BOOK OF ABSTRACTS

13 th IMIBIC YOUNG INVESTIGATORS MEETING

IMIBIC
INSTITUTO MAIMÓNIDES DE INVESTIGACIÓN BIOMÉDICA DE CÓRDOBA

UNIVERSIDAD D CÓRDOBA

Junta de Andalucía

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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 (13th OCT)

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

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

09:30 – 11:00 – SESSION I. Cancer I (IMIBIC Assembly Hall)

Chairs: **Dr. Ana Gordon & Dr. David García.**

Ia. 09:30 – 09:45 Tumor suppressor role of RBM22 in prostate cancer acting as a dual-factor regulating alternative splicing and transcription of key oncogenic genes. **Antonio Jesús Montero Hidalgo.**

Ib. 09:45 – 10:00 Adoptive transfer of human allogeneic Natural Killer cells for the improvement of anti-EGFR therapy in colorectal cancer: a preclinical study. **Carmen Navarrete Sirvent.**

Ic. 10:00 – 10:15 Left Atrial Strain Assessment in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. **Consuelo Fernández-Avilés Irache.**

Id. 10:15 – 10:30 Laparoscopic Versus Open Primary Interval Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Peritoneal Carcinomatosis from Epithelial Advanced Ovarian Cancer: a comparative study. **Manuel Durán Martínez.**

Ie. 10:30 – 10:45 Proteomic dysregulation of splicing machinery is associated to aggressive hepatocellular carcinoma. **Natalia Hermán-Sánchez.**

If. 10:45 – 11:00 Revealing DYRK2 as a new regulator of the key MAPK pathway and its implications in colorectal and breast cancer. **Lucía Suanes Cobos.**

11:00 – 11:30 – Coffee Break (IMIBIC Cafeteria)

11:30 – 12:45 – SESSION II. Multidisciplinary I (IMIBIC Assembly Hall)

Chairs: **Dr. Pedro Jesús Gómez & Dr. Antonio Romero.**

IIa. 11:30 – 11:45 Impact of KPC-producing Klebsiella pneumoniae relative bacterial load on all-site infection and all-cause mortality in patients with intestinal colonization: a prospective cohort study. **Alejandra Méndez Natera.**

IIb. 11:45 – 12:00 A pain-free home-based exercise program reduced kidney disease progression respect to the usual care in patients with claudication: an observational study. **Anna Crepaldi.**

IIc. 12:00 – 12:15 SARS-CoV-2's accessory proteins role in endothelial dysfunction. **Antonio Romero Guillén.**

IId. 12:15 – 12:30 Non-sense mediated decay as a potential source of biomarkers in chronic liver disease. **Betsaida Ojeda Pérez**.

IIe. 12:30 – 12:45 Characterization of extra-musculoskeletal manifestations and their influence on the phenotype of spondyloarthritis. Data from REGISPONSER registry. **Ignacio Gómez García.**

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

Chairs: **Dr. María Soledad Avendaño, Dr. Mario Frías & Dr. Alexander Batista**

PSI.a. Analysis of the contribution of p53 in the metabolic regulation of Kiss1 neurons at female puberty. **Silvia Daza Dueñas.**

PSI.b. Role of NADH-cytochrome b5 reductase 3 in acute kidney injury associated to massive intravascular hemolysis. **Cristina García Caballero.**

PSI.c. Quantification tool of intestinal microbiota for the prediction of developing diabetes mellitus type 2. **Javier Arenas Montes.**

PSI.d. Ecological and clinical impact of an antimicrobial stewardship program on the incidence of carbapenem resistant Klebsiella pneumoniae. **Teresa López-Viñau López.**

PSI.e. ZIF-8 nanoparticles incorporated in kidneys scaffolds: A novel approach in the uremic toxins depuration. **Victoria Pulido Escribano.**

PSI.f. Determining the Difficulties of Students with Dyslexia via Virtual Reality and Artificial Intelligence: An Exploratory Analysis. **José Manuel Alcalde Llergo.**

PSI.g. Lumbopelvic rhythm in patients with acute low back pain compared with axial spondyloarthritis and healthy subjects. **Sandra Alcaraz Clariana.**

PSI.h. Design of novel mRNA vaccine candidates for induction of antibodies, TCD4+ and TCD8+ cell responses. **Amina Aldebis Moreno.**

PSI.i. Inflammatory cytokines: definition of normal values in healthy population. **Paula Álvarez Romero.**

PSI.j. Real-life validation of prognostic risk stratification according to ELN 2017 in AML patients. **Clara Aparicio Pérez.**

PSI.k. The impact of expanding hepatocellular carcinoma as an indication for liver transplantation on the waiting list length and composition. **Ana Aparicio Serrano**.

PSI.l. Analysis of the hypothalamic expression of the Prader-Willi Syndrome-related genes Magel2 and Ndn and their predicted microRNAs throughout pubertal development in lean and obese female rats. **Álvaro Aranda Torrecillas.**

PSI.m The experience of childbirth and the subsequent appearance of a mental disorder. **Irene Cabedo Olaya.**

PSI.n. Early and late intestinal complications after combined pancreas-kidney transplantation. **Rafael Calleja Lozano.**

PSI.ñ. Pillar pain as a complication of carpal tunnel syndrome surgery. **Irene Calzado Álvarez de Lara.**

PSI.o. Study of cyclic hypoxia, agitation and differential glucose supply in adipogenic differentiation. **Marta Camacho Cardeñosa.**

PSI.p. Monitoring disease evolution and treatment response in pancreatic cancer patients using liquid biopsy-based epigenetic biomarkers. **Pablo Francisco Cano Ramírez.**

PSI.q. Identification of novel molecular signatures associated with the therapeutic response to DMARDs and TNFi therapies in Rheumatoid Arthritis patients through high throughput proteomics. **Tomás Cerdó Ráez.**

PSI.r. Prevalence and risk factors for peripheral artery disease in a population with coronary heart disease: from the cordioprev study. **Maria del Pilar Coronado Carvajal.**

PSI.s. High throughput transcriptomic analysis of peripheral mononuclear cells identifies molecular alterations associated with the active clinical phenotype of Axial Spondyloarthritis. **Laura Cuesta López.**

PSI.t. Potential anti-proliferative role of the Liver Enriched Antimicrobial Peptide 2 (LEAP2), a new component of the ghrelin system, in prostate cancer cells. **Isidoro Di Caro.**

PSI.u. Aortic valve infiltrating pro-inflammatory cells in aortic stenosis patients. **Jose Joaquín Dominguez del Castillo.**

PSI.v. Evaluation of the performance of artificial intelligence (AI) after one year of use in breast cancer screening practice. **Esperanza Elías Cabot.**

PSI.w. Computer-assisted navigated piezoelectric resection and CAD-CAM designed PEEK prosthesis for the surgical resection of tumors affecting facial bones. A synergy of new technologies to improve the surgical results. **Orlando Estevez Cordero.**

PSI.x. The impact of Robot-assisted and Virtual Reality-based Neuromotor Rehabilitation on Health-related Quality of Life: A Systematic Review and Meta-Analysis. **Naima Z. Farhane Medina.**

PSI.y. Surgical treatment of cervicomediastinal goiter: Experience at a single centre. **Alba María Fernández González.**

PSI.z. Threshold concepts applied to oncological surgical pathology. Preliminary results. **María José Gálvez Medina.**

PSI.aa. Splicing machinery dysregulation as a source of novel diagnostic, prognostic and therapeutic targets in craniopharyngiomas. **Miguel Eduardo García García.**

PSI.bb. Loss of metabolic health in normal-weight individuals: Identification of visceral adipose tissue biomarkers. **Olga García Ruiz.**

PSI.cc. Analyzing the molecular mechanisms underlying the resistance to somatostatin analogues in Pheochromocytomas and Paragangliomas. **Víctor García Vioque.**

PSI.dd. GSK-3β is a regulatory kinase of colorectal cancer immune microenvironment and the response to immunotherapy. **Aurora Rivas Crespo.**

PSI.ee. Immunotherapy followed by Cell Therapy in relapsed/refractory acute B cell lymphoblastic leukemia. **Ana Camila Gonzalez Teomiro.**

PSI.ff. Management and knowledge of soft tissue tumors / sarcoma: Update of primary care physicians. **Raquel Gracia Rodríguez.**

PSI.gg. SPARCC, MASES, LEI and MEI Indexes capture different patients with enthesitis in Axial Spondyloarthritis, Peripheral Spondyloarthritis and Psoriatic Arthritis. **Raquel Ena María Granados.**

PSI.hh. DNA Repair profile and temozolomide resistance in glioblastoma cells. **Inés Grávalos Cano.**

PSI.ii. Obesity induces central hypogonadism and metabolic comorbidities via miRNA-137/325 mediated repression of hypothalamic kisspeptin. **Yolanda Guerrero Ruiz.**

PSI.jj. Mindfulness-based Interventions in Adolescents with Type 1 Diabetes Mellitus: A Systematic Review. **Tamara Gutiérrez Domingo.**

PSI.kk. Functional Changes of CD4 and CD8 T-Cell Subsets with Age and CMV Infection. **Fakhri Hassouneh.**

PSI.ll. Validity of the isometric contraction test for the diagnosis of muscle temporomandibular disorders, with DC/TMD axis I as gold standard. **Marcos Iglesias Peón.**

PSI.mm. Upper limb muscle mechanical characteristics in women with multiple sclerosis: a case-control study. **Carmen Jurado Lora.**

PSI.nn. Change in miRNA expression is induced by healthy diets and associated to the carotid intima-media thickness in patients with coronary heart disease: CORDIOPREV study. **Yelizaveta Krylova.**

PSI.ññ. COPD in Severe Mental Illness: A three years longitudinal study. **David Laguna Muñoz.**

PSI.oo. The effect of FGF23 blockade on blood pressure control in hypertension. **Rodrigo López Baltanás**

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

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

Chairs: **Dr. María Isabel Martínez & Dr. Iván Arias**

IIIa. 15:45 – 16:00 Dysregulation of splicing machinery as early biomarker of diabetic nephropathy: From the CORDIOPREV study. **Alicia Podadera Herreros.**

IIIb. 16:00 – 16:15 Molecular and clinical implications of somatostatin receptor profile and somatostatin analogues treatment in high-grade astrocytomas. **Ana de la Salud De la Rosa Herencia.**

IIIc. 16:15 – 16:30 Role of Let-7b-5p and miR-191-5p in the development of early obesity and associated metabolic comorbidities. **Carmen Torres Granados.**

IIId. 16:30 – 16:45 Basketball exercise reduced plasma cytokines in prepubertal children. Bipic-study. **Cristina Castro Collado.**

IIIe. 16:45 – 17:00 Lessons from lean but metabolically unhealthy individuals: new highlights on adipose tissue dysfunction. **Elena Garrido Rascón.**

IIIf. 17:00 – 17:15 E-ducass Project: Educational strategy to improve cardiovascular health and food insecurity on a vulnerable population. **Esther Porras Pérez.**

17:15 – 18:30 – SESSION IV. Multidisciplinary II (IMIBIC Assembly Hall)

Chairs: **Dr. María Dolores Carmona & Dr. André Sarmento**

IVa. 17:15 – 17:30 MicroRNAs in lung epithelial cells expressing SARS-CoV-2 accessory protein ORF8 can regulate immunometabolism. **José Manuel Suárez Cárdenas.**

IVb. 17:30 – 17:45 Integrated high-throughput proteomics and machine learning analysis in systemic lupus erythematosus patients identify distinctive clinical profiles and novel biomarkers related to cardiovascular risk and lupus nephropathy. **Ismael Sánchez Pareja.**

IVc. 17:45 – 18:00 CMV in aortic stenosis. **Pablo Álvarez Heredia.**

IVd. 18:00 – 18:15 Effect of SARS-CoV-2 ORF7a on lung epithelial cells studying the microRNA and proteomic profiles. **Raúl Fernández Rodríguez.**

IVe. 18:15 – 18:30 Impact of ceftazidime-avibactam on clinical outcome in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing Klebsiella pneumoniae (INCREMENT-SOT Project). **Víctor Gálvez Soto.**

Day 2 (14th OCT)

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

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

Chairs: **Dr. Rafael González & Dr. Yolanda Jiménez**

Va. 08:30 – 08:45 Mutational and phenotypic clonal evolution in relapsed-refractory acute myeloblastic leukemia. **Esther Prados De la Torre.**

Vb. 08:45 – 09:00 Orphan base specificity of abasic sites processing during DNA Base Excision Repair. **Marina Jordano Raya**.

Vc. 09:00 – 09:15 Splicing factor SRSF6 as a novel therapeutic target for advanced prostate cancer. **Jesús Miguel Pérez Gómez.**

Vd. 09:15 – 09:30 Breaking the mucin barrier: Discovering and testing new therapeutic targets in Pseudomyxoma peritonei. **María Carmen Vázquez Borrego.**

Ve. 09:30 – 09:45 Exploring the potential therapeutic role of somatostatin/cortistatin endocrine system in prostate cancer. **Prudencio Sáez Martínez.**

Vf. 09:45 – 10:00 Alteration in RNA metabolism unveils new therapeutic opportunities in pancreatic adenocarcinoma. **Ricardo Blázquez Encinas-Rey.**

10:00 – 10:30 – Coffee Break (IMIBIC Cafeteria)

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

Chairs: **Dr. María Soledad Avendaño, Dr. Mario Frías & Dr. Alexander Batista**

PSII.a. Severe aortic stenosis, long-term survival analysis in patients treated with self-expandable prosthesis and surgery. **María Teresa Conejero Jurado**.

PSII.b. Proliferative T-cell response against SARS-CoV-2 in convalescent COVID-19 infected patients. **Raquel Fernández Moreno.**

PSII.c. Dysregulation and functional relevance of the RNA-exosome machinery in hepatocellular carcinoma. **Samanta Lozano de la Haba.**

PSII.d. High Phosphate intake promotes renal and cardiac fibrosis during chronic kidney disease. **Teresa Obrero Sojo.**

PSII.e. Impact of pulmonary artery pressure on early outcomes and survival after lung transplantation in patients with chronic obstructive pulmonary disease. **Eloísa Ruiz López.**

PSII.f. Association between Fibroblast Growth Factor 23 and pulse pressure in Chronic Kidney Disease Stage G5 patients. **Isabel López López.**

PSII.g. Quality of child development scales. A systematic review**. Sara María Luque de Dios.**

PSII.h. Novel insights to understand the potential of the somatostatin/cortistatin system in neuroendocrine tumors (NETs) and carcinomas (NECs). **Federica Mangili.**

PSII.i. Oncometabolic features of GSNOR-deficient colorectal tumors impact immune surveillance and impair response to immunotherapy. **Ana Mantrana Soldado.**

PSII.j. The key role of abnormal fat distribution for prediction metabolic disease. **Laura Martín Piedra.**

PSII.k. Obesity due to a high-fat diet impacts the development and progression of prostate cancer in the TRAMP mouse model. **Fernando Mata Ordóñez.**

PSII.l. Relationship between depression and pathological cognitive dysfunction in older people 65 years old. **María Morales Cabanillas.**

PSII.m. Characterization of the splicing process in pheochromocytomas and paragangliomas. **María Trinidad Moreno Montilla.**

PSII.n. Acute kidney injury associated to intravascular hemolysis increases chronic renal fibrosis. **Jose Luis Morgado Pascual.**

PSII.ñ. Serum magnesium and mortality risk in Chronic Kidney Disease (CKD). An independent effect of nutritional and inflammatory status. **Cayetana Moyano Peregrin.**

PSII.o. Spliceosome alterations in leucocytes from APS, SLE and SLE+APS patients are closely related to their main clinical features. **Laura Muñoz Barrera.**

PSII.p. Resistance to alkylating agents: role of the phosphatase PNKP. **Ariadna Muñoz Fernández.**

PSII.q. Adherence to the Mediterranean diet in childhood at risk of obesity: MELIPOP Study. **Belén Pastor Villaescusa.**

PSII.r. Improvement of left ventricular ejection fraction in patients with heart failure with reduced ejection fraction: mid-term clinical impact. **Jorge Perea Armijo.**

PSII.s. Biomechanical analysis of the voice, characterization method in Amyotrophic Lateral Sclerosis (ALS). **Margarita Pérez Bonilla.**

PSII.t. CYB5R3 overexpression and dietary nicotinamide riboside supplementation influence mitochondrial status: effects in mitochondrial complexes and mitochondrial population ultrastructure of kidney from female and male mice. **Miguel Pérez Rodríguez.**

PSII.u. Identification and characterization of novel positive allosteric modulators for CB1R. **Francisco José Ponce Díaz.**

PSII.v. Phase I/II study of the single-arm efficacy and safety of the use of neutral argon plasma in the cytoreduction of miliary implants on the peritoneal surface. **Alfonso Carlos Pontes García.**

PSII.w. Association between metabolic syndrome and uric acid: a systematic review and meta-analysis. **Elena Raya Cano.**

PSII.x. SARS-CoV-2 infection increases CMV-associated cardiovascular risk. **Ester Irene Reina Alfonso.**

PSII.y. Muscle mechanical properties of pelvic floor and paravertebral muscles, and lumbar range of motion in women with and without urge incontinence urinary: case-control study. **Mª Teresa Garzón Alfaro.**

PSII.z. Evaluation of the in vitro and in silico interaction of a cationic peptide against colistin-resistant P.aeruginosa membrane models. **Sandra Patricia Rivera Sanchez.**

PSII.aa. The novel multiagonist, GLP1-estrogen, improves the management of non-alcoholic fatty liver disease in lean and obese models of polycystic ovary syndrome. **Andrea Rodríguez Martín.**

PSII.bb. Metabolic adaptation of female mice overexpressing CYB5R3 and submitted to a caloric restriction intervention. **Luz Marina Sánchez Mendoza.**

PSII.cc. S-nitrosoglutathione reductase deficiency in colorectal cancer confers metabolic vulnerabilities that can be therapeutically exploited. **María Teresa Sánchez Montero.**

PSII.dd. Anti-glomerular basement membrane glomerulonephritis. A study in real life. **Marina Sánchez-Agesta Martínez.**

PSII.ee. Could the primary cilium predict progression from actinic keratosis to squamous cell carcinoma?. **Alicia Sanz Zorrilla.**

PSII.ff. Comparative Study of a Sjögren's Syndrome Cohort (Primary and Secondary). **José Miguel Sequí Sabater.**

PSII.gg. Analysis of the potential role of hepatic kisspeptin in energy and metabolic homeostasis. **Esperanza Uceda Rodríguez.**

PSII.hh. Oxidative environment and redox homeostasis in a rare malignant disease: Pseudomyxoma Peritonei. **Francisca Valenzuela Molina.**

PSII.ii. Ferroptosis is involved in acute kidney injury associated to massive intravascular hemolysis. **Mercedes Vallejo Mudarra.**

PSII.jj. Prognostic value of RAS mutation status changes in circulating tumor DNA of metastatic colorectal cancer patients. **Alicia Vargas Aliaga.**

PSII.kk. Gut microbial composition as a diagnostic tool for colorectal cancer. **Ana María Vega Rojas.**

PSII.ll. The role of physical activity on psychological well-being in children and adolescent with type 1 diabetes: preliminary data of a cross-sectional study. **Joaquín Villaécija Rodríguez.**

PSII.mm. Adipokines and hepatokines as potential biomarkers of hepatocellular carcinoma. **Javier Manuel Zamora Olaya.**

11:30 – 13:00 – Session VI. Nutrition, Endocrine and metabolic diseases II (IMIBIC Assembly Hall)

Chairs: **Dr. Clementina López & Dr. Cristian Rodelo**

VIa. 11:30 – 11:45 Personalized diagnostic and therapeutic potential of miR-191-5p in the pathophysiological relationship between obesity and prostate cancer. **Francisco Porcel Pastrana.**

VIb. 11:45 – 12:00 The role of intestinal microbiota in the different prevalence of coronary disease between genders. **Helena García Fernández.**

VIc. 12:00 – 12:15 Impaired metabolic and inflammatory profile in adult patients with a history extra-uterine growth restriction. **Laura Palomino Fernández.**

VId. 12:15 – 12:30 Micronutrients and their implications in the incidence of type 2 Diabetes Mellitus. Pieces of evidence from the CORDIOPREV study. **Lorenzo Rivas García.**

VIe. 12:30 – 12:45 Effect of diet on the expression of microRNAs and its relationship with aging in patients with coronary heart disease: CORDIOPREV study. **Maite Sánchez Giraldo.**

VIf. 12:45 – 13:00 Novel multiagonist therapy for efficient management of metabolic complications polycystic ovary syndrome. **Victor Serrano López.**

13:00 – 14:00 – Plenary Lecture: Immunometabolism and Inflammation. Dr. María Mittlebrunn (Centro de Biología Molecular Severo Ochoa, Madrid, Spain)

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

Description of the review process for selecting oral/poster presentations

Authors submitted their works through the Young Investigators abstract submission website from May 13th to June 9th. 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 113 abstracts were received. The Organizing Committee distributed all abstracts received amongst 28 external reviewers in a completely anonymized manner. All reviewers were selected based on their expertise in the scientific areas aligned with the abstracts submitted. The full list of the external reviewers can be found at the beginning of this book. Abstracts were peer-reviewed by the external reviewers, scoring the communications between 1 (very poor) and 5 (very good). It should be noted that the Organization Committee has not evaluated or scored any of the submitted abstracts.

On September 6th, 2022, the Organizing Committee held a meeting to distribute all abstracts evaluated into oral communications or poster presentations based on the scores provided by the external reviewers and the participants preferred presentation choice (oral vs. poster). Thus, oral communications were divided in 6 sessions, while poster presentations were distributed in 2 sessions. Considering the number and scores of oral presentations submitted for each category, the Organizing Committee decided to establish two sessions for Cancer, two sessions for Nutrition, and two Multidisciplinary sessions, 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 6 sessions. These awards will be selected based on the scores derived from the Scientific Committee, which includes 1 translational researcher and coordinator and 4 researchers (1 clinical and 3 translational), and all the chairs of the sessions (12 researchers). The full list of members of the Scientific Committee and chairs can be found at the beginning of this book. The Scientific Committee and chairs will score every presentation from 1 to 5, taking into consideration the following criteria: (i) scientific quality of the work, (ii) presentation skills of the presenter, and (iii) capacity to answer the questions raised by both the audience and chairs. The final score for each presentation will consist of the average of the score obtained by the Scientific Committee and chairs. The score of the external reviewers will only be used in the event of a tie. The six highest scored oral communications will compete for the Best Presentation Award of the Meeting. The best oral communication presented by a Resident Medical Intern will be also awarded by the “Colegio Oficial de Médicos de Córdoba”. To assess the poster presentations, three chairs will visit the 10 highest scored abstracts according to the

external reviewers. They will be scored following the same criteria applied for oral presentations. The highest scored poster per session will be awarded.

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

ORAL COMMUNICATIONS

Abstracts

SESSION I.

CANCER I.

Ia. Tumor suppressor role of RBM22 in prostate cancer acting as a dual-factor regulating alternative splicing and transcription of key oncogenic genes.

Authors: Antonio J. Montero Hidalgo[1,2,3,4], Juan M. Jiménez-Vacas[1,2,3,4], Enrique Gómez Gómez[1,3,5], Prudencio Sáez Martínez[1,2,3,4], Teresa González Serrano[1,3,5], Rafael Sánchez Sánchez[1,3,5], André Sarmento Cabral[1,2,3,4], Justo P. Castaño[1,2,3,4], Manuel D. Gahete[1,2,3,4]; Raúl M. Luque[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 (HURS), 14004 Cordoba, Spain; [4]CIBER Physiopathology of Obesity and Nutrition (CIBERobn), 14004 Cordoba, Spain; [5]Urology Service, HURS/IMIBIC, 14004 Cordoba, Spain; [6]Anatomical Pathology Service, HURS/IMIBIC, 14004 Cordoba, Spain.
Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: RBM22; splicing; prostate cancer; cell-cycle.

Abstract: Prostate cancer (PCa) is one the leading causes of cancer-related deaths among men worldwide, since the current therapeutic opportunities are very limited. Therefore, the identification of novel therapeutic targets is essential to improve patients' outcomes. In this scenario, our group has recently reported that elements of the cellular machinery controlling alternative-splicing might be used as potential novel strategies for PCa treatment; however, the presence and role of the key spliceosome component RBM22 in PCa remains unknown. For that reason, we aimed to evaluate the potential pathophysiological actions of RBM22 in PCa. To that end, RBM22 levels (mRNA and protein) were evaluated in four independent cohorts of patients and two preclinical mouse models (TRAMP and Hi-Myc). The functional (proliferation, migration, tumorsphere- and colony-formation) and molecular (RNA-seq, nCounter PanCancer Pathways) consequences of RBM22 modulation were assessed *in vitro* (using LNCaP, 22Rv1, and PC-3 cells) and *in vivo* (xenograft model). We found that RBM22 is downregulated in PCa samples, and its levels are inversely associated with key clinical aggressiveness features (e.g., extraprostatic extension, perineural invasion). Consistently, a gradual reduction of RBM22 from control to prostatic-intraepithelial neoplasia, and then to poorly differentiated PCa was observed in samples from two transgenic PCa mouse models (TRAMP and Hi-Myc). Notably, overexpression of RBM22 decreased aggressiveness features *in vitro*, and tumor-growth *in vivo* using a preclinical xenograft mouse-model. These actions were associated with the dysregulation of the splicing of numerous genes, alteration of the activity of oncogenic signalling pathways (e.g., cell-cycle progression), and to the downregulation of critical upstream regulators of cell-cycle (i.e., *CDK1*, *CCND1* and *EPAS1*). Altogether, our data demonstrate that RBM22 plays a critical functional role in the pathophysiology of PCa and invites to suggest that targeting negative regulators of RBM22 expression/activity could represent a novel therapeutic strategy to tackle this devastating pathology.

Ib. Adoptive transfer of human allogeneic Natural Killer cells for the improvement of anti-EGFR therapy in colorectal cancer: a preclinical study.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: colorectal cancer; NK cells; *in vivo* model; adoptive cell transfer; cetuximab.

Abstract: Anti-EGFR monoclonal antibodies (mAb) such as cetuximab has improved survival in metastatic colorectal cancer (mCRC) patients, but the prognosis is still very poor. Molecular heterogeneity of CRC and the lack of relevant preclinical models makes difficult to find alternative treatments. The Antibody-Dependent Cell Cytotoxic (ADCC) activity of Natural Killer (NK) cells has demonstrated to be essential in cetuximab anti-tumour activity. Therefore, the main goal of this work was the establishment of a valuable preclinical model for the assessment of the efficacy of human allogeneic NK cell-based adoptive transfer in potentiating anti-EGFR therapy in CRC.

