FSHβ, are reduced; an inverse relationship that is compatible with a repressive role on key elements of the HPG axis, that may contribute to OIH. Given the evolutionary conservation of these miRNAs, it is tenable that these miRNAs may also participate in the pathogenesis of OIH in humans; a possibility that we are currently exploring in human cohorts of men suffering obesity and central hypogonadism.

PSI.i. A Preliminary Study of Circulating Tumour Cells in Patients with Hepatocellular Carcinoma Undergoing Neoadjuvant Transarterial Chemoembolization.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: Hepatocellular carcinoma, transarterial chemoembolization, circulating tumour cells, liquid biopsy.

Abstract: Background: Circulating cells derived from tumours (circulating tumour cells or CTCs) are thought to be responsible for cancer progression and recurrence. Thus, CTCs count has been used as cancer biomarker associated with poor prognosis. The aim of this study was to analyze the relationship between CTCs count and the response of hepatocellular carcinoma (HCC) patients to transarterial chemoembolization (TACE) as neoadjuvant therapy.

Methods: Single-centre and prospective preliminary study including HCC patients undergoing TACE from 2019 to 2021. Enumeration of CTCs was performed in peripheral blood samples (7ml) using the IsoFlux® system immediately before TACE and 1 day and 30 days after treatment. Patients who revealed an increase of at least 20% in CTCs count after TACE compared to pretreatment were considered as unfavourable. We used the mRECIST criteria to confirm radiological tumour response to TACE at day 30. Patients were divided into response group (R; complete response) and non-response group (NR; partial or incomplete response). Then, we analyzed the correlation between radiological response to TACE and clinicopathological features and CTCs counts.

Results: 25 HCC patients were included (mean age 63.4±8.3; 88.5% male). Of them, 19 patients (76.0%) were completed and 6 failed at the last analysis point on day 30. 24 hours after TACE, CTCs count increased, remained stable and decreased in 60.0% (n=15), 4.0% (n=1) and 36.0% (n=9) of patients, respectively. After 30 days, CTCs count increased in 42.1% (n=8) and decreased in 57.9% (n=11), of patients. Logistic regression showed a significant relationship between NR group and unfavourable patients at 1 day after TACE (p=0.028).

Conclusions: An increase greater than 20% in CTCs count at 24 hours after TACE could serve as a quick indicator for the response to neoadjuvant TACE therapy in HCC patients. It is necessary to increase the patient cohort to confirm these preliminary results.

PSI.j. Social support in times of pandemic. Intervention study

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Scientific Program: Active aging and fragility.
Keywords: Social support, loneliness, ageing, social networks.

Abstract: Background: The type of social support available to older people in later life can affect their health. Social support can be defined as the help provided by family, friends, neighbours and other members of the community.
Aim: To find out the social support situation of people over 65 years of age living in the south of Spain, pre- and post-intervention, based on the ENRED@TE programme of the Spanish Red Cross.
Methods: Pre-post intervention study carried out with 95 people over 65 years of age, residents of a province in the south of Spain, who participated in the ENRED@TE programme of the Spanish Red Cross. The pre-test was carried out in the period November 2019-March 2020 and the post-test in March-May 2021. The variables collected, in addition to the intervention (ENRED@TE) of training in social resources and new technologies as specific supports, were socio-demographics and socio-family status, social support and loneliness. The situation of the COVID- 19 pandemic became an emerging variable.
Results: The participants were 88.4% female and had a mean age of 81.54. The number of people who were not lonely after the intervention was significantly higher (48.4% vs. 52.6%); however, severe loneliness increased (11.6% vs. 20%). In the socio-familial aspect, the perception of normality increased slightly (25.3% vs. 28.4%) but also that of social problems (2.1% vs. 3.2%) after the intervention. Regarding social support, participants perceived lower levels after the intervention (15.8% vs. 29.5%). Non-computer users were 4.42 times more likely to suffer from loneliness (p=0.03).
Conclusions: The results of the social intervention programme carried out with older people seem to be mediated by the impact of the health pandemic on loneliness, socio-familial assessment and perceived social support. The use of computers could protect against the presence of moderate or severe loneliness.

PSI.k. In vitro evaluation of the effect of exosomes derived from umbilical cord MSCs grown in normoxia and hypoxia on cell types involved in skin regeneration.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Cytochrome b5 reductase, aging, mitochondrial metabolism, longevity and skeletal muscle.

Abstract: Background: Mesenchymal stem cells (MSC) are cells with great potential for use in regenerative medicine due to their ability to differentiate into other cell types, regulation of physiological processes such as angiogenesis and their immunomodulatory activity. MSC can be obtained from different sources. Among them are those derived from umbilical cord. This tissue is easily accessible and presents no ethical problems in its use. The therapeutic effect of stem cells is partially mediated by the extracellular vesicles, such as exosomes, they secrete. The content and properties of exosomes depend on the physiological conditions of the source cells. In this study, MSC have been isolated from the umbilical cord. From these cells, exosomes have been obtained under normoxic and hypoxic conditions to evaluate their effect on cell types involved in skin regeneration.
Methods: Exosomes were isolated from MSC grown in normoxia (Exo-N) or hypoxia (1% O2) (Exo-H) during 48 h, by ultrafiltration and size exclusion chromatography, and characterized and quantified by dynamic light scattering (DLS) and Western Blot. We examined the effects of exosomes on viability and migration of dermal fibroblast, keratinocytes (HaCaT) and Human Umbilical Vein Endothelial Cells (HUVECs), in addition to angiogenesis with HUVEC.
Results: Exosomes increased the viability of HaCaTs, but not of fibroblasts or HUVECs. There was no difference between normoxia and hypoxia. Fibroblast migration was slightly induced by Exo-H. Exosomes increased the migration of HaCaT and HUVECs, mainly with Exo-N. Angiogenesis was also induced by exosome treatment, but no differences were observed between Exo-N and Exo-H.
Conclusion: Umbilical cord MSC-derived exosomes have the ability to promote angiogenesis and migration of cell types involved in skin regeneration, so they could potentially be used in therapies for healing skin wound such as diabetic ulcers. However, we did not observe an improvement with exosomes derived from preconditioned MSCs under hypoxia.

PSI.I. Improvement of cetuximab-dependent cellular cytotoxic activity of human NK cells against colorectal cancer cells.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: NK cells; cetuximab; monalizumab, ADCC; colorectal cancer.

Abstract: Cetuximab is an IgG1 monoclonal antibody directed against the epidermal growth factor receptor (EGFR) and has become one of the main treatments of metastatic colorectal cancer (mCRC) patients. However, 50-60% of the patients with wild-type RAS do not respond to cetuximab, whereas some patients carrying RAS-mutated tumours respond to cetuximab therapy. Alternative mechanisms involved, such as antibody-dependent cell mediated cytotoxicity (ADCC) exerted by natural killer (NK) cells, which recognize the Fc portion of cetuximab, have been suggested. Therefore, new combined treatments may improve ADCC and the clinical efficacy of cetuximab. In this study we first analysed the EGFR expression by flow cytometry and western blot analysis in human colon cancer cell lines (HCT116, HT-29, Caco2 cell lines) in order to find the optimal CRC target cells for ADCC assays. Next, we isolated human PBMCs from peripheral blood of healthy donors; highly pure NK cells were obtained by depletion of magnetically labelled cells (Miltenyi) and their NK immunophenotype was confirmed by flow cytometry. Finally, we tested their functional cytotoxic activity using cell-based ADCC assays with different effector/target cell ratios and doses of cetuximab. Among the tested CRC cell lines, HT-29 cells showed the highest EGFR expression and were selected as target cells for ADCC assays. On the other hand, 97% of purity was achieved in the isolation of human NK cells as confirmed by flow cytometry analysis. Our data show that cetuximab treatment of HT-29 cells enhanced their NK cell-induced cell death. Moreover, this ADCC activity was increased when cetuximab was combined with monalizumab, which is an anti-NKG2A antibody that potentiates the cytotoxic activity of NK cells. In conclusion, our results support that monalizumab improves the cetuximab-dependent cellular cytotoxic activity of NK cells, thereby suggesting that clinical efficacy may be increased by a combination of these drugs.

Fundings: PI20/00997 and PIP-0044-2020.

PSI.m. Health-Related Quality of Life in Cardiovascular Patients explicated by Positivity and Self-Efficacy.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Positivity; Cardiac self-efficacy; Self-regulation; Affect regulation; Cardiovascular disease; Health-related quality of life.

Abstract: Background. Psychological well-being and health-specific self-regulation have been associated with cardiovascular health. Objective. This study aimed to examine the longitudinal relationship of positivity and health-specific self-regulatory variables to health-related quality of life in patients with cardiovascular disease. Methods. A sample of 550 cardiac patients completed a number of instruments (positivity, regulatory emotional self-efficacy, and cardiac self-efficacy scales, and the general health questionnaire SF-12) on two occasions 9 months apart, assessing their level of positivity, health-specific self-efficacy beliefs, and health-related quality of life. Results. Mediational analyses demonstrated that health specific self-efficacy beliefs mediate the relationship between positivity and health-related quality of life. In terms of self-efficacy in managing negative affect, the despondency-distress factor showed both direct and indirect effects on health, while the anger factor showed only an indirect effect. The results of the structural equation model demonstrated suitable indices of fit. Conclusions. Positivity may act as a disposition helps patients to use motivational strategies related to health, be more confident in their ability to regulate their emotions, and follow the recommendations of their cardiac medical team, enabling them to perceive a higher quality of life. These findings indicate the need to promote psychosocial interventions that include these variables.

PSI.n. Peritonitis predictive factors in incidental patients in peritoneal dialysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Peritonitis, peritoneal dialysis, C reactive protein, serum magnesium.

Abstract: Introduction: Peritonitis remains the most common complication in peritoneal dialysis (PD) patients. Furthermore, it remains as the leading cause of peritoneal catheter dysfunction, removal, hospitalization and transfer to hemodialysis (HD). Therefore, Identifying the risk factors that can predict peritonitis is necessary to set up strategies in order to identify susceptible patients, and prevent new events.

Material and Methods: We retrospectively evaluated a cohort of PD patients that started peritoneal dialysis from January 2000 to January 2019. Patients should have been receiving PD for at least 90 days to be included. Those patients under PD because of chronic heart failure, previous HD as renal replacement therapy (RRT), and those with a previous renal transplant were excluded. Demographics, clinical and biochemical characteristics were recorded at the beginning and at 3,6 and 12 months of PD. Patients with at least one episode of peritonitis were compared with those who never had one. Multivariate analysis was performed to identify variables associated with peritonitis. Youden's J statistic identified the optimum cut-off point where a continuous variable predicted an increased risk of peritonitis.

Results: 178 patients started PD in the analysed period. The mean age was 51 ± 15.86 years, and 67.4% were male. 22.5% were diabetic, and 38.8% were hypertensive. Median follow-up time was 387 days (86 -4404 days). 22.5% (N=40) of patients displayed signs of peritonitis at any time throughout follow up. No statistically significant differences were found in age, sex, diabetes, and BMI between groups (Peritonitis vs no peritonitis). However, differences were found at the begining of the technique in patients with longer PD vintage (923.1 vs 524.8 days, $p < 0.01$), lower haemoglobin levels (11.05 g/dl vs 11.75 g/dl), serum albumin (3.5 vs 3.78 g/dl), and serum magnesium (1.78 vs 2.21 mg/dl). In multivariate analysis, the risk for a peritonitis episode was independently associated with higher levels of C-Reactive Protein (CRP), (OR 1.10 (1.03 -1.18), whereas serum magnesium levels seem to be a protective factor (OR 0.14 (0.30-0,56). Youden's J statistic identified CRP serum levels of 5.5 mg/l as the cut-off point for a higher risk of peritonitis.

Conclusions: Inflammation, as measured by CRP and serum magnesium levels are associated with a higher risk of developing a peritonitis episode in incident PD patients.

PSI.ñ. Role of the phosphatase PNKP in temozolomide resistance.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Glioblastoma, Temozolomide resistance, AP sites repair, PNKP.

Abstract: Glioblastoma (GBM) is an aggressive form of brain cancer. The treatment for GBM is surgery, followed by radiotherapy and chemotherapy with temozolomide (TMZ), an alkylating agent which causes damage to the purine bases of DNA. GBM has a low survival rate due to the resistance to TMZ, as a consequence of the action of DNA repair mechanisms. The principal types of lesions induced by TMZ include the methylation at position N7 and O6 of guanine and at N3 of adenine. The O6-meG is repaired by O6-methylguanine-DNA-methyltransferase (MGMT). Several studies have shown that in TMZ-sensitive patients the MGMT expression is low or absent, thus the repair of O6-meG is impaired. However, not all patients with low levels of MGMT are sensitive to TMZ, indicating that there are other repair mechanisms involved in resistance to this alkylating agent. On the other hand, the main lesion induced by TMZ is N7-meG, harmless by itself but prone to undergo spontaneous depurination, generating abasic (AP) sites highly cytotoxic and mutagenic effects. Recently, it has been shown that in Arabidopsis thaliana, the AP sites generated from N7-meG are processed through the AP lyase activity of the bifunctional DNA Glycosylase FPG. The incision catalysed by FPG generates a 3'-P end that is converted to 3'-OH by the 3'-phosphatase ZDP. There is homology between this FPG/ZPD pathway of Arabidopsis and a repair pathway of oxidative damage in human cells mediated by the NEILs/PNKP pathway. An important but still unaddressed question is whether the NEILs/PNKP pathway is involved in the repair of AP sites induced by TMZ. In this work we have used GBM cell lines to study the involvement of PNKP in the resistance to TMZ. The results showed that there is differential level of PNKP transcription and protein in TMZ-sensitive compare to resistant cells.

PSI.o. Relevance of an AP lyase / DNA 3'-phosphatase pathway in the repair of abasic sites in human cells.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords Base excision repair, N7-methylguanine, abasic sites, AP lyase, DNA 3'-phosphatase.

Abstract: Abasic sites (apurinic/apyrimidinic sites, AP sites) are ubiquitous DNA lesions that arise from spontaneous base loss or as intermediaries during repair of damaged bases. In addition, they may be induced indirectly by spontaneous release of alkylated bases such as N7-methylguanine (N7-meG). The addition of alkyl groups can be induced by alkylating compounds, such as temozolomide (TMZ), that are often used as chemotherapeutic agents. AP sites are mainly repaired through the Base Excision Repair (BER) pathway initiated by AP endonucleases or by AP lyases. A subset of AP lyases generates intermediaries with a blocked 3'-P end that must be processed by a DNA 3'-phosphatase to continue the repair pathway.

It has been shown that a deficiency in the DNA repair machinery correlates with an increased risk of developing cancer. Moreover, cancer treatments often combine anticancer drugs with specific DNA repair inhibitors. It is therefore important to study the role of DNA repair in tumour development and how it influences the efficacy of the different drugs used in cancer treatment.

In this work, we have analysed, in cancerous human cells, the relevance of an AP lyase/DNA 3' phosphatase pathway during repair of AP sites arising from spontaneous release of N7-meG, a major lesion induced by the anticancer drug TMZ. We show that human AP lyases may initiate the repair of cytotoxic AP sites regardless of their origin, enzymatic or from spontaneous N7-meG loss. Furthermore, our results indicate that the incision catalysed by AP lyases generates an intermediate with a 3'-P end that is converted to 3'-OH by the DNA 3' phosphatase activity of PNK. Altogether, the results obtained in this work suggest that an AP lyase/DNA 3'-phosphatase pathway may play a relevant role in the repair of AP sites in human cells.

PSI.p. Are smoking and alcohol associated with peripheral musculoskeletal involvement in patients with Spondyloarthritis? Results from the ASAS-PerSpA study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Spondyloarthritis, peripheral manifestations, alcohol, smoking.

Abstract: Background: There are controversies around the role of smoking and alcohol in manifestations of axial spondyloarthritis (axSpA) such as peripheral involvement. Objectives: 1) To evaluate the association between smoking/alcohol intake and the prevalence of peripheral articular manifestations; 2) to assess the association between smoking/alcohol intake and the location of such manifestations.
Methods: Patients from the cross-sectional ASAS-PerSpA study with available data for both the smoking status and alcohol intake were included. Mixed logistic regressions using the peripheral manifestation (or the location) as a dependent variable, the smoking status or alcohol intake and the presence of psoriasis as fixed effect and the country as random effect were used. The interaction between smoking and alcohol was tested.
Results: 4451 patients with either axSpA, peripheral SpA or Psoriatic Arthritis were included. 59.5% had smoked at any moment and 42.7% had been alcohol drinkers. Patients who have ever suffered arthritis showed a lower frequency of smoking habit (OR 0.72, 95%CI 0.63-0.82) and a lower alcohol consumption (OR 0.82, 95%CI 0.71-0.94). In addition, among patients with arthritis, smoking was associated with a predominantly upper limbs involvement (OR 0.78, 95%CI 0.65-0.94), while alcohol was associated with a predominant mono/oligoarticular involvement (OR 1.13, 95%CI 0.94-1.36).
Patients who have ever suffered enthesitis showed a lower frequency of smoking habit and alcohol intake (OR 0.75, 95%CI 0.63-0.89 and OR 0.69, 95%CI 0.57-0.83, respectively). No association was found with regard to the prevalence of dactylitis.
Current alcohol intake was associated with a lower prevalence of current arthritis (26.9% vs. 33.6% (OR 0.76, 95%CI 0.64-0.91)) and current enthesitis (21.1% vs. 34.6% (OR 0.78, 95%CI 0.62-0.96)).
Conclusion: Smoking and alcohol are associated with a lower prevalence of peripheral manifestations. Smoking seems to be associated with predominantly upper limbs arthritis while alcohol intake seems to be associated with a predominantly oligo/mono articular involvement.

PSI.q. Histological changes of major pectoralis muscle fibres after breast prosthesis implantation.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Capsular contracture, muscle fibres, breast prosthesis, histology.

Abstract: Background: Subpectoral prosthesis implantation is one of the two most frequent techniques available to achieve mammary volume augmentation. Although other studies refer radiological volume and isokinetic changes of major pectoralis muscle due to this surgical intervention, the possible existence of histological changes, and the role that they may play in some pathologies of the breast such as the mammary periprosthetic capsular contracture remain unclear.
Objectives: The aim of this study was to describe the histological changes of major pectoralis muscle after prosthesis implantation.
Methods: 10 women who underwent subpectoral augmentation mammoplasty and had to be reoperated were selected. 10 female patients who had no mammary implants were also introduced in the study as controls. Major pectoralis muscle of each patient was biopsied, and the samples were processed in order to undertake their histological, histochemical and immunohistochemical study. Histological changes observed were compared between the two groups.
Results: From the 10 studied muscle samples, lymphocytic infiltration (chronic) in the muscle bundles was observed only in two samples. Muscle atrophy of the types of fibres was observed in one muscle sample due to perimysial thickening. Neither myo- nor neuropathy histological changes were found. These changes are not related to the fibrosis and retraction of the mammary capsule.
Conclusions: Mammary capsular retraction does not cause histological changes consistent with denervation or fibrotic contiguity myopathy. Chronic inflammatory processes in the breast area impair the skeletal muscle. Further studies should be undertaken, including ultrastructural ones, that would allow deeper knowledge of the histological changes of the capsule-muscle transition as the step prior to the finding of targeted therapies that would reduce capsular fibrosis.

PSI.r. Inhibition of dipeptidyl peptidase 8/9 negatively affects human mesenchymal stem cell differentiation in vitro.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: DPP4, DPP8/9, MSC, osteoblasts, adipocytes, diabetes, sitagliptin, vildagliptin.

Abstract: The dipeptidyl peptidase (DPP) 4 family includes four enzymes, DPP4, DPP8, DPP9 and fibroblast activation protein (FAP). DPP4 is a ubiquitous exopeptidase and occurs as a cell membrane-bound protein as well as in soluble and extracellular forms. DPP4 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 is used for the treatment of patients with type 2 diabetes as they increase GLP-1 and GIP levels, increasing insulin secretion, inhibiting glucagon release and reducing blood glucose levels. Diabetes-associated bone loss decreases with gliptins. Mesenchymal stem cells (MSCs) are precursors of adipocytes and osteoblasts. Aging and diabetes enhance MSC differentiation through the adipogenic lineage at the expense of the osteoblastic phenotype, which promotes bone loss and osteoporosis. Previous work by our group has shown that the gliptin Vildagliptin inhibits osteogenic and adipogenic differentiation of MSCs in vitro. However, vildagliptin is an inhibitor of DPP4 and with less intensity of DPP8/9, so its effect can be achieved through any of these two peptidases.
AIM: to study the effect of DPP4 family inhibitors on MSC differentiation into osteoblasts and adipocytes.
MSC cultures were induced to differentiate into osteoblasts and adipocytes with sitagliptin (specific DPP4 inhibitor), vildagliptin (non-specific DPP4 inhibitor) and 1G244 (specific DPP8/9 inhibitor).
The results show that a high concentration of 1G244 decrease MSC viability and activate cell apoptosis, while gliptins do not affect. In addition, in MSC differentiated into osteoblast or adipocytes, gene expression of osteoblastic or adipogenic genes, respectively, it is lower in cultured treated with 1G244, followed by those treated with vildagliptin.
The results suggest that DPP8/9 have an important role in MSC viability and differentiation.

PSI.s. MicroRNAs involved in oxidative stress from patients with cardiovascular disease in response to two cardio-healthy diets: from CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: miRNAs, oxidative stress, Mediterranean diet, cardiovascular disease.

Abstract: Introduction and Objective: According to the WHO, the mortality rate by chronic diseases associated with aging (T2DM, obesity, CVD) will be increased significantly in the coming years. Recent studies have shown that epigenetic markers such as miRNAs play an important role in the development of these diseases. Our objective was to analyze the relationship between miRNAs and markers of oxidative stress in response to two cardio-healthy diets in patients with cardiovascular disease.

Material and Methods: The present study preliminarily included 90 patients with established cardiovascular disease participating in the CORDIOPREV study. Oxidative stress markers were determined and the expression of 17 miRNAs was analyzed by RT-PCR at the beginning of the study and after 4 years of dietary intervention. Finally, based on studied parameters, repeated measures ANOVA analyzes were carried out through the SPSS software.

Results: The results showed that total glutathione and GSH levels increased in patients whose miR-126 expression decreased after 4 years of intervention with the Mediterranean diet (both $p < 0.01$). Furthermore, LPO levels decreased in patients who showed increased expression of miR-133 after following a Mediterranean diet ($p < 0.01$). Finally, a decrease in GPx activity was observed in patients who showed lower expression of miR-31 after 4 years of intervention with the Mediterranean diet ($p = 0.048$).

Conclusion: Diet constitutes a regulatory tool for the expression of miRNAs involved in processes such as oxidative stress which is directly related to diseases associated with ageing in patients with cardiovascular disease.

PSI.t. Evolution of metabolic phenotypes of obesity after 5-year intervention with two healthy diets. Cordioprev study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Metabolic Phenotypes; Obesity; Diet Intervention; Mediterranean Diet; Low-Fat Diet.

Abstract: Obesity is a well-known risk factor for cardiovascular disease and other comorbidities. The risk of developing obesity-associated diseases varies widely among obeses with same body mass index (BMI), being necessary new tools to understand this condition, such as metabolic phenotypes. They are defined on BMI degree and the presence/absence of metabolic disorders. In the present study we aimed to study the evolution of Metabolic Healthy Obese (MHO) and Metabolic Unhealthy Obese (MUO) after two diets over a 5-year period.

A subgroup of 221 obese cardiovascular patients from CORDIOPREV study was selected. They were randomized to Low-Fat (LFD) or Mediterranean diet (MD). Anthropometric measures and biological variables were carried out during a 5-year follow-up.

MHO represented 14% among obeses at baseline: 72.6% of them continued being obese and 62.9% became unhealthy. Number of metabolic abnormalities increased ($p< 0.001$) from a mean(SD) of 0.74(0.44) to 2.02(1.17) after follow-up. Despite of a statistically significant decrease in BMI ($p=0.046$), insulin resistance and atherogenic dyslipidaemia progressed in MHO: HOMA-IR increased from 1.7(0.8) to 2.4(1.5), $p<0.001$; HDL decreased from 48.5(9.0) to 45.3(9.4), $p= 0.001$.

Most of MUO (73.9%) remained in this phenotype. 16.3% became non-obese; 9.7% became healthy and 2.1% improved both characteristics. BMI decreased, especially in LFD [from 34.3(3.6) to 33.4(4.0), $p<0.001$]. Triglycerides and glucose levels improved without differences between diets. Inflammation declined more with MD [from 2.8(2.2) to 2.4(1.9), $p=0.006$].

In conclusion, obesity could be understood as a dynamic and complex process. First stage (MHO) is less frequent, being a relatively fast transition to MUO. By contrast, it is more difficult for MUO to recover a healthy metabolic state. Chronic intervention with healthy diets could influence the evolution of metabolic phenotypes. More studies are needed to know how to slow down the process from healthy to unhealthy obese, and to accelerate the reverse evolution.

PSI.u. Role of intestinal microbiota in the sex-dimorphism differences in the cardiovascular diseases.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: microbiota, cardiovascular diseases, sex-dimorphism, CORDIOPREV.

Abstract: CVD is currently considered the main cause of death in the western countries. The incidence of CVD is influenced by gender and appears more frequently in men than women. However, this apparent cardioprotection in women disappears after menopause, which suggests that sex steroid hormones contribute to the degree of susceptibility to the disease. We hypothesized that the alterations in the intestinal microbiota associated to cardiovascular diseases (CVD) are different in men and women, which may influence the sex-dimorphism in its incidence, and that the consumption of healthy diets may differentially shape intestinal microbiota according to gender. We aim to evaluate the differences between the intestinal microbiota of women and men with coronary heart disease as compared with non-CVD women and men. DNA from feces was isolated by the QIAamp DNA kit Stool Mini Handbook (Qiagen, Hilden, Germany) and gut microbiota composition was determined by 16S metagenomic. Sequencing data were analyzed by Qiime2 software. Discriminant Analysis Size Effect showed a higher Firmicutes and lower Bacteroidetes abundance in CVD patients than in non-CVD individuals. These differences were observed in CVD vs non-CVD men, but women only differ in Bacteroidetes abundance. Moreover, the gut microbiota of CVD men was enriched in Prevotella and Roseburia genera, the gut microbiota of CVD women was enriched in Allistipes, Parabacteroides, Bifidobacterium and Bilophila genera. By contrast, the gut microbiota of non-CVD men was enriched by Collinsella whereas the gut microbiota of non-CVD women was characterized by higher Akkermansia, Oscillospira and Streptococcus genera. In conclusion, our results suggest that gut microbiota composition between men and women with CVD is different, and the alterations observed as compared with non-CVD individuals differ between genders. In addition, our results suggest the potential involvement of differences in gut microbiota in the unequal incidence of CVD between genders.

PSI.v. Role of DNA repair mechanisms in temozolomide resistance.

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

Abstract: Temozolomide (TMZ) is a DNA methylating agent used in the treatment of glioblastoma (GBM), an aggressive form of brain cancer with a low survival rate, due in large part to resistance to TMZ. The main lesions generated by TMZ are N7-meG, N3-meA and O6-meG. The resistance to therapy is a consequence of the repair of such methylated bases by DNA repair mechanisms. A role in TMZ resistance has been proposed for high expression of repair proteins such as MGMT, (O6-meG DNA methyltransferase) that directly demethylates O6-meG lesions or AAG (Alkyladenine DNA Glycosylase), that repairs N7-meG and N3-meA via Base Excision Repair (BER). However, increased levels of MGMT or AAG only explain a small percentage of cases of tumours resistant to TMZ. N7-meG, the major lesion induced by TMZ, is frequently lost from DNA generating toxic abasic sites (AP sites). AP sites are repaired through a pathway initiated either by AP endonucleases or by AP lyases. It is generally assumed that AP endonucleases play a major role, but the contribution of AP lyases to TMZ-resistance in GBM remains largely unknown. Furthermore, unprocessed AP sites may generate single- and double-strand DNA breaks, channelling repair through alternative, BER-independent routes. Since DNA repair mechanisms contribute to TMZ resistance, tumour-specific DNA repair signature may be used as predictive biomarker of patient response to treatment. Here, we have used a panel of GBM cell lines described as TMZ resistant (T98G, U373 and LN18) or TMZ sensitive (A172, LN229 and CCF-STTG1) to analyse the expression of DNA repair genes. The results showed that there are differences in the expression levels of some of these genes between TMZ-resistant and TMZ-sensitive GBM cells.

PSI.w. Enhancing subjective well-being in cardiovascular disease patients through a mHealth psychological intervention in emotion regulation.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Cardiovascular disease; emotion regulation; mHealth, Psychological intervention.

Abstract: Previous studies have supported the relationship between being diagnosed with a cardiovascular disease with psychological distress. Also, it has been found that emotion dysregulation could become a risk-factor for cardiovascular diseases. Therefore, training patients in emotion regulation might act as a barrier to develop psychological disorders such as depression or anxiety. Given that this comorbidity could worsen the recovery and quality of life of patients with cardiovascular disease, we proposed a psychological intervention in emotion regulation to enhance subjective well-being of these patients. To do so, a randomized controlled prospective study was undertaken comparing two groups, experimental and control group. The study sample (N = 69) were patients from the Cardiology Unit at the University Hospital Reina Sofía. The experimental group received an emotion regulation psychoeducational session, and a later, 2-weeks mHealth psychological intervention in emotion regulation. The subjective well-being was the variable analyzed in this study, measured by the positive and negative affect scale (PANAS). Five evaluation were conducted over a period of 6 weeks: at baseline, after the psychoeducational session, after the mHealth psychological intervention and two follow-ups. Results showed a higher positive and lower negative affect in the experimental group after the psychoeducational session. A repeated measures analysis showed an enhanced subjective well-being in the experimental group over time. The results of this study provide evidence of the benefits of implementing psychological interventions in emotion regulation to improve the subjective well-being of patients with cardiovascular disease. This type of interventions may serve to avoid psychological distress, to facilitate adaptation to the disease and to favor a better quality of life in these patients.

PSI.x. Medium-term clinical impact of the ejection fraction recovery in patients with severe left ventricule dysfunction.

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Affiliations: None.
Scientific Program: Chronic and Inflammatory diseases.
Keywords: HFrEF, ejection fraction recovery.

Abstract: Introduction: In heart failure (HF) with reduced ejection fraction (HFrEF), there is a percentage of patients who present improvement in left ventricular ejection fraction (LVEF) during the follow-up and whose prognosis remains uncertain. Our aim was to determine the percentage of patients with HFrEF who improve LVEF according to the new universal definition of HF and to analyze the medium-term prognosis in terms of mortality and hospital readmissions for HF.
Material and methods: Retrospective study of a cohort of patients with HFrEF. The percentage of patients who improved LVEF according to the new definition (Group 1) and those who maintained dysfunction (Group 2) were analyzed and compared. Clinical, echocardiographic and treatment variables were collected, and it was analyzed mortality and hospital-readmissions for HF medium-term.
Results: A total of 90 patients were analyzed. The mean age of the cohort was 68.5±11 years with a male predominance (73.9%). The principal etiology was ischemic(32.2%) followed by idiopathic(28.9%) and tachycardiomyopathy(10%). A total of 45 patients(50%) improved LVEF(group 1) and 45 patients(50%) did not improve LVEF(group 2). In group 1, the mean time to LVEF improvement was 12.8±6 months. There were no significant differences in the prescription of medical treatment in both groups at the start of follow-up. Despite not having improved LVEF, group 2 had a higher proportion of the prescription of Sacubitril-Valsartan (77.8%vs51.1%;p=0.008), inhibitors of SGLT-2 (iSGLT-2) (55.6%vs28.9%;p=0.01) and implantable cardioverter defibrillator (ICD) (26.7%vs4.4%;p=0.004). With a mean of 19±1 months of follow-up, group 1 had a lower rate of hospital readmission (3.1%vs24.9%;p=0.003) and lower mortality rate from HF (0%vs24.4%;p=0.003).
Conclusion: 50% of the patients had improved LVEF according to the new universal definition. This improvement in LVEF does not appear to be related to a greater prescription of sacubitril-valsartan, iSGLT-2 or ICD. To medium-term, patients with improved LVEF had a lower rate of hospital-readmission and lower mortality from HF.