Firstly, human NKs from healthy donors were isolated by magnetic immuno-depletion and their immunophenotype was assessed by flow cytometry. For in vitro activation, NKs were exposed to human IL2 and IL15 during 14 days. Xenografts models were established by subcutaneously injecting EGFR-positive HT29 cells in NSG mice that were randomly divided in three groups: control (HT29), HT29+activated NKs, HT29+cetuximab and HT29+combined treatments (NKs+cetuximab). Mice were euthanised when tumours reached 2,000 mm3 and Tumour-Infiltrating NK cells (TINKs) were isolated and immunophenotyped to evaluate ADCC.

The results indicated that the in vitro activation of NKs up-regulated markers involved in activation, cytotoxicity and immunosurveillance, and potentiated the conversion of CD56Dim NK cells into CD56Bright NK cells which are associated with anti-tumour cytotoxicity. Secondly, tumours treated with NKs plus cetuximab were significantly smaller than the rest of the experimental groups, whereas the immunophenotype of TINKs showed a significantly higher expression of activation markers CD25, CD57, NKp30 and NKp46.

Altogether, our results support that adoptive transfer of allogeneic NK cells may constitute a valuable strategy to improve current anti-EGFR treatments in advanced CRC. Besides, our in vivo preclinical model will be useful to evaluate other NK-based strategies, such as anti-NKG2A mAbs promoting anti-tumour immunity by unleashing NK cells.

Fundings: ISCIII-PI20/00997.

Ic. Left Atrial Strain Assessment in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: cardio-oncology; cardiotoxicity; diastolic dysfunction; left atrial strain; echocardiography; childhood cancer survivors.

Abstract:

Background: Long-term survivors of childhood acute lymphoblastic leukemia (ALL) are susceptible to developing left ventricular systolic dysfunction due to the chemotherapeutic treatments received. Diastolic function may also be compromised, but previous studies showed inconclusive results, which is partly explained by the lack of robust parameters of diastolic function. Left atrial strain (LAS) is a novel echocardiographic measurement that seems to be an early and more reproducible marker of diastolic dysfunction. However, no study to date has evaluated LAS in long-term childhood ALL survivors. **Purpose:** To examine diastolic function, by means of LAS and conventional echocardiographic parameters, in a cohort of long-term childhood ALL survivors. **Methods:** ALL survivors diagnosed before 18 years of age in our center between 1985-2015 and a control group of healthy siblings were recruited. Conventional diastolic function parameters and LAS were compared, the latter measured by a Machine Learning-Enabled Fully Automated Software (AutoStrain, Tomtec) and divided into three phases, according to current recommendations: reservoir (PALS), conduit (LACS) and contraction (PACS). Group differences were accounted with inverse probability of treatment weighting (IPW). Covariates included in the propensity score were sex, age, body mass index, heart rate and diastolic blood pressure. **Results**: 90 survivors (37.8% female, time from diagnosis 18 [11-26] years) and 58 controls were analyzed. PALS and LACS were significantly reduced compared to the control group: 46.4±11.2 vs 52.1±11.7 (p=0.003) and 32.5±8.8 vs 38.2±9.3 (p=0.003), respectively. The differences remained significant in the IPW models. PACS, conventional diastolic parameters (E/A, e', E/e') and LA size were similar between groups. **Conclusion:** In a cohort of long-term childhood ALL survivors, PALS and LACS were reduced compared to a control group despite similar conventional diastolic measurements. Longitudinal data is needed to validate the usefulness of LAS as an early marker of diastolic dysfunction in these patients.

Id. Laparoscopic Versus Open Primary Interval Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Peritoneal Carcinomatosis from Epithelial Advanced Ovarian Cancer: a comparative study.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Ovarian Cancer; Peritoneal Carcinomatosis; Peritonectomy; Interval Cytoreductive Surgery; HIPEC; Laparoscopy.

Abstract:

Background: Ovarian cancer (OC) is the leading cause of gynaecologic cancer death in developed countries. Currently, the standard treatment for advanced OC is the combination of optimal cytoreductive surgery (CRS) followed by platinum and taxol intravenous chemotherapy regimens. Alternative, neoadjuvant chemotherapy prior to interval CRS plus Hyperthermic intraperitoneal chemotherapy (HIPEC) is acceptable and has demonstrated favourable oncologic outcomes. This study aims to compare our experience with the use of laparoscopic interval CRS + HIPEC for patients with advanced epithelial OC. **Material and methods:** A retrospective analysis of a prospectively maintained database was performed. A total of 254 patients with confirmed epithelial ovarian cancer carcinomatosis (FIGO stage IIIC and IV) treated at our institution with CRS + HIPEC between January 2016 and December 2021 were assessed for inclusion. Patients with primary disease and limited carcinomatosis (total PCI ≤ 10) treated by interval CRS + HIPEC by open (O-CRS + HIPEC) or laparoscopic (L-CRS + HIPEC) approach were included in the final analysis. Analysis of overall survival (OS), disease-free survival (DFS), and perioperative outcomes were performed. **Results**: Between January 2016 and December 2021, 53/254 patients were selected for the study. Of these, 14 patients were treated with L-CRS+HIPEC and 39 with O-CRS+HIPEC. Two-years OS was 100% in the L-CRS+HIPEC group and 92% in the O-CRS+HIPEC group (p = 0.96). DFS at one year and two-year was 73% and 50% in the L-CRS+HIPEC group versus 78% and 57% in the O-CRS+HIPEC group, respectively (p = 0.79).The L-CRS+HIPEC group had higher PCI (4.1 ± 1.2 vs 6.3 ± 2.9; p = 0.027) and mean operative time (437.9 ± 83 vs 317.9 ± 60 min; p < 0.001) than the O-CRS+HIPEC group. Patients undergoing L-CRS+HIPEC had a shorter mean length of stay (5.6 ± 1.9 vs 9.7 ± 9.8 days; p < 0.001) and shorter time to re-administration of systemic chemotherapy (4.3 ± 1.9 vs 10.3 ± 16.8 weeks; p = 0.003). **Conclusions**: Treatment of limited ovarian carcinomatosis by interval L-CRS+HIPEC is safe and effective in strictly selected patients, obtaining

oncological and safety results similar to the open approach, with a reduction in hospital stay and time to re-administration of systemic chemotherapy. Randomized trials are needed to evaluate these findings.

Ie. Proteomic dysregulation of splicing machinery is associated to aggressive hepatocellular carcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: hepatocellular carcinoma; proteomics; SNRPD1; LSM2.

Abstract: The genome and transcriptome of hepatocellular carcinoma (HCC) has been widely described. In contrast, the proteome, which reflects the molecular targets with the highest clinical potential, is mostly unknown. Herein, we performed the first quantitative proteomic analysis (SWATH-MS) in a representative, well-characterized cohort of HCC samples. Cytosolic and nuclear proteomes of liver tissues from HCC patients (n=42; HCC vs. adjacent tissue) and healthy controls (n=5) were determined by SWATH-MS. The results were analyzed in IPA, Reactome, Metaboanalyst and GenePattern. In vitro assays (proliferation, migration, colonies/tumorspheres formation) were performed in three liver cancer cell lines (HepG2, Hep3B, SNU-387) after silencing SNRPD1 and LSM2 with specific siRNAs. SWATH-MS proteomics revealed the dysregulation of the cytosolic and nuclear tumor proteomes (n=507 and n=925 proteins, respectively). Interestingly, the proteomic fingerprint defined a subgroup of HCC patients with lower survival and higher recurrence, which was associated to the dysregulation of the splicing machinery. Indeed, the altered proteins in HCC samples were associated, by enrichment analysis, with cellular functions such as mRNA processing. The dysregulation of the splicing machinery was further confirmed in two retrospective cohorts of samples [(HCC vs. adjacent tissues, n=93); (HCC vs. adjacent tissue, n=58; cirrhosis, n=39; healthy, n=5)] and 5 in silico HCC cohorts (mRNA and protein). From the 94 splicing factors identified in the proteomic analysis, 31 were validated in the retrospective and in silico cohorts which were associated to clinically relevant parameters (tumoral diameter, dedifferentiation, survival, recurrence). Based on these results, SNRPD1 and LSM2, two structural spliceosome components, where further analyzed. In vitro silencing of SNRPD1 and LSM2 reduced proliferation and dedifferentiation capacity in liver cancer cell lines. Altogether, this study demonstrates the usefulness of quantitative proteomics for the identification of tumoral subgroups in HCC and the potential of the splicing machinery as a tool for the management of HCC.

If. Revealing DYRK2 as a new regulator of the key MAPK pathway and its implications in colorectal and breast cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: DYRK2, MAPK, B-RAF, MEK1, ERK, Activation, Phosphorylation, Cancer.

Abstract: The MAPK/ERK cell signalling pathway, one of the most active in cancer, is considered key in the control of a variety of biological processes such as cell growth, division and differentiation. This pathway consists in the cascade activation of RAS-RAF-MEK-ERK, which promotes the activation of relevant transcription factors. As a consequence, its hyperactivation is related to proliferation, migration, or metastasis. Despite its relevance, the known modulators of MAPK pathway are insufficient to explain the resistance to targeted-treatment, which makes it necessary to increase our knowledge of this pathway. Here we describe for the first time the Dual specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2) as a new component of the MAPK/ERK pathway, positively regulating the activation through the phosphorylation of its components. First, we show that DYRK2 stabilizes B-RAF protein levels through a post-transcriptional mechanism dependent on DYRK2 kinase activity and independent of the known B-RAF E3 ubiquitin ligase FBXW7. DYRK2 phosphorylates B-RAF and MEK1 directly, resulting in ERK activation and its targets. Functional analyses demonstrated the existence of DYRK2-dependent regulatory mechanisms for key MAPK/ERK cascade targets in several colorectal and breast cancer cell lines (HT29, MDA-MB-468, etc). Additionally, we prove that pharmacological modulation of DYRK2 modifies B-RAF levels and/or pathway activity. Furthermore, DYRK2 is key in controlling the proliferation and migration of colon and breast cancer cell lines with the pathway hyperactivated. In the same sense, MAPK/ERK pathway inactivation with different antitumor treatments promotes DYRK2 stabilization. Overall, these relevant results show DYRK2 as a new key member of the MAPK/ERK pathway and point it as a potential therapeutic target for patients with drug-resistant colorectal and breast cancer.

SESSION II.

MULTIDISCIPLINARY I.

IIa. Impact of KPC-producing Klebsiella pneumoniae relative bacterial load on all-site infection and all-cause mortality in patients with intestinal colonization: a prospective cohort study.

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Scientific Program: Infectious and Immunological diseases.
Keywords: KPC-producing Klebsiella pneumoniae, intestinal bacterial load, clinical Outcome.

Abstract:

Background: Increased relative bacterial load of KPC- producing Klebsiella pneumoniae (KPC-KP) within the intestinal microbiota has been associated with KPC-KP bacteremia. We aimed to study the prognostic significance of bacterial load in patients with intestinal colonization by KPC-KP. **Methods:** Prospective observational study of KPC-KP adult carriers with a hospital admission at recruitment or within the three prior months (January 2018-February 56 2019). A qPCR-based assay was developed to measure the relative load of KPC-KP in rectal swabs (RLKPC, proportion of blaKPC relative to 16S rRNA gene copy number). We generated Fine-Gray competing risk and Cox regression models for survival analysis ofall-site KPC-KP infection and all-cause mortality, respectively, at 90 and 30 days. **Results:** The median RLKPC at baseline among 80 KPC-KP adult carriers was 0.28% (range 0.001%-2.70%). Giannella Risk Score (GRS) was independently associated with 90-day and 30-day all-site infection (adjusted SHR 1.23, 95% CI 1.15-1.32, p<0.001). RLKPC (adjusted HR 1.04, 95% CI 1.01-1.07, p=0.008) and age (aHR 1.05, 95% CI 1.01-1.10, p=0.008) were independent predictors of 90-day all-cause mortality in a Cox model stratified by length of hospital stay (LOHS) ≥20 days. An adjusted Cox model for 30-day all-cause mortality, stratified by LOH ≥14 days, included RLKPC (aHR 1.03, 95% CI 1.00- 1.06, p=0.027), age (aHR 1.10, 95% CI 1.03-1.18, p=0.004), and severe KPC-KP infection (INCREMENT-CPE score >7, HR 2.96, 95% CI 0.97-9.07, p=0.057). **Conclusions:** KPC-KP relative intestinal load was independently associated with allcause mortality in our clinical setting, after adjusting for age and severe KPC-KP infection. Our study confirms the utility of GRS to predict infection risk in patients colonized by KPC-KP.

IIb. A pain-free home-based exercise program reduced kidney disease progression respect to the usual care in patients with claudication: an observational study.

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Scientific Program: Active aging and frailty.
Keywords: exercise; rehabilitation; chronic kidney disease; peripheral artery disease; outcomes.

Abstract:

Aims: This longitudinal observational study aims to monitor at long-term the indexes of kidney function in patients with concomitant chronic kidney disease (CKD) and peripheral artery disease (PAD) when exposed or not to a structured pain-free home-based exercise program. **Methods:** Sixty-six patients at KDOQI stages III or IV and PAD at Rutherford's stage I-III were included in the study within 2011 and 2016. Thirty-two patients received a home-based walking program that encompassed two daily 10-minute interval walking exercise at a weekly increasing speed (Exercise, Ex). The remaining 34 patients underwent usual nephrological care (Control, Co). Primary outcome was kidney function, yearly measured with estimated glomerular filtration rate (eGFR) over 5 years. Secondary outcomes included admission to dialysis, all-cause hospitalizations and PAD-related revascularizations. **Results:** At baseline the two groups were matched for age, nephropathy, diabetes, comorbidities and PAD severity. Patients of Ex group completed the 9-month program successfully without any adverse event. In Ex group, eGFR showed almost stable values (Y0: 29±12; Y1: 29±13; Y2: 26±13; Y3: 25±12; Y4: 26±12; Y5: 28±13 mL/min/1.73m2), whereas a progressive significant decreasing trend was observed for Co group (Y0: 30±11; Y1: 25±11; Y2: 25±13; Y3: 24±12; Y4: 23±10; Y5: 18±10 mL/min/1.73m2; $p<0.001$). The between group overtime analysis showed significant differences after one year ($p=0.015$) and five years ($p=0.017$). Five patients were admitted to dialysis within the follow up; they all belonged to Co group ($p=0.025$). A significant higher risk was also observed for Co group for both all-cause hospitalizations (hazard ratio: 1.69; 95%CI: 1.01-2.86; $p=0.047$) and lower limbs revascularizations (hazard ratio: 3.21; 95%CI: 1.02-5.30; $p=0.046$).**Conclusion:** A home-based low-intensity exercise program was feasible in CKD-PAD patients, slowed down kidney function decline and favored long-term clinical outcomes. These preliminary observations need to be confirmed in properly designed randomized trials.

IIc. SARS-CoV-2's accessory proteins role in endothelial dysfunction.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: COVID-19, endothelial dysfunction, accessory proteins, hypofibrinolysis.

Abstract: Since the start of the ongoing COVID-19 outbreak, it has increasingly been reported the development of thrombotic complications in COVID-19 patients that contribute to the boost of the mortality rate. COVID-19-associated coagulopathies are complex and of unknown origin. We hypothesize that they could be produced either directly through infection of endothelial cells or indirectly as a consequence of inflammatory processes initiated in the alveolar epithelium after infection. In this study, we analyzed the role of SARS-CoV-2 ORF3d, ORF7b, ORF8 and ORF9c accessory proteins in the induction of the endothelial dysfunction. By transducing these proteins into HUVEC cells using a lentivirus vector, we first investigated their potential role in fibrinolytic and coagulation pathways. The direct effect of accessory proteins on endothelial dysfunction was determined by analyzing prothrombotic mediator levels and conducting angiogenic assays. Secondly, we examined the effect of the alveolar epithelium in the initiation of intra-alveolar coagulation and how the accessory proteins affect this process. For this purpose, two different approaches were carried out. In the first, the effect of conditioned medium derived from alveolar epithelial A549 cells expressing accessory proteins on the procoagulant activity of HUVEC cells was studied. In the second, transduced A549 cells and HUVEC cells were co-cultured in a transwell system. Our results demonstrate (1) that ORF3d, ORF7b and ORF9c could be directly related to the endothelial dysfunction by promoting the overexpression of F3 and SERPINB2 genes in HUVEC cells, as well as inducing angiogenic alterations, and (2) that ORF8 induces the overexpression of VWF, ANGPT2 and SERPINE1 genes in HUVEC cells co-cultured with A549 cells which could contribute to the creation of a procoagulant antifibrinolytic environment in the alveolar compartment. These results may shed light in the understanding of COVID-19's coagulopathies and help in the development of more efficient therapeutic strategies.

IId. Non-sense mediated decay as a potential source of biomarkers in chronic liver disease.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: NMD, NASH, alternative splicing, hepatocarcinoma, SMG7, SMG8.

Abstract: Non-sense mediated decay (NMD) machinery is involved in the control of gene expression by eliminating aberrantly produced and/or incorrectly spliced mRNAs. Indeed, NMD and splicing machineries share common components. Scattered works suggest dysregulations of these cellular machineries in chronic liver disease (CLD), including non-alcoholic fatty liver disease, non-alcoholic steatohepatitis (NASH) and hepatocarcinoma (HCC). This study focuses on discovering NMD machinery alterations in chronic liver disease to find new potential biomarkers and/or therapeutic targets. Expression (mRNA) of 22 NMD components and their correlation with splicing factors and variants were analyzed in a retrospective HCC cohort [n=89 HCC and non-tumor adjacent tissues (NTAT)] by microfluidic-based qPCR array and validated in five in silico cohorts with healthy, NASH, cirrhotic, HCC, and/or NTAT samples (TCGA, Roessler 2, Zhou liver, Wurmbach, and GSE164760). Prognostic potential of NMD components was interrogated in the Human Protein Atlas. MetaboAnalyst was used to obtain VIP scores. The expression of at least 45% of NMD components was altered and associated with unfavorable prognosis in HCC samples, including RBM8, SMG8, or PABPC1. RBM8 and SMG7 also exhibited higher expression in NASH and NASH-derived HCC samples compared to healthy livers. Remarkably, SMG7 and SMG8 were consistently overexpressed in all HCC cohorts (top-10 VIP scores in all cases). Additionally, the expression of several NMD components, including SMG7 and SMG8, was correlated with that of key splicing factors and/or splicing variants (RBM39, HNRPL, SNRPF, or CD44V6) in the retrospective HCC cohort. In conclusion, NMD machinery is dysregulated in CLD and could serve to improve the diagnosis, prognosis, or treatment of these patients. Particularly, SMG7 and RBM8 are elevated in the early phases of CLD, and could be useful in early diagnosis, while SMG7 and SMG8 could represent new potential targets in HCC.

IIe. Characterization of extra-musculoskeletal manifestations and their influence on the phenotype of spondyloarthritis. Data from REGISPONSER registry.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Spondyloarthritis, uveitis, psoriasis.

Abstract:

Objectives: To describe the time of onset of acute anterior uveitis (AAU) and psoriasis relative to the appearance of rheumatic symptoms and to determine the association with a clinical phenotype and a rheumatologist's diagnosis in patients with Spondyloarthritis (SpA). **Methods:** This was a cross-sectional study with data extracted from the REGISPONSER (Spondyloarthritis Registry of the Spanish Rheumatology Society) registry. All patients had data available for AAU, psoriasis and SpA dates of onset. Patients were classified into two groups depending on the time of appearance of AAU and psoriasis: before rheumatic symptoms or after rheumatic symptoms. The clinical characteristics, disease activity, radiographic damage and treatments were compared between the two groups. Moreover, the rheumatologists' diagnoses were compared between the two groups. Univariate and multivariate logistic regressions were conducted to evaluate the factors associated with each group. **Results:** A total of 379 (16.2%) and 433 (18.3%) of 2367 patients had at least one episode of AUU and psoriasis, respectively. Patients with AAU before rheumatic symptom onset had better function, less structural damage, older at SpA symptom onset and had a shorter diagnosis delay than patients with AAU after rheumatic symptom onset. Patients with psoriasis before rheumatic symptoms had a shorter disease duration and a lower body mass index, a lower prevalence of both HLA-B27 antigens and AAU, a higher prevalence of dactylitis and an increase in levels of the erythrocyte sedimentation rate (ESR). Furthermore, a higher prevalence of psoriatic arthritis (PsA) diagnoses (78.1% vs. 56.4%) and a more frequent fulfilment of the CASPAR criteria (57.5% vs. 42.2%) were found in these patients vs. those with psoriasis after rheumatic symptoms. **Conclusion:** The presence of psoriasis before rheumatic symptoms could determine a clinical phenotype and a more frequent diagnosis of PsA by rheumatologists, while the presence of AAU is associated with a less severe SpA.

POSTER SESSION I.

PSI.a. Analysis of the contribution of p53 in the metabolic regulation of Kiss1 neurons at female puberty.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Puberty; p53; Kiss1 neurons; pifithrin-α p-nitro; virogenetic overexpression; KipKO.

Abstract: Puberty is a fundamental developmental event in the lifespan of any individual, which is determinant to achieve reproductive capacity in adulthood. This process is controlled by Kiss1 neurons at the hypothalamic arcuate nucleus (ARC), as a key regulatory element of the hypothalamic-pituitary-gonadal axis. Currently, there are numerous unknowns about the molecular regulation of puberty; yet, the worrying trends of advanced puberty, especially in girls, urges for action, since alterations in the timing of puberty can entail serious health consequences later in life. The tumor suppressor p53, recently recognized also for its metabolic function, has been suggested as one of the main regulatory components of a gene network whose hypothalamic expression increases during puberty. Notwithstanding, the functional role of p53 in pubertal control and its metabolic regulation remains unexplored. Here, we define hypothalamic expression profiles of p53 (acetylated and phosphorylated isoforms) during postnatal/pubertal maturation in female rats, including changes that occur under conditions of early-onset undernutrition and obesity. Furthermore, we have performed two different in vivo approaches in female rats: 1) inhibition of p53 by intracerebroventricular treatment with pifithrin-α p-nitro, and 2) virogenetic p53 over-expression in the ARC. Finally, to reveal the possible action of p53 directly on Kiss1 neurons, conditional ablation of p53 in cells that are expressing Cre-recombinase under the Kiss1 promotor was implemented in mice. Our results showed that hypothalamic expression of p53 isoforms is nutritional- and developmentally regulated and may be relevant for the control of pubertal onset. Both pharmacological inhibition in rats and Kiss1 cell-specific p53 KO (KipKO) mice showed that the absence of p53 causes a moderate delay in phenotypic features of female puberty. In contrast, p53 over-expression resulted in a tendency of an earlier puberty onset. Overall, we suggest that p53 has functions related with the control of puberty, possibly acting on Kiss1 neurons.

PSI.b. Role of NADH-cytochrome b5 reductase 3 in acute kidney injury associated to massive intravascular hemolysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: CYB5R3, AKI, intravascular hemolysis, oxidative stress.

Abstract: Severe intravascular hemolysis is a typical feature of several hematological diseases and surgical procedures. In this pathological context, hemoglobin (Hb) and its heme-derivates are released to plasma and then accumulated in the kidney, inducing renal toxicity. Renal cell exposure to Hb and heme promote oxidative stress, inflammation and cell death, leading to acute renal injury (AKI). The flavoenzyme NADH-cytochrome b5 reductase 3 (CYB5R3) catalyzes the oxidation of NADH to NAD+, thus protecting against oxidative stress. Transgenic mice overexpressing CYB5R3 showed improvement of mitochondrial function, with reduced oxidative stress and inflammation. However, no previous studies have analyzed the role of CYB5R3 in AKI associated to intravascular hemolysis. We performed an experimental model of massive intravascular hemolysis by intraperitoneal injection of phenylhydrazine (150 mg/kg) in transgenic mice that overexpress the CYB5R3 enzyme (CYB5R3-Tg) and wild type control mice. We euthanized the animals 72 hours after induction of hemolysis and collected serum, urine, and renal samples. We determined renal function as well as oxidative stress, inflammation and markers of tubular and podocyte damage in the kidney. Our results showed that induction of hemolysis altered renal function, as demonstrated by increased creatinine and BUN serum levels, and promoted morphological changes in the kidney, mainly in the proximal tubular epithelium, a pathological effect that was confirmed by the enhanced expression of the tubular injury marker (NGAL). However, the magnitude of these pathological effects was lower in CYB5R3-Tg mice as compared to wild type mice. We also observed higher oxidative stress (HO-1, Ferritin), lipid peroxidation (MDA) and inflammation (IL-6, CCL2) in the kidneys from mice with intravascular hemolysis, although this effect was lower in CYB5R3-Tg mice as compared with wild type mice. Podocytes were also identified as potential cellular targets of Hb-mediated harmful effects in the kidney, as demonstrated by decreased expression of synaptopodin and nephrin, two functional proteins of the glomerular filtration barrier. Interestingly, hemolysis-mediated decrease of these proteins was lower in CYB5R3-Tg than in control mice. In conclusion, our results suggest that CYB5R3 may play a potential protective role against Hb-mediated harmful effects in intravascular hemolysis associated-AKI.

PSI.c. Quantification tool of intestinal microbiota for the prediction of developing diabetes mellitus type 2.

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

Abstract: The simultaneous presence of cardiovascular disease and diabetes mellitus type 2 considerably increases the risk of macrovascular complications and mortality. Thus, is especially important to develop strategies for the prevention of the apparition of DM2 in patients with cardiovascular disease (CVD). In a previous study, we developed a predictive model combining the basal microbiome with clinical biomarkers. We aim to develop prediction tools for DM2 for its clinical use based on determining a reduced number of bacterial taxa by qPCR. This study includes all patients of the CORDIOPREV study without DM2 at the beginning of the study (n=462); 107 of them developed DM2 after a follow-up of 60 months. The intestinal microbiota composition was analyzed by specific oligonucleotides designed for the ten bacterial taxa mainly present in the prediction of DM2. The designed oligonucleotides for the ten most important bacteria of the model showed specificity and efficiency of amplification nearly to 100 %. The quantification carried out with these oligonucleotides showed a differential profile of intestinal microbiota associated with to development of DM2. Our results suggest that it is possible to predict the development of DM2 in patients with CVD through a platform applicable to clinical practice. The identification of patients with CVD with a risk of DM2 allows treating more efficiently those patients. It means a decrease in cardiovascular risk.

PSI.d. Ecological and clinical impact of an antimicrobial stewardship program on the incidence of carbapenem resistant Klebsiella pneumoniae.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: antimicrobial stewardship program; carbapenems; antimicrobial resistance; carbapenem-resistant Klebsiella pneumoniae; carbapenemases.