PSI.y. Healthy habits intervention program. WhatsApp broadcast.

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Scientific Program: Endocrine and metabolic diseases.
Keywords: Healthy habits, clinic advice, Whatsapp distribution disease.

Abstract: Primary care is the ideal setting for motivation in healthy habits. After the pandemic, a worsening has been detected in patients diagnosed with diabetes, dyslipidemia or obesity. Follow-up of patients with metabolic disease is essential. This includes dietary advice, exercise advice, and emotional health, which have been shown to influence motivation to change habits. The time for consultation is very limited and the care load is high, so the transmission of healthy advice through WhatsApp has been tried. The objective of the study is to assess whether the use of a WhatsApp distribution list is a useful tool for the educational health council in metabolic processes.

E an experimental study. Patients have been selected from a quota who fulfilled the condition of Type 2 Diabetes or obesity or Dyslipidemia with or without medical treatment. Those who have agreed to participate and have been given initial advice on healthy eating, physical exercise and relaxation habits. A lipid and glycosylated profile has been analyzed in diabetics, as well as BMI in obese patients. The work has been developed for 12 weeks, to 47 patients, receiving twice a week on their WhatsApp, a reminder about food, physical exercise and relaxation. A new subsequent determination of lipid profile and BMI has been made. A satisfaction survey of the process has been passed.

97% have shown high satisfaction in this type of advice. Most report having been motivated to do some exercise and eat well. Less than 10% have carried out relaxation or meditation exercises. 80% have lowered their total cholesterol.

It would be necessary to give continuity to this intervention to be able to show the benefit of the technological diffusion of health council.

PSI.z. Severe aortic stenosis survival and mortality analysis, in a series of patients, clinical and economic factors.

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Scientific Program: Active aging and fragility.

Keywords: TAVI; CoreValve; surgery; mortality.

Abstract: Introduction and objectives: 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, along with other associated diagnoses, treated with TAVI (CoreValve) or conventional surgery. We evaluated the cost, survival, major complications, and other factors associated with mortality in these patients.

Methods: From January 1, 2010 to December 31, 2011, 143 patients were studied, 79 (55.2%) underwent surgery and the remaining 64 underwent the TAVI procedure. The mean age was 77.7 years; 93 patients (65%) had isolated SAS. The mean log euroSCORE was 12%, with no differences between the groups. The mean follow-up time was 6.15 years (0–9.28).

Results: There were no significant differences in the incidence of mortality ($p = 0.34$). The mean basic cost was higher in the TAVI group ($p < 0.001$), with more or these patients also requiring pacemakers ($p < 0.01$). Age and arterial hypertension were significantly associated with mortality, and antilipemic treatment was significantly inversely associated with mortality (HR = 0.69). The median survival was 8.2 years ($p = 0.25$).

Conclusions: There were no significant differences regarding mortality during the follow-up, but because TAVI was a more expensive procedure, patients had to be selected. The role of antilipemic therapy in survival remains to be determined.

PSI.aa. Rare indications of lung transplantation in Andalucia.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Lung transplant, rare diseases, lung diseases, respiratory insufficiency.

Abstract: Lung transplantation is an accepted treatment for adequately selected patients with advanced lung disease, that improves quality of life. The most frequent indications are chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, followed by cystic fibrosis, as reported by the International Registry (International Society for Heart and Lung Transplantation, ISHLT). Other diseases classified as infrequent account for 1% and have inferior results and survival following lung transplantation. We present our single-centre experience.
Objetives: To determine the most frequent pathologies within the group of rare indications of lung transplantation. To assess the overall survival (OS) and the incidence of chronic lung allograft dysfunction (CLAD) in patients with rare indications receiving lung transplant.
Patients and methods: Single-centre, retrospective cohort study of all patients with rare lung diseases who underwent lung transplantation between 1996 and 2020. The survival curves were estimated with Kapplan Meier and compared by long-rank analysis.
Results: In our series of 687 patients, 49 were selected from the group of infrequent pathologies. The median age was 42 years-old. The largest group was the "other diagnoses" subgroup (49%), followed by histiocytosis X, lymphangioleiomyomatosis and sarcoidosis. With a median follow-up of 11.7 years, the OS of the series was 44.5 ± 0.7%. In the analysis by diagnosis, the patients with histiocytosis obtained a better OS of 80%, although not significant. OS in single-lung transplantation was higher than in double-lung transplantation (OS 60% vs 32%, p: 0.078). The incidence of CLAD was 11%, occurring more frequently in single lung transplantation. A total of 6 patients, (5 of them with single-lung transplantation) received induction therapy with basiliximab, observing better OS in this group, although without reaching statistical significance (p: 0.109).
Conclusions: Based on our data, lung transplantation in patients with rare diseases have a similar survival to other more frequent pathologies.

PSI.bb. Phase I / II single-arm efficacy and safety study of the use of neutral argon plasma in the debulking of miliary implants on the peritoneal surface.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Carcinomatosis, debulking surgery, miliary implants.

Abstract: Introduction: Peritoneal carcinomatosis is a rare form of intraabdominal dissemination of cancer. It's considered a malignant tumor in which the complete debulking surgery offers patients survival rates above previously expected. One of the major limitations for obtaining a complete cytoreduction is the miliary involvement of the mesentery, which sometimes requires large intestinal resections or the removal of the mesenteric peritoneum and the electrofulguration of the tissues using monopolar energy, which increases morbidity and the possibility of non-repairable vascular injuries.
Neutral argon plasma uses a pure argon flow that achieves superficial tissue destruction with penetration of less than 0.2 mm and a larger action diameter than electrofulguration. Thus, this system could meet the requirements to achieve an oncological debulking of miliary lesions, minimizing the associated morbidity.
Hypothesis: Neutral argon plasma vaporization causes minimum damage to normal tissue and allows complete removal of tumor tissue.
Objective: To evaluate the effectiveness and safety of neutral argon plasma on peritoneal implants with different dosimetry in vivo and ex vivo.
Design: Prospective inclusion of patients with peritoneal carcinomatosis of different origin with indication for debulking surgery. Samples of mesenteric peritoneum with tumor involvement will be obtained, to each of which will be applied neutral argon plasma with two different powers during different times of action and different application distances.
A control sample will be taken to which no treatment will be applied, and another sample to which electrofulguration will be applied.
The in-vivo effect of the application of electrofulguration and argon plasma will be evaluated in terms of damage to the serosa or vascularization.
Subsequently, the histopathological analysis will be performed to evaluate the presence of tumor cells and the degree of tissue destruction in the samples. In addition, the depth of vaporization of the tissue will be evaluated as well as the lateral thermal damage.

PSI.cc. Late complications in patients with Stent-treated coarctation of the aorta: Long-term follow-up.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: HCV, PBMCs, viral relapse, DAA.

Abstract: Introduction: Coarctation of the aorta (CoA) is one of the most frequent congenital heart diseases. Complications after stenting are rare and may occur immediately and in early or late follow-up. The aim of the study was to describe the prevalence of stent fracture in the long-term follow-up of patients with stent-treated CoA and its correlation with the incidence of aortic injury.

Methods: Observational, analytical and prospective study including patients with stent-treated CoA in the period from 1993 to 2018.

Results: A total of 108 patients (76% male) were included. Mean age at the time of implantation was 15 ± 14 years. The CoA was native in 73 patients (68%), post-angioplasty in 17 patients (16%), and post-surgery (with or without associated angioplasty) in 18 patients (17%). After a mean follow-up of 137 ± 74 months, 46 Stent fractures (43%) and some type of damage to the aortic wall were observed in up to 17 patients (18%), with no relationship between them. There were 6 fractures (14%) associated with damage to the aortic wall and 38 fractures of stent (86%) not associated, without significant differences. Male sex (4.305; 95% CI 1.479-12.528 p = 0.007), age <18 years (5.319; 95% CI 1.841-15.368 p = 0.002) and the residual gradient (1,139; 95% CI 1,033-1,255 p = 0.009) were found as independent predictors of risk of stent fracture. Mean survival was 190 ± 89 months.

Conclusions: Percutaneous treatment of CoAo is a safe and effective technique, however there is a higher incidence of stent fractures than described before, without association with a higher incidence of damage to the aortic wall.

PSI.dd. Management and knowledge of soft tissue tumors / sarcoma: Update of primary care physicians.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Sarcoma, Soft Tissue Neoplasms, Primary Health Care, General Practitioner.

Abstract: Sarcomas are tumors which are originated in soft tissue with a fatal evolution if they are not detected and a therapeutic strategy is established as early as possible. To my knowledge, there are no studies summarizing the extent to which primary care doctors know, recognize and react to signs and symptoms of sarcoma.
Objective: To evaluate the knowledge, protocols and practices of primary care doctors towards the implementation of clinical guides and diagnostic tools which may allow early detection and treatment of sarcoma.
Materials and methods: This will be an observational, descriptive, cross-sectional study. For a 5% alpha-error, 3% accuracy, and a proportion of 50% it is necessary to include 1012 primary care doctors. Spanish and Andalusian family medicine members and medical residents in their specialization in family medicine will be invited to participate in the study. All the members will be contacted via the administrative departments of these associations. Once they agree to participate in the study, they will complete an online survey. A descriptive, inferential statistical analysis will be performed (bivariate and multivariate analysis, a p-value lower smaller than 0.05 will be accepted as statistically significant). In the second phase, 30 participants will be randomly chosen to participate in a sarcoma-focused training, and their knowledge will be registered before and after the training. In this phase, a descriptive and inferential analysis for dependent and independent samples will be performed using parametric or non-parametric test, as appropriate.

SESSION III. Nutrition, Endocrine and metabolic diseases

IIIa. Long-term consumption of a Mediterranean diet or a low-fat diet on kidney function in coronary heart disease patients: an analysis of the CORDIOPREV randomized controlled trial.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: chronic kidney disease, Mediterranean diet, diabetes.

Abstract: Lifestyle and dietary habits influence kidney function, having an important role in the prevention and development of chronic kidney disease (CKD). The effectiveness of the Mediterranean diet in preserving kidney function has been seen in primary prevention however, no scientific evidence is currently available in secondary cardiovascular prevention. Thus, our aim was to evaluate the efficacy of the long-term consumption of two healthy dietary patterns -a Mediterranean diet and a low-fat diet- in delaying the impairment of kidney function in coronary heart disease (CHD) patients. Methods: CHD patients (n = 1002) from the CORDIOPREV study were randomized to follow a Mediterranean diet or a low-fat diet. Kidney function was assessed by the determination of serum creatinine-based estimated glomerular filtration rate (eGFR) at baseline and after 5-years of dietary intervention. Patients were also classified according to their baseline eGFR (normal eGFR: ≥ 90; mild-impaired eGFR: 60 to <90, severe-impaired eGFR: <60 mL/min/1.73 m2) with the aim to study their influence on the progression of kidney function. Results: Although, eGFR declined after both dietary interventions compared to baseline (all $p < 0.001$), the Mediterranean diet produced a lower decline of eGFR compared to the low-fat diet ($p = 0.033$), particularly in those with type 2 diabetes at baseline. This differential effect of the Mediterranean diet was also mainly observed in patients with mild-impaired eGFR in which this diet slowed eGFR progression ($p = 0.002$). Conclusions: Long-term consumption of a Mediterranean diet rich in EVOO, when it is compared to a low-fat diet, may preserve kidney function, as shown by a reduced eGFR decline in patients with CHD. These findings reinforce the clinical benefits of the Mediterranean diet in the context of secondary cardiovascular prevention.

IIIb. Molecular Diagnosis of Polycystic Ovary Syndrome in Obese and Non-Obese Women by Targeted Plasma miRNA Profiling.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: MicroRNA, obesity, molecular diagnosis, polycystic ovary syndrome (PCOS).

Abstract: Background: Polycystic ovary syndrome (PCOS), the most common endocrinopathy of women at reproductive age, is characterized by a heterogeneous clinical presentation, often confounded by concurrent conditions (obesity, insulin resistance, etc.). MicroRNAs have recently emerged as putative pathophysiological and diagnostic factors in PCOS. However, their contribution to metabolic complications of the disease remains unsolved and no reliable method for molecular diagnosis of PCOS based on miRNAs has been reported so far. Our group has developed a novel method for accurate molecular diagnosis of PCOS, in obese and non-obese women, by applying targeted miRNA profiling of plasma samples.

Methods: miRNA analyses using NanoString and targeted qPCR validation, were applied in blood samples from a case-control PCOS cohort including 170 women classified into four groups: non-PCOS/lean; non-PCOS/obese; PCOS/lean; and PCOS/obese. Statistics were applied to build classification algorithms.

Results: The geometric mean of circulating hsa-miR-103a-3p, hsa-miR-125a-5p and hsa-miR-1976, selected among 125 unchanged miRNAs, was defined as optimal reference for internal normalization. Ten miRNAs were identified and validated as differentially expressed across the groups. Multinomial LASSO Regression and decision-tree models were built to discriminate PCOS vs. non-PCOS in non-obese women, with the performer miRNAs being hsa-miR-191-5p, hsa-miR-93a-5p, hsa-miR-126-3p, hsa-miR-28-3p and hsa-miR-142-3p. A similar approach was used to discriminate PCOS vs. non-PCOS in obese women, with hsa-miR-93a-5p, hsa-miR-28-3p, hsa-miR-143-3p and hsa-miR-539-5p being selected as performer miRNAs.

Conclusions: We define herein a robust method for molecular detection and classification of PCOS, based on the unbiased identification of miRNA biomarkers and decision-tree protocols. This method allows not only the reliable diagnosis of lean women with PCOS, but also the discrimination between PCOS and obesity.

IIIc. Evaluation of the effect of COVID-19 on body composition and the development of obesity in Spanish preschool children: Coral Study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Obesity, COVID-19, children, anthropometry.

Abstract: Introduction: Childhood obesity is considered as a pandemic due to its increasing trend. Despite the great amount of studies in other age groups, there is little known about the incidence of obesity and its risk factors in European preschoolers. Restrictions by COVID-19 could condition lifestyle changes according to the new measures established. The aim of this study was to evaluate changes in weight in a cohort of Spanish preschoolers followed for two years, and to determine the impact of lifestyle changes on obesity in childhood.
Methods. A subsample of 61 children (5-6-years-old) from the Spanish CORAL study was selected. In first (June 2019) and second visit (March 2021), anthropometric measurements and blood pressure (BP) were collected. Body Mass index (BMI) Z-score and waist-to-height ratio were calculated. Children with normal-weight, overweight and obesity were classified by Cole, 2004. Parents were asked to complete questionnaires related to children's diet and physical activity. A pair-wise comparison in the two different times was made by t-test student, and effect size (ES) was calculated using Cohen's d.
Results. 55.8% of children studied were girls. The percentage for excess weight (children with overweight or obesity) changed from 22.95% to 42.62% ($p<0.001$). It was observed an increase in BMI-Z-score mean ($\Delta=0.45 \pm 0.61$; $p<0.001$; ES=0.371). An increase in the fat mass percentage was observed ($\Delta=3.4 \pm 3.3$ %; $p<0.001$; ES=0.678). Moreover, differences in the waist-to-height ratio were found ($\Delta=0.49 \pm 0.04$; $p<0.001$; ES=0.958). Finally, there was an elevation in systolic BP at the second visit, ($\Delta=6.3 \pm 13.1$ mmHg; $p=0.001$; ES=0.565), but no differences were found regarding diastolic BP ($p=0.179$).
Conclusions. There was an alarmingly increasing trend in the development of overweight and obesity after COVID-19 pandemic in this group of very young children that could be due to lifestyle changes linked to this pandemic.
Results. 55.8% of children studied were girls. The percentage for excess weight (children with overweight or obesity) changed from 22.95% to 42.62% ($p<0.001$). It was observed an increase in BMI-Z-score mean ($\Delta=0.45 \pm 0.61$; $p<0.001$; ES=0.371) and in the fat mass percentage ($\Delta=3.4 \pm 3.3$; $p<0.001$; ES=0.678). Moreover, differences in the waist-to-height ratio were found ($\Delta=0.49 \pm 0.04$; $p<0.001$; ES=0.958). Finally, there was an elevation in systolic BP at the second visit, ($\Delta=6.3 \pm 13.1$mmHg; $p=0.001$; ES=0.565), but no differences were found regarding diastolic BP ($p=0.179$).
Conclusions. There was an alarmingly increasing trend in the incidence of weight excess and fat mass accumulation after COVID-19 pandemic in this group of very young children that could be due to lifestyle changes linked to this pandemic.