Abstract: Carbapenem-resistant Enterobacteriaceae are a critical public health threat, and carbapenem use contributes to their spread. In 2012, an outbreak of carbapenemase KPC-producing Klebsiella pneumoniae (KPC-Kp) was reported in Reina Sofia University Hospital (HURS) following the transfer of an infected patient from an Italian hospital, causing a mortality rate of 30%. To combat this problem, an antimicrobial stewardship program (ASP) was implemented in 2014, which achieved a substantial reduction in carbapenem consumption and the incidence density (ID) of KPC-kp isolates two years after starting the program (López-Viñau T, et al. doi: 10.3390/antibiotics10050586).The aim to this study is to assess whether this reduction in KPC-kp isolates was indeed associated with a decrease in KPC-kp infections and associated mortality.

A quasi-experimental study was conducted in HURS one year before (January 2013- January 2014) and two years after (February 2014- February 2016) the implementation of an ASP aimed at hospitalised adult patients treated with carbapenems. We assessed monthly ID of KPC-kp isolates and 30-day crude death rate associated per 1000 occupied-bed days. The clinical category was classified according to the EUCAST breakpoints. Joinpoint regression analysis was used to model trends over time and identify the estimated location of any significant change in the slope of a trend line (Joinpoint Regression Program, version 4.9.1.0). A two-sided p-value of <0.05 was considered significant. Infection control indicator trends remained steady during study period. A substantial reduction in KPC-kp ID was observed during post-intervention period, with a monthly change in slope of −2.9% (95% CI, −4.5 −1.3, p=0.01). The crude death rate of KPC-kp infections also showed a significant reduction after the intervention, with a monthly change in slope of −5.1% (95% CI, −8.5 −1.7, p=0.005). The implementation of this ASP contributed to decreasing the DI of KPC-kp infections and the associated mortality.

PSI.e. ZIF-8 nanoparticles incorporated in kidneys scaffolds: A novel approach in the uremic toxins depuration.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Metal-organic frameworks; uremic toxins; chronic kidney disease; kidney scaffolds.

Abstract: Metal-organic frameworks (MOFs) are a new type of porous crystalline materials consisting of polydentate organic ligands attached to metal ions that conform a highly porous network. Their high porosity gives them a great potential for its application in adsorptive purification. Recent studies have shown that MOFs offer higher uremic toxins efficiency removal than adsorbents commonly used in the treatment of uremia. Therefore, we proposed to investigate the potential of nanosized MOFs to remove uremic toxins such as p-cresol (PC) and indoxyl-sulfate (IS). We used Zeolitic-imidazolate Framework-8 (ZIF-8) MOFs that were synthesized at nanoscale (nanoZIF-8) and stabilized with a polymer to confer them biocompatibility. The adsorption efficiency was evaluated by incubating nanoZIF-8 with solutions of PC and IS under static conditions. Furthermore, nanoZIF-8 were immobilized on biological kidney scaffold which were also perfused with the toxins solutions for 24 h at a flow rate of 12 also ml/h in a closed-loop bioreactor. The levels of uremic toxins were quantified by reversed-phase liquid chromatography coupled to a diode array detector (RP-HPLCDAD). The results showed that under static conditions, nanoZIF-8 achieved a removal efficiency of 87.5 % for PC and 66 % for IS. Under flow conditions and with nanoZIF-8 retained in a kidney scaffold, a significant decrease in the concentration of toxins in the perfusate was observed. The removal efficiency was 76 % for PC and 34 % for IS. Moreover, reusability studies displayed that the adsorptive efficiency persisted after up to 3 reuses, with a decrease in efficiency of less than 30% on the third reuse. In conclusion, nanoZIF-8 designed show a high efficiency in the removal of several uremic toxins. In addition, it has been achieved the immobilization of these nanoparticles in kidney scaffold maintaining their adsorption capacity under flow conditions. These promising results support their potential to be implemented in extrarenal depuration techniques.

PSI.f. Determining the Difficulties of Students with Dyslexia via Virtual Reality and Artificial Intelligence: An Exploratory Analysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Inclusiveness, Machine Learning, Reading Disorder, Learning Difficulty, Virtual Reality.

Abstract: Learning disorders are neurological conditions that affect the brain's ability to interconnect communication areas. Dyslexic students experience problems with reading, memorizing, and exposing concepts; however the magnitude of these can be mitigated through both therapies and the creation of compensatory mechanisms. Several efforts have been made to mitigate these issues, leading to the creation of digital resources for students with specific learning disorders attending primary and secondary education levels. Conversely, a standard approach is still missed in higher education. The VRAIlexia project has been created to tackle this issue by proposing two different tools: a mobile application integrating virtual reality (VR) to collect data quickly and easily, and an artificial intelligence-based software (AI) to analyze the collected data for customizing the supporting methodology for each student. The first one has been created and is being distributed among dyslexic students in Higher Education Institutions, for the conduction of specific psychological and psychometric tests. The second tool applies specific artificial intelligence algorithms to the data gathered via the application and other surveys. These AI techniques have allowed us to identify the most relevant difficulties faced by the students' cohort.

PSI.g. Lumbopelvic rhythm in patients with acute low back pain compared with axial spondyloarthritis and healthy subjects.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Lumbopelvic rhythm, Low back pain, Lumbar spine, Pelvis, Lordosis, axSpA.

Abstract: Low back pain (LBP) is one of the most common musculoskeletal problems worldwide, topping the list as the main cause of disability. Observation of the posture and movement of the subject with LBP should be part of any initial clinical evaluation, as well as the control of clinical evolution. In order to improve the understanding of lumbopelvic rhythm (LPR) alterations in low back pain of different origins, the objective of this study was to identify differences between posture and compensatory strategies present in the LPR of subjects with non-specific mechanical LBP and inflammatory LBP, present in axSpA, compared to healthy subjects. Socio-demographic, Clinical variables and lumbopelvic kinematics were obtained in 39 subjects with acute LBP, 39 with axSpA, and 39 healthy control subjects. The results showed that from the second quartile of spinal flexion, the group with acute LBP behaved differently from the other two groups with less lumbar movement (14.43°, CI 95% 26.74-3.15), and less pelvic motion ($p<0.001$). Trunk movement during the third quartile established differences between low back pain (17.90° 95% CI 44.54-2.65) and AxSpA (23.86°, 95% CI 35.27-11.53) and healthy controls (23.32°, CI 95% 36.52-12.68). But it will only happen with axSpA in the fourth quartile and not with healthy controls. Within extension movement, pelvic motion in the second quartile was significantly reduced in the acute group (13.85°, 95% CI 32.12-3.47) compared to the axSpA group (16.97°, 95% CI 30.12-3.47). Trunk movement in the second and third quartiles was significantly reduced in the acute group compared to the other two groups ($p = 0.001$ and $p = 0.007$, respectively). Differences shown by the acute pain group in third quartile lumbar motion were also found. In conclusion, lumbopelvic kinematics change in the presence of pain and behave differently depending on the origin or time of evolution.

PSI.h. Design of novel mRNA vaccine candidates for induction of antibodies, TCD4+ and TCD8+ cell responses.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: mRNA-based vaccines, SARS-CoV2, COVID19, TCD4+ response, TCD8+ response.

Abstract: mRNA-based vaccines have been a pilar to fight against current COVID19 pandemic. However, many vaccines in use today, are not optimal to induce TCD4+ and TCD8+ responses and protection, for asymptomatic infection and disease, drops after few months. We have designed in this work a new type of mRNA molecules for increased antibody response and a Th1 TCD4+ response or even more an antibody, Th1 TCD4+ and TCD8+ response for diseases like certain viruses or cancer that may need both antibody and TCD8+ cytotoxic response. As a virus model we have selected SARS-CoV2 virus and we have selected the receptor-binding domain (RBD) of spike protein. A synthetic gene was designed and cloned including a polymerization domain along with TCD4+ T cell epitopes from carrier proteins and a known Th2 TCD4+ epitope of OVA (OVA 323-339) for Balb/c mice. A group of 6 Balb/c mice of 10 weeks average age was immunized with one intramuscular dose of plasmid (1ug per animal) induced an average antibody response of 1/28.000 as measured by an indirect ELISA with a range between 1/10.000 to over than 1/40.000. When we compared two intraperitoneal doses of 2 micrograms/dose of OVA, the first in ACF and the second in AIF, with a first dose of plasmid and the second one of OVA in AIF we observed a higher level of interferon gamma with plasmid plus protein when compared with two doses of protein after in vitro stimulation of spleen cells with OVA 323-339 peptide. This demonstrates that designed nucleic acids induce a Th1-biased response that might be optimal for vaccine design. Results are being protected for further development of vaccine candidates for both viral diseases and cancer.

Fundings: CPP21 EBV-IMMUNOVAC. Project of Ministerio de Ciencia e Innovación.

PSI.i. Inflammatory cytokines: definition of normal values in healthy population.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: cytokines; inflammation; reference range; health; inflammaging.

Abstract: Inflammatory cytokines are signalling molecules involved in the immune system homeostasis, but also in many pathological processes. Due to their diagnostic, prognostic and predictive values, determining their serum concentration has become a routine practice, despite the heterogeneity in quantitation methods. The aim of this study was to determine inflammatory cytokine levels by flow cytometry in a healthy population according to age in order to stablish normal ranges.

Samples were obtained from 152 healthy volunteers, who were stratified into 3 or 6 groups of age. Those with chronic diseases, immunological alterations, infections or metabolic syndrome or under immunomodulation drugs were excluded, except >70 y.o people. Circulating IL-1β, IL- 6, IL-8, IL-10, IL-12p70, TNF-α, IFN-γ, MCP-1 and IP-10 were measured in 1:4 diluted serum samples using Cytometry Bead Array on a FacsCanto II and analysed with FCAP Array.

Results: IL-1β, IL-6, IL-10, IL-12p70, TNF-α and IFN-γ were undetectable. Results did not show significant differences considering gender, allergy or smoke habits. Correlation analyses revealed a decreased in IL-8 ($r=-0.44$) and an increased in IP-10 levels ($r=0.37$) with age ($p<0.05$). IL-8, MCP-1 and IP-10 levels were affected by diabetes, hypertension, hypercholesterolemia and cardiopathy ($p<0.05$).

Inflammatory cytokines values (pg/mL):

Group 1 (19-29 y.o.): IL-8 (0.00-2587.92); MCP-1 (0.00-259.48); IP-10 (21.35-218.93).
Group 2 (30-39 y.o.): IL-8 (0.00-643.38); MCP-1 (7.40-395.38); IP-10 (22.09-397.89).
Group 3 (40-49 y.o.): IL-8 (0.00-798.08); MCP-1 (8.33-263.83); IP-10 (11.01-215.24).
Group 4 (50-59 y.o.): IL-8 (1.69-211.63); MCP-1 (7.63-371.05); IP-10 (67.27-200.97).
Group 5 (60-69 y.o.): IL-8 (0.00-447.39); MCP-1 (14.15-427.84); IP-10 (55.16-584.00).
Group 6 (>70 y.o.). IL-8 (0.00-10.37); MCP-1 (11.35-83.97); IP-10 (83.35-1339.49).

Group A (<40 y.o.): IL-8 (0.00-2319.76); MCP-1 (4.07-320.64); IP-10 (21.76-371.76).
Group B (40-59 y.o.): IL-8 (0.00-616.66); MCP-1 (7.86-345.91); IP-10 (16.85-210.60).
Group C (>60 y.o.): IL-8 (0.00-447.39); MCP-1 (11.35-427.84); IP-10 (55.16-1339.49).

In conclusion, inflammatory cytokine levels in healthy individuals change with age and the presence of chronic diseases.

PSI.j. Real-life validation of prognostic risk stratification according to ELN 2017 in AML patients.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Next Generation Sequencing (NGS), Acute myeloblastic leukemia (AML), European LeukemiaNet (ELN), prognostic risk.

Abstract: Recently, a census of mutated genes in AML has been described but their value in clinical practice is not fully elucidated. The revised 2017 European LeukemiaNet (ELN) recommendations for genetic risk stratification of AML have been widely adopted, but have not yet been validated in large cohorts of AML patients.

The objective of this work is to analyze to study whether the application of ELN 2017 scale improves prognostic risk stratification with respect to ELN 2010 and Medical Research Council (MRC).

We included 112 adult AML patients diagnosed in our center between Jun2017 and Dec2021 and who were studied at diagnostic using the spanish PLATFOLMA PETHEMA. The prognostic risk was established according to MRC, ELN2010 and ELN2017 classification.

NPM1 and FLT3-ITD were determined by melting curve analysis and standard PCR-EC technique according to Thiede et al (Blood 2002) in ABI 3130 Analyzer (Thermofisher). For NGS, the commercial panel Myeloid SolutionTM (Sophia Genetics) KAPA Kit amplification libraries and sequencing on ILUMINA Myseq platform were used. Variant analysis was performed using DDM software (Sophia Genetics).

Re-stratifying according to ELN 2017, the 53% of patients categorized within the intermediate risk group according to MRC change prognostic group: 28.9% became redefined as unfavorable risk and 24.1% as favorable.

The overall survival analysis shows statistically significant differences taking into account either ELN 2017 or ELN 2010 and MRC. However, according to ELN 2017 there are greater differences between intermediate and unfavorable groups than in the other classifications.

Conclusions: 1. NGS proves its usefulness by detecting more clinically relevant alterations than conventional cytogenetic techniques and PCR, and stratifies a larger group of patients as favorable and unfavorable. 2. ELN 2017 establishes greater survival differences between the intermediate and unfavorable group than ELN 2010 and MRC redefining the intermediate group.

PSI.k. The impact of expanding hepatocellular carcinoma as an indication for liver transplantation on the waiting list length and composition.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: Liver transplant; Milan criteria; Waiting list.

Abstract:

Objectives: To evaluate the impact of the expansion of hepatocellular carcinoma (HCC) criteria, from Milan to 'up-to-seven', on the liver transplant (LT) waiting list. **Methods:** Retrospective study including a consecutive cohort of LT candidates from our center. Taking into account the nationwide consensus document for expanding HCC criteria in 2019, we compared the pre-expansion period (from January, 2016 to December, 2018) with the post-expansion period (from January, 2019 to August, 2021) in terms of waiting list length and composition. **Results:** In all, 284 candidates for LT (pre-expansion n=167; post-expansion n=117) were included, with a similar HCC prevalence in both periods (42.5% vs 39.3%; p=0.59). The main etiologies of liver disease were hepatitis C (59.4%) and alcohol (51.6%). The frequency of patients exceeding Milan criteria at waitlist inclusion was comparable between groups (14.3% vs 15.6%; p=0.85), as it was serum alpha-fetoprotein (4.9 vs 5.4 µg/ml; p=0.99). No significant differences were found regarding the length of the waiting list for patients included due to hepatic insufficiency or special indications before and after expansion (84 vs 99 days; p = 0.50). The waiting time was shorter for HCC patients during the post-expansion period (181 vs 121 days; p = 0.03). Delisting due to HCC progression was comparable in both groups (9,9% vs 15,2%; p=0,383). Histological features of more aggressive HCC did not change after expanding criteria: microvascular invasion (37.8% vs 38.7%; p=0.93), number of nodules (1,54±0,75 vs1,48±0,81; p=0,70), and main nodule diameter (28.2±12,7 vs 28.3±11,2 mm; p=0.97). As expected, after expanding criteria a higher proportion of patients had a tumor beyond Milan criteria in the explanted liver (20% vs 43%; p=0.023). **Conclusion:** A moderate expansion of HCC criteria for LT had no relevant impact on the waiting list length and composition. A more liberal expansion in the future could be considered.

PSI.I. Analysis of the hypothalamic expression of the Prader-Willi Syndrome-related genes Magel2 and Ndn and their predicted microRNAs throughout pubertal development in lean and obese female rats.

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Scientific Program: Nutrition, Endocrine and metabolic.
Keywords: Prader-Willi; puberty; hypothalamus; miRNAs.

Abstract: Prader-Willi Syndrome (PWS) is a rare neurogenetic disorder caused by loss of expression of imprinted, paternally inherited genes on chromosomal region 15q11q13. The most common endocrine manifestations associated with this syndrome include alterations in the timing of puberty onset. Among the inactivated genes in PWS, MAGEL2 and NDN are especially relevant. In fact, recent evidence suggests that hypothalamic alterations induced by the loss of expression of these genes might contribute to the pubertal disorders associated with PWS. However, the regulatory elements that might modulate these genes and participate in these alterations remain unknown. In this work, we analyzed the hypothalamic expression of Magel2 and Ndn throughout pubertal development under normo- and over-nutrition conditions and their potential regulation by miRNAs, which are considered relevant modulatory factors in the control of puberty. Our findings reveal that the hypothalamic expression of Magel2 and Ndn decreases during the pubertal-adult transition in both lean and obese female rats with precocious puberty. Furthermore, in the latter, such a decline is associated with an increase in the hypothalamic expression of miR-30b-5p and miR-200b-3p, which are predicted miRNAs for Magel2 and Ndn regulation, respectively. Overall, our findings suggest a potential interplay between miR-30b/Magel2 and miR-200b/Ndn in obesity-induced precocious puberty. However, further research is needed to validate and expand such preliminary findings.

PSI.m. The experience of childbirth and the subsequent appearance of a mental disorder.

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Scientific Program: Active ageing and fragility.
Keywords: Mental disorder.

Abstract: The experience of childbirth and the subsequent appearance of a mood disorder is closely related. In respected childbirth, the preferences of the pregnant woman must be taken into account when making decisions and carrying out any intervention, so as not to act unjustifiably and without informing the pregnant woman. The professional attends, listens, speaks and understands the mother if she shows any concern or setback. A respected birth depends too much on the care provided by health professionals and to a lesser extent on the place where it is carried out.

Once the delivery is over, the needs, complications or situations that have arisen and in which it was necessary to intervene in one way or another should be evaluated, for example, artificial rupture of the membranes (amniotomy), administration of synthetic oxytocin, episiotomy or other type of actions.

PSI.n. Early and late intestinal complications after combined pancreas-kidney transplantation.

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Keywords: Pancreas-kidney transplantation; Enteric complications; Enteric drainage; Duodenojejunostomy.

Abstract:

Introduction: Combined pancreas-kidney transplantation (PKT) is the treatment of choice in patients with type 1 diabetes and end-stage renal disease, as it improves survival and quality of life. Currently, enteric exocrine drainage is the most commonly used. Enteric complications continue to be a major cause of post-transplant morbidity despite improvements in surgical technique. Enteric complications have been poorly described in the literature. The aim of this study was to retrospectively analyse early and late intestinal complications. **Methods**: We performed a retrospective analysis of 100 adult patients undergoing PKT between January 2009 and December 2019. Venous drainage performed was systemic and for exocrine secretion enteric drainage with manual duodenojejunal anastomosis was performed. Statistical analysis was performed using SPSS v2. **Results:** Ten patients (10%) had early intestinal complications. Intestinal complications were: paralytic ileus (n = 4); intestinal obstruction (n = 2); intestinal obstruction due to pancreatic graft volvulus (n = 1); duodenal graft fistula (n = 1); and jejunal fistula after pancreas transplantation (n = 1). Two cases required re-laparotomy: graft repositioning by volvulus and y de roux conversion (n = 1); y de roux conversion (n = 1). Eight patients (8%) had episodes of late bowel obstruction of which two required surgery for resolution with 100% postoperative mortality. **Conclusions:** Patients undergoing PKT with enteric drainage via duodenojejunostomy have a low rate of short- and long-term postoperative bowel complications. Interventions for intestinal obstruction in transplant patients have a high mortality risk and should be performed in reference transplant centres.

PSI.ñ. Pillar pain as a complication of carpal tunnel syndrome surgery.

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Keywords: carpal tunnel syndrome, pillar pain, incidence.

Abstract: The conventional surgery for carpal tunnel syndrome has remarkably good results both in the short and long term with regard to resolving the compressive clinic of the median nerve. Nevertheless, these results are overshadowed due to the appearance of various adverse effects such as pillar pain. Pillar pain is a deep pain associated with a sensation of dysesthesia and allodynia at the thenar and/or hypothenar eminences (sometimes described as peri-inflammatory pain). **Objectives**. The objective of this study was to estimate the incidence of pillar pain in a sample of patients undergoing conventional carpal tunnel syndrome surgery, as well as the correlation between pillar pain and gender and age. **Methods**. The incidence of pillar pain in a sample of 78 patients undergoing median nerve exoneurolysis throughout 2021 (chosen consecutively) after 4-6 weeks post-surgery has been analyzed. Chi-square statistics have been used to analyze the relationship between gender and age of these patients. **Results**. Of the total of 78 patients in the sample, 28 suffered postoperative pillar pain (35.9%). 23 women (37.7%) and 5 men (29.4%) suffered post-surgical pillar pain. 7 patients over 60 years of age (26.9%) and 21 patients under 60 years of age (26.9%) suffered pillar pain. The occurrence of pillar pain and gender, or the occurrence of this complication in both age groups, did not show statistically significant associations (p-value of 0.528 and 0.958 respectively). **Conclusions**. Currently, complete release of the transverse carpal ligament is the most widely used procedure for resolving the compressive symptoms of the median nerve. However, pillar pain is an adverse effect, estimated in the literature with a 41% incidence in the first month after surgery. Therefore, it is a common complication, which seems to have no relation to age and gender, and which often overshadows the results perceived by patients.

PSI.o. Study of cyclic hypoxia, agitation and differential glucose supply in adipogenic differentiation.

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Scientific Program: Active aging and frailty.
Keywords: adipocyte; hypoxia; agitation; fat; diet.

Abstract: It has been described that pre-adipocyte express RANKL contributes to the osteoclastic activity and bone resorption, which is associated to aging. In this sense, it may be important to develop strategies which promote the decrease of adipogenesis during aging, while promoting bone formation. Physical exercise, diet and hypoxic exposure could be an alternative. Oxygen requirement is greater during fatty acid oxidation than glucose oxidation, a switch in substrate preference away from fatty acids represents a mechanism of adaptation to hypoxia. Combined with elevated basal metabolism (mechanical stimulus, as agitation), the energy deficit could be a more potent metabolic stimulus. Lower blood glucose concentrations contribute also to a shift in substrate selection to support energy needs. There is a lack of knowledge in the scientific literature about predominant metabolic pathways when combining a mechanical and hypoxic stimulus with increased or decreased energy intake. Thus, the aim of this study is to know how the combination of agitation and cyclic hypoxia during adipogenesis, with a greater or lesser supply of nutrients, could influence on the cell differentiation.

Cultures of human bone marrow mesenchymal stem-cells were induced to adipocytes and exposed 4 days (2 h/day) per week to agitation, hypoxia or both stimuli. The culture medium was changed twice or three times per week. Expression of adipogenic genes and lipid droplets formation were studied.

When the culture medium was changed 2 days per week, subjected to hypoxia or agitation and hypoxia lower levels of lipid droplets were observed. Expression of PPARG and FASN1 genes in pre-adipocytes were lower, while the expression of LPL gene was maintained. Furthermore, OPG/RANKL gene expression was higher in the cultures exposed to agitation and hypoxia.

Agitation, hypoxia and controlled diet may improve body composition through loss of fat mass, at the same time as bone remodelling processes are enhanced.

PSI.p. Monitoring disease evolution and treatment response in pancreatic cancer patients using liquid biopsy-based epigenetic biomarkers.

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

Abstract:

Background and aims: Pancreatic cancer (PC) is the most lethal cancer with five-year survival rates of around 5%, mainly due to diagnosis at advanced stage and ineffective treatments. Circulating CA19-9 levels and computed-tomography (CT) imaging are the main standard criteria for assessment of disease evolution and treatment response. This study was aimed to explore the utility of liquid biopsy-based epigenetic biomarkers to monitor the response to treatment in patients with metastatic PC (mPC). **Material and Methods**: Plasma was obtained from fifteen mPC patients at diagnosis and during follow-up of disease. The median survival of patients was 13.1 (11.1-26.2) months and most of them (80%) received first-line gemcitabine-based regimes. Cell-free DNA (cfDNA) levels were determined, and circulating levels of methylated NPTX2, SPARC, BMP3, SFRP1 and TFPI2 cfDNA were measured using digital droplet PCR (ddPCR). BEAMing technique was performed for quantitation of RAS mutation allele fraction (MAF) in cfDNA and tumor marker CA19-9 was measured using standard techniques. **Results:** All five genes previously reported to be methylated in pancreatic tumors were found methylated in at least one of the analyzed plasma samples. However, NPTX2 was the most highly and frequently methylated gene in cfDNA samples from metastatic mPC patients. Dynamics of NPTX2 methylation levels correlated with the disease progression and response to therapy estimated by standard criteria, such as CA19-9 and CT imaging. A significant correlation was found between RAS MAF, CA19-9 levels and circulating NPTX2 methylation levels, but not with cfDNA concentration. Remarkably, in some cases therapy failure was anticipated by the rise in circulating NPTX2 methylation levels, before the confirmation of progression of disease by CT imaging. **Conclusions:** Our data support that circulating levels of methylated cfDNA are biomarkers of disease progression in mPC patients and may constitute a valuable tool for clinical decision-making and tailored patient care.

PSI.q. Identification of novel molecular signatures associated with the therapeutic response to DMARDs and TNFi therapies in Rheumatoid Arthritis patients through high throughput proteomics.

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

Abstract:

Background: The clinical outcome of the most common therapeutic options of rheumatoid arthritis (RA) patients, such as conventional disease-modifying antirheumatic drugs (DMARDs) and TNF inhibitors (TNFi) is still unpredictable, since a high percentage of patients do not response to the therapy. Innovative analyses combining high-throughput technologies and thorough clinical assessments are needed to gain insight about the management of this prevalent autoimmune disorder. **Objectives:** To evaluate the systemic inflammatory proteome of RA patients, to identify useful biomarkers associated with distinctive clinical outcomes. **Methods:** Serum samples from 140 subjects, including 40 healthy donors (HC) and 100 RA patients with high activity disease (mean DAS28=4.7), were profiled with the innovative proteomic methodology "proximity extension assay" (Olink) which analyses one panel of 92 pro-inflammatory proteins. Samples from RA active patients included 40 from newly-diagnosed RA patients before taking conventional DMARDs and 100 from biologics-naïve patients (mean disease duration=10 years) before receiving TNFi drugs. Clinical outcomes were evaluated following EULAR criteria after 6 months of treatment and patients were classified as responders or non-responders to the different therapeutic interventions. Unsupervised hierarchical clustering methodologies were applied to identify subgroup pf patients based on the proteomic profiles. Gene ontology enrichment were used to interrogate the biological meaning of the distinctive molecular signatures identified. **Results:** The inflammatory proteome analysis identified 33 proteins differentially expressed and upregulated in RA patients compared with HC including several chemokines (CCL-11, -19, -20, -23, -28; CXCL-10, -11, -9; MCP-1, -3), interleukins (IL-6, -8, -18, -10, -17c), and other relevant proinflammatory mediators (VEGFA, CD40, MMP-1, CSF-1, OPG, FGF23) among others (FDR<0.05). Most of these molecules were associated with disease activity (DAS28) and the autoimmunity profile (Rheumatoid factor and ACPAs antibodies) of RA patients. The unsupervised clustering analysis using the proteomic profile of RA patients before TNFi identified two subgroups of patients. Cluster 1 (C1) was characterised by patients with higher levels of several pro-inflammatory mediators compared with Cluster 2 (C2), where a signature of 16 chemokines was significantly enriched (CCL-3, -4, -10, -11, -20, -23; CX3CL1; CXCL-1, -10, -11, -5, -6, -9; MCP-1, -3, -4). Clinically, 25% of the non-responders' patients was included in C2, while 75% was located in C1, suggesting that a prominent circulating chemotaxis profile prior therapy is associated with a

poor clinical outcome. These data were similarly observed in patients before receiving DMARDs, where a signature of upregulated chemokines and pro-inflammatory mediators characterised a cluster with a high % of non-responder patients. **Conclusions:** A pro-inflammatory signature, where chemokines are predominantly up-regulated in the serum of RA patients before therapy, is associated with a poor clinical outcome. This newly identified signature, which deserves a more in-depth analysis, might be clinically useful guiding precision medicine and novel therapeutic approaches.

PSI.r. Prevalence and risk factors for peripheral artery disease in a population with coronary heart disease: from the cordioprev study.

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Scientific Program: Nutrition, endocrine and metabolic diseases.
Keywords: Peripheral artery disease, lipoprotein, risk factors, lipid panel, ankle-brachial index.

Abstract: Peripheral artery disease (PAD) refers to an atherosclerotic disease that affects arteries that supply blood to the lower extremities. Due to chronic occlusion of arteries, the disease is characterized by intermittent claudication, leg pain and limb ischemia. Global prevalence of PAD in people older than 25 years old has been established in 5.56 % (3.79-8.55%), with Spain among the 15 countries that contained more than two thirds of PAD cases reported in 2015. Coexisting PAD and coronary heart disease (CHD) has been positively associated with coronary event recurrence, which might unfold even in patients who have risk factors under control. The aim of the present study was to determine the relationship between different traditional risk factors and PAD in a CHD population from the CORDIOPREV study. To that end, CHD patients (n=981) from the CORDIOPREV study were classified according to the presence or absence of PAD, defined as an ankle-brachial index ≤ 0.90. Logistic regression models were designed to calculate the odds ratios of 14 risk factors for peripheral artery disease. In our CHD population, the number of patients suffering from PAD was 195. Traditional risk factors associated to the presence of PAD were age, smoking (former and current) hypertension, diabetes, renal impairment, inflammation, and hyperfibrinogenemia. However, in the studied population dyslipidemia, defined as the presence of hypercholesterolemia, low HDL-c, high LDL-c or high triglycerides levels, was not found associated to PAD. In this regard, statin treatment (undergone by approximately 85% of the study population) might have attenuated the associations of lipid panel parameters and PAD. As future work, we pretend to combine the information provided by PAD traditional risk factors and lipoprotein subfractions obtained by nuclear magnetic resonance to describe a risk profile that might help us to better explain factors that promote the presence of PAD in a CHD population.

PSI.s. High throughput transcriptomic analysis of peripheral mononuclear cells identifies molecular alterations associated with the active clinical phenotype of Axial Spondyloarthritis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: axial spondyloarthritis; transcriptomic analysis; gene modules.

Abstract: Significant progress has been made in the identification of molecular profiles involved in the pathogenesis of chronic autoinflammatory diseases. However, few studies have been carried out in axial spondyloarthritis (axSpA), which would allow the identification of new therapeutic targets and disease biomarkers. Objectives: 1) To identify clusters of highly correlated genes enriched in biological functions and molecular pathways involved in the pathogenesis of axSpA; 2) To study the association between molecular signatures and the disease's clinical-analytical profile. Methods: Cross-sectional study including 20 healthy donors and 105 axSpA patients from the CASTRO cohort who underwent a clinical and analytical evaluation. RNA from PBMC was isolated and sequenced using Illumina. For the identification of patient subgroups and the generation of co-expressed gene modules, the "hierarchical clustering" and WGCNA ("Weight gene correlation network analysis") methodologies were used. EnrichR platform was used to identify enriched pathways and functions from each gene module and hub genes were measured through high throughput PCR (Fluidigm). Association and correlation studies between the molecular and the clinical profiles were performed. Results: Analysis of the transcriptome revealed two "clusters" of axSpA patients, differentiated by their molecular and clinical profile. Specifically, the molecular analysis distinguished patients with a longer disease duration, greater disease activity, radiographic damage and cardiovascular risk. WGCNA identified 11 highly co-expressed modules. Among them, six were differentially expressed between the two clusters, being responsible for the molecular and clinical distinction of those groups. The functional analysis of these modules revealed the enrichment in pathways related to inflammation, oxidative metabolism, proliferation of B and T lymphocytes, immune response and the increase of cell survival. Finally, key genes were identified within each module, whose expression was associated with a more active phenotype. Conclusions: 1) The whole transcriptomic analysis by RNAseq distinguished subgroups of patients with distinctive clinical profiles 2) Analysis of gene modules identified new pathways and molecular functions potentially involved in the pathophysiology of the disease.

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PSI.t. Potential anti-proliferative role of the Liver Enriched Antimicrobial Peptide 2 (LEAP2), a new component of the ghrelin system, in prostate cancer cells.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Prostate Cancer; Ghrelin system; LEAP2.

Abstract: Ghrelin system is an endocrine-metabolic and pleiotropic regulatory system involved in cancer pathophysiology. Some ghrelin system components have been associated to prostate cancer (PCa) development, progression, and aggressiveness. Recently, the existence of a novel endogenous ghrelin receptor antagonist, the liver-expressed antimicrobial peptide-2 (LEAP2) protein, has been reported to be expressed in liver and intestine, and to be involved in some metabolic actions (i.e. hormonal secretion and blood glucose balance); however, the presence and pathophysiological role of LEAP2 in cancer tissues have been poorly explored. Therefore, we aimed to interrogate the expression profile of the components of the ghrelin system [ghrelin (GHS), In1-ghrelin splicing variant, ghrelin receptor 1a (GHSR1a) and 1b (GHSR1b) and LEAP2] and the functional role of LEAP2 in PCa cells. To that end, the normal-like prostate cell line (PNT2) and different PCa cell lines (22Rv1, LNCaP, PC3) were used as experimental models, and different doses of LEAP2 were used alone [physiological concentrations (15 and 30 ng/mg), and a supraphysiological concentration (150 ng/ml)], or in combination with GHS (10 nM)] in different PCa cells. Our data revealed that GHS was only expressed in the normal-like prostate cells (PNT2) but not in PCa cells, while In1-ghrelin variant and GHSR1a were found to be highly expressed in 22Rv1 cells as compared to LNCaP, PC3 and the normal-like prostate cell line (PNT2). In contrast, LEAP2 was found to be expressed in the normal-like prostate cells and in all the PCa cell lines analyzed. Interesting, high dose of LEAP2 was able to significantly reduce the proliferation rate, but not the migration capacity or the formation of colonies and tumorspheres, in 22Rv1 and LNCaP cells. Altogether, our data revealed a dose and cell-line dependent anti-proliferative role of LEAP2 in PCa cells.

PSI.u. 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 an atherosclerotic-like disease, 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 fully characterized in any study regarding AS, and only to molecular level, but not to cellular level. Up to date there is no other treatment for the valve stenosis other than the replacement of the valve itself. Therefore, the profound characterization of the cells implicated in the inflammatory processes of the valvular degeneration is of outmost importance in order to develop new therapies for AS patients. Here we present a novel protocol, using multi parametric flow cytometry, for the phenotypic and functional characterization of aortic valve infiltrating immune cell populations. This methodology has allowed us to assess for the first time the frequency of the different infiltrating lymphocyte subsets and to compare the level of infiltration between diseased aortic valves and healthy ones. **Results:** In contrast to other studies in which the molecular analysis of the valve infiltrate showed a predominance of CD8+ T cells, our cytometric analysis showed a 47,9% of CD4+ T cells and 37,2% of CD8+ population cells, closer to the peripheral distribution. Moreover, we have observed NK cells presence, both CD56dim and CD56brigth subsets and a new NK CD56dim cell subpopulation that lacks CD16 receptor which is not present in peripheral blood. **Conclusions:** Our protocol opens new opportunities for the characterization of the immune cells implicated in the immunopathology of cardiovascular diseases as well as for the development of novel strategies to tackle them.

PSI.v. Evaluation of the performance of artificial intelligence (AI) after one year of use in breast cancer screening practice.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Artificial intelligence; Breast cancer screening; Digital Breast Tomosynthesis; Digital mammography.

Abstract:

Purpose or Learning Objective: To evaluate the impact of using an AI system as support for human double reading in a breast cancer screening program and its ability to correctly stratify these exams according to probability of cancer. **Methods or Background:** We reviewed all digital mammography (DM) or digital breast tomosynthesis (DBT) screening examinations between March 2021 and March 2022 that were double read (without consensus) by radiologists concurrently with AI support at our hospital. The AI system used in this study categorises each exam into three categories (low, intermediate, elevated) representing the probability of cancer and highlights suspicious areas (1-100 score). We computed the number of examinations, cancers, recalls and positive predictive value (PPV) of the recalled studies globally and in each AI category, as well as the overall cancer detection rate (CDR) and recall rate (RR) during the study period. We compared these data with the same 12 months period one year earlier (CDR 5.5/1000, RR 6.1%, PPV 9%), prior to the implementation of AI, using the Chi2 test. **Results or Findings:** 11998 screening examinations were included and classified as low: 7917 (65.9%), intermediate: 3730 (31%) and elevated: 351 (2.9%). 108 cancers were detected, which were categorised as low: 1 (0.9%), intermediate: 32 (29.6%), elevated: 75 (69.4%). AI correctly marked 101 cancers. CDR, RR and PPV were 9/1000 (+3.5/1000, $p<0.001$); 6.1 % (0 %, $p=0.9$) and 14.6% (+5.6%, $p<0.001$), respectively. **Conclusion**: AI used concurrently in clinical practice is able to stratify the examinations according to probability of cancer. AI increases cancer detection rate and PPV of the recalled women. **Limitations:** A longer time frame, including interval cancers, is needed to support these findings.

PSI.w. Computer-assisted navigated piezoelectric resection and CAD-CAM designed PEEK prosthesis for the surgical resection of tumors affecting facial bones. A synergy of new technologies to improve the surgical results.

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Keywords: Facial Bones Tumors; CAD-CAM; Surgical Navigation; PEEK Prosthesis; Facial Surgery; Piezosurgery.

Abstract:

Objectives: Computer Assisted Navigated Piezoelectric Surgery applies the computer planning and surgical navigation to a piezoelectric device in such a way that the piezoelectric device becomes "navigable". Our objective is to present our experience treating facial intraosseous tumors with Computer-Assisted Navigated Piezoelectric Surgery and CAD-CAM design and to evaluate the advantages and disadvantages of this new surgical technique. **Materials and Methods**: This is a series of patients with facial bones tumors treated between June of 2017 and May of 2022. DICOM CT data were imported into the planning BrainLab software. The tumors are segmented and sent to Materialise® (as .STL file), who made a custom- made PEEK prosthesis and resection guides using Surgicase®. Intraoperative BrainLab navigation was used to guide resection. The handpiece of a Vercelotti type pie- zoelectric device, with a cutting saw tip was registered with a calibration matrix. From then on, real-time navigation could be done. The osteotomy was performed with CANPS and with the aid of the surgical guides over the bone surface. Then in depth, with the aid of the CANPS, in the orbital roof as well the orbital and maxillary walls. **Results:** Computer Assisted Navigated Piezoelectric Surgery was successfully performed, excising the bone lesions in a more accurate maner. CANPS was an excellent tool for good control of the margins of the resection. **Conclusion:** Bone Tumors resection can benefit of using the Computer Assisted Navigated Piezoelectric Surgery and CAD-CAM technologies. CAD-CAM facilitates the manufacture of PEEK prosthesis that can be im- mediately adapted to the defect. CANPS allows performing osteotomies according to the planning, maximizing the precision safety of surgery.

PSI.x. The impact of Robot-assisted and Virtual Reality-based Neuromotor Rehabilitation on Health-related Quality of Life: A Systematic Review and Meta-Analysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Robot-assisted therapy, Virtual Reality, Rehabilitation, Neurological Diseases, Health-related Quality of Life, Systematic Review, Meta-Analysis.

Abstract: Over the past two decades, promising evidence on the efficacy of robot-assisted therapy (RAT) and virtual reality (VR)-based neuromotor rehabilitation on neurological disease patients' recovery has been reported. Depending on the study population, diverse functional (e.g., balance, gait, autonomy in activities of daily living, occupational performance) and motor (e.g., mobility, muscle strength, spasticity, dexterity) outcomes have been investigated to better understand the clinical impact of technology on the patient's recovery pathway. However, the effects of this innovative rehabilitation procedure on patient's health-related quality of life (HRQoL) and psychological aspects remain still unclear. This research intends to systematically describe and review the literature regarding the impact of RAT and VR-based rehabilitation on the HRQoL and the psychological status in patients suffering from various neurological diseases (e.g., stroke, Parkinson's disease, multiple sclerosis). Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review of studies published between 2000 and 2021 in PubMed, Web of Science, Cochrane Library, CINAHL, Embase, and PsychINFO electronic databases was carried out. The search identified a total of N = 3,025 records of which 130 were included and analysed trough the National Heart Lung and Blood Institute (NHLBI) quality assessment tools. Descriptive data regarding the study design, participants, technological devices, interventions, and main results were extracted and meta-synthetized. Finally, according to the technological device implemented and the clinical population, meta-analyses on the effects estimated from each study specifically concerning patients' HRQoL pre-post intervention changes were conducted. The analyses of the present work are ongoing and will be discussed. This contribution will not only shed light on the effects of robotics and VR beyond motor improvement, but it will also provide precious insights into the specific technological device applicability and the related effectiveness on patient's quality of life.

PSI.y. Surgical treatment of cervicomediastinal goiter: experience at a single centre.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: goiter; cervicomediastinal; cervical approach; thoracotomy; sternotomy.

Abstract:

Objectives: The aims of this study were: 1) To analyze the results of thyroidectomy for cervico-mediastinal goiters (CMG) 2) To identify conditions that might predict the need for an extra-cervical approach. 3) To determine risk factors for complications. **Methods:** Retrospective analysis of 261 consecutive patients undergoing thyroidectomy for CMG between 1986 and 2021. Pre-, intra-, and postoperative recipient variables, surgical technique, pathological analysis, complications and mortality were analyzed. Risk factors for complications and predictive factors for an extra-cervical approach were studied. **Results:** 203 (78%) women and 58 (22%) men underwent surgery for CMG. CMG, 250 patients and intrathoracic ectopic goiter, 11. Surgical approaches: cervicotomy (n=234; 90%); cervico-sternotomy (n=18; 7%), sternotomy (n=3; 1%); thoracotomy (n=3; 1%), and cervico-sternotomy (n=3; 1%). 147 (56%) total thyroidectomies, 36 (14%) subtotal and 78 (29%) hemithyroidectomies were performed. Histological findings revealed 187 (72%) colloid goiters, 28 (11%) hyperplasia, 21 (8%) adenomas, 15 (6%) carcinomas and 10 (3%) thyroiditis. The morbidity rate was 22% (58 patients): recurrent laryngeal nerve paralysis (n=35; 13%), transient hypoparathyroidism (n=21; 8%), bleeding (n=7; 3%), infection (n=2; 1%), tracheomalacia (n=2; 1%). 14 patient (5%) needed revision surgery, and 30-day postoperative mortality was 3% (8 patients). Risk factors for complications were total thyroidectomies (n=44, 30%; p=0.02), thyroidectomies for carcinoma (n=8, 53%; p=0.03) and vertical diameter (uncomplicated vs. complicated: 8.3±2 cm vs. 9.3±2 cm; p=0.03). The risk factor for mortality was reoperation for bleeding (n=3; 21%; p=0.006). Risk factors for the need for an extra-cervical approach were dyspnea (n=13, 50%; p=0.02), preoperative recurrent laryngeal nerve palsy (n=3, 33%; p=0. 04), ectopic intrathoracic goiters (n=9, 82%; p<0.001) and goiters with large retro-visceral progression (n=9, 37%; p=0.003). **Conclusions:** Thyroidectomy for CMG is a safe procedure with low morbidity and mortality. Ectopic goiters, cervical goiters with extensive retrosternal progression and thyroid carcinomas have a higher incidence of complications and predict the need for an extra-cervical approach.

PSI.z. Threshold concepts applied to oncological surgical pathology. Preliminary results.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Threshold concepts, Pathology, learning proccess.

Abstract:

Background & objectives: Students' cognitive perceptions (SCP) are considered important variables for high-quality learning. In this study, SCP were used to identify histopathological threshold concepts (TC) in medical curricula. The objective is to analyse the perception of medical students' about TC in Pathology. **Methods:** A questionnaire was developed and validated to characterize SCP of TC in pathology. A sample of 180 medical students' participated in the study. Different items were evaluated by means of a Likert-type scale (1-5) on their consideration of each TC in pathology. Statistical analysis was performed (Student's t test) comparing the values by gender and the differences between different sections. **Results:** The result of questionnaires related to morphostructural TCs was very distributed in the interval from 1 to 5, being the mean value 3.2/5. TC related to two-dimensional microscopic identification were scored 4.2/5. Additionally, students identified TC related to the general histogenesis of neoplasms as critical to understanding and learning in pathology. The most valued concepts were those of the tissue injury section (4.7/5). 60% of the students did not know the concepts of clinical autopsy or concepts related to the tissue neoplasms section. 45% of the students did not consider Pathology as essential for the exercise of the medical profession. **Conclusion:** The identification of threshold concepts through students' perceptions is potentially useful to improve the teaching and learning process in health sciences curricula. The differences observed must be taken into account in the organization in the teaching programming of the Pathology subject and in the entire Medicine degree, to guarantee an autonomous learning process based on specific competencies.

PSI.aa. Splicing machinery dysregulation as a source of novel diagnostic, prognostic and therapeutic targets in craniopharyngiomas.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Craniopharyngioma, splicing, diagnostic/prognostic biomarkers, therapeutic target.

Abstract:

Craniopharyngiomas (CP) are relatively benign epithelial tumors that typically arise in the sellar/suprasellar region, and are classified in adamantinomatous (ACP) and papillary (PCP). Diagnosis is usually performed when tumor development is already advanced, and serious comorbidities are present. The first-line therapy is usually surgery, but frequently the resection is not complete, causing high recurrence rates. Therefore, the identification of alternative diagnostic/prognostic/therapeutic tools to improve CP management is necessary. Recently, growing evidence indicates that defects in the splicing-process are frequent in cancer, leading to the appearance of altered spliceosome components (SCs), splicing-factors (SFs) and/or aberrant splicing-variants (SVs), which are associated with the development/progression/aggressiveness of various cancer types. Therefore, our aim was to explore the putative oncogenic role of key splicing-related factors in CP through: 1) interrogating the expression profile of key splicing machinery components in ACP (n=36) and PCP (n=4) vs. control samples [n=11; normal-pituitaries (NP)]; and 2) implementing different bioinformatic and functional approaches (RNAseq and CP primary cell-cultures). Our results revealed a substantial number of SCs and SFs drastically altered in ACP vs. NP, and also when primary vs. recurrent ACP were compared. Specifically, RAVER1, RBM22, FBP11, and PRPF8 were identified as the most discriminating diagnostic/prognostic factors, being corroborated in additional human cohorts, and associated with key clinical parameters suggesting a potential oncogenic role in CP. Dysregulation of RAVER1 and PRPF8 was also corroborated in RNAseq of 18 ACP vs. 3 NP. In vitro overexpression of PRPF8 and RAVER1 in primary ACP-derived cells revealed a critical functional role of these factors in CP. Finally, key SVs

that are associated to CP development/progression (e.g., GNAS) were identified as potential oncogenic linkers with the observed splicing-machinery dysregulation. In conclusion, spliceosome is drastically altered in CP wherein RAVER1 and PRPF8 could represent attractive novel diagnostic/prognostic and therapeutic targets for this endocrine pathology.

PSI.bb. Loss of metabolic health in normal-weight individuals: Identification of visceral adipose tissue biomarkers.

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

Abstract:

Obesity is considered a global health problem and is commonly associated with insulin resistance, which is a major risk factor for the development of type 2 diabetes, cardiovascular disease, hypertension, and certain types of cancer, among other diseases. In particular, accumulation of visceral adipose tissue (VAT) contributes to unhealthy obesity and associated insulin resistance. Interestingly, certain normal-weight individuals (MONW) also suffer from insulin resistance and other obese-like features including excess VAT and ectopic fat deposition, adipose tissue inflammation and altered inflammatory and adipokine profiles. To elucidate the precise mechanisms underlying the pathogenic processes leading to the metabolic alterations observed in MONW, we carried out a comparative proteomic analysis of VAT from lean individuals with normoglycemia (NG) or with pre-diabetes (PD) using LC-MS coupled with diaPASEF for sample analysis. This enabled the identification of a total of 2032 proteins, from which 1365 were significantly different between lean NG vs. PD. Functional classification of differentially expressed proteins identified two major clusters, namely, metabolism and environmental information processing, that included proteins with important roles in insulin signaling and glucose/lipid metabolism. A subsequent analysis of the extracellular matrix (ECM) was carried out, which enabled the identification of 135 proteins belonging to the matrisome, with 111 differentially expressed proteins between the two groups. According to the classification of ECM proteins, ECM regulators and glycoproteins were the two major differentially regulated groups, along with ECM-affiliated proteins. In sum, we can conclude that MONW individuals exhibit metabolic and ECM alterations similar to those observed in obese individuals, which opens new perspectives in the treatment of metabolic disease.

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PSI.cc. Analyzing the molecular mechanisms underlying the resistance to somatostatin analogues in Pheochromocytomas and Paragangliomas.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: pheochromocytomas, paragangliomas, neuroendocrine tumors, somatostatin analogs, treatment resistance.

Abstract: Pheochromocytomas and paragangliomas (PPGLs) constitute rare neuroendocrine neoplasms (NENs) derived from chromaffin cells of the neural crest, arising in the adrenal medulla and the sympathetic and parasympathetic ganglia, respectively. One of the main NENs characteristics is the overexpression of somatostatin receptors (SSTs), an ideal target for NENs due to the diagnostic/therapeutic potential of somatostatin analogs (SSAs). PPGLs also exhibit a high proportion of SSTs in their membrane, but unlike other NENs, SSAs are not as effective. Therefore, the main objective was to explore the molecular mechanism underlying the resistance of PPGLs to SSAs, with the ultimate aim to seek potential tools to overcome this obstacle. In silico analyses of a 204 PPGLs fresh tissue samples cohort revealed a clearly distinct SSTs expression pattern according to mutational clusters. Next, we confirmed the expression of SSTs by qPCR in two PPGLs cell models: PC-12 (derived from rat pheochromocytoma) and SK-N-AS (human neuroblastoma cell line, which shares the cell origin with PPGL) wild-type and SDHB mutant. To evaluate their response to SSAs we performed drug response assays to: somatostatin, cortistatin, octreotide and pasireotide. Results did not show any significant antitumor effects in terms of cell proliferation, migration, and colony formation assays in response to any of the drugs. Ongoing experiments will allow to evaluate further cellular parameters, including free cytosolic calcium, cAMP production and membrane potential, that would help to determine the existence of any relevant cellular response resulting from the binding of different ligands to the SSTs, using specific receptor-agonist. Altogether, our results provide novel insights on the presence of SSTs in PPGLs and offer in vitro evidence for the lack of response of PPGL cell models to SSAs. These findings underscore the necessity to perform further molecular analysis to elucidate the molecular basis for the low efficacy of SSAs in PPGLs.

PSI.dd. GSK-3β is a regulatory kinase of colorectal cancer immune microenvironment and the response to immunotherapy.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: GSK-3, isoforms, PD-1, tumor microenvironment, PDXs.

Abstract:
Background and aims: Glycogen synthase kinase-3 (GSK-3) is a multifunctional serine-threonine kinase with a variety of critical regulatory functions. GSK-3 has been reported to play an important role in the pathophysiology of several cancers, including colorectal cancer (CRC). In mammals, there are two isoforms of GSK-3 encoded by separate genes: GSK-3-α and GSK-3-β. However, the relevance and role of these enzymes in the tumor microenvironment are largely unknown. The aim of the study was to analyze the relevance of GSK-3 in the tumor immune microenvironment of CRC. **Material and Methods:** The expression of GSK-3α, GSK-3β and the immune checkpoint protein PD-1 were evaluated by immunohistochemistry (IHC) in 33 CRC clinical samples. To assess in vivo the effect of GSK-3 inhibition (SB415286, GSK-3i) on the immunotherapeutic efficacy of nivolumab (anti-PD1), humanized PDXs were generated in NGS mice using human PBMCs and a DNA mismatch-repair deficient (dMMR) human CRC tumor. Cancer-associated fibroblasts (CAFS) were evaluated by IHC. **Results:** IHC analysis showed that although GSK-3α was prevalent in CRC clinical samples, only the expression of GSK-3-β was significantly associated with adverse clinicopathological factors (advanced TNM stages, poor progression-free survival and right-sided location). Furthermore, GSK-3β expression negatively correlated with PD-1 expression, confirming its association with a pro-tumorigenic microenvironment. As expected, in the in vivo assay a clear antitumoral effect was observed in anti-PD-1 treated mice, which was consistent with the proven efficacy of nivolumab in dMMR tumors. Remarkably, GSK-3i alone did not affected tumor growth but abolished the anti-tumoral effect of nivolumab. Interestingly, a significant increase of CAFs was observed in GSK-3i-treated tumors. **Conclusions:** Our findings support that GSK-3β expression may constitute a clinically relevant marker in CRC, and suggest that this kinase modulates the tumor stroma and microenvironment thereby influencing the response of CRC tumors to immunotherapy.
Fundings: PID2019-105256RB-I00, P20-00967.