IIId. Microvascular endothelial function, long-term dietary intervention and cardiovascular risk of recurrence: from the cordioprev study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: microvascular endothelial function, coronary heart disease, healthy dietary intervention, Mediterranean diet, low-fat diet.

Abstract: Introduction: Microvascular circulation controls tissue perfusion. Its dysfunction is implicated in damage to target organs such as the myocardium and is a predictor of cardiovascular events. It is known that factors related to diet may influence microvascular endothelial function (MEF). No studies are evaluating the long-term effect of healthy diet patterns on MEF in patients with coronary heart disease (CHD) and whether this effect is modified by the risk of CHD recurrence assessed by the TIMI Score for Secondary Prevention (TRS2P).

Hypothesis: the consumption of healthy diets improves the MEF of CHD patients in the long-term, and this effect is interrelated with the risk of CHD recurrence.

Methods: In the CORDIOPREV study, dietary intervention with a Mediterranean diet or a low-fat diet was carried out in 1002 patients with CHD. The effect of this dietary intervention on basal microvascular flow (BF) and reactive hyperemia area (RHA) to hypoxia was evaluated in 664 patients by laser-Doppler flowmetry at baseline and after 6 years of intervention. The risk of recurrence of CHD in patients was evaluated according to the TRS2P score.

Results: BF (97.78 ± 2.79 vs. 179.31 ± 5.06 arbitrary perfusion units, $p<0.001$) and RHA (4233.3 ± 127.73 vs. 9695.9 ± 205.23 arbitrary perfusion units per time, $p<0.001$) improved after the dietary intervention in the cohort, without finding differences due to the diet ($p>0.05$ for the diet-effect). When patients were stratified to low, medium or high-risk of recurrence, BF was similarly increased in all three groups. However, RHA was improved to a greater extent in patients at the low-risk group compared with those at medium or high-risk.

Conclusion: Long-term consumption of a healthy dietary pattern improves MEF in patients with CHD, but this improvement was greater in patients at the low-risk category compared with those at the medium and high-risk groups.

IIIe. Hypothalamic lipid sensing: a new player in the metabolic control of puberty.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: Puberty, Metabolism, Hypothalamus, FFARs, PPAR-g.

Abstract: Puberty is a complex developmental phenomenon highly sensitive to metabolic and nutritional cues. Conditions of energy excess have been associated with precocious puberty; a phenomenon that has been linked to worsening health. Emerging evidence suggests that alterations in hypothalamic pathways implicated in the control of energy balance, including those involving lipid-signaling molecules, contribute to such phenomenon. However, the targets and underlying mechanisms remain largely unknown.

We report here a series of expression and functional analyses addressing the role of relevant receptors sensing and transducing free fatty acids signals, including membrane receptors of the family of G Protein-Coupled Receptors known as Free Fatty Acid Receptors (FFARs), and the nuclear peroxisome proliferator-activated receptor-g (PPAR-g), in the central control of puberty under normal and/or stress metabolic conditions.

Hypothalamic mRNA expression of the short-chain FFAR Gpr43 and the medium/long-chain FFAR Gpr84 was significantly increased in early overfed female rats with precocious puberty. Moreover, mRNA levels of Gpr43, Gpr84, and Ppar-g dynamically changed in the hypothalamus of lean female rats throughout pubertal development. In particular, Gpr43 expression maximally increased at the infantile period, while Gpr84 and Ppar-g content drastically augmented from the neonatal to the prepubertal stage. Yet, Ppar-g expression, unlike Gpr84, remained persistently high until the peripubertal period. Further functional studies involving the central inhibition of PPARg signaling in prepubertal lean female rats resulted in delayed puberty, as evidenced by the age of vaginal opening and first ovulation. However, no significant changes in other relevant reproductive and metabolic parameters, such as LH levels, uterus weight, body weight, and food intake, were observed.

Collectively, these preliminary data suggest the potential contribution of the FFARs Gpr43 and Gpr84 to obesity-induced precocious puberty and the potential involvement of PPAR-g signaling in the central control of puberty onset. Yet, further experiments are required to fully validate this conclusion.

IIIf. Relationship between Physical Activity, Oxidative Stress, and Total Plasma Antioxidant Capacity in Spanish Children from the GENOBOX Study.

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Scientific Program: Physical activity; accelerometry; oxidative stress; plasma total antioxidant capacity; 8-hydroxy-20-deoxyguanosine; isoprostane F2.

Keywords: Obesity, COVID-19, children, anthropometry.

Abstract: The World Health Organization has recommended performing at least 60 min a day of moderate-to-vigorous physical activity (MVPA) and reducing sedentarism in children and adolescents to offer significant health benefits and mitigate health risks. Physical fitness and sports practice seem to improve oxidative stress (OS) status during childhood. However, to our knowledge, there are no data regarding the influence of objectively-measured physical activity (PA) and sedentarism on OS status in children and adolescents. The present study aimed to evaluate the influence of moderate and vigorous PA and sedentarism on OS and plasma total antioxidant capacity (TAC) in a selected Spanish population of 216 children and adolescents from the GENOBOX study. PA (light, moderate, and vigorous) and sedentarism (i.e., sedentary time (ST)) were measured by accelerometry. A Physical Activity-Sedentarism Score (PASS) was developed integrating moderate and vigorous PA and ST levels. Urinary 8 hydroxy-20-deoxyguanosine (8-OHdG) and isoprostane F2 (F2-IsoPs), as markers of OS, were determined by ELISA; and TAC was estimated by colorimetry using an antioxidant kit. A higher PASS was associated with lower plasma TAC and urinary 8-OHdG and F2-IsoPs, showing a better redox profile. Reduced OS markers (8-OHdG and F2-IsoPs) in children with higher PASS may diminish the need of maintaining high concentrations of antioxidants in plasma during rest to achieve redox homeostasis.

IIIg. Circulating miRNA profile in childhood early obesity and metabolic syndrome.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: circulating miRNAs, childhood, obesity, metabolic syndrome.

Abstract: Background: Childhood obesity is reaching epidemic dimensions and represents one of the major public health problems nowadays. Nonetheless, not all obese children exhibit metabolic complications (insulin resistance, hypertension or dyslipidemia), which has led to the concept of metabolically healthy obese (MHO), versus obese patient suffering metabolic complications (metabolically unhealthy obese: MUO). However, there is a lack of consensus to define the risk of appearance of metabolic syndrome (MetS) in the pediatric population, which led us to explore the profile of circulating miRNAs, as putative non-invasive biomarkers.

Methods: Circulating miRNA profiles were identified using the high-throughput NanoString nCounter® technology in plasma samples obtained from a cohort of prepubertal girls, classified as normal-weight metabolically healthy controls (n=16), MHO (n=15) and MUO (n=22). Subsequently, miRNAs candidates found as differentially expressed were validated by qPCR in the same cohort and correlations with relevant clinical variables were carried out.

Results: Expression analysis identified a profile of several miRNAs altered: 3 downregulated in the C vs MHO comparison; 2 downregulated in the C vs MUO comparison; 1 downregulated and 2 upregulated in the MHU vs MUO comparison. Results from this panel of miRNAs were technically confirmed by qPCR validation in the same cohort, showing consistent differences mainly due to the obese condition. Interestingly, significant correlations of miRNAs candidates were found with anthropometric (BMI, body weight, hip and waist circumference and waist/hip ratio), metabolic (Glucose, HDL and systolic blood presure) and inflammatory (TNF, IL-8) variables.

Conclusions: Our high-throughput analyses have identified a profile of altered circulating miRNAs as potential biomarkers of childhood obesity and/or MetS. This signature of deregulated miRNAs in child obesity has been confirmed by PCR. These results are being validated in an independent cohort.

SESSION IV. **Cancer II**

IVa. GSK-3 inhibition as an immunotherapeutic approach in colorectal cancer.

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Scientific Program: Cancer II.

Keywords: Colorectal cancer, immunotherapy, PDX, T-cells, tumor budding, anti-PD1, anti-GSK-3.

Abstract: Improvement in the efficacy of immunotherapy in colorectal cancer (CRC) is hampered by the great complexity and heterogeneity of tumor microenvironment. In this regard, tumor budding (TB) is an adverse histological feature related with higher tumor invasion and metastasis and promoted by an immunosuppressive microenvironment. Besides, glycogen synthase kinase 3 (GSK-3) is a serine/threonine protein kinase that affects immune tumor microenvironment by regulating PD1 expression in T cells. However, no relationship between GSK-3 and TB has been previously described. Therefore, in this study we first evaluated the expression of PD1 and PDL1 immune checkpoints and GSK-3 by qRT-PCR and immunohistochemistry (IHQ) in a cohort of 208 CRC patients according to their TB grade. Secondly, we analyzed the response to immune checkpoint blockade (anti-PD1) and GSK3 inhibition (SB415286) in humanized CRC patient-derived xenografts (PDXs). Our results showed that a high grade of TB was associated with poor prognosis clinicopathological factors and with an increased expression of PD1, PDL1 and GSK-3. In the in vivo assay with humanized PDXs, a reduced tumor size, increased tumor necrosis and a decrease of tumor buds was observed in anti-GSK-3 treated mice compared to control and anti-PD1 treated mice. By flow cytometry analysis, we observed that whereas anti-PD1 treatment drastically decreased PD1 expression in T cells, GSK-3 inhibition upregulated PD1+CD8+ T cells, NK cells and TCRγδ T cells in tumor infiltrating lymphocytes (TILs) and PDL1 expression in tumor cells. In addition, both treatments increased double-negative T cells (CD3+CD4- CD8- T cells) in peripheral blood along with naïve T cells in peripheral blood and TILs with anti-PD1 treatment. Altogether, our findings demonstrate the applicability of GSK-3 inhibitors as a potential immunotherapeutic approach for CRC with high-grade TB and support the value of humanized PDXs as relevant preclinical models for development of personalized immunotherapy in CRC.

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IVb. SF3B1 inhibition disrupts malignancy and prolongs survival in glioblastoma patients through the imbalance of BCL2L1-splicing and mTOR/ßcatenin-pathways.

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Scientific Program: Cancer II.

Keywords: SF3B1 inhibition disrupts malignancy and prolongs survival in glioblastoma patients through the imbalance of BCL2L1-splicing and mTOR/ßcatenin-pathways.

Abstract: Glioblastomas are one of the most devastating cancers worldwide based on their locally aggressive behavior and because they cannot be cured by current therapies. Therefore, identification of new diagnostic, prognostic and therapeutic tools to deal with this type of brain tumors is urgently needed. In this sense, defects in alternative splicing process are frequent in cancer. Recently, we demonstrated that spliceosome dysregulations are directly associated with glioma development, progression and aggressiveness. Hence, we analyzed several human cohorts and a dataset from different glioma mouse models to determine the mutation frequency and the mRNA and protein levels between tumor and control samples of the splicing-factor-3B-subunit-1 (SF3B1), an essential and druggable spliceosome component. SF3B1 expression was also explored at single cell level across all cell subpopulations and transcriptomic programs. The association of SF3B1 expression with relevant clinical data in different human cohorts was also analyzed. Different functional and mechanistic assays were performed in three different glioblastomas cell models (human primary cultures and two cell lines) and in a GBM-xenograft-model in response to SF3B1 blockade (using pladienolide-b). Our data provide novel evidence demonstrating that the SF3B1 is scarcely mutated in gliomas (1%) but widely overexpressed in glioblastomas compared with control samples from the different human cohorts and mouse models included in the study, wherein SF3B1 levels are associated with key molecular and clinical features (e.g., overall survival, poor prognosis and/or drug-resistance). Remarkably, in vitro and in vivo blockade of SF3B1 activity with pladienolide-b drastically altered multiple glioblastoma pathophysiological processes (i.e., reduction in proliferation, migration, tumorspheres-formation, VEGF-secretion, and increase in apoptosis) likely by suppressing AKT/mTOR/ß-catenin pathways, causing an imbalance of BCL2L1 splicing. Together, we highlight SF3B1 as a potential diagnostic and prognostic biomarker and an efficient pharmacological target in glioblastoma, offering a clinically relevant opportunity worth to be explored in humans.

IVc. The emerging role of the dual-specifity tyrosine-regulated kinase 2 (DYRK2) regulating FBXW7 tumor suppressor in cancer development and progression.

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Scientific Program: Cancer II.

Keywords: FBXW7, DYRK2, ubiquitin ligase, kinase, DDR pathway and carcinogenesis.

Abstract: FFBXW7 is a relevant E3 ubiquitin ligase that targets proteins for proteasomal degradation. It is one of the main tumour suppressors, due to its essential role in the degradation of significant oncoproteins such us c-Jun, c-Myc, Cyclin E1 and Notch1, which regulate cellular processes, such as the cell cycle or differentiation. FBXW7 is widely mutated and protein levels are commonly downregulated in cancer. For these reason, knowing how FBXW7 is regulated could lead to improved the potential design of effective anticancer therapies. In this work, we report for the first time the identification of DYRK2 kinase, a protein with a central role in maintaining cellular homeostasis, as a novel FBXW7 regulator. Through different experimental approaches, we demonstrate how DYRK2 regulates FBXW7 expression at post-transcriptional level in a kinase activity-dependent manner via phosphorylation. Additionally, this reduction of FBXW7 expression is proteasome-mediated and is independent of FBXW7 ubiquitin ligase activity. We described the residues/regions responsible for this event which the interaction between both proteins takes place. We prove how these events happen in an oncogenic stress response context, involving the DNA damage response pathway (DDR), but not affecting dimerization capacity. Intriguingly, an enhanced degradation and a higher colocalization of these two proteins in the nucleus after exogenous DNA damage were observed. These data were verified modifying DYRK2 expression through the use of siRNAs and the generation of different DYRK2-/- cell lines using CRISPR/Cas9 methodology. Finally, we demonstrated that DYRK2 profoundly enhances degradation of multiple FBXW7 substrates, implicating DYRK2 as a general modulator of FBXW7 activity with consequences in tumor progression and proliferation. In summary, we reveal a novel regulation mechanism for the relevant tumor suppressor FBXW7 which might help us to better understand its role in cancer biology, with important consequences on cell-cycle control and DNA damage response pathway in cancer cells.

IVd. Dysregulation of the splicing machinery in rare tumors: The splicing process is altered in Pseudomyxoma Peritonei.

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Scientific Program: Cancer II.

Keywords: Pseudomyxoma peritonei; Alternative Splicing; Splicing machinery.

Abstract: Pseudomyxoma peritonei (PMP) is a rare peritoneal malignancy, with an incidence of 1–2 per million, which is usually caused by the perforation of appendiceal mucinous tumor and the redistribution of mucus and tumor cells. The chronic mucus accumulation is one of the major clinical features of PMP, which gradually leads to intraperitoneal organ adhesion, bowel obstruction, and eventually cachexia and death. Aggressive cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is the primary therapeutic approach used providing best results to benefit PMP patients' life. However, after this treatment patients suffer from relapse, presenting aggravated symptoms. For that, the exhaustive study of the molecular mechanisms underlying this disease is of great relevance, in order to further understand its origin and progression, and identify novel biomarkers and potential therapeutic tools. In this context, alteration of alternative splicing has recently emerged as a new relevant field of study, as it is a common feature of tumor pathologies, becoming a novel cancer hallmark. Generation of abnormal splicing variants with oncogenic potential is often the result of a dysregulated splicing machinery. Accordingly, the main objective of this work was to evaluate the expression of the splicing machinery in these rare tumors in comparison with normal tissues and to determine the possible contribution of the dysregulations found to the diagnostic of this disease. To this end, 62 splicing components were measured in 29 patient samples by a microfluidic qPCR array. The results unveiled a previously unknown profound dysregulation of the expression profile of key splicing machinery components, with an important discriminatory potential (between tumoral and non-tumoral samples). These findings support the idea that the dysregulation of the splicing process could contribute relevantly to this rare tumor pathology, and its study could help to identify novel biomarkers with potential as prognostic and therapeutic tools for future studies.

IVe. The Combination of Neutrophil–Lymphocyte Ratio and Platelet–Lymphocyte Ratio with Liquid Biopsy Biomarkers Improves Prognosis Prediction in Metastatic Pancreatic Cancer

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Scientific Program: Cancer II.

Keywords: NLR; PLR; circulating tumor DNA; pancreatic ductal adenocarcinoma; RAS mutation; neutrophil elastase.

Abstract: Liquid biopsy is emerging as a promising tool for the non-invasive analysis of pancreatic cancer, that is one of the most deadly malignancies, with a dismal five-year survival rate of 5%. The vast majority of pancreatic tumors are pancreatic ductal adenocarcinomas (PDAC), which are characterized by pronounced inflammation. Therefore, the present study was aimed to evaluate the prognostic value of combining biomarkers of systemic inflammation with liquid biopsy-based biomarkers. Plasma was obtained from 58 patients with histologically confirmed metastatic PDAC, and without previous chemotherapy or radiotherapy. Neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) were determined and circulating cell-free DNA (cfDNA) was extracted from plasma. The OncoBEAM™ RAS assay was used for the analysis of RAS mutations in cfDNA and the determination of RAS mutant allelic fraction (MAF). Neutrophil elastase in plasma was used as a marker of neutrophil activation. We found that NLR was significantly associated with both overall survival (OS) and progression-free survival. Remarkably, NLR was an independent risk factor for poor OS. Moreover, NLR and PLR positively correlated, and combination of both inflammatory markers improved the prognostic stratification of metastatic PDAC patients. NLR also showed a positive correlation with cfDNA levels and MAF. Besides, we found that neutrophil activation contributed to cfDNA content in the plasma of metastatic PDAC patients. Finally, a multi-parameter prognosis model was designed by combining NLR, PLR, cfDNA levels, RAS mutation, RAS MAF, and CA19-9, which greatly improved prognostic power and provided accurate survival risk stratification. In conclusion, our study supports that the use of systemic inflammatory markers along with circulating tumor-specific markers may constitute a valuable tool for the clinical management of metastatic PDAC patients.

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IVf. Spliceosome dysregulation accompanies diet-induced chronic liver disease progression towards hepatocellular carcinoma in mouse models.

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Scientific Program: Cancer II.
Keywords: Hepatocellular carcinoma; non-alcoholic steatohepatitis, spliceosome; alternative splicing; mouse models.

Abstract: The molecular characterization of metabolic-associated fatty liver disease (MAFLD) progression, an emerging cause of hepatocellular carcinoma (HCC) development, remains essential. Aberrant mRNA splicing and altered splicing machinery (spliceosome) have been described in several tumor types, including HCC. Here, we explore the spliceosome expression landscape in mouse models that recapitulate the pathological progression of chronic liver disease.

RNA expression levels of 69 spliceosome components were measured in mouse models (C57BL/6J) of diet-induced MAFLD/non-alcoholic steatohepatitis (NASH)/HCC [high-fat diet (HFD, n=12) vs. low-fat diet (LFD, n=12); methionine and choline-deficient diet (MCD, n=32) vs. methionine-supplemented diet (MSD, n=14); high-fat, high-cholesterol, high-fructose diet (HFHCHFD, n=19) vs. low-fat, low-cholesterol, low-fructose diet (LFLCLFD, n=14); and choline-deficient, high-fat diet (CDAHFD, n=12) vs. methionine and choline-sufficient, high-fat diet (MSHFD, n=10)] alone and/or after Cre/loxP-mediated knockdown of Pparγ, a master regulator of hepatic lipid metabolism.

Six spliceosome components (9%) were dysregulated in early-stage MAFLD. MCD-mediated mild NASH was characterized by the alteration of 15 spliceosome components (22%). HFHCHFD-associated advanced NASH and fibrosis resulted in the dysregulation of 37 spliceosome components (54%), while 49 (71%) of the analyzed genes were altered in severe NASH and HCC after CDAHFD administration. Mbnl2 and Nova1 overexpression was detected as an early event in MAFLD, while downregulation of Nova1, Rbm4, Rnu6, Srrm4 and U2af1 characterized NASH stages prior to the development of HCC. Pparγ knockdown improved NASH by decreasing spliceosome dysregulation [MCD: Pparγ+ (15 spliceosome components) vs. Pparγ− (1 spliceosome component); HFHCHFD: Pparγ+ (32 spliceosome components) vs. Pparγ− (13 spliceosome components)], yet it promoted pathogenesis in HCC by increasing spliceosome dysregulation [CDAHFD: Pparγ+ (27 spliceosome components) vs. Pparγ− (44 spliceosome components)].

The alteration of the splicing machinery accompanies the pathological progression of chronic liver disease, wherein Mbnl2 and Nova1 overexpression could represent novel early diagnostic biomarkers.
Fundings: ISCIII (ERDF/ESF, "Investing in your future") (PI20/01301), JdA (BIO-0139, PEMP-0036-2020) and CIBERobn.

IVg. Incidence of cancer in the native lung after single lung transplantation.

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Scientific Program: Cancer II.
Keywords: Lung transplantation, lung cancer, COPD.

Abstract: Objective: To assess the incidence of primary lung cancer in the native lung and its impact on survival in patients undergoing single lung transplantation (SLT).
Methods: Retrospective analysis of 258 consecutive lung transplants performed between June 2012 and June 2019 in our Institution. Among them, 161 single lung transplants were selected for the analysis.
The incidence of carcinoma in the native lung and its influence on patient survival was determined. Pre, intra, and postoperative recipient variables, tumour stage, treatment options, and survival, were analysed and compared between patients with and without native lung cancer. The analysis was adjusted for transplant indication (emphysema and pulmonary fibrosis). Both univariable and multivariable analyses were performed. Kaplan Meier with log-rank test was used to assess differences in survival between patients with and without native lung cancer.
Results: There were 161 patients (126M/35F; 57±7 years) transplanted for emphysema (COPD) (n=72), pulmonary fibrosis (IPF) (n=77), or other indication (n=12).
Eleven emphysema patients (7%) developed lung cancer in the native lung after SLT. Lung cancer did not appear in any of the SLT for pulmonary fibrosis.
Five cases were in stages I/II and underwent lung resection, and 6 cases were in stages III/IV and underwent chemo/radiotherapy.
Survival (1,3,5 years) without vs. with native lung carcinoma: COPD (89%, 86%, 80% vs. 86%, 71%, 51%; p=0.04). The occurrence of carcinoma in the native lung predicted survival in COPD patients (OR: 2.55; p=0.07).
Conclusion: Lung cancer in the native lung is a frequent and devastating complication after single lung transplantation in COPD patients, which negatively affects long-term survival.
This should be taken into consideration when choosing the transplant procedure in COPD patients.

POSTER SESSION II

PSII.a. Oncometabolism as a potential target in the poor prognosis subtype of colorectal cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: Colorectal cancer, GSNOR, S-nitrosylation, GLUT1 and 2-deoxyglucose.

Abstract: We have previously shown that low expression of denitrosilase enzyme GSNOR/ADH5 is associated with aggressive breast tumors and poor survival in breast cancer patients. Besides, recent research in our laboratory also connects GSNOR/ADH5 deficiency in colorectal cancer (CRC) with worse prognosis, poor survival and, remarkably, with a metabolic shift from oxidative phosphorylation to aerobic glycolysis. On the other hand, increased expression of glucose transporter GLUT1 has been related to an unfavorable prognosis in CRC. Therefore, this study was aimed to analyze the relationship between the expression of GSNOR/ADH5 and GLUT1 in the different molecular subtypes of CRC and also to explore the targeting of glucose metabolism in CRC cells as a potential therapy for poor prognosis tumors.

For this purpose, in a cohort of 80 patients, CRC tumors were classified into the CMS molecular subtypes and GSNOR and GLUT1 expression was evaluated using immunohistochemistry. On the other hand, CRC ADH5-knockout (ADH5-KO) cells were evaluated for their glucose metabolism and sensitivity to 2-deoxyglucose (2DG) in comparison with their parental counterparts.

A significant association was found between low GSNOR/ADH5 expression, poor clinico-pathological features and the CMS4 worst prognosis subtype. In addition, an upward trend was observed for GLUT1 expression in the case of CMS4 and GSNOR-low tumors.

Besides, ADH5-KO cells exhibited low basal ATP content and higher lactate production compared with parental cells, indicating a shift of pyruvate carbons away from TCA cycle and towards fermentation at the expense of oxidative phosphorylation. Importantly, ADH5-KO cells also displayed a higher sensitivity to the anti-tumoral effect of 2DG compared to parental cells.

In conclusion, our data support that attacking the metabolic vulnerabilities associated with metabolic rewiring in GSNOR-ADH5 low tumors may constitute a promising approach for improving therapeutic strategies in poor prognosis colorectal cancer.

PSII.b. Pharmacological inhibition of Nox4 protects against acute kidney injury associated to massive intravascular hemolysis.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Intravascular hemolysis, AKI, Nox4, GKT137831.

Abstract: Intravascular hemolysis is a common characteristic of surgical procedures and several diseases. In this pathological context, free hemoglobin (Hb) and heme are accumulated in the kidney, promoting oxidative stress, inflammation, and cell death, thus leading to acute kidney injury (AKI). NADPH oxidase 4 (Nox4) is the principal source of reactive oxygen species (in the kidney. In this study, we investigated whether Nox4 inhibition protected against Hb/heme-mediated renal damage in vivo and in vitro.

We performed an experimental model of massive intravascular hemolysis by intraperitoneal injection of phenylhydrazine (200 mg/kg) in C57BL/6J mice with the Nox4 inhibitor (GKT137831, 10 mg/kg/day, i.p.). Animals were sacrificed 72 hours after hemolysis induction. We also conducted experiments in primary cultures of tubular and podocytes stimulated with Hb (200µg/ml) and heme (5µM) in presence/absence of GKT137831 (5 µM).

Our results show that induction of hemolysis promoted acute loss of renal function, histological damage, increased expression of the tubular and podocyte injury markers, oxidative stress, inflammation, and cell death. All these pathological effects were significantly attenuated in mice treated with the Nox4 inhibitor. We also observed that administration of GKT137831 reduced intravascular hemolysis-mediated podocyte damage, as demonstrated by amelioration of the podocyte injury markers synaptopodin and nephrin. Nox4 inhibition did not influence the severity of hemolysis, suggesting that the beneficial effects of this treatment were related to a direct protective role in renal parenchymal cells. To confirm this hypothesis, we performed in vitro experiments in tubular cells and podocytes. Stimulation with heme and hemoglobin time- and dose-dependently increased oxidative stress, lipid peroxidation and cell death in both cells, effects that were diminished after Nox4 inhibition with GKT137831.

In conclusion, inhibition of Nox4 reduces renal associated to hemolytic crisis. These findings may have important implications for the treatment of patients with these disorders.

PSII.c. Autophagy and mitochondrial alterations by anti-aging interventions with NAD+ boosters and CYB5R3 overexpression are sex dependent in mice kidney.

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Scientific Program: Active aging and fragility.
Keywords: CYB5R3, cytochrome b5 reductase 3, NAD+, NAD+ boosters, NR, Nicotinamide Riboside, aging, autophagy, mitochondria, sexual dimorphism, kidney, mice.

Abstract: Interventions aimed at maintaining or increasing NAD+ levels have engaged a great interest since the maintenance of this compound has been related with the prevention of metabolic diseases and the promotion of healthy aging. Among them, cytochrome b5 reductase 3 (CYB5R3) overexpression and dietary supplementation with NAD+ boosters have reported relevant results. The aim of our studies was to analyze in kidney from male and female mice how CYB5R3 overexpression and/or dietary supplementation with the NAD+ booster nicotinamide riboside (NR) modify key markers of two key pathways related with the hallmarks of aging, namely autophagy and mitochondrial function.
Autophagic and mitochondrial biomarkers, as well as levels of CYB5R3, were assessed by Western blot. Kidney samples were obtained from male and female 7-month mice of wild-type and CYB5R3-transgenic genotypes. Animals were fed ad libitum with a standard chow from weaning until they reached 3 months of age. Thereafter, they were transferred to a purified AIN93M diet, supplemented or not with NR.
The levels of CYB5R3, changes of LC3I and LC3II (autophagy markers), PARKIN (mitophagy marker), and VDAC (mitochondrial mass marker) were evaluated as a function of sex, genotype, and diet. Results depicted a consistent pattern of changes. Briefly, CYB5R3 overexpression induced the upregulation of the biomarkers in both sexes. In wild-type mice, NR supplementation produced similar effects to those of CYB5R3 overexpression and this effect was also observed for both sexes. However, the effect of NR supplementation in CYB5R3-transgenic mice was found dependent of sex, increasing the levels of the biomarkers in males while decreasing in females.
In conclusion, NR supplementation produces a pattern of changes in the analyzed markers that is similar to that produced by CYB5R3 overexpression, both in males and females, while NR supplementation enhances the effects of CYB5R3 overexpression in males but reverts the effects in females.

PSII.d. Utility of copy number variation analysis detected by next generation sequencing in acute myeloid leukemia patients.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: CORDIOPREV study, gene-diet interactioN, oxidative stress, FOXO1A genetic variants, Mediterranean diet, Low fat diet..

Abstract: Introduction: The analysis of chromosomal alterations by conventional karyotype is one of the most important diagnostic tools to determine the prognosis of acute myeloid leukemia (AML) patients, where more than 50% of cases are affected. However, the sensitivity of the technique could not detect small genetic alterations (Copy Number Variation, CNV) that could affect the pathophysiology and prognosis of the disease significantly.

Objective: To analyse CNV of genes related to LAM by Next Generation Sequencing (NGS) and to evaluate their connection with the mutational profile and its possible influence on the clinical-biological phenotype and prognosis of the disease.

Materials and methods: The CNV and mutational profile were analysed in samples from 348 AML patients, belonging to PLATAFO-LMA reference centers (IMIBIC, Córdoba and Dr Negrín Las Palmas de Gran Canaria) by NGS, applying a panel of 29 genes (154 regions) related to myeloid neoplasms (Sophia Myeloid Solution) on Ilumina Myseq platform.

Results: The NGS detected 357 CNV in 29 genes analysed, affecting 123 AML patients (35.3%). The median number of genes affected by CNV was 2 (1-12). When comparing with the karyotype information, CNV provided additional information to conventional cytogenetics in 51% of the cases.

The chromosomes 7, 11 and 21 were most CNV affected, occurring in 88 (72.5%), 46 (37.4%) and 47 (38%) patients, respectively. The gains of genetic material occurred more frequently on chromosome 21 in U2AF1 and RUNX1 genes, in 17 and 16 patients, respectively. The loss of genetic material in EZH2 and BRAF genes occurred mutually. Interestingly, 7 patients had losses in TET2 gene and shorter overall survival compared to cases without CNV in this gene (0 months vs. 6 months, p = 0.005).

Moreover, 484 mutations were detected by NGS, distributed in 28 genes in 119 LAM with CNV. Only 4 patients did not have any mutation in genes analysed. The median number of mutations was 3 (range 0-14). The distribution and frequency of genes affected by CNV and by mutations was different.

Conclusions: The CNV of genes related to myeloid neoplasms are frequent in LAM patients (35.3%) and provides additional information to the conventional karyotype in half of the cases. The use of NGS with CNV analysis provides important information on copy number alterations not detected by the karyotype, which could significantly affect the pathophysiology of LAM and with potential clinical impact, especially in patients with normal karyotype.