PSI.ee. Immunotherapy followed by Cell Therapy in relapsed/refractory acute B cell lymphoblastic leukemia.

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Keywords: acute lymphoblastic leukemia, immunotherapy, cell therapy.

Abstract: Acute lymphoblastic leukemia (ALL) is an hematological neoplasm whose prognosis in relapse or refractoriness(R/R) is very poor.

New therapies based on immunotherapy (IT) against tumor antigens expressed by leukemia cells such as CD22 or CD19 (Inotuzumab or Blinatumomab) have shown a higher ratio of complete remissions and elimination of the leukemic population compared to conventional chemotherapy, with an acceptable safety profile. Therefore, they can be used as a bridge therapy to subsequent cell treatments (HSCT, DLI, CAR-T) in a greater number of patients, which may lead to an improvement of their survival.

We retrospectively analyzed 12 R/R B-ALL patients treated with immuno and cell therapy in our institution; 50% had previous Allo-HSCT. Patients received at least one cycle of Inotuzumab(n=6) or Blinatumomab (n=6).

Minimal Residual Disease (MRD) and the normal B lymphopoiesis pattern were quantified by Flow Cytometry in a FACSCanto II Cytometer.

Regarding the clinical response, all patients achieved a complete response following first IT cycle; 91.7% was consolidated with cellular therapy (8 underwent Allo-HSCT, one received DLI, and 2 patients CAR-T therapy). Only one patient progressed at the end of the 2nd cycle, not receiving subsequent treatment. 79% of cases showed negative MRD prior to receive cell therapy.

Regarding the safety profile, 100% of the patients presented grade II-IV hematological toxicity and two patients presented grade II hepatic and neurological toxicity, both reversible. Two patients who received Allo-HSCT suffered from hepatic veno-occlusive disease (HVOD), both treated with Inotuzumab and previous HSCT.

The overall survival probability estimated using Kaplan-Meier method was 44.6 +/- 17.6%, with 7 patients alive at the end of the follow-up period.

In conclusion, the treatment strategy with immunotherapy combined with cell therapy, achieves high rates of negative MRD in advance B-ALL, constituting a curative treatment option.

PSI.ff. 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: Background: 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.

PSI.gg. SPARCC, MASES, LEI and MEI Indexes capture different patients with enthesitis in Axial Spondyloarthritis, Peripheral Spondyloarthritis and Psoriatic Arthritis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Enthesitis, Spondyloarthritis, Psoriatic Arthritis.

Abstract:

Introduction. Reliable clinical instruments have been developed to assess enthesitis in Spondyloarthritis (axial (axSpA), peripheral (pSpA)) and psoriatic arthritis (PsA)): SPARCC, LEI, MASES and MEI. The aim was to evaluate whether the prevalence of patients with at least one enthesitis across the three subtypes of SpA differs depending on the use of SPARCC, LEI, MASES and MEI indexes. **Methods. 4185** patients from the cross-sectional ASAS-PerSpA study with a diagnosis of axSpA (2719), pSpA (433) and PsA (1033) according to the Rheumatologist were included. The location of enthesitis during the study visit were evaluated according to the four indexes. The prevalence of patients with at least one enthesitis according to the different indexes were compared across the three diseases and pair-wise agreement between indexes were evaluated using the Cohen's kappa. **Results.** In the overall population, 10.7%, 8.3%, 13.5% and 17.2% of patients showed at least one enthesitis according to the SPARCC, LEI, MASES and MEI indexes, respectively. Figure 1 shows that, among patients with axSpA, MEI and MASES indexes capture the majority of patients with at least one enthesitis (98.7% and 82.4%, respectively), while in pSpA and PsA, MEI and SPARCC are the indexes which capture the majority of patients with enthesitis (100% and 84.6% for MEI and SPARCC in pSpA, and 97.3% and 77% for MEI and SPARCC in PsA, respectively). In the total population, MASES and MEI showed the strongest agreement for patients with at least one enthesitis (absolute agreement 96.3%; Cohen's kappa: 0.86). Similar results were found among axSpA patients (97.3%; 0.90). In pSpA patients, SPARCC and MEI showed the strongest agreement (97.2%; 0.90), as well as among PsA patients (95.4%; 0.82). **Conclusions.** These results suggest that the prevalence of enthesitis across entities differ depending on the disease and on the use of the different indexes.

PSI.hh. DNA Repair profile and temozolomide resistance in glioblastoma cells.

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

Abstract: Resistance to antitumor therapies is a major problem in the treatment of cancer patients. The resistance to therapy has been correlated, among other causes, with the action of DNA repair mechanisms that repair the damage caused by an antitumor agent. Glioblastoma (GBM) is an aggressive form of brain cancer with a low survival rate, due in large part to resistance to temozolomide (TMZ), a DNA alkylating agent used in combination with radiotherapy as first-line treatment after surgery. A role in TMZ resistance has been proposed for high expression of DNA repair proteins such as MGMT, (O6-meG DNA methyltransferase), or MPG (N-Methylpurine DNA Glycosylase). However, increased levels of MGMT or MPG only explain a small percentage of cases of tumours resistant to TMZ, suggesting that the resistance to such alkylating agent is not mediated by a single molecular mechanism. Moreover, in recent years there has been increasing interest in studying the role that epigenetic silencing of DNA repair genes plays in tumour generation and in antitumor therapy. Since DNA repair mechanisms contribute to TMZ resistance and are epigenetically regulated, tumour-specific DNA repair and epigenetic signatures in GBM may be used as predictive biomarkers of patient response to treatment. Here, we have characterized a panel of GBM cell lines analysing their sensitivity to TMZ, studying the expression and DNA methylation levels of different DNA repair genes. We have found significant differences between TMZ-resistant and TMZ-sensitive GBM cells in the expression levels of some genes involved in a DNA repair pathway that has not been previously implicated in the repair of TMZ lesions. Our results may help to identify novel predictive genetic biomarkers and/or therapeutical targets in GBM treatment.

PSI.ii. Obesity induces central hypogonadism and metabolic comorbidities via miRNA-137/325 mediated repression of hypothalamic kisspeptin.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: obesity, obesity-induced hypogonadism, miRNAs, metabolism, kisspeptin, reproduction.

Abstract:

Introduction/Aim: Obesity is a life threatening condition associated with numerous comorbidities. Among them, central hypogonadism, defined by low circulating testosterone, has been recently suggested to contribute to metabolic complications of obesity, especially in men. Yet, the mechanisms for obesity-induced hypogonadism (OIH), and its actual role in the generation/evolution of the metabolic alterations linked to obesity remain ill defined. Recent data suggest that OIH may be bound to suppression of the hypothalamic Kiss1 system, which is a major activator of the reproductive axis. Yet, the mechanisms for Kiss1 suppression in obesity remain unknown. Considering our recent evidence for a role of microRNAs (miRNAs) in the modulation of the Kiss1 system, here we aimed to identify novel miRNAs capable of regulating kisspeptin expression and evaluated their potential contribution to OIH. **Methods/Results:** Bioinformatic analyses on the KISS1 gene were conducted with different algorithms to seek for potential miRNA regulators. Selection of miRNA candidates was based on the following criteria: 1) to be identified in at least two databases; 2) to show an evolutionary-conserved seed region (rat, mouse, human); and 3) to be deregulated by metabolic alterations. Using these criteria, the miR-137-3p/miR-325-3p tandem was selected, as putative modulators of a common, evolutionary conserved seed region at KISS1 3'-UTR. A repressive action of miR-137-3p/miR-325-3p at the human KISS1 3'-UTR was documented using luciferase reporter assays. In addition, central injection of a miR-137-3p mimic induced a decrease in kisspeptin levels, together with a drop in circulating testosterone in lean male rats. A Target Site Blocker (TSB), tailored to selectively block the repressive interaction of miR-137-3p/miR-325-3p at the Kiss1 3'-UTR, was centrally injected to obese male rats, displaying reduced testosterone (T) and gonadotropin (LH) levels. TSB infusion increased hypothalamic kisspeptin levels and enhanced LH and T concentrations. Of note, this model of OIH suffered also marked cardio-metabolic alterations, including increased systolic blood pressure, altered vascular reactivity, glucose intolerance and insulin resistance, that were ameliorated by TSB administration. Notably, reversal of OIH by TSB was more effective than that induced by chronic kisspeptin or testosterone treatments in obese rats. Conversely, over-expression of miR-137 in Kiss1 neurons reduced Kiss1/kisspeptin levels and partially replicated reproductive and metabolic alterations of OIH in lean mice. **Conclusions:** Our data provide conclusive evidence for a relevant role of miR-137-3p/miR-325-3p, as repressors of kisspeptin, in the pathophysiology of

OIH, and strongly suggest that central hypogonadism is a key contributor for the metabolic complications of obesity.

PSI.jj. Mindfulness-based Interventions in Adolescents with Type 1 Diabetes Mellitus: A Systematic Review.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Type 1 diabetes mellitus, adolescence, mindfulness-based interventions, emotional well-being, health related quality of life.

Abstract:

Background: Type 1 diabetes mellitus in adolescence is one of the main chronic diseases worldwide in this population group, affecting their well-being and health related quality of life. **Objective:** To know the impact of mindfulness-based interventions as a strategy for regulating emotional well-being in adolescent patients with type 1 diabetes mellitus. **Methodology:** A systematic review of randomized controlled trials published in the period 2012-2022 was carried out through a bibliographic search in electronic databases (Web of Science, MEDLINE, and SciELO). The quality of the studies was assessed using the CONSORT Statement. **Results and discussion**: In light of the reviewed results, albeit modestly, mindfulness-based interventions could be presented as an effective strategy to improve the emotional well-being and health related quality of life of adolescent patients with type 1 diabetes mellitus. **Conclusion:** Psychological intervention in the promotion of health and wellbeing, from the guidelines for the control of type 1 diabetes mellitus, should take into account to intervene in the adolescent population through interventions based on mindfulness programs.

PSI.kk. Functional Changes of CD4 and CD8 T-Cell Subsets with Age and CMV Infection.

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Scientific Program: Active aging and frailty.
Keywords: CD57; T-cell response; aging; cytomegalovirus.

Abstract: Memory T cells undergo replicative senescence upon prolonged proliferation by chronic antigen stimulation. In humans, senescent T cells are marked in part by loss of CD28 expression and acquired expression of CD57. However, these senescent T cells can still produce large quantities of pro-inflammatory cytokines and cytotoxic mediators. CMV infection also induces the expansion of CD57+ T-cells, but whether this has a beneficial, detrimental, or neutral role for immunity is still debated. The increased functionality of CD57+ T-cells can be considered useful, but a growing body of evidence suggests that these cells may have pathogenic potential in conditions like chronic kidney rejection, cancer, atherosclerosis, and myocardial infarction, underscoring the detrimental roles of these cells in various chronic inflammatory responses. We have demonstrated that CMV-seropositivity is associated with the expansion of polyfunctional CD57+ T-cells in young and middle-aged individuals in response to different stimuli. Here, we expand our results on the effects of age and CMV infection on T-cell functionality in a cohort of healthy middle-aged and older individuals stratified by CMV serostatus. Specifically, we studied the polyfunctional responses (degranulation, IFN-γ and TNF-α production) of CD4+ and CD8+ T-cells according to CD57 expression in response to Staphylococcal Enterotoxin B (SEB). Results showed that CD57+ T-cells were mainly expanded in CMV-seropositive individuals and clearly demonstrate that in the absence of CMV, age has no effect on the size or polyfunctionality of both the CD4 and CD8 T-cell responses to SEB. The study shows that CD57+ T-cells are more polyfunctional than CD57− T-cells in any age group. Our results also show that CMV, but not aging, has a significant role in the expansion CD57+ T-cells. This data could be of clinical importance because CMV infection can be treated, and the expansion of such cytotoxic proinflammatory cells could potentially be prevented.

PSI.II. Validity of the isometric contraction test for the diagnosis of muscle temporomandibular disorders with DC/TMD axis I as gold standard.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: temporomandibular disorders; test accuracy; muscle dysfunction; orofacial pain.

Abstract:

Objective: The aim of this study was to determine the validity of the Isometric contraction test of the occlusive masticatory muscles (ICTest), to diagnose the axis I myalgia of DC/TMDs. **Methods:** The study was carried out with 63 participants, being 33 subjects with DC/TMD of the Axis I, and 30 age matched healthy controls. One of the evaluators applied the DC/TMD criteria of the Axis I (gold standard), both at a general level, called myalgia, and in its different subgroups: local myalgia, myofascial pain and myofascial pain with referral. Another evaluator applied the ICTest, held for 40 seconds. The validity analysis between the DC/TMD and the ICTest determined sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and Youden's index. **Results:** The validity of the ICTest showed high sensitivity and specificity values for all the analyses, with the exception of the sensitivity, negative LR+ and Youden's index of the myofascial pain with referral, that showed low ability (<50%) to detect DC/TMD of the axis I cases. In all cases, specificity was higher than sensitivity, which determine agood capacity of ICTest to be a confirmatory test for muscle TMDs. Likelihood ratios showed acceptable probabilities of suffering the DCT/TMD of the axis I or not, depending on the positive or negative result of the ICTest. **Conclusions:** The ICTest is valid to diagnose subjects with DC/TMD of the axis I. Specificity values are higher than sensitivity values, both for Myialgia and the subtypes of Myalgia. Myofascial pain with referral showed the worst validity values, with sensitivity below 50%. The ICTest can be applicable in clinical practice, although further knowledge of other metric features is required.

PSI.mm. Upper limb muscle mechanical characteristics in women with multiple sclerosis: a case-control study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Women; Multiple Sclerosis; Tone; Cognitive Tests; MyotonPro.

Abstract: Spasticity is one of the most common symptoms of multiple sclerosis (MS), which increases severely as the disease progresses. The aim of this study was to identify the differences in the muscle mechanical characteristics (MMC) of the upper limb muscles between women with MS and healthy women. A cross-sectional observational study of cases and controls with non-probabilistic recruitment of consecutive cases was carried out. The sample consisted of 25 women with multiple sclerosis and 30 healthy women. Clinical and cognitive scales, and the MyotonPro device were applied to identify the clinical status and the MMC, respectively. For the between groups comparison, the Student's t test for independent samples and the Mann-Whitney U test were applied depending on the data distribution. For bivariate correlations within the groups, the Spearman´s test and Pearson´s tests were used. The “Time 25 Foot Walk”, “9 HDT non- dominant”, “9 HDT dominant” and “Symbol Digit Modalities Test (SDMT)” tests showed statistically significant differences, with lower results for the MS group, as well as in the tone of the left anterior brachialis muscles (p=0.003) and right (p=0.011) and left (p=0.039) extensor digitorum muscles, being higher in the women with MS. In the MS, the higher age, the higher EDSS score (rho= 0.448; p=0.013), and the higher "VAS", the higher "PENN Scale" score. "Time 25 Foot Walk" was positively correlated with the tone of the left triceps brachial muscle and the extensor digitorum creep. It is concluded that the resting tone of the upper limb in women with multiple sclerosis is higher than that of healthy women, and it is associated with cognitive tests results.

PSI.nn. Change in miRNA expression is induced by healthy diets and associated to the carotid intima-media thickness in patients with coronary heart disease: CORDIOPREV study

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Scientific Program: Nutrition, Endocrine and Metabolic Diseases.
Keywords: microRNA, atherosclerosis, Mediterranean diet, low fat diet, cardiovascular disease.

Abstract:

Background and Objective: Cardiovascular disease has the greatest mortality rate worldwide. It originates and progresses due to atherosclerosis, a chronic thickening of the carotid intima-media. Previous studies have shown the role of miRNAs in this process, and their expression may be regulated by dietary components. Our objective was to study the effect of the diet on miRNA expression in relation to the 5-year change in carotid intima-media thickness (cIMT) in patients with coronary heart disease. **Material and Methods:** The present study included 240 participants from the CORDIOPREV study: 120 with the greatest cIMT progression after 5 years of consuming the low-fat diet (LF)(n=58) or the Mediterranean diet (Med diet)(n=62), and 120 with the greatest cIMT regression after consuming either diet (n=51 and 69, respectively). Expression of 28 miRNAs in peripheral blood mononuclear cells before and after 5 years of intervention was determined by RT-PCR. Repeated measures ANOVAs were conducted separately by diet. **Results:** After consuming the LF diet, miR-21 expression decreased in patients whose cIMT regressed (p=0.009), while miR-92a expression increased in patients whose cIMT progressed (p=0.001). After consuming the Med diet, miR-150 expression decreased and miR-365 expression increased in patients whose cIMT regressed (p<0.001 both). The increase in miR-365 expression was associated with a lower consumption of total fat and saturated fat (p<0.001 both). **Conclusion:** The two healthy diets induce different changes in the miRNA expression profile, which could be associated with intima media thickness in patients with coronary heart disease. An understanding of this epigenetic regulation may allow a more personalized selection of the appropriate dietary model to lower the risk of atherosclerosis development.

PSI.ññ. COPD in Severe Mental Illness: A three years longitudinal study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: COPD, Severe Mental Illness.

Abstract:

Background: People with Severe Mental Illness (SMI), such as schizophrenia or bipolar disorder, have up to 20 years less life expectancy, with respiratory causes being one of the most frequent causes of death. Those produced by Chronic Obstructive Pulmonary Disease (COPD) are up to 9 times more frequent in SMI. Smoking is the first preventable factor, with consumption rates that triple those of the general population. Very few works have evaluated these patients using spirometry, the Gold Standard test in the study of pulmonary function and the diagnosis of COPD. None have done so longitudinally, as occurs with other factors associated with lung damage, including inflammation and metabolic syndrome. **Objectives:** 1. Evaluate, longitudinally, the presence of lung damage in patients with schizophrenia and bipolar disorder. 2. Evaluate the evolution of respiratory function and its analytical, clinical, cognitive and functional impact. **Ongoing research Project:** Observational, prospective and multicenter study lasting 36 months. 390 individuals grouped into 4 samples will be followed: SMI-Smoker; SMI-Non Smoker; Population without mental illness – Smoker; Population without mental illness – Non Smoker between 40 and 70 years old. In them, lung function will be studied by spirometry, including the diagnosis of COPD and its staging. Likewise, other variables that will be analyzed in individuals are those related to their psychopathological and functional evolution, such as PANSS, and inflammatory markers such as protein C. Finally, smoking habits, comorbidities, neuropsychological performance and global functioning will be evaluated in each session. **Conclusions:** Follow-up for 3 years will make it possible to define, for the first time, the critical times for primary and secondary prevention. The promotion of early diagnosis of respiratory damage should favor the evolution of the mental disorder and control a determining factor in the risk of morbidity and mortality.

PSI.oo. The effect of FGF23 blockade on blood pressure control in hypertension

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: None.

Abstract:

Introduction: FGF23 is a hormone elevated during the chronic kidney disease. Several studies suggest a hypertensive effect of FGF23. We have already observed a relationship between FGF23 and arterial stiffness through phenotypical switching of vascular smooth muscle cells (VSMC). Now, a direct effect of FGF23 on hypertension will be explored. **Methods:** FGF23 (20ng/mL) was added to VSMC and human umbilical vein endothelial cells (HUVEC) for 9 days or 48 hours respectively. Intracellular calcium levels were measured by fluorescence using Cal-520 AM calcium dye in cells treated with FGF23 vs. control cells after AngII (100nM) stimulation. Thapsigarnin was used to evaluate intracellular calcium stored in the endoplasmic reticulum (ER). In vivo, WKY, SHR and SHR + FGF23 blockade (anti-FGF23) rats were used for 14 days. Changes in blood pressure (BP), mineral metabolism, endothelin-1 (ET-1) and angiotensinII-IV were evaluated as well as histological changes in the thoracic aorta. **Results:** Results showed an increase in intracellular calcium levels in FGF23-treated VSMCs and HUVECs respect to control cells. High levels of FGF23 increased also the calcium stored in the ER of VSMC. IP3 inhibition by 2-APB avoided the FGF23-induced calcium entry. In vivo, FGF23 blockade on SHR reduced urinary P excretion, increased phosphate and calcitriol in plasma and significantly reduced BP and ET-1 levels. There was a positive correlation between FGF23 and ET-1. Interestingly, FGF23 blockade increased AngII-IV concentrations. Histological analyses revealed a larger diameter of thoracic aortas in anti-FGF23-treated rats than in SHR. Other histological changes such as changes in the structure of elastin fibers, vascular remodeling, and a differential expression of calcium channels were observed after FGF23 blockade. **Conclusions**: A direct effect of FGF23 on calcium entry of vascular cells is demonstrated. In vivo, FGF23 blockade decreased BP and ET-1 levels, however, with an increased AngII concentration and structural changes on the vascular tissue.

SESSION III.

NUTRITION, ENDOCRINE AND METABOLIC DISEASES I.

IIIa. Dysregulation of splicing machinery as early biomarker of diabetic nephropathy: From the CORDIOPREV study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: diabetes, splicing, cardiovascular disease, kidney.

Abstract:

Introduction: Diabetic nephropathy (DN) is the main cause of chronic kidney disease (CKD) initiated by uncontrolled diabetes. In fact, the concomitant presence of renal and cardiovascular disease is closely related to a higher probability of associated comorbidities than separately. This context shows the need to characterize the mechanisms involved in these diseases, since they share risk factors that can be addressed jointly. Alternative splicing is involved in different pathologies such as diabetes and CKD, however, few has been described in the identification of changes in the splicing machinery responsible for key isoforms in DN. **Methods:** 190 patients with type 2 diabetes mellitus, recently diagnosed, and with coronary heart disease from the CORDIOPREV study were evaluated. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) at baseline. Patients were classified into quartiles (Q1=low eGFR vs Q4=high eGFR). Expression of 93 genes associated with splicing machinery and related isoforms was measured in peripheral mononuclear cells of the study patients. **Results:** Partial least squares regression analysis (VIP score PLS-DA) made it possible to discriminate 3 genes of the 72 associated with the splicing machinery in the comparison of the extreme quartiles Q1 vs Q4, with hnRNP2, esrp2 and mbnl1 being the ones that obtained the highest punctuation. In the analysis of covariance, the expression of esrp2 (Q1=1.024e+004±4.153e+004 vs Q4=1.372e+005±4.537e+004, p=0.029) was lower in Q1 compared to Q4 while the CD44 isoform levels were higher in Q1 than in Q4 (Q1=1.15e+007±2.38+006 vs Q4=1.12e+007±2.42e+006, p=0.029). **Conclusions:** Our results suggest that the expression of the esrp2/cd44 axis is associated with renal function in the diabetic population and, therefore, act as a potential biomarker for the development of diabetic nephropathy.

IIIb. Molecular and clinical implications of somatostatin receptor profile and somatostatin analogues treatment in high-grade astrocytomas.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: somatostatin receptors; somatostatin analogs; glioblastoma; diagnostic/prognostic biomarker; therapeutic target.

Abstract: High-grade astrocytomas (HGAs) remain the most prevalent and malignant brain tumor based on its locally aggressive behavior, being glioblastoma (grade-IV astrocytoma) the most lethal. The current standard treatment for glioblastomas consists of surgery followed by radiotherapy and/or chemotherapy. However, the average period of survival is still only around 14 months after the first intervention. Therefore, there is a clear need for the identification of novel diagnostic/prognostic tools and therapeutic strategies to manage and treat these brain pathologies. In this context, somatostatin analogues (SSA) are efficacious and safe treatments for a variety of tumors, but the presence of somatostatin receptors (SSTRs) and pharmacological effects of SSA on HGAs are poorly known. In this study, we demonstrated that the expression levels of 5 canonical receptors (SSTR1-5) were significantly down-regulated in HGAs compared to non-tumor samples in different available human cohorts (both internal and external cohorts). Notably, SSTRs expression levels were inversely correlated with the tumoral grade, and, consequently, with the aggressiveness of HGAs. Moreover, ROC curve and survival analysis demonstrated the potential value of SSTRs, mainly SSTR1 and SSTR2, as novel diagnostic and prognostic biomarkers. Additionally, lower expression levels of SSTRs were associated with aggressive parameters (i.e., IDH wildtype status, classical/mesenchymal subtypes, etc.) showing a potential pathophysiological role in HGAs. Notably, treatment with different somatostatin analogues and specific receptor-agonists (especially octreotide, pasireotide and SSTR1/SSTR2/SSTR5 agonists) significantly reduced cell proliferation in primary patient-derived glioblastoma cell cultures. Altogether, this study demonstrated that SSTRs expression is dysregulated in HGAs vs. control brain tissues and could represent novel diagnostic/prognostic biomarkers, since their expression is associated with critical clinical/pathological features. Moreover, our data unveil clearantitumoral effects of SSAs on HGAs, opening new avenues to explore their potential as targeting therapy for these devastating brain pathologies.

IIIc. Role of Let-7b-5p and miR-191-5p in the development of early obesity and associated metabolic comorbidities.

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

Abstract: Obesity is a public health problem with >340 million children and adolescents suffering from overweight/obesity, according to WHO data in 2016. This condition increases the risk of developing other comorbidities in adulthood, including metabolic and reproductive disorders. MicroRNAs (miRNAs) have emerged as promising biomarkers and therapeutic targets in different pathologies. Previous high-throughput analysis from our group identified different circulating miRNAs dysregulated between normal-weight and obese prepubertal girls, suggesting their potential involvement in the development of childhood obesity. Validation of these results in Wistar rats allowed us to select two miRNAs (Let-7b-5p and miR-191-5p), as potential targets involved in the mechanisms underlying the development of obesity and associated comorbidities. Blockade of these specific miRNAs with LNA technology (antagomirs; LNA-let-7b and LNA-miR-191) in a model of infantile obesity in female rats resulted in significant metabolic and reproductive changes. In detail, treatment with LNA-miR-191 affected the reproductive system, increasing the estrous cycle length. In addition, LNA-let-7b and LNA-miR-191 treatments, during the peripubertal period, produced an increase in body length and worsened different metabolic parameters during the adult period, including increased body weight, glucose intolerance and insulin resistance, being these effects more pronounced in LNA-miR-191 treated animals. Further analyses suggested that these metabolic manifestations could be associated with an increase in food intake and lower energy expenditure, the latter related with a significant diminution in the thermogenic activity of the brown adipose tissue. All in all, our results suggest that the suppression of the actions exerted by both LNA-let-7b and LNA-miR-191, during the peripubertal period, worsens the metabolic conditions associated with obesity during the adult stage. These findings point out a protective role for these miRNAs against the development of late-onset and long-lasting metabolic consequences of infantile obesity.

IIId. Basketball exercise reduced plasma cytokines in prepubertal children. Bipic-study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: healthy, fitness, physical activity, childhood, youth sports.

Abstract:

Objective: The aim is to evaluate the effects of a basketball training in combination of dietary recommendations based on the Mediterranean diet on inflammatory biomarkers. **Methods:** Two basketball teams (20 players) of healthy prepubertal boys (7 -11 years old) were selected to engage in an exercise program. It was divided into two periods: a pre-season (6 weeks), including 5 training sessions per week of 2 hours each one (Monday to Friday); and immediately afterward, a season for 32 weeks, including 3 training sessions per week of 2 hours each one (after school) and a game during the weekend. The sample was divided in two group, an intervention group which received individualized dietary recommendations, teaching material and group workshops on nutritional education, and a control group which did not receive dietary advice. Body composition components were obtained by bioelectrical impedance analysis. C-reactive protein was determined using a high-sensitivity. Luminex ® 200™ System to determine: adiponectin, resistin, leptin, plasma hepatic growth factor (HGF), interleukin 6 (IL-6), IL-8, MCP1, nerve growth factor (NGF), plasminogen activator inhibitor-1 (PAI-1), and TNF-α. Standardized Eurofit battery tests were performed to evaluate fitness. **Results:** 17 players finished the intervention. When it was compared the basal evaluation with the intervention, the group of players showed a decrease in the average BMI percentile and Z-score BMI decreased ($P<0.005$); an increase in the aerobic and anaerobic capacity tests ($P<0.001$) and in the strength tests ($P<0.001$); and a reduction in the inflammation variables: PAI and MCP-1 ($P=0.008$) and resistin ($P=0.048$). The diet group showed reduction on IL-6 ($P>0.05$). No significant differences were found between diet group and control group in both measure time. **Conclusions:** Practice basketball three days per week and two hours each one, joint to diet recommendations seems an effective option to reduce the increase of obesity during childhood.

IIIe. Lessons from lean but metabolically unhealthy individuals: new highlights on adipose tissue dysfunction.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Insulin resistance, obesity, prediabetic lean, inflammation, fibrosis.

Abstract: Metabolic diseases such as insulin resistance are generally associated with obesity though it can also develop in lean individuals (BMI< 25 kg/m2), who are thus referred as to "metabolically unhealthy, normal-weight (lean) individuals" or "metabolically-obese, normal-weight' phenotype". The pathophysiological mechanisms underlying metabolic dysfunction despite a lean phenotype are far from being understood. In fact, metabolically-obese lean individuals represent a valuable group for studying the mechanisms underlying the development of metabolic disease independently of weight gain. In these individuals, insulin resistance may be related to altered body composition and fat distribution (visceral obesity) as well as to differences in adipocyte differentiation and altered lipid turnover. However, it is unknown whether subcutaneous adipose tissue, which has been proposed to be even protective in obesity from a metabolic point of view, may be altered in these group of individuals. In this scenario, the main objective of the study is to analyze the proteome of subcutaneous adipose tissue of lean individuals with different degrees of insulin sensitivity in order to identify possible biomarkers of insulin resistance associated to adipose tissue dysfunction. **Methods:** A comparative proteomic study (LC-MS, diaPASEF) of whole adipose tissue samples from lean normoglycemic vs. prediabetic subjects was performed. Bioinformatic analysis of the proteomic data was carried out using different softwares (Spectronaut™, IPA, Reactome,…). In addition, in vitro models of insulin resistance in adipocytes were used for validation of selected biomarkers. **Results:** A total of 2031 proteins were detected in the proteome of human subcutaneous fat, with 966 being significantly different between the two groups (Q-value <0.01). Differentially expressed proteins are mainly involved in processes related to actin signalling or integrin signalling, and processes related to metabolism were up- and down-regulated, respectively, in prediabetic subjects. Specific analysis of the components of the extracellular matrix, i.e., matrisome, was carried out to explore the possible role of fibrosis in the development of insulin resistance in lean individuals. This analysis identified 146 matrisome proteins, among which 70 were significantly different between the two groups (Q-value <0.01). Most of the major groups of proteins composing the extracellular matrix (glycoproteins, fibrotic collagens, proteoglycans, and affiliated proteins) were found overexpressed in prediabetes but secreted factors, which were down-regulated in these metabolically unhealthy individuals. In **conclusion**, our study is the first to describe the main

components underlying the transition from health to prediabetes in lean individuals and highlights a role of the extracellular matrix in the development of insulin resistance independently of weight gain.

Fundings: MICINN/FEDER (PID2019-108403RB-I00); PRE2020-095163. CIBERobn (ISCIII).

IIIf. E-ducass Project: Educational strategy to improve cardiovascular health and food insecurity on a vulnerable population.

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

Abstract: Food insecurity is involved in the most important health problem: the increasing of noncommunicable diseases. The majority of strategies aimed to lifestyle improvement are frequently expensive and effective only in the short-term. Our hypothesis is that an educational program on a healthy lifestyle, with an initial intervention and subsequent reinforcements, which promotes health literacy, could improve the long-term health status, and mitigate food insecurity. The main objective is to perform a 24-month intervention improving cardiovascular health (Life's Simple 7, American Heart Association), in a group of vulnerable families at risk of food insecurity.

The first phase includes an initial training through workshops (basic intervention model). Then, volunteers will be randomized in three groups, 1. Non-intervention; 2. Motivational workshops, every 3 months and with limited cost (traditional advanced intervention model), and 3. Educational workshops, every 15 days, with videos from YouTube channel or WhatsApp/text message (e-learning advanced intervention model).

The study population is composed by 460 subjects (12-80 years), 43% men y 57% women. 46,6% of adults (19-80 years) and the 12,7% of young (12-18 years) suffers from obesity and 21,9% of adults and the 22,2% of young have overweight. The levels of triglycerides in adults were 172±7mg/dl, for 19-49 years and 200±13mg/dl, for >50 years; LDL-cholesterol levels were 90±2mg/dl, for 19-49 years and 103±5 mg/dl, for >50 years, and the fasting glucose levels were 99±1mg/dl, for 19-49 years and 109±3mg/dl, for >50 years.

E-ducass program pretends to offer an educational strategy as a tool to improve cardiovascular health in vulnerable populations, in an effective, secure, and sustainable way. At the beginning of the program our population overtake the obesity rate described in Spanish population (46,6%vs17,4% for adults y 12,7%vs10,3%, for young), with plasmatic glucose levels in prediabetes range and lipid parameters above recommended.

SESSION IV.

MULTIDISCIPLINARY II.

IVa. MicroRNAs in lung epithelial cells expressing SARS-CoV-2 accessory protein ORF8 can regulate immunometabolism

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: SARS-CoV-2; accessory proteins; ORF8; microRNA; immune response; metabolism; COVID-19.

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the causative agent of COVID-19 pandemic that has caused more than 6.2 million deaths worldwide (WHO, 30 May 2022). The molecular mechanisms of SARS-CoV-2 infection and virus–host interactions are still unclear. The SARS-CoV-2 genome contains multiple open reading frames that code for a total of eleven accessory proteins. Although none of these are essential for virus replication, some appear to have a role in virus pathogenesis. In addition, it has been shown that changes in miRNA expression are linked to severity of COVID-19 however the role played by miRNA-mRNA networks in disease etiology remains to be elucidated. Here, we examined changes in the mRNA and miRNA expression of A549 pulmonary epithelial cells to identify the transcriptomic regulatory networks associated with SARS-CoV-2 accessory proteins ORF8 expression. A total of 1,066 differentially expressed genes and 119 differentially expressed miRNAs were identified. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Ingenuity Pathways Analysis (IPA) were carried out. We show that the most microRNAs may regulate the expression of genes involved in metabolic pathways firstly, MAPK signaling pathway and cytokine-cytokine receptor interaction. UGT8 gene is differentially expressed compared to the control cell. Silencing of this gene has been shown to impair glycolysis. Moreover, miRNA hsa-miR-124-3p could regulate the expression of the IPTKB and PLCB1 genes, which are related to the metabolism of inositol triphosphate (IP3). Also, IPTKB regulates immune cell function and is required for T and B cell development. This study demonstrates that ORF8 induces a robust host miRNA response, which could be involved in metabolic reprograming and immune dysregulation.

IVb. Integrated high-throughput proteomics and machine learning analysis in systemic lupus erythematosus patients identify distinctive clinical profiles and novel biomarkers related to cardiovascular risk and lupus nephropathy.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Systemic lupus erythematosus, serum inflammatory profile, cardiovascular risk, renal involvement.

Abstract:
Background: Systemic lupus erythematosus (SLE) is a remarkably heterogeneous autoimmune disease. At present, our knowledge of serum protein patterns related to cardiovascular (CV) risk and renal involvement is limited.
Objectives: To characterize clinical phenotypes in SLE patients through serological analysis of proteomic profiles. **Methods:** Proximity extension immunoassay (PEA, Olink) was used to assess the serum levels of 184 inflammation and organ damage-related proteins in 141 SLE patients and 28 healthy donors (HD). The contribution of molecular profiles to disease features was evaluated by unsupervised machine learning clustering analyses. Gene ontology enrichment analysis were performed to interrogate the biological meaning of the molecular signatures identified. **Results:** Several circulating proteins related to inflammation and organ damage were coordinately altered in the serum of SLE patients in relation to HD. Unsupervised clustering analyses differentiated 2 patients clusters presenting different proteomic profiles. Clinically, patients belonging to cluster 1 were characterized by higher status of disease activity (SLEDAI over 5,3) and prevalence of positivity for anti-ENA and anti-dsDNA antibodies in relation to patients belonging cluster 2. These patients further showed high incidence of dyslipidemia, obesity and hypertension (higher CV-risk) and preponderance of lupus nephritis (LN) and proteinuria. Sixty-seven proteins were found deregulated between clusters, including inflammatory mediators and numerous proteins related to renal disease and increased CV risk. Of note, 50 proteins were found altered in patients with LN vs patients without LN. Logistic regression analyses identified several proteins whose levels distinguished LN patients, including specific proteins involved in renal damage not previously reported in the serum of SLE patients. **Conclusions:** 1) The proteomic analysis in the serum of SLE identified molecular patterns distinguishing patients with high disease activity, enhanced CV-risk and active LN, including several novel SLE biomarker-candidate proteins. 2) Combination of novel and traditional disease-specific biomarkers may improve diagnosis and management of SLE.

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IVc. CMV in aortic stenosis.

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

Abstract:

Aims: During ageing immune cells suffer alterations which lead to a decline of both the adaptive and innate immune responses, also known as “immunosenescence”. Immunosenescence is not always a consequence of chronological ageing, and situations involving chronic stimulation of the immune system by persistent antigens can lead to “early or accelerated immunosenescence”. In this regard, our group has demonstrated that the expansion of proatherogenic and proinflammatory CD28null T cells is driven by cytomegalovirus (CMV) chronic infection and not an effect of age. In the past years, CMV latent infection has also been associated with several autoimmune conditions, and CMV-seropositivity has been associated with an increased risk of cardiovascular death by up to 20%. Recent studies suggest that aortic stenosis (AS) is an active inflammatory atherosclerotic-like process. Furthermore, the expansión of peripheral CD28null T cells has been observed in AS patients, suggesting that CMV infection could have a role in the degeneration of the aortic valve. **Methods:** We performed a detailed phenotypical and functional characterization of both peripheral and valvular T cells from AS patients (49-80 years), and sex/age matched healthy volunteers (HD) by multiparametric flow cytometry. The analysis included the identification of infiltrating CMV-specific T cells in the aortic valve tissue and the response of these cells to CMV peptides. **Results:** CMV-associated pro-atherosclerotic and highly cytotoxic (granzyme B) T cells were increased in peripheral blood and valvular tissue in AS patients in comparison to HD. Furthermore, we found both CD4+ and CD8+ CMV-specific T cells (tetramer positive) infiltrating the aortic valve tissue of AS patients. The presence of CMV-specific T cells in the diseased valves was further corroborated by functional assays against CMV peptides (TNF and IFN-γ production). **Conclusions:** Our results show for the first time an association of AS with CMV chronic infection and supports a potential role of CMV in the degeneration (calcification) of the aortic valve, probably mediated, at least in part, by CMV-specific T cells and by the CMV-driven expansion of proinflammatory T cells.

Fundings: This research was funded by the Spanish Instituto de Salud Carlos III from the Ministry of Health, grant number PI19/00075 (awarded to Pera A.) and FI20/00194 (awarded to AlvarezHeredia P.).

IVd. Effect of SARS-CoV-2 ORF7a on lung epithelial cells studying the microRNA and proteomic profiles.

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: SARS-CoV-2; microRNA; accessory protein; ORF7a; metabolism; COVID-19; proteomic.

Abstract: The coronavirus SARS-CoV-2 is the cause of the ongoing pandemic of COVID-19. Since there are no effective treatments for SARS-CoV-2, a molecular understanding of how the virus affects host cells is urgently required. The SARS-Cov-2 genome encodes 31 proteins, including 11 accessory proteins that have been implicated in infection and pathogenesis through their interaction with cellular components. In the present study, we investigated the SARS-CoV-2 accessory protein ORF7a, whose role in the viral pathogenicity is poorly understood. ORF7a is a type-I transmembrane protein of 121 amino acid residues that possesses an Ig-like ectodomain containing an integrin binding site. In this study, we have used a cellular model of lung epithelial A549 cells expressing SARS-CoV-2 ORF7a (A549-ORF7a) to analyse alterations in the proteome and microRNA-omic profiles. Label-free quantitative proteomic analysis revealed that 244 proteins were differentially expressed in A549-ORF7a. A significant number of proteins were detected in A549-ORF7a cells, but not in control cells, indicating that the expression of ORF7a causes higher abundance of these proteins. The miRNA expression profiling identifies 150 miRNAs with statistically significant expression changes. We demonstrated that ORF7a can cause host pathway deregulation, specifically protein folding, RNA processing, cell adhesion, and metabolism pathways, such as glycolysis or pentose phosphate pathway. Integration of miRNA and proteome expression data with miRNA target prediction algorithms generated a potential regulatory network. The miRNA-protein network analysis suggests that miRNAs are involved in immune response by controlling TRIM25 and TKFC mediated cellular antiviral response. In addition, the results indicate that miRNAs play a relevant role in the promotion of metabolism reprograming by modulating the expression of critical proteins related to glycolysis/glyconeogenesis and pentoses phosphate pathway such as DLD, PFKL or TKT. Together, these results provide important new information on the role of accessory proteins in SARS-CoV-2 pathogenesis, representing an important step towards developing new therapies and biomarkers.

IVe. Impact of ceftazidime-avibactam on clinical outcome in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing Klebsiella pneumoniae (INCREMENT-SOT Project).

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Scientific Program: Infectious and Immunological diseases. Organ transplantation.
Keywords: ceftazidime-avibactam, carbapenem-resistant Klebsiella pneumoniae, solid organ transplantation, infections, INCREMENT-SOT Project.

Abstract:
Purpose: Solid organ transplant recipients (SOTR) are at particular risk of developing carbapenem-resistant Enterobacterales infections, which are associated with high mortality. Until Ceftazidime-avibactam (CAZ-AVI) was licensed in 2015, the therapeutic alternatives for these infections were based on the 'best available therapy' (BAT), which included drugs considered as second-line antibiotics such as gentamicin, colistin, tigecycline or fosfomycin. Ceftazidime/avibactam exhibits activity against class A β-lactamases, including Klebsiella pneumoniae carbapenemase (KPC), class C and some class D β-lactamases, such as OXA-48. The purpose of this study was to compare the efficacy of CAZ-AVI versus BAT for the treatment of SOTR with bloodstream infections caused by carbapenemase-producing Klebsiella pneumoniae (CPKP-BSI). **Materials and Methods:** Retrospective (2016-2021), observational cohort in 15 centers from the INCREMENT-SOT consortium (ClinicalTrials.gov identifier: NCT02852902). Outcomes: 14 and 30-day clinical success and 30-day all-cause mortality. Multivariable logistic and Cox regression models including propensity-score to receive CAZ-AVI.

Results: Among 210 SOTR with CPKP-BSI, 166 received an active primary therapy with CAZ-AVI (85/166) or BAT (81/166). INCREMENT-SOT-CPE score predicted 30-day mortality with an area under the receiver operating characteristic curve (AUROC) of 76.3% (95% CI 0.69-0.83) and a cut-off point of 8. Patients treated with CAZ-AVI versus BAT had significantly higher 14-day (81.2% vs 58.0%, P=0.001) and 30-day (81.2% vs 60.5%, P=0.004) clinical success and significantly lower 30-day mortality (12.9% vs 27.2%, P=0.036). In the adjusted analysis, CAZ-AVI was associated with higher 14-day (adjusted odds ratio [aOR] 5.16, 95% confidence interval [CI] 1.64-18.14, P=0.007) and 30-day clinical success (aOR 3.95, 95%CI 1.27-13.37, P=0.021) in patients with high INCREMENT-CPE-SOT mortality risk score (ICS-SOT≥8). CAZ-AVI therapy was not associated with all-cause mortality, after adjusting by severity of the BSI. In the CAZ-AVI subcohort, administration of combination therapy was not associated with better outcomes. **Conclusion:** CAZ-AVI may be considered a first-line therapeutic option for SOTR with CPKP-BSI.

SESSION V.

CANCER II.

Va. Mutational and phenotypic clonal evolution in relapsed-refractory acute myeloblastic leukemia.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: acute myeloid leukemia, relapse, refractory, bone marrow, phenotypic profile, NGS.

Abstract:

Introduction: Acute myeloblastic leukemia (AML) is a heterogeneous and dynamic clonal neoplasm caused by the accumulation of somatic acquired mutations that generate competing clones during evolution and resistance to treatment. The aim of this work is to analyze the evolution of the phenotypic profile at relapse-refractoriness and the possible correlation with the evolution of the mutational profile. **Methods:** We included 12 patients studied in PLATAFO-LMA PETHEMA at our center, between July-2013 and October-2021, who presented relapse or refractoriness after induction treatment. Bone marrow samples obtained at diagnosis and at relapse/refractoriness were analyzed. Immunophenotypic analysis was performed with a 14 common markers panel with FACSCanto II cytometer acquisition and InfinicytTM v1.7 software. A mutational analysis was also performed by Next Generation Sequencing (NGS) using the commercial panel MyeloidSolutionTM (SophiaGenetics) KAPA Kit for library amplification and sequencing on ILUMINA Myseq platform with variant analysis according to DDM software (SophiaGenetics). Statistical analysis was performed using SPSS v23.0. **Results:** All patients presented at least one phenotypic change at relapse with a median of 4 changes (range 1-10). 45.5% increased CD56 expression and 36.4% lost CD38 expression without associated loss or gain of another phenotypic marker. Three patients with CBF AML presented more stable phenotypes. The multidimensional phenotypic stability of one patient with no changes except loss of CD19 and the clonal phenotypic evolution of another patient with 10 changes were studied. Four patients showed mutational stability and eight showed mutational changes being frequent changes in FLT3 and acquisition of TP53 and RUNX1. However, we found no statistically significant correlation with phenotypic evolution (defined as at least change in 4 markers). **Conclusions:** Phenotypic clonal evolution is very frequent in relapsed refractory AML, however, there is no association with the presence of mutational changes. CBF AML appears more stable to relapse without phenotypic or mutational changes.

Vb. Orphan base specificity of abasic sites processing during DNA Base Excision Repair.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: DNA repair, Base Excision Repair, abasic sites, AP endonucleases.

Abstract: It is well known 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 molecular basis of DNA repair to design new therapies and treatments against cancer.
Abasic (apurinic/apyrimidinic, AP) sites are ubiquitous DNA lesions that arise through spontaneous base loss or as intermediates during Base Excision Repair of modified bases. AP sites may be processed by either AP endonucleases or AP lyases, but the relative roles of these two types of enzymes are not well understood. We hypothesized that the sequence flanking the AP site and/or the identity of the orphan base on the opposite DNA strand may determine the enzyme responsible for AP site processing. We have analyzed AP endonuclease and AP lyase activity from human, bacteria and plant cells using DNA substrates containing an abasic site opposite G or C in different sequence contexts. We found no preference for the orphan base neither in the main human AP endonuclease (APE1) nor in the AP lyase activity detected in human cell extracts. In contrast, the major Arabidopsis AP lyase (FPG) showed preference for AP sites opposite C, whereas the main plant AP endonuclease (ARP) exhibited higher activity on AP sites opposite G. Interestingly, bacterial AP endonucleases such as Exo III behave similarly to the plant AP endonuclease.
Through structural and homology models we found that residue Met270 in human APE1, which is predicted to contact the orphan base, has not been conserved neither in Arabidopsis ARP (Arg488) nor in E. coli Exo III (Arg216). We generated two mutant versions of ARP at this position (R488G and R488M) and we found that they lack the capacity to distinguish the orphan base. We propose that opposite base specificity is an ancestral feature of AP endonucleases that has been lost in the metazoan lineage. Our results offer new insights into the evolution of an important DNA repair enzyme that is a druggable target in cancer.

Vc. Splicing factor SRSF6 as a novel therapeutic target for advanced prostate cancer.

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Keywords: Prostate Cancer, SRSF6, Splicing, Diagnostic-therapeutic tool.

Abstract: Prostate cancer (PCa) represents the most diagnosed tumour among men population in developed countries. Androgen-deprivation-therapy (ADT) represents the main pharmacological treatment for advanced PCa, which consists in blocking the androgen receptor (AR) signalling pathway. However, some of the patients will eventually become resistant, developing castration-resistant prostate cancer (CRPC), which remains lethal nowadays. Consequently, new exploitable therapeutic targets to manage advanced PCa are urgently necessary. In this scenario, RNA-splicing process alteration has raised as a new hallmark of cancer. Herein, we studied the presence/pathophysiological role of the key splicing factor SRSF6 in PCa. To that aim, SRSF6 mRNA and protein levels were interrogated in two well characterized cohorts [PCa biopsies (n=42) vs. control samples (n=9); and PCa samples and non-tumour adjacent tissues (n=84) taken from radical prostatectomies]. Additionally, functional, and mechanistic assays were performed in different normal prostate-like, AR dependent and CRPC cell models in response to SRSF6 silencing. Moreover, the effect of SRSF6 silencing was also tested in vivo using a CRPC xenograft mouse model. Our results revealed that SRSF6 is upregulated (at mRNA/protein level) in PCa samples and its levels are associated with key clinical and molecular parameters of PCa aggressiveness (e.g., Gleason score, AR signalling pathway). These data were validated in five additional and available in silico cohorts of patients. Furthermore, SRSF6 silencing significantly decreased functional aggressiveness related parameters (i.e., proliferation, migration, tumorspheres and colony formation capacity) of AR-dependent and CRPC cell lines. Consistently, the treatment with SRSF6 siRNA reduced the growth of CRPC derived tumours (i.e., 22RV1) in vivo. Mechanistically, SRSF6 silencing altered the splicing of the oncogenic AR-variant 7 and key pathways involved in PCa progression (e.g., E2F, DNA-repair). Taken together, our results demonstrate that SRSF6 impact key PCa-related pathways and its targeting could represent a novel and promising therapeutic strategy for the treatment of advanced PCa.

Vd. Breaking the mucin barrier: Discovering and testing new therapeutic targets in Pseudomyxoma peritonei.

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

Abstract:

Introduction: Pseudomyxoma peritonei (PMP) is a rare malignant disease characterized by progressive accumulation of mucin and secretion of tumour cells within the abdominopelvic cavity. As a result, patients suffer from cachexia and malnutrition, leading to a fatal ending. Newly, the combination of macroscopic cytoreduction surgery and multi-visceral resections associated with microscopic chemical cytoreduction through intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), has shown better survival rates for patients. However, despite the positive results obtained in surgery, a considerable percentage of patients suffer a tumoral relapse. In this context, molecular characterization is necessary to classify the tumour, improve the prognosis, and develop effective therapeutic strategies. **Methods:** Our research group has developed a new protocol based on a liquid chromatography approach followed by a mass spectrometry platform, to isolate the protein fraction from mucinous tumours. Furthermore, proteomic approaches followed by bioinformatic analysis were implemented to find the best candidates as new therapeutic targets. Besides, protein expression of the selected candidates, which are expressed and secreted extracellularly, were validated in the hole cohort by Western Blot and ELISA. **Results and Conclusions:** The first high-throughput approach has allowed us to describe the premier proteomic profile of PMP with more than 1500 different protein species, reaching two putative candidates as new therapeutic targets for PMP thanks to bioinformatic analysis. The validation of these targets showed aberrant expression in mucin tumours (hard and soft) compared with control tissue. To test the use of these new targets as good candidates to develop new treatment strategies and parallelly study their pathophysiological role in the tumour's genesis, a new analysis platform based on primary cell cultures and patient-derived xenografts of PMP has been developed.

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Ve. Exploring the potential therapeutic role of somatostatin/cortistatin endocrine system in prostate cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Somatostatin, Cortistatin, Prostate Cancer, Therapeutic Tool.

Abstract: Somatostatin (SST), cortistatin (CORT), neuronostatin (NST) and their receptors (sst1-5/sst5TMD4-TMD5/GPR107) comprise a hormonal system involved in the regulation of multiple pathophysiological functions. Certain components of this system are dysregulated in different endocrine-related cancers (ERC), playing a critical role in the development/progression of these diseases. However, the presence and therapeutic role of SST and CORT in prostate-cancer (PCa), one of the commonest diagnosed ERC, has not been fully explored. We perform functional (proliferation/migration/colonies-formation) and mechanistic (Western blot/qPCR/microfluidicbased-qPCR-array) assays in response to SST and CORT treatment (10-7M) and siRNA-induced CORTsilencing in different PCa cell-lines [androgen-dependent (AD): LNCaP; and androgen-independent (AI): 22Rv1 and PC-3; hormone-sensitive and Castration-Resistant PCa (CRPC) models, respectively], and in the normal prostate cell-line RWPE-1. SST/CORT-treatment inhibited key tumor parameters (proliferation/migration/colonies-formation) only in AI-PCa cells. Mechanistically, the antitumor capacity of SST/CORT was associated with a significant down-regulation of genes involved in proliferation/migration/PCa-aggressiveness (e.g. CDK4/MKi67/MMP9/EGF/EZH2) and with the modulation of oncogenic signaling-pathways (PTEN/AKT/JNK/AR/ERK). 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 mediated through sst5. Remarkably, CORT was highly expressed, while SST was not detected, in all prostate cell-lines analysed, suggesting that endogenous CORT could exert antitumor actions in PCa-cells through an autocrine/paracrine mechanism. Consistently, CORT-silencing drastically modulated aggressiveness (e.g. enhanced proliferation) of AI-PCa cells. Moreover, CORT-silencing also blunted the antitumor activity of Pasireotide, an SST/CORT-analogue commonly used as medical therapy in different ERC, probably as a consequence of the sst5-downregulation observed after CORT-silencing. Finally, we found that CORT was overexpressed and correlated with key clinical parameters (GleasonScore/metastasis) in PCa samples from an internal (n=69) and two external in silico cohorts of patients (Grasso/Taylor).