PSII.e. SARS-CoV-2 and CMV chronic infection.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Ageing, Chronic inflammation, Immune senescence, Inflammatory disease, viral infections.

Abstract: Aims: SARS-Cov-2 infection (COVID-19) causes an inflammatory immune response followed by a significant reduced number of CD4 and CD8 T-cell counts. The severity of COVID-19 increases with age, so it has been speculated its association with immunosenescence. Expansion of peripheral CD28null CD8+ and CD4+ T cells is associated with cytomegalovirus (CMV) infection. We have demonstrated that CD57+ T cells are highly proinflammatory, cytotoxic and polyfunctional, as well as a hallmark of CMV infection. CD28null T cells express CD57 and CX3CR1 chemokine receptor. Vascular endothelial cells produce fracktalkine (CX3CR1 ligand) in response to proinflammatory cytokines. Thus, here we studied the expression of CD57 and CX3CR1 on CD28null T cells and their potential association with SARS-Cov-2 and CMV.
Methods: Expression of CD28, CD57 and CX3CR1 on peripheral blood T-cells from severe and mild COVID-19 patients (24-85 years), and sex/age matched healthy volunteers (HD) was analysed by flow cytometry.
Results: The percentage of CD28nullCD57+CX3CR1+ CD8+ T-cells was increased in mild COVID-19 patients compared with HD (p=<0.01), but only in the context of CMV chronic infection. Additionally, we found a difference in CMV seropositive prevalence between severe patients (80%) and mild patients (40%) and HD (60%).
Conclusions: Our results support that CMV chronic infection is associated with a worst outcome of SARS-Cov-2 infection. Furthermore, the expansion of CD28nullCD57+CX3CR1+ CD8+ T cells in mild CMV+ COVID-19 patients suggests that SARS-Cov-2 infection boosts early immunosenescence in CMV+ individuals.
Fundings: This research was funded by Fondo COVID-19 Supera Santander / CRUE Universidades (EudraCT: 2020-001364-29/ENCEMECO).

PSII.f. Circadian biorhythm and cardiometabolic risk among patients with coronary heart disease.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: circadian rhythm, cardiovascular disease, chronodisruption, lipids, meal timing.

Abstract: Introduction: Cardiovascular diseases (CVD) are the most common cause of morbidity and mortality worldwide. Chronodisruption has been associated with CVD, established it as a novel cardiometabolic risk factor.
Objective: The aim of this work was to determine the relation between chronotype measured by temperature, activity and position biorhythm, and cardiometabolic risk.
Material and Methods: Daily rhythm was recorded in a subset of 169 participants with coronary heart disease from the CORDIOPREV study (NCT00924937) during consecutive 7 days using an external device. Based on the acrophase of an integrative variable TAP (Temperature (T), Activity (A), Position (P)) we classified the participants as morning, intermediate and evening subjects. Lipid profiles were measured at baseline and every year during the 4 years of follow-up. During the first years of study information about meal and sleep timing was collected for one week. The timing of the three main meals of the day was reported, and the midpoint of intake was determined by calculating the midpoint between breakfast and dinner timing. To determine the differences in baseline between chronotypes we used analysis of variance (ANOVA). On the 4-year follow-up, we used a general linear model of repeated measures of each year of the study. Potential confounding factors were age, gender, BMI, dietary intervention (low-fat or Mediterranean diet), use of statins, fibrates, omega-3 or other lipids drugs, smoker status and alcohol intake and they were included as covariates in the tests.
Results: Evening subjects showed higher triglycerides levels at baseline ($p=0.04$) and on the 4-year follow-up ($p=0.03$) compare to morning subjects. In addition, evening subjects showed latter meal timing (breakfast, lunch and dinner) ($p=0.02$, $p<0.01$, $p<0.01$, respectively), and latter midpoint of intake ($p<0.01$).
Conclusions: Our work demonstrated in coronary heart disease patients, that subjects classified as evening by daily rhythm had higher cardiometabolic risk.

PSII.g. The Yin-Yang of Adipose Tissue Fibrosis.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Extracellular matrix, proteoglycans, fibrosis, adipose tissue, obesity.

Abstract: Fibrosis, commonly attributed to excessive deposition of collagen, is strongly associated with adipose tissue dysfunction. Understanding the molecular mechanisms that control fibrosis is fundamental for the knowledge of metabolic disorders in obesity. However, traditional approaches have been hampered by the inability of 2D in vitro models to recapitulate fibrosis. Here, we set up a three-dimensional (3D) adipocyte culture system mimicking the microenvironment of the adipose tissue in obese individuals with different degrees of insulin resistance. To this end, 3T3-L1 adipocytes were cultured in collagen-I matrices, in the presence of other extracellular matrix components shown to be dysregulated in the adipose tissue from obese individuals with insulin resistance, lumican and collagen VI (COLVI). Scanning electron microscopy and physical tests were employed for ultrastructural characterization of the collagen matrices, and adipocyte differentiation was evaluated by lipid droplet staining (Nile Red). Expression analyses of adipogenesis and cell stress markers were also carried out. A phosphoproteomic approach was used to characterize signalling pathways responsive to changes in the extracellular matrix (ECM). Results show that adipocytes grown in obesogenic 3D matrices containing lumican exhibit impaired adipogenesis and reduced glycolytic and lipogenic rates. Our analysis demonstrated that lumican-containing matrices activate mechanotransduction pathways affecting the nuclear envelope protein, lamin, in adipocytes. In contrast, adipogenesis and glycolysis were increased in the presence of COLVI. In addition, insulin increased glucose uptake in adipocytes grown in 3D matrices containing COLVI, alone or with lumican, via noncanonical insulin intracellular signaling. In sum, our studies unveil distinct ECM-responsive transduction pathways that impair adipocyte differentiation and metabolism, which may be relevant for the development of adipose tissue (dys)function and metabolic disease in obesity.
Fundings: MICINN/FEDER (BUF2016-76711-R; BFU2017-90578-REDT; PID2019-108403RB-I00); CIBERobn (ISCIII).

PSII.h. Improvement of "off-the-shelf" allogeneic CAR-T cells.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: CAR T cells; Immunotherapy; Gene editing; CRISPR-Cas9.

Abstract: Therapy based on T cells expressing chimeric antigen receptors (CAR) is a novel treatment for lymphoid neoplasms, which has already proven promising results. Currently antitumor T cells grafts are obtained from autologous T cells, which increases the cost and reduces the efficacy of the treatment. Additionally, several clinical trials involving CAR T cells have been impacted by T cells intrinsic factors, mainly associated with their phenotype. To avoid these major drawbacks, the use of allogeneic products in combination with the selection of defined CAR T cells subsets with greater in vivo persistence is being considered and tested. In this project, we expect to generate off-the-shelf allogeneic CAR-CD19 T cells with a defined phenotype.

We first generated universal HLA-I and T-cell receptor (TCR) double-knockout (dKO) T cells, by simultaneous disruption of B2M and TRAC genes through Cas9/sgRNA ribonucleoporation. When transduced with a CD19 CAR-T, the dKO-CAR T retained similar antitumoral activity in comparison with unedited CAR T cells. Ongoing work is focused in testing whether our dKO-CAR T cells reduce both rejection and graft versus host disease, and in the improvement of the persistence and antitumoral activity of these cells, by selection of specific T cells subsets.

To sum up, the combination of gene editing of CAR-T lymphocytes by TCR and B2M loci disruption, with the isolation of specific T subsets is an in vitro procedure developed with the translational objective of improving the clinical results of CAR T cells infusions in patients with refractory or relapsing B neoplasms.

PSII.i. Alterations of mitocondrial ultrastructure due to aging and CYB5R3 overexpression.

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Scientific Program: Active aging and fragility.

Keywords: Cytochrome b5 reductase, aging, mitochondria, longevity, and skeletal muscle.

Abstract: Aging is a natural and progressive process characterized by functional decline with increased risk of disease and death. Sarcopenia, the age-associated decline in skeletal muscle mass and function, is a hallmark of aging and is partially attributed to changes in mitochondria. Caloric restriction (CR) is the most effective non genetic intervention to extend both healthspan and lifespan. However, due to the difficulty of implementing this kind of diet in humans, nowadays there is great interest in identifying enzymes which promote healthy aging and even allow to increase longevity. One of such enzymes is NADH-cytochrome b5 reductase-3 (NADH:ferricytochrome b5 oxidoreductase, EC1.6.2.2, CYB5R3), which has been documented to increase longevity, protect against induced cancer, increase insulin sensitivity, and improve mitochondrial function in transgenic mice. CYB5R3 catalyzes electron transfer from NADH to cytochrome b5 and also to alternative electron acceptors as plasma membrane coenzyme Q or several exogenous compounds. Whereas mitochondrial function is a known CYB5R3 target, no study has been undertaken to elucidate the impact of CYB5R3 overexpression on mitochondrial ultrastructure. Thus, the aim of our work was to study by electron microscopy the ultrastructural features of mitochondria in red gastrocnemius samples from skeletal muscle of young (7 m.o.) and old (24 m.o.), wild-type and CYB5R3-transgenic mice. Our results show that old wild-type mice exhibited mitochondrial fragmentation whereas CYB5R3 overexpression increased mitochondrial size in old transgenic mice. CYB5R3 overexpression seems to avoid the effects of aging upon mitochondrial morphology in red and white fibers of skeletal muscle. Optimization of mitochondrial physiology thus emerge as a key mechanism related with the antiaging effect of CYB5R3 overexpression. Moreover, our data suggest that therapies aimed on increasing CYB5R3 levels or activity might be feasible antiaging approaches.

PSII.j. Influence of low back pain, sequenced movement, short-term rest, and age on lumbar muscle mechanical properties.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Spinal pain, myotonometry, spinal biomechanics.

Abstract: The aim was to identify the influence of the clinical status of the patient, the performance of movement or rest, and age in the muscle mechanical properties (MMPs) of the lumbar tissues. A longitudinal case-control study was designed with 75 subjects, 33 with acute low back pain (LBP) and 42 healthy controls. The MMPs were evaluated with a hand myotonometry (MyotonPRO®) before and after sequenced movements and after 5 minutes of rest. Three-way analysis of variance (ANOVA) was used to determine the interaction among the study factors. Double interactions and main factors were also of interest. The confidence level was set at 95% and the level of statistical significance was $p < 0.05$.
Regarding the comparative results, there was no triple interaction among the three factors (clinical status, age and movement or rest) on the behavior of the MMPs, except for the Decrement that decreased by 0.07 Ø in the third measurement with respect to the baseline of the young healthy subjects.
The interaction between clinical status and time of evaluation reported that subjects with LBP showed a decrease in Relaxation between the second measurement and after rest with $p < 0.05$. Likewise, the time of evaluation interacted with age showing that, after rest, the young subjects increased the Stiffness and Creep of 0.03 Deborah Number ($p<0.05$).
Finally, the evaluation of the main factors only showed differences for the age. Thus, subjects >35 years old presented a higher Frequency, Stiffness and Decrement and a lower Relaxation, than the youngers ($p<0.05$).
In conclusion, the age and the time of evaluation of the MMPs can modify MMPs.

PSII.k. Low fat diet modulates oxidative stress through FOXO1A genetic variant in coronary heart disease patients with type 2 diabetes.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: CORDIOPREV study / gene-diet interaction / oxidative stress / FOXO1A genetic variants / Mediterranean diet / Low fat diet.

Abstract: Background: We explored whether long-term consumption of two healthy dietary patterns (low-fat (LF) diet or Mediterranean diet (MedDiet)) interact with the Forkhead box protein O1 A (FOXO1A) single nucleotide polymorphisms rs2755209, rs2721069 and rs2755213 modulating oxidative stress in coronary heart disease (CHD) patients with type 2 diabetes mellitus (T2D).

Methods and results: We selected 136 patients with T2D from the CORDIOPREV study with genotyping and oxidative stress measurements at baseline and after four years follow up. After four years of follow-up, we found a gene-diet interaction between the FOXO1A rs2755213 SNP and LF diet. Specifically, C-allele carriers in the LF diet group showed a significant increase in total glutathione (p = 0,04) and superoxide dismutase (p = 0.02) plasma levels compared with TT subjects. No other gene-diet interactions were observed.

Conclusions: The long-term consumption of a LF diet modulates oxidative stress through FOXO1A genetic variant in CHD patients with T2D. This gene-diet interaction may contribute to a more precise dietary advice in these patients.

PSII.I. Sensitisation Profile Of Patients Allergic To Apis Mellifera.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Allergy, bee venom, hymenoptera time.

Abstract: Introduction: The beekeeping sector generates approximately 14.2 million Euros annually. However, 3% of the general population and between 14 and 43% of beekeepers are allergic to bee venom. Continuous contact with bee venom can lead to a high risk of adverse symptoms, anaphylaxis and even death.

Currently, most diagnostic techniques involve exposure of the patient to the allergen, which leads to adverse symptoms. In addition, many of them fail immunotherapy.

Objective: To study the sensitisation protein profile of patients allergic to bee venom. Comparison of an allergenic extract of Hymenoptera venom and Hymenoptera venoms extracted directly from the bee sting.

Materials and Methods: This study compares the protein extraction of purified and freeze-dried commercial bee venom with a protein extraction of bee venom obtained directly from bee stingers after their sacrifice with CO2.

Two phases, a soluble phase and a precipitate phase, were observed in the commercial venom protein extraction.

The sensitisation profiles of 10 patients allergic to Apis mellifera venom were characterised using ImmunoCAP, SDS-PAGE and Immunoblot techniques in all the aforementioned samples (commercial extract - soluble phase and precipitate - and venom extract extracted directly from the stingers).

One patient was negative for all allergenic components of Apis mellifera using the ImmunoCAP technique but suffered anaphylaxis after a bee sting.

Results: The results showed large differences in recognition between the soluble phase and the precipitate. Five of them showed recognition of a band with a molecular weight of 16 KDa coinciding with the size of Api m 1. Another patient showed a complex band recognition profile with molecular weights between 15 and 100 KDa, and also did not recognise any band in the pellet. However, the Immunocap negative patient showed a complex profile in the pellet, recognising bands with molecular weights between 14 and 100 KDa that could correspond to the allergens Api m 1 (16 kDa), Api m 10 (50-55 kDa), Api m 11 (50-60 kDa), Api m 8 (70 kDa) and Api m 9 (60 kDa) among others. Two patients showed no recognition at any stage. Protein extraction from venom extracted directly from stingers showed a higher number of bands compared to the commercial extract. In addition, when the serum of the patients was contacted it revealed a broad protein sensitisation profile between 250 and 50 kDa and 15 kDa.

Conclusion: Currently, there are very few techniques developed for the extraction of allergens from Hymenoptera extracts and all procedures reported in the literature select the supernatant from the extraction process. This study can show how there are proteins that can develop sensitisation in Hymenoptera-allergic patients that are not being considered.

Methods involving direct measurement of allergen recognition need to be developed.

PSII.m. Impact of the use of diuretics after the onset of hemodialysis.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Diuretic, residual diuresis, hemodialysis.

Abstract: The use of diuretic treatment (DT) is frequent in patients with chronic kidney disease, not always we keep the treatment on hemodialysis. DT help to maintain residual diuresis, with proved clinics and prognostic advantages. The purpose of the study was to analyze the effects of continue DT after the onset of hemodialysis.

We performed an observational study with incidents on hemodialysis during the years 2017 and 2019 (n=248). We divided the sample into patients that continue DT (n=165) vs patient that not (n=83).

Demographic and biochemical variables were collected, hemodialysis type, Charlson index, residual diuresis, left ventricular ejection fraction (LVEF), hospital admissions and number of deaths at first year after start hemodialysis.

From total 248 patients, 165 (66.5%) were on DT. The sample of DT had a Charlson index higher (≥3) [152 (92,1%) vs 73 (87,9%); p=0,038], more LVEF <50% [137 (90,13%) vs 76 (97,4%); p=0,045] and higher interdialytic weight gain at 6 month of the onset hemodialysis (1.96 ± 0.68 vs 1.73 ± 0.71; p=0,013) and at 12 months of the onset hemodialysis (2.15 ± 0.78 vs 1.88 ± 0.69; p=0,028). We also found a higher dry weight at 12 months of the onset hemodialysis (75.58 ± 16.07 vs 69.26 ± 16.54; p=0,013). No differences were found in the rest of the variables studied. In terms of survival univariate analysis, we found differences at 6 months on CRP, phosphorous, hemoglobin, sodium and albumin; and at 12 months on interdialytic weight gain, dry weight, CRP, calcium and hemoglobin. These results did not reach statistical significance in the multivariate analysis.

In conclusion, the maintenance of DT after start hemodialysis is more frequent in patients with higher comorbidity, worse cardiac function and with worse volume management, without higher number of hospital admissions. DT could bring benefits on interdialytic weight gain, plasmatic sodium and dry weight.

PSII.n. Preliminary results on the establishment of an animal model of pseudomyxoma peritonei with human xenograft.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: pseudomyxoma peritonei; animal model; xenograft; Ki67; CK7; CK20.

Abstract: Pseudomyxoma Peritonei (PMP) is a rare disease characterized by mucinous ascites and peritoneal implants originating from a perforated mucinous tumor of the appendix. The low number of cases makes it difficult to know the molecular mechanisms of genesis, proliferation and recurrence of this rare tumor.

The global objective of this line is to develop xenograft mouse models to replicate human PMP and use it as a tool to test new target therapies in future studies. The animal models developed so far are based on the implantation of intraperitoneal human tumor tissue. This procedure has been developed by different reference groups in the study of PMP, located in Pittsburgh, Paris, Oslo and Beijing.

We present the development of the first Spanish PMP animal model. We have analyzed the gene expression levels of three human tumor biomarkers (Ki67, CK7 and CK20) by qPCR in the tumor collected from the patient (HT) before and after being transplanted into the mouse (MT). In addition, mouse ovaries (MO) were used as a negative control. In both cases, HT and MT, the tumor biomarkers Ki67, CK7 and CK20 were positive; likewise, MOs were negative for CK7, CK20 and Ki67, showing that MT is a human tumor.

This advance will be essential to find specific biomarkers of this kind of tumor, as well as to develop new drugs with the ability to stop the progression and/or the recurrence of this malignant disease.

Fundings: National Institute of Health Carlos III (ISCIII). Reference: PI19/01603.

PSII.ñ. Additive antitumor effect of metformin and simvastatin combination in glioblastoma: evidence for a potential drug repurposing.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: Glioblastoma, metformin, simvastatin, senescence.

Abstract: Glioblastomas (GBMs) remain the deadliest human brain tumors, with a poor prognosis despite years of research. Currently, standard therapeutic strategies to treat GBM are not efficient. Thus, the identification of new therapeutic tools to tackle GBMs is crucial. In this sense, some metabolic drugs [e.g., metformin (MF) and simvastatin (SVT)] have emerged as potential antitumor agents against several endocrine-related cancer types. For that reason, our aims were to: 1) evaluate the putative in vivo association between MF and/or SVT treatment with key clinical parameters in GBM patients; and, 2) analyze the direct effects of MF, SVT, and their combination, on key functional endpoints and associated signaling mechanisms in GBM cells. Specifically, an exploratory/observational retrospective cohort with GBM patients (n=61) was analyzed, and human GBM cell lines and patient derived GBM cells were used to measure a set of key functional parameters and signaling pathways in response to MF, SVT, and their combination. Our results showed an association of the MF/SVT combination with longer overall survival in GBM patients. Moreover, MF and SVT exerted strong antitumor actions in terms of proliferation, migration, tumorsphere formation, VEGF secretion, and apoptotic activity in vitro. Remarkably, MF+SVT combination further decreased these critical pathophysiological parameters, wherein these actions were mediated through the modulation of key oncogenic signaling pathways (AKT/JAK-STAT/NFkB/TGFß). Interestingly, an enrichment analysis uncovered an activation of the TGFß pathway and ERK1/2 proteins together with the AKT inactivation in response to the combination MF+SVT, which might be tightly linked to an induction of senescence-associated secretory phenotype. Moreover, this phenotype was associated with the activation of telomerase/shelterin complex and dysregulation of the splicing cellular machinery. Therefore, given the demonstrated clinical safety of MF and SVT, and their antitumor effects observed in GBM, our results suggest a potential therapeutic role for these drugs, especially their combination, in GBMs.

Fundings: MINECO (PID2019-105564RB-I00/FPU16-05059), Junta de Andalucía (BIO-0139) and CIBERobn.

PSII.o. Impact of the number of comorbidities on the outcome measures and on the retention rate of the first anti-TNF in patients with Ankylosing Spondylitis. Two-year follow-up REGISPONSER-AS.

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Keywords: spondyloarthritis, anti-TNF, comorbidities.

Abstract: Objectives: To evaluate the impact of the number of comorbidities on the outcome measures after 2 years of follow-up in patients with ankylosing spondylitis (AS) and to determine whether the number of comorbidities influences the retention rate to the first anti-TNF.
Methods: Observational and prospective study during 2 years of follow-up that includes a subgroup of 749 patients with AS (REGISPONSER-AS). The patients were divided into 3 groups according to the number of comorbidities at baseline. Linear regression models were performed using the Patient Reported Outcomes (PROs) as the dependent variable and the 3 groups of patients as the explanatory variable. Additional models adjusting for disease duration were explored. After that, the impact of the number of comorbidities on PROs over 2 years of follow-up was evaluated using mixed models for repeated measures. Finally, we compared the retention rate to the first anti-TNF across the 3 groups of patients using a Kaplan-Meier curve and Log-rank test.
Results: 749 patients were included. We found that patients with 2 or more comorbidities showed an increase in all PROs compared with patients without comorbidities. In general, patients with 2 or more comorbidities showed higher scores during the 2 years of follow-up in Global VAS, BASDAI, ASDAS, BASFI and worse levels from the SF12. We found a higher probability of discontinuation of the first anti-TNF in patients with 2 or more comorbidities compared with the other 2 groups, although these differences were not significant (Log-rank test: p-value = 0.180).
Conclusion: In patients with AS, the presence of 2 or more comorbidities was associated with poorer scores on the outcome measures after 2 years of follow-up. Despite the 3 groups showed a similar use of anti-TNF, a greater tendency of discontinuation of the first anti-TNF was observed in patients with 2 or more comorbidities.

PSII.p. Outcomes in patients with anti-gbm glomerulonephritis in a multicentric spanish cohort.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Anti-glomerular basement membrane disease, end-stage kidney disease, kidney survival, plasma exchange.

Abstract: Background: Plasma exchange and immunosuppressive agents are the main therapy for treating anti-glomerular basement membrane (anti-GBM) disease. The aim of the study was to assess the clinical and pathological features that predict evolution to end-stage kidney disease (ESKD) and if plasma exchange has a beneficial effect in kidney survival.
Methods: Retrospective multicentric observational study including 72 patients from 18 nephrology departments with biopsy proven anti-GBM was carried out from 1999 to 2019. ANCA positive patients were also included. Progression to ESKD in relation to clinical and histological variables was evaluated.
Results: The creatinine at admission was 8.6(±4) mg/dl. Sixty-one patients (84.7%) required dialysis at presentation. Sixty-five patients (90.3%) undergo plasma exchange. 22 patients (30.6%) had pulmonary haemorrhage. Seventeen patients (23.6 %) underwent a renal transplant. No difference in dialysis dependence at admission and ESKD development were observed in double positive patients. The discrimination value for a creatinine> 4.7 mg/dl and for 50.5% percent of crescents had an AUC of 0.9 (95% CI 0.82 0.97; p < 0.001) and 0.77 (95% CI 0.56 0.98; p =0.008) respectively. Kidney survival at 1 and 2 years was 13.5% and 11%. Kidney survival was worse in patients with creatinine > 4.7 mg/dl(3 %vs 44% p<0.01) and in patients with >50% of crescents in the renal biopsy (6% vs 49%; p=0.03). Dialysis dependency at admission and creatinine> 4.7 mg/dl remained independent significants predictors of ESKD in multivariable analysis (HR 3.13(1.25-7.84); HR 3(1.01-9.14; p<0.01). No patients exhibited evidence of relapse in the graft.
Conclusions: In patients with antiGBM disease a creatinine higher than 4.7 mg/dl and the presence of >50 % crescents in renal biopsy are associated with ESKD development. These patients may be refrained of plasma exchange treatment. There is not evidence of relapse in the 17 patients that underwent a renal transplant.

PSII.q. Lipoprotein subclasses, particle sizes and standard lipid panel and their relationship with peripheral artery disease in coronary heart disease patients: from the CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Peripheral artery disease, lipoprotein, lipid panel, NMR metabolomics, ankle-brachial index.

Abstract: Peripheral artery disease (PAD) refers to a partial or complete occlusion of arteries of the upper or lower limbs caused by atherosclerosis plaque. Although frequently asymptomatic, patients suffering from PAD are at high risk of cardiovascular events. Traditional risk factors are similar to those of coronary heart disease (CHD), and include smoking, hypertension, or dyslipidemia. Nevertheless, despite having risk factors correctly under control, CHD patients remain at high risk of recurrence. Thus, to effectively protect this sensitive population, it is crucial to understand the underlying mechanisms not captured by traditional risk factors. The objective of this research work has been to assess whether lipoprotein subclasses measures obtained by nuclear magnetic resonance (NMR) spectroscopy and standard lipid panel are associated with the presence of PAD in CHD patients enrolled in the CORDIOPREV study. Results showed that total cholesterol, LDL cholesterol, apolipoprotein B and non-HDL cholesterol positively correlated with IDL, LDL and very small VLDL particles, whereas triglycerides positively correlated with all VLDL particles except very small VLDL. Finally, HDL cholesterol positively correlated with large HDL particles, and apolipoprotein A1 with large and medium HDL particles. In multivariable-adjusted models comparing extreme tertiles, triglycerides (OR 1.8, 95% CI:1.1-2.7), non-HDL cholesterol (OR 1.5, 95% CI: 1.0-2.28) and total cholesterol: HDL cholesterol (OR 1.80, 95% CI: 1.2-2.8) were associated with the presence of PAD. Regarding NMR data, HDL particle size was inversely associated with PAD (OR 0.7, 95% CI: 0.4-0.99), but associations of PAD with lipoprotein subclasses particle concentration were not found. As future work, we aim to test whether NMR-derived lipoprotein subclasses lipid composition measures are associated with the presence of PAD, with the aim of provide a lipoprotein signature for PAD in coronary heart disease patients.

PSII.r. Evaluation of Sedentary Behavior and Physical Activity Levels using Different Accelerometry Protocols in Children from the GENOBOX study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: Lifestyle; accelerometer; child; exercise.

Abstract: Objectives. The present study aimed to examine the sedentary behavior (SB) and physical activity (PA) levels in children using six selected accelerometry protocols based on diverse cut-off points.
Methods. Clinical examination, anthropometric measurements, and PA evaluation by accelerometry were assessed in 543 selected children (10 ± 2.4 years old) from the Spanish GENOBOX study. The ActiLife data scoring program was used to determine daily min spent in SB, and light, moderate, vigorous and moderate-vigorous PA using six validated accelerometry protocols differing in their cut-off points.
Results. Very different estimations for SB and PA intensity levels were found in children, independently of the non-wear-time algorithm selected, and considering puberty stages, age and body mass index. The time spent in daily SB varied from 471 to 663.7 min, PA ranged from 141 to 301.6 min, and the moderate-vigorous PA was reported between 20.7 and 180.2 min.
Conclusion. The choice of a particular accelerometry protocol considering these factors is important to evaluate SB or PA intensities to suit the characteristics of the sample researched. It seems necessary to establish future lines of research that include different analytical approaches to measure SB and PA by accelerometry based on standardized and validated methodology.

PSII.s. Pediatrics eating disorders during the sars-cov19 pandemic in Reina Sofia University Hospital.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Eating disorders, pandemic, Covid 19, adolescents, Paediatric.

Abstract: Introduction: With the arrival of SARS-Cov 19, eating disorders have increased, especially in children.
Aim: To evaluate the clinical profile of paediatric patients with eating disorders (ED) analyzing the triggering factors, specially the confinement due to COVID-19.
Methods: Retrospective study in paediatric patients with ED from Reina Sofia Hospital during the pandemic of SARS-Cov2 was carried out. Demographic, anthropometric and clinical parameters as well as diagnosis and treatment data have been studied.
Results: 10 patients with ED severe (9 girls/1 boy) since March 2020 until March 2021 were selected. The average range was between 8 and 17 years. 70% of them identified the origin of their interest into lose weight during confinement, starting the restriction of the intake. 100% of the patients associated an impulsive increase of exercise. 40% of them had a weight below percentile 10 in the first visit with an average of body mass index about 15,1 kg/m2. The average of fat mass was of 11,01% (13,56-26,62), 89,04% (73,34-86,39) of lean mass and 65,2% (45,65-60,69) of water weight.
Changes in biochemical analysis were detected in 70% of patients. 60% of them presented changes in sex hormonal levels. 60% of them needed hospitalization, with an average of 21 days. We highlight a patient with pericardial effusion. 70% of the patients showed symptoms of anxiety, and 40% of depression.
All of them received and integral personalized treatment. There has not been any medical discharge for healing. 50% needed nutritional supplements, and a minimal sample used nasogastric tube. 80% needed intensive psychological support and pharmacological treatment.
Conclusions: In Covid 19 pandemic, eating disorders in pediatric patients with a rapid progression has increase. It is necessary to advance in the knowledge of these diseases and to promote an early detection and an integral treatment by the development of multidisciplinary paediatric teams.

PSII.t. A proposal for modification of PSOGI classification according to Ki-67 proliferation index in pseudomyxoma peritonei.

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Scientific Program: Cancer (Oncology and Oncohematology).

Keywords: Pseudomyxoma peritonei, PSOGI classification, Ki67, PMP.

Abstract: Background and objective: Pseudomyxoma peritonei (PMP) is a rare malignant disease characterized by the progressive and multifocal accumulation of abundant mucinous tumor tissue in the peritoneal cavity. It is generally associated with a perforated epithelial neoplasm of the appendix. The Peritoneal Surface Oncology Group International (PSOGI) has recently published a consensus statement about the diagnosis and treatment of mucinous appendiceal tumors and PMP. It recommends, whenever possible, cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) in reference centers. The PSOGI classification divides PMP into three groups and excludes acellular mucinous-type lesions from its definition. These three groups are defined as PMP with low-grade histological characteristics (LG-PMP), PMP with high-grade histology (HG-PMP), and PMP with the presence of signet ring cells (SC-PMP). Ki67 proliferation index has been proved to be a prognostic factor for a huge variety of tumours. It is not always studied but its analysis can be useful to stablish patient outcomes since a high Ki-67 index generally shows poor prognosis in clinical conditions.

Methods: We have conducted a prospective study using a collected tissue samples from a retrospective cohort of patients with PMP treated in our Unit by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) from 1997 to 2020. All the patients signed their informed consent to analyze the samples of tissue and it was approved by our local ethics committee. The entire cohort was classified according to the new PSOGI LG-PMP, HG-PMP, or SC-PMP groupings and cases with acellular mucin.

In addition, Ki67 proliferation index was determined immunohistochemically in HG-PMP samples.

Results: At the time of this study, 76.2% of patients were alive and the median follow-up time was 47 months (0–240). The 5 years OS were 72% and 22% for Ki67 less or equal to 15% and greater than 15%, respectively. After previous analysis the HG-PMP group was divided in two subcategories using the Ki67 15% cut-off (PSOGI-Ki67). The multivariate analysis showed as only prognostic factor for overall survival and for disease free survival the PSOGI-Ki67 variable: OS 161+/-14; 128+/-17 y 31+/-8 months for LG-PMP, HG-PMP-Ki67<15% and HG-PMP-Ki67>15%. The mean DFS was 138+/-10; 66+/-9 and 19+/-5 months in each group. Mean DFS at 5 years was 100%, 70% and 24%, and mean DFS at 5 years was 90%, 40% y 0%, in each group.