Altogether, our results indicated that SST, CORT and their synthetic analogues could represent a potential new therapeutic alternative for PCa, especially for CRPC.

Vf. Alteration in RNA metabolism unveils new therapeutic opportunities in pancreatic adenocarcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pancreatic cancer; RNA; RNA-exosome; biomarkers.

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers, mainly due to the lack of precise biomarkers and effective therapies. Alterations in RNA metabolism have been found in many cancers, and may offer new cues to solve those problems in PDAC. RNA-decay and RNA-exosome are macromolecular complexes that maintain RNA metabolism homeostasis. Our aim was to characterize these complexes in PDAC and identify their association with clinical features. To this end, we evaluated expression of 46 genes from the RNA-decay and RNA-exosome complexes, using a microfluidic qPCR custom-made array, in a cohort of 79 tumor vs. non-tumor adjacent samples from PDAC patients, and analyzed their association with clinical parameters. The findings were validated through biocomputational analyses in an additional cohort of 94 samples, and in TCGA database. The functional role of selected components of the RNA-exosome complex are then tested in vitro using two PDAC cell lines, BxPC-3 and MIAPaCa-2. Most components of the RNA-decay and RNA-exosome complexes were dysregulated in PDAC: namely, 21 and 7 were down- and up- regulated, respectively. Biocomputational analyses revealed that the NEXT complex, involved in degradation of non-coding short-lived RNAs, displayed a particularly high diagnostic capacity. Moreover, some components were associated with survival or metastasis. Further analyses on RNAseq data showed that expression of the NEXT complex was linked to a specific gene signature in PDAC. Interestingly, NEXT complex expression is linked to dysregulated splicing, including correlations with splicing machinery core components and to differential splicing events of RNA metabolism genes. Ongoing in vitro studies are aimed to elucidate the precise role on functional endpoints. These results indicate that the RNA surveillance system is dysregulated in PDAC and associated to clinical features, opening the way to explore their value as potential biomarkers and therapeutic targets.

POSTER SESSION II.

PSII.a. Severe aortic stenosis, long-term survival analysis in patients treated with self-expandable prosthesis and surgery.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: TAVI, CoreValve, Surgery, Survival.

Abstract:

Introduction: Severe aortic stenosis (SAS) has a high prevalence in developed countries. Both standard surgery and percutaneous procedures are used to treat SAS. Here we present a series of cases, treated with TAVI (CoreValve) or conventional surgery. We evaluated survival, major complications, and other factors associated with mortality. **Methods:** We followed up 121 patients treated between 1 January 2010 and 31 December 2011, until February 2022. 64 patients underwent the TAVI procedure (CoreValve) and the remaining 57 patients underwent surgery. The mean age was 75,88 years IC (74,93-76,83) in the surgery group and 79,96 years IC (78,95-80,96) in the TAVI group. 57.9% of patients undergoing surgery were male, while 70.3% of patients in the TAVI group were female. The mean logistic Euroscore value for the surgery group was 10.46% and 11.66% in the TAVI group. **Results:** Median survival in the surgery group was 98.95 months 95% CI (85.85-111.99) and 92.94 months 95% CI (81.99-103.89) in the TAVI group, p=0.231. Gender was not associated with mortality, p=0.715. There was no difference in in-hospital mortality during the procedure, p=0.816, nor in the development of periprocedural stroke, p=0.471. The TAVI group required more definitive endocavitary pacemaker implants, p<0.008. **Conclusions:** Treatment options for severe aortic stenosis have expanded. Long-term differences between groups with respect to survival are not significant. Individualized indication could optimize the results obtained for each patient in terms of better survival and better use of available economic resources.

PSII.b. Proliferative T-cell response against SARS-CoV-2 in convalescent COVID-19 infected patients.

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Scientific Program: Infectious and Immunological Diseases.
Keywords: SARS-CoV-2, FASCIA assay, T-cell response, lymphocyte proliferation.

Abstract:

Rationale: Most studies initially published on the immune response against SARS-CoV-2 focused primarily on immunoglobulins and cytokines analysis. However, T-cell response against SARS-CoV-2 (T-SARS-CoV-2) is crucial to maintain the virus under control. Likewise, immunological memory generated after SARS-CoV-2 infection is essential to control future infections. **Objective:** To analyze whether COVID-19 patients with asymptomatic/mild infection develop a different T-SARS-CoV-2 compared to severe patients. **Methods:** This cross-sectional study was carried out in convalescent positive SARS-CoV-2 PCR patients (PCR+SARS-CoV-2). Patients were classified as asymptomatic/mild or severe according to whether they required oxygen therapy. Healthy volunteers were used as controls. A single blood sample was taken from all patients. T-SARS-CoV-2 was assessed by the Flow-cytometric Assay for Specific Cell-mediated Immune-response in Activated whole blood (FASCIA) assay, which measures the proliferation capacity (blasts formation) using a mix of SARS-CoV-2 peptides, cytomegalovirus (CMV) lysate and Staphylococcus aureus enterotoxin A and B (SEA+SEB) as stimulus. **Results:** A total of 59 PCR+SARS-CoV-2 patients and 33 negative controls were recruited (33 asymptomatic/mild and 26 severe COVID-19 patients). PCR+SARS-CoV-2 patients had higher blast proliferation with SARS-CoV-2 peptides than the controls (median, 114.0 vs. 15.3 cells/µL; $p < .001$). They also showed increased proliferation with CMV lysate (median, 86.4 vs. 34.9 cells/µL; $p = .037$) but no significant differences were found with SEA+SEB (median, 2306.4 vs. 2493.9 cells/µL; $p = .603$). A ROC curve analysis was then performed and showed that the number of SARS-CoV-2-specific blasts, CD3 and CD4 were useful to discriminate between controls and COVID-19 patients (AUC 0.859; 0.838 and 0.853, respectively; all $p < .001$). The cut-offs with best sensitivity and specificity were 28 cells/µL, 6 cells/µL and 5.5 cells/µL, respectively. With these cut-offs more than 80% of COVID-19 patients had positive TSARS-CoV-2. Nevertheless, these parameters were not able to discriminate between asymptomatic/mild and severe patients. **Conclusion:** The proliferative assay is useful to determine T-SARS-CoV-2. Moreover, the number of blasts, CD3 or CD4 allowed discriminating the convalescent COVID-19 patients from the controls. However, with this sample size, the proliferative response was not able to discriminate asymptomatic/mild from severe patients.

PSII.c. Dysregulation and functional relevance of the RNA-exosome machinery in hepatocellular carcinoma.

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

Abstract: Hepatocellular carcinoma (HCC) represents the most common type of liver cancer and exhibits increasing incidence, aggressive behavior, and poor outcome. In HCC and other cancer types, a profound dysregulation of the molecular machineries responsible for RNA processing and metabolism has been observed. One of these machineries is the RNA-exosome, a ribonuclease complex that cooperates with multiple cofactors in the processing, quality control and degradation of virtually all classes of RNAs. Here, we aimed to identify novel RNA-exosome machinery related factors with pathogenic implication in HCC development and progression, as it could be helpful to discover early changes, new diagnostic/prognostic biomarkers, as well as possible molecular targets for HCC management. To that end, the expression levels of the components of the RNA-exosome machinery have been determined in two retrospective and five in silico HCC cohorts, including tumor and non-tumor adjacent tissues. Functional assays were carried out in the HCC cell line SNU387. Our results showed a profoundly dysregulated expression pattern of the components of the RNA-exosome machinery in the different cohorts. Specially, we found a consistent RNA and protein overexpression of Exosome Component 4 (EXOSC4), Poly(A) Binding Protein Nuclear 1 (PABPN1) and Zinc Finger C3H1-Type Containing (ZFC3H1) factors in most HCC cohorts. Remarkably, the expression of these components was associated with clinical (e.g., reduced overall survival) and molecular (e.g., MKi67-, CDK1-, c-MYC-expression) parameters. Finally, in vitro approaches indicated that PABPN1-silencing using two specific siRNAs (validated at mRNA and protein levels) reduced key tumor parameters such as proliferation and capacity to form colonies and tumorspheres in SNU387 cells. Altogether, our results indicate that EXOSC4, PABPN1 and ZFC3H1 could represent potential candidates for the design of novel diagnostic/therapeutic strategies in HCC, capable of reducing the lethality of this pathology and/or improving patients quality of life.

PSII.d. High Phosphate intake promotes renal and cardiac fibrosis during chronic kidney disease.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Renal fibrosis; Cardiac fibrosis; Phosphate.

Abstract: Renal and cardiac fibrosis (RF/CF) are pathologies linked to inflammatory processes and oxidative stress that condition the prognosis of patients with chronic kidney disease (CKD). It is known that a high phosphate diet increases inflammation and oxidative stress. Now, the effect of Phosphate on RF and CF in CKD will be evaluated.
A model of CKD was generated by 5/6 nephrectomy (Nx) in rats fed with normal Phosphate (0,6%) or high Phosphate (0.9%) for two months. Sham animals were fed with normal Phosphate. Plasma creatinine and phosphorus were determined by colorimetric assay. Fibrosis was quantified in plasma by TGFβ (ELISA). In kidney αSMA was measured by immunohistochemistry. The grade of renal and cardiac fibrosis was quantified after Masson trichrome and Sirius red staining. Oxidative stress was evaluated by malonyl dialdehyde quantification in renal tissue. Changes in Klotho expression were evaluated through renal immunohistochemistry and ELISA in urine.
Nx rats with high phosphate diet developed RF/CF (related to type IV cardiorenal syndrome) finding increased TGFβ levels, αSMA expression, oxidative stress and a larger percentage of renal and cardiac fibrosis than in Nx rats with normal phosphate. High Phosphate in the diet decreased significantly renal Klotho expression and increased urine klotho (see table).
In conclusion, in an experimental model of CKD, a high phosphate content in the diet, promotes renal and cardiac fibrosis (cardiorenal syndrome type IV) with a negative impact on CKD progression.

	Sham (0.6% Ca +0.6% P)	Nx 5/6 (0.6% Ca + 0.9% P)
n	14	9
Creatinine (mg/dl)	0.43±0.08	0.82±0.17***
Phosphorus (mg/dl)	6.03±1.29	9.24±3.67**
Ionic calcium (mg/dl)	1.25±0.05	1.11±0.09***
TGFβ (pg/ml)	5422±1248	7460±2131*
α-SMA (IHC, %)	2.51±1.54	7.84±1.72***
Renal Klotho (IHC, %)	20.16±4.80	10.37±4.18***
Urine Klotho (ng/ml)	0.63±0.29	1.13±0.42**
MDA (µM)	0.78±0.30	1.17±0.33*
Renal Fibrosis (%):		
Sirius red	7.11±2.54	22.37±3.85***
Masson trichrome	6.94±3.61	21.12±7.26***
Cardiac Fibrosis (%):		
Sirius red	10.86±4.97	24.21±10.34**
Masson trichrome	8.14±3.91	25.67±4.08***

Data expressed as mean +/- standard deviation. T test: * p<0.05 vs Sham+0.6%P; ** p<0.01 vs Sham+0.6%P; *** p<0.0001 vs Sham+0.6%P

PSII.e. Impact of pulmonary artery pressure on early outcomes and survival after lung transplantation in patients with chronic obstructive pulmonary disease.

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Keywords: Lung Transplantation, Pulmonary Artery Pressure, Outcomes, Survival.

Abstract:
Objectives: Whether a double lung transplant (DLT) rather than a single lung transplant (SLT) should be performed in patients with chronic pulmonary obstructive disease (COPD) and pulmonary artery hypertension remains controversial. We aimed at investigating the influence of pre-transplant pulmonary artery pressure (PAP) on survival after either SLT or DLT. **Methods:** Retrospective analysis of 208 COPD consecutive patients transplanted at a single Centre. Patients were compared based on their PAP (normal mPAP <25 mmHg vs. high mPAP ≥25 mmHg), type of transplant (SLT vs. DLT) and age (≤60 years vs. >60 years). Early mortality and survival were analyzed by univariable, Kaplan-Meier, and Cox regression analyses, adjusting for age and type of transplant. **Results:** There were 136 (65%) SLT and 72 (35%) DLT. Normal mPAP in 130 (63%) and high mPAP in 78 (37%). 30-day mortality: 22 patients (10%), presenting higher mPAP (25±6 mmHg vs. 29±10 mmHg; p=0.002). mPAP groups did not differ in terms of age, BMI and lung allocation score. There was no difference in survival between SLT vs. DLT patients (80%, 70%, 62%, 59% vs. 73%, 64%, 59%, 55%, at 1,3,5,7 years respectively; p=0.50). Patients with high mPAP did not have different survival from patients with normal mPAP (figure). There was also no difference in survival between the two age groups (p=0.44). Only those high mPAP patients older than 60 years and receiving a SLT presented worse survival (normal mPAP: 88%, 78%, 61%, 61% vs. high mPAP 65%, 58%, 58%, 44%, at 1, 3, 5, 7 years respectively; p=0.04). The Cox model identified the ichemic time in DLT patients as the unique independent predictor of survival (OR: 1.02; p=0.02). **Conclusions:** COPD patients with pre-transplant pulmonary artery hypertension present higher 30-day mortality after lung transplantation, but they can safely undergo a SLT with similar long-term survival than those receiving a DLT.

PSII.f. Association between Fibroblast Growth Factor 23 and pulse pressure in Chronic Kidney Disease Stage G5 patients.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Pulse Pressure, Fibroblast Growth Factor 23, chronic kidney disease.

Abstract:

Background: Fibroblast Growth Factor 23 (FGF23) is associated with increased cardiovascular events and mortality in chronic kidney disease (CKD) patients. Non-classical biological effects of FGF23, such as left ventricular hypertrophy and vascular remodeling, may potentially explain this association. Experimental models suggest that FGF23 stimulates renal tubular sodium reabsorption and volume overload. It is plausible that FGF23 also increases blood pressure. The linking of FGF23 increment with blood pressure control may help identify novel risk factors of mortality in CKD patients. Therefore, we aimed to evaluate the relationship between FGF23, blood pressure control, and indirect signs of arterial stiffness in subjects with CKD G5. **Methods:** Clinical and analytical variables were analyzed in 159 patients with CKD G5 patients immediately before starting kidney replacement therapy with hemodialysis. The association between these variables and the levels of intact FGF23 (iFGF23) was evaluated with linear regression models. Pulse pressure (PP) was estimated with systolic blood pressure (SBP) and diastolic blood pressure (DBP) and was used as an indirect surrogate of arterial stiffness. Statistics were performed using R 3.6.2. **Results:** The median (IQR) SBP was 159 (144,166) mmHg, whereas the median DBP was 87 (80,94) mmHg, and the median PP was 72 (60,80). The median iFGF23 was 468 (297,729) pg/ml. iFGF23 was positively correlated with serum phosphate ($p < 0.001$), plasma sodium ($p = 0.02$), C-reactive protein ($p < 0.01$), SBP ($p < 0.001$), DBP (<0.01) and PP ($p = 0.02$). Linear multivariable analysis showed that iFGF23 was independently associated with the increase in SBP, DBP and PP (after adjustment by overhydration state and residual renal function). **Conclusions:** The increase in FGF23 is associated with higher SBP, DBP, and PP. These data suggest that iFGF23 may increase the risk of cardiovascular events in patients with CKD G5 through increasing blood pressure and arterial stiffness.

PSII.g. Quality of child development scales. A systematic review.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Development Scales. Psychometry. Systematic review. Evaluation instruments. Evolutive development.

Abstract: The development scales aimed at children from 0 to 6 years of age have experienced slow progress. They present a broad conceptual framework and their metric validation is insufficient and could be improved. The objective of this systematic review is to analyze its psychometric quality and point out aspects that can be improved. The PRISMA (2020) methodology and the WOS and PROQUEST databases have been followed, finding 72 related documents. The results show a small number of studies dedicated to the independent statistical measurement of the scales. The works found are heterogeneous and apply adaptations of the common metric to this discipline. Most of the articles perform cross-cultural, concurrent and forecasting validations of the tests. It is necessary to improve the metric quality of the scales, pointing out common aspects that they suffer from: scarcity and heterogeneity of the samples and cultural biases. It concludes by underlining the importance of applying metric advances in the elaboration of development scales and betting on computerized versions that make them more comfortable and efficient.

PSII.h. Novel insights to understand the potential of the somatostatin/cortistatin system in neuroendocrine tumors (NETs) and carcinomas (NECs).

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pancreatic Neuroendocrine tumors; Somatostatin analogs; Cortistatin.

Abstract: Neuroendocrine tumors (NETs) and carcinomas (NECs) comprise a heterogeneous group of malignancies with increasing incidence worldwide, due in part to enhanced awareness and diagnosis improvements. Surgery is often effective for local disease, but a successful pharmacological approach for disseminated or metastatic disease is still lacking. Pancreatic (Pan)NETs and Pan-NECs frequently express somatostatin receptors (SSTs), providing the target for treatment with somatostatin analogs (SSAs). Nevertheless, a significant proportion of patients are still unresponsive or become resistant to these drugs and the underlying causes remain incompletely understood, thus, search for alternative strategies is required. The neuropeptide cortistatin (CST), a natural somatostatin analogue with comparable affinity to SSTs, emerged as anti-inflammatory player, with inhibitory potential as antisecretory and antitumoral drug. This study aims to determine the effect of CST and a novel set of CST analogs as compared with classic SSAs on different functional parameters and to characterize the somatostatin/CST/SSTs phenotype on Pan-NETs and NECs cells models. SSAs and CST analogues effects were evaluated on cell proliferation, apoptosis, migration, colony formation and intracellular signaling in classical (BON-1, QGP-1), and novel Pan-NETs and NECs (NT-18LM, NT-38) cell lines.Treatment with SSAs tested exerted dose-related effects in cell proliferation and migration, in BON-1, QGP-1 and NT-18LM cells while NT-38 cells appeared less responsive. Moreover, SSAs determined a significative reduction in BON-1 colony formation. CST analogues exerted a different, but significative reduction in cell proliferation in almost all cell lines, which displayed a unique SSTs expression profile that may underlie the differential functional responses observed. Overall, this study opens original avenues to explore novel therapeutical approaches in NETs and NEC with CST analogs. In addition, an initial characterization and response to various SSAs, of novel Pan-NETs and Pan-NECs cell models, more precisely mimicking the behavior of human tumors, is provided.

PSII.i. Oncometabolic features of GSNOR-deficient colorectal tumors impact immune surveillance and impair response to immunotherapy.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Colorectal cancer, GSNOR, Immunotherapy, Oncometabolism, humanized xenografts.

Abstract:

Background and aims: S-nitrosoglutathione reductase (GSNOR) is a denitrosylase enzyme that has been suggested to play a tumor suppressor role. We have previously shown that GSNOR-deficient colorectal cancer (CRC) cells are characterized by an oxidative phosphorylation to glycolysis switch that induces an aggressive and immunoevasive phenotype. Therefore, the aim of this study was to evaluate to what extent this metabolic switch affects tumor immune microenvironment and the response to immunotherapy. **Material and methods:** GSNOR expression and tumor infiltration of cytotoxic CD8+ T lymphocytes was evaluated by immunohistochemistry in a cohort of 43 CRC patients. The anti-tumor effect of the immune checkpoint inhibitor nivolumab (anti-PD1) was evaluated in peripheral blood mononuclear cells (PBMC)-humanized NSG mice engrafted with HCT116-GSNOR knockout (KO) or HCT116-wildtype (WT) CRC cells. **Results:** CRC tumors with high GSNOR expression were characterized by a significantly higher percentage of CD8+ T tumor infiltration compared to CRC tumors with low GSNOR expression (1.711 vs 1.008, p= 0.0339) supporting that GSNOR-deficiency in CRC confers an immunosuppressive tumor microenvironment. Importantly, in our humanized murine models the anti-PD1 treatment with nivolumab effectively reduced the growth of GSNOR-WT tumors, but not of GSNOR-KO tumors. Moreover, tumor volumes correlated with the percentage of tumor infiltrating lymphocytes (TILs) observed in each experimental group. Thus, TILs levels increased in GSNOR-WT tumors after anti-PD-1 treatment, but decreased in GSNOR-KO tumors when PD-1 was blocked. The immunophenotype of TILs revealed an increase in active cytotoxic populations in GSNOR-WT tumors with PD1 blockade, which was not observed in GSNOR-KO tumors. **Conclusions:** Altogether, our results suggest that GSNOR-deficiency in CRC confers an immunosuppressive tumor microenvironment and hampers the immune response to PD1 blockade. Our in vivo humanized models will be useful to evaluate targeting metabolic

vulnerabilities in combination with anti-PD1 therapies for boosting immunotherapy effectiveness in these aggressive tumors.

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PSII.j. The key role of abnormal fat distribution for prediction metabolic disease.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: fatty liver index, liver fat, body mass composition, cardiometabolic abnormalities, metabolic disease.

Abstract: Obesity contributes directly to increase incident cardiovascular diseases and other comorbidities, also increases all-cause mortality and reduce life expectancy. Body mass index (BMI) is not a proper indicator to assess the cardiometabolic risk associated with increased adiposity. Studies highlight the need to quantify fat depots including ectopic fat as liver fat. Fatty liver index (FLI) is an indirect measure of non-alcoholic fatty liver disease and could play a pivotal role in the development of metabolic disease. The aim of this study is to assess the association between BMI and FLI, and which anthropometric tool had better prediction of metabolic disease after two diets after 5-years.
All obese cardiovascular patients from CORDIOPEV study (n=476) were selected and randomized to Low-Fat (LFD) or Mediterranean diet (MD). Anthropometric and biological variables were measured over a 5-year period. FLI was calculated using the standard mathematical formula. Cardiometabolic abnormalities analyzed were: elevated blood pressure, elevated triglycerides, decreased HDL-c, elevated glucose, insulin resistance and systemic inflammation. We defined metabolic disease ≥ 2 abnormalities.
We observed a good overall correlation between BMI levels and a liver fat content, estimated by FLI (r= 0.579). We studied correlation between FLI and number of cardiometabolic abnormalities (r=0.432, p< 0.001), and BMI and these abnormalities (r=0.321, p<0.001), at baseline. FLI had a best area under the receiver operating characteristic curve (AUROC, 95% CI) 0.65 (0.57-0.73) at predicting metabolically unhealthy status after 5 years, than BMI 0.53 (0.45-0.62).
In conclusion, excess of adiposity would not be responsible for the different metabolic health on the obesity spectrum. The difference in the distribution of ectopic fat, especially when it accumulates in the liver, was best predictor of metabolic disease. More studies are needed to study how liver fat may play a key factor in the development of metabolic diseases (adiposopathy).

PSII.k. Obesity due to a high-fat diet impacts the development and progression of prostate cancer in the TRAMP mouse model.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Prostate cancer; obesity; high fat diet; TRAMP model.

Abstract: Prostate cancer (PCa) and obesity are diseases with high incidence worldwide. Although obesity has been associated with a higher recurrence and worse prognosis of PCa, the relationship between both pathologies remains controversial. Therefore, our objective was to clarify the direct impact of a high-fat diet on the development and/or progression of different stages of PCa, using the transgenic adenocarcinoma of mouse prostate (TRAMP) mice, a model that mimics the progression of human PCa over time. Specifically, TRAMP mice and wild-type (WT) littermates (used as controls) were fed a high- or low-fat diet (HFD or LFD respectively), starting at 5 weeks of age, and euthanized at 16 (established adenocarcinoma) or 21 weeks of age (established advanced adenocarcinoma) (n=11-14/experimental group). Glucose tolerance test (GTT) and indirect calorimetry was performed. Our results revealed that both WT and TRAMP mice fed a HFD showed increased body weight, due to increased adipose tissue, and worse response to GTT, comparing with WT or TRAMP controls (fed a LFD). Of note, 21-week-old TRAMP LFD and HFD mice presented lower body fat mass compared with 21-week-old WT LFD and HFD, respectively. Furthermore, indirect calorimetry revealed that there were no significant differences on the nutritional source to generate energy; however, the activity of the TRAMP mice was significantly lower. Moreover, 16-week-old TRAMP-HFD mice presented a heavier tumor-free prostate gland. Although we could not observe a significant impact of diet on tumor incidence or tumor size, 21-week-old TRAMP-HFD mice showed higher mortality compared to the TRAMP-LFD control group. In summary, our data suggest that obesity due to a HFD diet could enhance the development and progression of PCa. Further studies are being currently performed to elucidate the molecular factors involved in the observed pathophysiological interplay between obesity and PCa in the TRAMP model.

PSII.I. Relationship between depression and pathological cognitive dysfunction in older people 65 years old.

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Scientific Program: Active ageing and fragility.
Keywords: depression; cognitive dysfunction; dementia; aging.

Abstract:

Introduction: The WHO estimates that by 2050 the geriatric population will have almost doubled compared to 2015. In addition, this increase in life expectancy is accompanied by an increase in the prevalence of diseases associated with age, such as depression, pathological cognitive impairment and subsequent dementia. **Objective:** To review and synthesize the existing scientific literature to verify the possible relationship between pathological cognitive impairment and depression in people over 65 years of age. **Methodology:** A search strategy has been carried out in Medline, through Pubmed, which has been replicated in Scielo, through WOS. This strategy has included as terms: depression, cognitive impairment and older people. In Pubmed, the type of article (metaanalysis, reviews and systematic reviews) and the date of publication (published in the last 10 years) have been activated as limiters, and in Scielo, only the date of publication (in the last 10 years). **Results and Discussion:** 15 studies have been identified and they describe a connection between the depressive process and cognitive impairment, mainly focused on common pathophysiological processes that help explain the high risk of progression to Alzheimer's disease. To explain this association, various hypotheses have been proposed, including the neuroinflammatory one, where the neuroinflammatory process is described as the connection between both pathologies. **Conclusion:** A better understanding of the mechanisms that link depression and dementia, as well as an early diagnosis and effective treatment of depression, would allow establishing goals for the prevention of dementia and avoiding the development of Alzheimer's disease.

PSII.m. Characterization of the splicing process in pheochromocytomas and Paragangliomas.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: pheochromocytoma, paraganglioma, splicing dysregulation, splicing machinery, pladienolide B.