Conclusion: The division of the HG-PMP category into the PSOGI PMP classification according to the Ki67 proliferation index provides two sub-categories well defined with significant differences for overall survival and disease free survival. This new proposal modification must be validated in an international collaborative study.

PSII.u. Rab34 or how to turn lipid storage on and off.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Rab34; adipocyte; lipogenesis; lipolysis.

Abstract: Rab proteins are known for their ability to act as molecular switches that turn on (GTP-bound) or turn off (GDP-bound) the transport mechanisms between intracellular compartments, as well as the transport of proteins or lipids to a target organelle. Previous studies from our laboratory unveiled Rab34 binding to surface of lipid droplets (LDs) in cells specialized in lipid accumulation, the adipocytes. In this work, the role of Rab34 in LD dynamics and lipid metabolism in adipocytes was analysed. We observed that Rab34 overexpression increased the accumulation of triglycerides (i.e., lipogenesis) while decreasing the release of glycerol (i.e., lipolysis), whereas the opposite effects were observed upon Rab34 silencing. A role for Rab34 in lipid accumulation was further confirmed in overexpression experiments using a constitutively active (Q111L) and an inactive (T66N) Rab34 variant, which also induced an imbalance in the availability of intracellular glycerol. The expression of a battery of metabolic markers was also evaluated in silenced and overexpressing cells by Western blot, which suggested the participation of Rab34 in de novo lipogenesis. Biochemical analysis of Rab34 interactome demonstrated the interaction between this small GTPase and fatty acid binding proteins (FABPs), which act as intracellular lipid chaperones regulating both lipogenesis and fatty acid release. Interestingly, Rab34 colocalized and coimmunoprecipitated with FABP5, whose levels decreased in cells overexpressing Rab34. This, together with the decreased expression of adipose triglyceride lipase (ATGL) observed in these cells (among other expression changes), suggested that Rab34 causes a shift in the energy balance towards lipogenic pathways. Altogether, our results suggest that Rab34 participates in the regulation of lipogenesis in adipocytes, which is in line with our observations on the increased expression of this GTPase in the adipose tissue of genetically or diet-induced obese animals. Thus, Rab34 could represent a promising target to control lipid accumulation in adipocytes.

PSII.v. Prevalence and Associated Factors of Low Bone Mineral Density in the Femoral Neck and Total Hip in Axial Spondyloarthritis: Data from the CASTRO Cohort.

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Scientific Program: Chronic and Inflammatory diseases.

Keywords: Axial spondyloarthritis; bone mineral density; osteopenia.

Abstract: Studies on osteoporosis in axial spondyloarthritis (axSpA) have focused on the lumbar segment, and few studies have assessed bone mineral density (BMD) in the hip and femoral neck in these patients. The aim of this study was to evaluate the prevalence of low BMD and osteopenia in the total hip or femoral neck and the factors associated with these conditions in axSpA patients. This was a single-centre, observational, cross-sectional study among consecutive patients with axSpA according to the ASAS criteria from the CASTRO registry. All patients underwent total hip and femoral neck DXA BMD measurements. Low BMD was defined as a Z-score less than −1, and osteopenia was defined as a T-score less than −1. Multivariate logistic and generalised linear regressions were used to evaluate factors independently associated with low BMD and osteopenia in the hip or femoral neck and those associated with variability in BMD, respectively. A total of 117 patients were included, among which 30.8% were female and the mean age was 45 years. A total of 36.0% of patients had low BMD (28.1% in the total hip and 27.4% in the femoral neck), and 56.0%
of patients had osteopenia (44.7% in the total hip and 53.8% in the femoral neck). A multivariate logistic regression showed that age, radiographic sacroiliitis and ASAS-HI were independently associated with low BMD in the total hip or femoral neck. Factors that were independently associated with osteopenia were Body Mass Index, disease duration, radiographic sacroiliitis and ASAS-HI. In conclusion, 36% of the patients with axSpA had low BMD in the total hip or femoral neck. A younger
age and radiographic sacroiliitis were the most important factors associated with decreased BMD.It is possible that these patients with negative C3 deposit represent a MN with evolution to SR and in these patients and that these patients do not need immunosuppressive treatment.

PSII.w. Relationships between Body Mass Index and Psychosocial variables to predict the well-being of children and adolescents: a preliminary study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: healthy, well-being, support, young people, obesity, weight, body mass index.

Abstract: Poor eating habits in childhood have become a serious public health problem that is also causing child overweight rates to continue to grow. The consequences of these bad habits can be very dangerous when it occurs in young people who already have a diagnosed disease such as diabetes or obesity. Without disregarding biomedical variables, this study aimed to explore the relationships between psychosocial variables regarding well-being, self-efficacy to food intake and social support in relation to parents and peers for healthy and unhealthy eating. The study sample (n = 299) were children and adolescents aged 9-18 years. The parents of these young people, after informed consent, provided information on the sex, age, height and weight (to calculate body mass index) of their children, as well as the socioeconomic level of the family. Subsequently, the children and adolescents completed an online questionnaire on well-being, self-efficacy for food intake and social support. SPSS v.25 was used to analyze the collected data. Correlational analysis showed relationships between the studied variables. The body mass index correlated negatively with well-being and with self-efficacy to food intake, while well-being with parent and peer social support for unhealthy eating. In contrast, wellbeing correlated positively with self-efficacy to food intake and parent support healthy. With these results, we can conclude that a higher body mass index is detrimental to the well-being perceived in children and adolescents, and that a greater self-efficacy for food intake is associated with a more optimal body mass index, as well as the importance to the support of family and peers in choosing healthy or unhealthy foods.

PSII.x. Construccion of a predictive test for postpartum depression.

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Scientific Program: Active aging and fragility.
Keywords: Pregnancy, postpartum depression, mental disease, childbirth.

Abstract: Postpartum depression is most suffered mental disorder by the female population worldwide. We know that pregnancy, childbirth and the puerperium are periods of high vulnerability for the development of depressive symptoms. In fact, on many occasions the symptoms already began in pregnancy and continue in the postpartum period. The worldwide frequency of this disease ranges from 10% to 20% of postpartum women according to some authors, or from 10% to 15% according to others. Its prevalence is three times higher in developing countries than in developed countries, and it is more frequent in women of low socioeconomic status. The main objective of this work is to carry out and validate a screening test for postpartum depression that allows to identify risk factors by obstetric health professionals that predispose a pregnant woman to present this mood disorder during the puerperium. In order to carry out our main objective we will investigate which risk factors present during pregnancy participate in the development of depressive pathology in the postpartum.

PSII.y. Intratumoral Bromelain and Acetylcysteine for Recurrent and Unresectable Pseudomyxoma Peritonei. A Phase I/II, unicentric study.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pseudomyxoma peritonei, Bromelain, N-Acetylcysteine.

Abstract: Background: Mucinous neoplasms with peritoneal spread constitute an infrequent entity known as Pseudomyxoma Peritonei. The massive intraabdominal affectation contrast with the optimistic prognosis owing to its low grade histological classification. Cytoreductive surgery and HIPEC are the standard treatment but yet locoregional recurrences are described to occur in 20-30% of the cases. The scarce success of intravenous chemotherapy compels to iterative surgeries as the best treatment for recurrences. Hence, patients with several surgeries have an inadmissible morbidity risk for another cytoreduction in case of new relapses, being the supportive care the only available treatment.
This clinical trial is focused on the treatment for PMP abdominal recurrences in inoperable patients. The objective is to assess the effectiveness of the combination of Bromelain and Acetylcysteine (BromAc). Its synergistic activity results in the dissolution of tumour-produced mucin both in vitro and in vivo, along with a cytotoxic effect and improved chemosensitivity.
Methods: For this phase I/II, unicentric trial, 10 patients will be selected (inoperable abdominal mucin masses or mucin ascites). The BromAc will be administrated as a minimally invasive treatment through a percutaneous catheter directly to the mucin for a total of three days. Doses will be adjusted to the tumour volume.
Conclusions: We aim to assess the safety, feasibility, and effectiveness of the BromAc to dissolve mucin masses, relieve symptoms, and to control tumour progression.
Fundings: Project granted by the Foundation of Health and Families of the Junta de Andalucía. Reference: PI-0064-2020.

PSII.z. Aortic valve infiltrating pro-inflammatory cells in aortic stenosis patients.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Aortic Stenosis, Cardiovascular disease, inflammation, immunopathology.

Abstract: Aortic valve stenosis (AS) is a frequent cardiac disease in the elderly and is characterized by valvular calcification, fibrosis and inflammation, however its pathogenesis is not well known. AS has been traditionally considered a passive chronic degenerative process due to the accumulation of damage with age. Nevertheless, recent studies suggest that AS is similar to atherosclerosis, being an active inflammatory process. Particularly, it has been suggested that several immune cell types, present in the valve infiltrate, might contribute to its degeneration and to the progression towards stenosis. However, the valve inflammatory infiltrate has not been well characterized in any study regarding AS. Up to date there is no other treatment for the valve stenosis other than the replacement of the valve itself. Therefore, the characterization of the cells implicated in the inflammatory processes of the valvular stenosis is of outmost importance in order to develop new therapies for AS patients.
Here we present the evolution in the results of a recently developed protocol for the phenotypic characterization of aortic valve infiltrating cell populations in AS patients.

PSII.aa. Ventilatory therapies and Intensive Care admissions for patients with COVID-19: a systematic review.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: ARDS, SARS-CoV-2, mechanical ventilation, Intensive Care Unit.

Abstract: Introduction: SARS-CoV-2, which affects humans, was first detected in December 2019 in Wuhan city, Hubei province, China. Acute Respiratory Distress Syndrome (ARDS) is among the most serious manifestations caused by SARS-CoV-2. This manifestation triggers severe respiratory failure requiring, in most cases, mechanical ventilation for recovery.
Objective: To synthesize and analyse the scientific production related to the ventilatory therapies used in patients with COVID-19 in ICUs, the parameters of invasive mechanical ventilation used and the clinical characteristics in such patients were studied.
Methods: A systematic review was carried out through the PubMed, Embase, Web of Science and Cochrane Library databases. Studies published between 05/31/2019 and 05/31/2020 were included in which reference was made to ventilatory therapies used in patients with COVID-19 in ICUs.
Results: 30 studies were included for qualitative analysis. A total sample of 48,743 patients was analysed, of which 17.66% were admitted to the ICU, dying 6.4% of them. Patients analysed which required some type of respiratory were 44.4% - specifically 12.8% had invasive mechanical ventilation, 9.7% had non-invasive support mechanical ventilation and 29.7% had high-flow nasal oxygen.
Conclusion: COVID-19 has led to a high number of admissions to the ICU. It has been a challenge for ICUs to provide the best ventilatory therapy available to admitted patients. The available figures for ICU admissions and the use of ventilatory therapies are similar across continents, although the data seem to suggest that geographic areas with higher ICU admission rates have lower mortality rates. The lack of specification in clinical records limits obtaining more conclusive results.

PSII.bb. Analyzing the Role of Autophagy in the Control of Puberty and Reproductive Function

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Scientific Program: Nutrition, Endocrine and metabolic diseases.

Keywords: Autophagy, Puberty, Reproduction, Kiss Neurons.

Abstract: Puberty is a key developmental event for humans and other species, when sex maturity and reproductive function are achieved. Puberty is controlled by the hypothalamic-pituitary gonadal (HPG) axis, compounded by three major elements: (i) GnRH neurons, producing gonadotropin-releasing hormone, (ii) gonadotroph cells, that secrete LH and FSH, and (iii) gonads, that release steroidal and peptide hormones. A major regulator of GnRH neurons are kisspeptins, a family of proteins produced by hypothalamic Kiss1 neurons that, thereby, are master elements in the control of puberty and reproduction. Among its multiple functions, autophagy, a major intracellular degradation pathway, is gaining attention in the last years, as key mechanism for central energy homeostasis. Autophagy eliminates unfolded/misfolded proteins and other dysfunctional cellular elements, allowing the recycling of numerous cell components. Autophagy is closely linked to endoplasmic reticulum (ER) stress responses, so that defective autophagy may severely perturb cellular homeostasis and function.

Departing from our recent evidence suggesting a role of hypothalamic ER stress in the control of puberty, in this study we aimed to address the role of hypothalamic autophagy in the physiological regulation of puberty and reproduction, with particular emphasis on its pathophysiological contribution in mediating the impact of obesity and its function in Kiss1 neurons. Our initial data showed an increase in the expression of the gene encoding the autophagy-related factor, Atg7, in the hypothalamus during the infantile-to-juvenile transition, while it trends to decline at puberty. In addition, hypothalamic expression of Atg-7, but not Atg-12, mRNA was suppressed in female rats suffering early obesity and advanced puberty. We are currently generating a novel mouse line with conditional ablation of Atg7 in Kiss1 neurons, as model to address the putative role of autophagic processes in Kiss1 neurons in the regulation of puberty and fertility, and their modulation by obesogenic insults.

PSII.cc. Relation between Helicobacter spp. isolated in bile and biliary tract malignancies.

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Scientific Program: Cancer II.

Keywords: Pancreatic cancer, Helicobacter, cholangiocarcinoma.

Abstract: The increased incidence of neoplastic lesions of the biliary tract, as well as their high mortality, require measures to detect factors associated with their development. Helicobacter spp. has been related to this type of cancer, however, there are big differences in the results, depending on geographic factors and the methods used for the detection. Demonstrating the association of Helicobacter spp. in bile would increase our knowledge of these malignancies and their prevention.

Objectives: To compare the proportion of Helicobacter spp. in bile of patients with malignant or benign biliary obstruction. To describe the baseline characteristics, laboratory values, and comorbidities of these patients, as well as characteristics related to ERCP or PTC procedures and their complications.

Methods: Cases and controls prospective study. We included 125 patients between April 2019 and January 2021, who underwent a bile drainage procedure by ERCP or PTC. Helicobacter spp. detection was carried out by polymerase chain reaction. Demographic data variables, comorbidities, hospital stay and related to drainage procedure were collected. Descriptive statistical calculation of the variables of interest, differentiating between the presence of malignancy or not was performed. We analyzed the data with SPSS using Chi-square test for qualitative variables and Mann-Whitney test.

Results: We studied 72 men and 53 women, who underwent PTC 12% (15), ERCP 88% (110) due to biliary obstruction. Average age 72.5 (28-94) years. Average time from diagnosis to admission 21 days (SD 5). Mean hospital stay 7.7 days (SD 6.7). Cause of biliary obstruction: 50.2% (74) choledocholithiasis, 35.2% (44) malignant obstruction (40.5% (17) pancreatic cancer, 33.3% (14) cholangiocarcinoma, 7.1% (3) ampuloma, 19.1% (8) malignant extrinsic compression of other origin), 4.8% (6) benign stenosis, 0.8%(1) biliary fistula. Previous ERCP 20.8%(26). Previous biliary stent 13.6% (17) and 40% (50) required biliary stent for the first time. Post-procedure complications 4%(5): 0.8% (1)pancreatitis, 2.4% (3) hemorrhage and 0.8% (1) other complication. Global detection of Helicobacter spp. in bile samples 13.6%. Helicobacter was isolated in 17.7% (3) of the malignant lesions. No association between Helicobacter in bile and neoplasia was found (16.9% vs 7.1%, P=0.1). None of the PTC bile samples were positive to Helicobacter spp.

Statistically significant association was found between neoplasia and alcohol misuse (7.2% vs 19%, p=0.048), death during admission (2.4% vs 14.3%, p=0.01), hospital stay (5 vs 13 days, p=0.0001), absence of cholecystectomy (65.1 vs 95.2, p = 0.0001), age (72.2 vs 71.5, p=0.0001), prothrombin activity value (86% vs 76%, p = 0.0001) and bilirubin value(2 vs 9.7mg/dL, p = 0.0001).

Conclusions: No association was found between Helicobacter spp and bile tract malignancies.

A significant percentage of Helicobacter spp was detected in ERCP bile samples whereas none was detected in PTC bile samples, although the small sample size could be related to this finding. Statistic association was found between neoplasia and higher bilirrubin value, decreased prothrombin activity, as well as being related to the absence of cholecystectomy, alcohol misuse, death during admission and longer hospital stay.

BOOK OF ABSTRACTS

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