Abstract: Although pheochromocytomas and paragangliomas (PPGL) are benign catecholamineproducing neuroendocrine tumors (NETs), up to 25% of patients develop distant metastases or aggressive behavior. According to their genomic characterization, the current classification of PPGL comprises three genetic clusters: pseudohypoxia-profile, MAPK-pathway alteration, and Wnt-pathway dysregulation. However, to date, there are no biomarkers that could stratify patients based on their prognosis. The dysregulation of the splicing process has emerged as a novel common cancer hallmark, frequently linked to a more aggressive phenotype in several tumors, including NETs. We have recently observed changes in the splicing machinery in pancreatic and lung NETs. In contrast, the splicing process has been scarcely investigated in PPGL to date. Here, we aim to determine the splicing machinery profile in PPGL, investigate its association with clinical/molecular features, and explore the functional role of splicing inhibitors in vitro using an appropriate cell model, the neuroblastoma cell line SK-N-AS harboring SDHB mutation (using the wildtype as control). Analysis of the expression of 310 splicing-related genes in the TCGA dataset, which comprise 151 patients (29 paragangliomas, PGL, and 122 pheochromocytomas, PCC), revealed that them expression of splicing machinery components differed between PCC and PGL, as well as between the three genetic clusters. In addition, more than 20 genes were linked to aggressive behavior, development of metastases, existence of somatic mutations, and even patient survival. Interestingly, inhibition of the splicing process using Pladienolide B in vitro in SK-N-AS cells decreased key functional tumoral aggressiveness features, including cell proliferation, migration, and tumorsphere and colony formation. Altogether, our findings indicate that the splicing machinery is disrupted in PPGL, associated with the clinical evolution of the disease and that its pharmacological modulation may help to decrease aggressive tumor behavior.

PSII.n. Acute kidney injury associated to intravascular hemolysis increases chronic renal fibrosis.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Kidney, fibrosis, hemolysis, acute injury, cronic kidney disease.

Abstract:

Introduction: Massive intravascular hemolysis is one of the possible causes of acute renal failure due to direct toxicity of hemoglobin to the proximal tubular cells. The presence of hemoglobin in the kidney causes a local inflammatory response that, if it becomes chronic over time, may induce an increase in the deposition of extracellular matrix components, such as Fibronectin and Collagen I, III and IV, leading to a fibrotic process. This renal process is mediated by different cells, including tubuloepithelial cells, infiltrating immune cells and interstitial fibroblasts, the latter being the cells that synthesize most of the extracellular matrix. However, it has not been analyzed whether repeated exposure to hemoglobin in the kidney causes a fibrotic response as well as the possible underlying mechanisms. **Material and methods:** We performed an experimental model of massive and chronic intravascular hemolysis by intraperitoneal administration of phenylhydrazine (150 mg/kg) in C57BL/6J mice. The mice were sacrificed 30 days after the induction of hemolysis and blood and kidney samples were collected to analyze markers of tubular damage and fibrosis. **Results:** Our results show an increase in mRNA expression levels of different profibrotic markers such as PAI-1, Fibronectin, Collagen 1 and Collagen IV in the kidneys of mice with chronic hemolysis. We also observed an increase in classic extracellular matrix components such as Fibronectin and collagen I, as well as a marked inflammatory infiltrate of CD3+ and F4/80+ cells in mice subjected to chronic hemolysis. We also observed an increase in the gene expression of both KIM-1 and NGAL, two biomarkers of kidney damage. **Conclusion:** Our results show that, in a model of sustained damage caused by massive intravascular hemolysis, there is an increase in the synthesis of extracellular matrix, with activation of a fibrotic response. Therefore, new therapeutic approaches may be necessary to reduce the chronic consequences of kidney damage caused by severe intravascular hemolysis.

PSII.ñ. Serum magnesium and mortality risk in chronic kidney disease (ckd). an independent effect of nutritional and inflammatory status.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: magnesium, chronic renal disease, mortality.

Abstract:

Introduction: Magnesium (mg) deficiency has been related to cardiovascular disease and mortality in the population with and without chronic kidney disease (CKD). Magnesium levels depend among other variables on nutritional status and inflammation. Therefore, the objective of our work is to find out if the impact of serum mg on mortality is independent of nutritional and inflammatory status in patients with advanced CKD. **Material and methods:** Cross-sectional study in 1271 patients with CKD-G4 evaluated between 2008 and 2018. Demographic, clinical and biochemical variables were evaluated. Nutrition/inflammation profiles were constructed according to local laboratory reference values for reactive C protein (CRP) and serum albumin, obtaining 4 groups: normal albumin/normal CRP, low albumin/elevated CRP, normal albumin/elevated CRP, and low albumin/normal CRP. The multivariate Cox predictive model was used to assess the impact of magnesium levels on all-cause and cardiovascular mortality (heart failure (HF), stroke, or coronary artery disease (CHD)). **Results:** 186 subjects died during 5 years of follow-up, 66 from HF, 38 from CHD, and 29 from stroke. The risk of dying from HF was 3.06 (1.61—5.82) times, 3.33 (1.43—7.74) times from IC, and 10.1 (2.24—45.7) times from stroke in subjects with mg<2.1 mg/dl. Magnesium levels were comparable between the 4 groups according to the nutrition/inflammation profile. The adjusted Cox model (figure 1) including the different albumin/CRP profiles as a covariate showed that lower magnesium levels were independently associated with a higher risk of death from all causes and from cardiovascular causes. **Conclusion:** Lower serum magnesium levels are associated with a higher risk of all-cause and cardiovascular mortality in patients with CKD-G4, regardless of nutritional-inflammatory status.

PSII.o. Spliceosome alterations in leucocytes from APS, SLE and SLE+APS patients are closely related to their main clinical features.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Splicing, Autoimmune diseases, Antiphospholipid syndrome (APS), Systemic lupus erythematosus (SLE).

Abstract: To date, no study has fully characterized the potential role of posttranscriptional regulatory mechanisms such as alternative splicing on Antiphospholipid Syndrome (APS), Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome + Lupus (APS+SLE). **Objective:** To identify differential changes in the splicing machinery of immune cells from APS, SLE and APS+SLE patients, and their involvement in disease activity and clinical profiling. **Methods:** Monocytes, lymphocytes and neutrophils from 80 patients (22 APS, 35 SLE, 23 APS+SLE) and 50 healthy donors (HD) were purified. Selected splicing machinery elements were evaluated by microfluidic qPCR array (Fluidigm) and an extensive clinical/serological evaluation was performed. Clustering analyses and correlation/association studies were developed. **Results:** Patients displayed significant alterations in splicing components compared to HD, specific for each leukocyte subset and associated with distinctive clinical features. APS, APS+SLE and SLE clustering analyses identified for each disease two patient subgroups representing different molecular profiles regarding the expression levels of splicing machinery components. Clinically, APS cluster 1 and APS+SLE cluster 2 characterized patients with more recurrent thrombotic episodes, increased adjusted global APS score (aGAPSS), and presence of inflammatory mediators, while the incidence of lupus nephropathy (LN) was similarly distributed. The two SLE subgroups showed distinctive clinical features: one characterized most of the anti-dsDNA antibody-positive patients, further suffering LN, a high proportion also presenting atheroma plaques and increased inflammation. Correlation studies further demonstrated that several deranged splicing components in immune cells (SF3B1tv1, PTBP1, PRP8 and RBM17) were linked to these diseases' autoimmune profile. Accordingly, in vitro treatment of HD lymphocytes with aPL-IgG or anti-dsDNA-IgG changed the expression of components also altered in vivo, modulating also inflammatory cytokine expression, changing monocyte adhesion and regulating NETosis. **Conclusion:** 1) The splicing machinery, altered in leukocytes from APS, APS+SLE and SLE patients, is closely related to their activity, autoimmune and inflammatory profiles. 2) Splicing machinery analysis allows patient segregation, with specific components explaining the CV risk and renal involvement in these autoimmune disorders.

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PSII.p. Resistance to alkylating agents: role of the phosphatase PNKP.

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

Abstract: Cancer treatments generally involve the use of chemical agents that cause DNA damage. However, the efficacy of chemotherapy is counteracted by the action of DNA repair mechanisms making it necessary to combine anticancer drugs with specific DNA repair inhibitors. Therefore, it is essential to understand the DNA repair mechanisms involved in tumour resistance for the rational design of cancer therapies. Temozolomide (TMZ) is a DNA alkylating 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 this alkylating agent. The main lesion induced in the DNA by TMZ is N7-meG, harmless by itself but prone to generate abasic (AP) sites highly cytotoxic and mutagenic. 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. Recently, it has been shown that in Arabidopsis thaliana, the AP sites generated from N7-meG are processed through an AP lyase/DNA phosphatase pathway mediated by the lyase FPG and the phosphatase ZDP. In human cells, the homologous proteins are the lyases NEILs and the phosphatase PNKP. An important unaddressed question is whether the NEILs/PNKP pathway is involved in the repair of AP sites induced by TMZ. In order to address this, we have used TMZ resistant and sensitive GBM cell lines to specifically block the activity of the phosphatase PNKP. Our data suggest that a specific PNKP inhibitor sensitize GMB cells to TMZ treatment, pointing toward a role of the AP lyase/DNA phosphatase repair pathway in the resistance to TMZ. Our results may help to identify novel therapeutical targets in GBM treatment.

PSII.q. Adherence to the Mediterranean diet in childhood at risk of obesity: MELIPOP Study.

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Scientific Program: Chronic and inflammatory diseases.
Keywords: Children, obesity, eating habits, Mediterranean diet, lifestyle intervention.

Abstract:

Background: Childhood obesity has become a major public health problem in every country in the world. It was estimated that in 2016, more than 41 million children under 5 years of age worldwide had overweight or obesity. Particularly, in Spain, 23.2% of children between 6 and 9 years old have overweight and 18.1% have obesity, being these among the highest prevalence in Europe. Although the development of obesity is partly explained by genetic susceptibility, some modifiable risk factors such as diet and a sedentary lifestyle contribute to its development. MELI-POP (Mediterranean Lifestyle in Pediatric Obesity Prevention) is the first multicenter, parallel, randomized and controlled clinical trial that promotes a healthy lifestyle program (diet and physical exercise) to mitigate the incidence of childhood obesity from the early years of life, as well as its complications in comparison with usual pediatric health care. **Aims:** To assess, in a cohort of children aged 3 to 6 years at high risk of obesity, whether a healthy lifestyle intervention based on the promotion of a Mediterranean eating pattern and regular physical activity, compared to a control group might contribute to 1) increase the adherence to a Mediterranean diet pattern (MDP) and the adherence to an active lifestyle; 2) decrease the incidence of obesity; 3) improve body composition and physical condition; and 4) decrease cardiovascular risk factors associated with obesity. **Preliminary results:** A total of 82 children (intervention=44 vs. control=38) were included to assess the efficacy of the lifestyle intervention to improve adherence to the MDP for the first year of the study. Based on General Linear Models for Repeated Measures, children randomized to the intervention group showed a higher adherence to the MDP at one year compared with those in the control group (18-Item Mediterranean Diet Assessment Tool for children: intervention group, 11.5 (SE 0.4) at baseline vs. 13.1 (SE 13.1) points at 1 year; control group, 10.7 (SE 0.5) at baseline vs. 10.6 (SE 0.4) points at 1 year, time x group interaction p=0.011, adjusted for age and center). Moreover, parents from the intervention group increased their adherence to the MDP vs. the control group (14-Item Mediterranean Diet Assessment Tool for adults: Parents intervention group, 8.5 (SE 0.3) at baseline vs. 9.3 (SE 0.3) points at 1 year; Parents control group, 8.2 (SE 0.3) at baseline vs. 7.6 (SE 0.4) points at 1 year, time x group interaction p=0.015, adjusted for center). **Conclusion:** Our preliminary findings show that a lifestyle intervention program successfully promotes healthier eating habits both in children and parents. It might contribute to reducing the risk of obesity and its long-term complications.

PSII.r. Improvement of left ventricular ejection fraction in patients with heart failure with reduced ejection fraction: mid-term clinical impact.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: HFrEF, HFimpEF, ejection fraction recovery.

Abstract:

Introduction: A percentage of patients with heart failure with reduced ejection fraction (HFrEF) improve left ventricular ejection fraction (LVEF) in the evolution. This entity, defined for the first time in an international consensus of 2021 as heart failure with improved ejection fraction (HFimpEF), could have a different clinical profile and prognosis than HFrEF. Our main aim was to analyse the differential clinical profile between the two entities, as well as the mid-term prognosis. **Material and methods:** Prospective study of a cohort of patients with HFrEF who had echocardiographic data at baseline and follow-up. A comparative analysis of patients who improved LVEF with those who did not was made. Clinical, echocardiographic and therapeutic variables were analysed, and the mid-term impact in terms of mortality and hospital readmissions for HF was assessed. **Results:** A total of 121 patients were analyzed. The mean age of the cohort was 66.6±11.5 years with a male predominance (71.9%). The principal etiology was ischemic (30.6%) followed by idiopathic (24.8%) and tachycardiomyopathy (10.7%). A total of 55 patients (45.5%) improved LVEF (group 1) and 45 patients (54.5%) didn't improve LVEF (group 2). In group 1, the mean time to LVEF improvement was 13.6±7.4 months. Group 1 had a more favourable clinical profile: lower prevalence of cardiovascular risk factors [diabetes mellitus (34.5%vs56.1%;p<0.05), hypertension (52.7%vs77.3%;p<0.05), dyslipidemia (50.9%vs74.5%;p<0.05)], chronic kidney disease (21.8%vs59.1%;p<0.01), and anemia (14.5%vs43.9%;p<0.01), higher prevalence of de novo HF (78.2%vs36.4%;p<0.01), lower prevalence of ischemic etiology (18.2%vs40.9%;p<0.05) and higher prevalence of tachymyopathy etiology (20.0%vs3.0%;p<0.05). Although at the end of follow-up (mean 21±1 months) group 2 had a higher proportion of prescription of Sacubitril-Valsartan (43.6%vs74.2%;p<0.01), SGLT2 inhibitors (21.8%vs47.0%;p<0.01) and implantable cardioverter defibrillator (1.8%vs28.8%;p<0.01), group 1 had a lower hospital readmission rate (2.3%vs44.9%; p<0.001), as well as lower mortality (0%vs43.2%;p<0.001). **Conclusion:** Patients with HFimpEF seem to have a better mid-term prognosis in terms of reduced mortality and hospital admissions according to the new Universal Definition of Heart Failure. This improvement could be conditioned by the clinical profile of patients HFimpEF.

PSII.s. Biomechanical analysis of the voice, characterization method in Amyotrophic Lateral Sclerosis (ALS).

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Scientific Program: Active ageing and fragility.
Keywords: Amyotrophic Lateral Sclerosis (ALS) and biomechanical analysis of voice and evolution.

Abstract:

Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive disease of the nervous system that affects nerve cells in the brain and spinal cord, causing loss of muscle control. Hypophonia, dysarthria, and anarthria are common symptoms in the ALS patient. Dysarthria can be present in up to 80%. Its origin includes weakness of the orofacial muscles, atrophy of the tongue and lips, and spasticity, among others. The patient presents a forced, slow production of speech, with short sentences, inappropriate pauses, articulatory imprecision, hypernasality, strangled and strained voice, more serious and low volume. In the case of the voice, a hyper-abduction or abduction mechanism can be observed depending on whether it is predominantly bulbar or corticobulbar, respectively. **Method:** The study carried out is a prospective observational cohort in which a sample of patients with ALS is compared with another without voice pathologies that affect the biomechanics of the voice. In all of them, a voice biomechanical study is carried out through App Online Lab (Voice Clinical System). The specific voice biomechanical profile alterations in ALS patients will be defined afterwards. **Results:** A total of 24 patients with a male predominance (62.5%) were analyzed. After evaluation of phonation types and the rest of the biomechanical parameters such as GAP, Asymmetry, Phases and tension, it was observed statistically significant results related to muscle control and instability (Pr13, Pr14 and Pr15). The muscle tensión parameters (Pr14 and Pr15) were decisive, with Pr15 being indicative of pathology severity. **Conclusion:** Through the biomechanical analysis of the voice in ALS with Voice Clinical System, we could have a characterization of the pathology, its degree and its evolution.

PSII.t. CYB5R3 overexpression and dietary nicotinamide riboside supplementation influence mitochondrial status: effects in mitochondrial complexes and mitochondrial population ultrastructure of kidney from female and male mice.

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

Abstract: The mitochondrial free radical theory of aging proposes mitochondrially-derived free radicals as the main trigger factor of aging since these free radicals can damage cellular components cumulatively throughout life. Interventions aimed to preserve or improve mitochondrial quality and function have engaged a great interest. Among them, those focused on NAD+ maintenance or increase have reported relevant results, as they may improve key markers of mitochondrial population status and other aging-related processes. Our aim was to analyze in kidney from male and female young/adult mice how CYB5R3 overexpression and/or dietary supplementation with the NAD+ booster nicotinamide riboside (NR) influence electron transport chain and mitochondrial population ultrastructure as descriptors of mitochondrial status. Markers related with mitochondrial mass, electron transport chain components and function, oxidative stress response and mitochondrial ultrastructure that may be related with the quality and function of mitochondria were analyzed using Western blot and quantitative electron microcopy techniques. Our data have shown a sex dependent effect of the interventions. CYB5R3 overexpression elicited changes that can be interpreted as beneficial in male mice, showing a synergistic effect with consumption of a NR-supplemented diet. In female mice however, CYB5R3 overexpression did not produce the same consistent pattern of changes, and the combined interventions of CYB5R3 overexpression and dietary NR-supplementation even seem to induce some detrimental effects. Taken together, our data stablish a novel starting point for further analysis and long-term aging studies to understand the effect of anti-aging approaches in mice of both sexes.

PSII.u. Identification and characterization of novel positive allosteric modulators for CB1R.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: CB1R, Positive allosteric modulators, Podophyllotoxin, Lignans.

Abstract: Cannabinoid receptors (CB1R and CB2R), as part of the endocannabinoid system (ECS), play a critical role in numerous human physiological and pathological conditions. From a natural products perspective, it is expected that small molecules targeting CB receptors may show special relevance.
We have screened a large collection of plant spices on ECS targets. Among the whole collection, a Juniper communis CO2 extract showed a potent and selective activity as a positive allosteric modulator (PAM) for CB1R. While showing no orthosteric activity, this extract enhanced cAMP levels, activation of ERK-1+2 and recruitment of β-arrestin. After bio-guided fractionation and compound isolation, podophyllotoxin (PPT), a lignan that prevents cell division by destabilizing microtubules through tubulin dimers binding, was identified as the major bioactive compound in the extract. PPT retains the effects of Juniper extract on cAMP, ERK1+2 and β-arresting signalling. PAM activity of PPT was confirmed in a GTPγS binding assay for CB1R as well. PPT enhanced CP55,940-stimulated [35S]GTPγS binding at low concentrations (10-12 and 10-15M) in transfected cell membranes. To get insight into the Structure-Activity Relationship (SAR) of PPT and other lignans with CB1R, docking analysis were performed. The most promising binding site was discovered at the exosite located between transmembrane helixes 1,2 and 4.
The identified binding site was confirmed using CB1R single and double mutants. While retaining response to orthosteric ligands, mutants showed no response to PPT PAM activity. Afterwards, an in silico screening of a large collection of 225 natural and semisynthetic lignans was performed, and 15 candidates were selected for additional in vitro studies.
The development of CB1R allosteric modulators has become an area of immense importance within the cannabinoid field. It is clear that enormous potential exists to successfully target CB1R through allosteric sites for the treatment of different types of pain, neurological diseases and metabolic diseases.

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

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Cytoreductive surgery, Peritoneal carcinomatosis, PlasmaJet®.

Abstract:

Introduction: Cytoreductive surgery (CRC), associated with hyperthermic intraperitoneal chemotherapy (HIPEC), is limited in many cases by the degree of involvement of the mesentery, which determines the complete resectability of the disease and increases the morbidity of surgery. In this context, different methods have emerged -not exempt from morbidity- for the treatment of miliary involvement of the mesentery. Recently, a new tool has emerged that allows the treatment of affected surfaces by vaporization with neutral argon plasma, called Plasmajet®. Its use presents little damage to normal tissue and allows complete removal of tumor tissue. The main objective of this research will be to try to evaluate the effectiveness and safety of the use of neutral argon plasma on peritoneal implants. **Material and methods:** Phase I/II study of a single arm to evaluate the safety and efficacy of the use of neutral argon plasma in the eradication of tumor implants at the mesenteric level, with different doses, application distances and time. It will also be compared in-vivo with monopolar electrofulguration control therapy. Patients diagnosed with peritoneal carcinomatosis, different tumor strains that meet criteria for treatment by CRS + HIPEC, clinicaltrials.org (NCT04904042), will be includ. **Results:** 10 patients were included. The mean PCI was 22.4, and the distribution by tumor origin was 5 ovarian cancer, 2 peritoneal pseudomyxomas, 1 endometrial cancer, 1 colon cancer, and 1 peritoneal mesothelioma. The mean size of the tumor implants studied was 4.34 mm. A total of 120 samples from 10 patients were obtained, in which the macroscopic destruction of the implants was verified. None of the samples showed viable tumor tissue in the treated area, penetration and destruction were greater for distances of 1cm and application of 4 seconds. The dose of 80% and 2 seconds at a distance between 2-3 cm were the ones that presented the best safety and effectiveness profile. In-vivo use did not show complications associated with the procedure and a subjective perception of less smoke formation than electrofulguration. No differences between the different tumor strains. **Conclusions:** These findings suggest that the PlasmaJet® device is an innovative, efficient and safe surgical device for tumor cytoreduction surgery, recommending a dose of 80%, máximum 2 seconds at a distance of 2-3cm.

PSII.w. Association between metabolic syndrome and uric acid: a systematic review and meta-analysis.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: metabolic syndrome, uric acid, biologic marker, early diagnosis.

Abstract: This systematic review and meta-analysis aim to provide the best evidence on the association between metabolic syndrome (MetS) and uric acid (UA) by determining the size of the effect of this biomarker on MetS. The review protocol is registered with PROSPERO (CRD42021231124). The search covered the PubMed and Scopus databases. Methodological quality was assessed with the STROBE tool, overall risk of bias with RevMan (Cochrane Collaboration) and quality of evidence with Grade Pro. Initially, 1,582 articles were identified. Then, after excluding duplicates and reviewing titles and abstracts, 1,529 articles were excluded from applying the eligibility criteria. We included 43 papers (56 groups) comparing UA concentrations between subjects 91,845 with MetS and 259,931 controls. Subjects with MetS had a higher mean UA of 0.57 mg/dl (95% CI 0.54-0.61) ($p<0.00001$). Given the heterogeneity of the included studies, the researchers decided to perform subgroups analysis. Men with MetS have a higher UA concentration mg/dl 0.53 (95% CI 0.45-0.62, $p<0.00001$) and women with MetS 0.57 (95% CI 0.48-0.66, $p<0.00001$) compared to subjects without MetS. Assessment of UA concentration could provide a new avenue for early diagnosis of MetS, as a new biomarker and the possibility of new therapeutic targets.

PSII.x. SARS-CoV-2 infection increases CMV-associated cardiovascular risk.

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

Abstract:

Aims: SARS-CoV-2 infection causes COVID-19. As the severity of COVID-19 increases with age, it has been speculated its association with immunosenescence. Expansion of peripheral CD28nullCD8+ and CD4+ T cells is associated with cytomegalovirus (CMV) infection, considered one of the main factors driving early immunosenescence. CMV has been associated with an increased risk of cardiovascular disease (CVD). An increment of cardiovascular events leaded by SARS-CoV-2 infection has also been observed. CD28null T cells express CD57, are proinflammatory, cytotoxic and polyfunctional, and express CX3CR1 chemokine receptor. We hypothesized that CD28nullCD57+CX3CR1+ T cells can infiltrate the vasculature, attracted by fractalkine (CX3CR1 ligand) produced by vascular endothelial cells in response to proinflammatory cytokines. Thus, we aim to study the proportion of CD28nullCD57+CX3CR1+ T cells subset as a marker of cardiovascular risk. **Methods:** We analyzed, by multiparametric flow cytometry, the expression of CD28, CD57 and CX3CR1 on peripheral blood T-cells from mild COVID-19 patients (30-54 years) 3-6 months and one year after infection, CVD patients (42-79 years), and sex/age matched healthy volunteers (HD), all of them stratified by CMV-serostatus. **Results:** The percentage of CD28nullCD57+CX3CR1+ T-cells was increased in asymptomatic/mild COVID-19 patients 3-6 months after infection compared to HD ($p<0.0001|p<0.05$, CD8+ and CD4+ respectively), but only in the context of CMV chronic infection. This expansion was observed even one year after SARS-CoV-2 infection ($p<0.001|p<0.05$). Remarkably, COVID-19 patients and CVD patients exhibited similar percentages of these proatherogenic cells ($p=0.8|p=0.4$). **Conclusions:** Our results suggest that, in patients with asymptomatic/mild COVID-19, SARS-CoV-2 accelerates CMV-associated cardiovascular risk. This effect was observed in individuals 20 years (medium age) younger than CVD patients, alerting of a potential increased risk of developing cardiovascular events at younger ages in these patients. Given the high prevalence of both CMV and SARS-CoV-2 worldwide, this could suppose a serious global health problem in the foreseeable future.

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ciencias de la salud en Andalucía 2021, co-funded by European Union (FEDER Andalucía 2014-2020) (to Pera, A. and Juan Molina). Grant FI20/00194 (to Álvarez-Heredia, P.).

PSII.y. Muscle mechanical properties of pelvic floor and paravertebral muscles, and lumbar range of motion in women with and without urge incontinence urinary: case-control study.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Urinary Incontinence; Pelvic Floor; Women; Biomechanical behavior; Lumbar Motion.

Abstract: Deficit in the function of the Pelvic Floor Muscles (PFM) can compromise their action and result in involuntary urination, called by the International Continence Society as Urinary Incontinence (UI). Although no single factor completely explains the etiology, particularly the condition of the pelvic floor muscles (PFMs) has been analized. However, relationships between urge urinary incontinence (UUI) and muscle mechanical properties (MMPs) of the pelvic floor muscles (PFMs) and spinal range motion have not been fully elucidated. The objective was to identify potential differences in MMPs of PFMs and in biomechanical behaviour in patients with UUI and healthy controls.
The participants of this cross-sectional study comprised 21 women with UUI (UUI group) and 20 continent women (continent group). Sociodemographic and pelvic floor symptoms were obtained using clinical questionnaires. The muscle mechanical properties (MMPs) of the pelvic floor muscles (PFMs) was assessed with a hand-held tonometer device called the MyotonPRO and inertial sensors “Inertial Measuring Unit” (IMU) were used to determine lumbar range of motion (LROM). Between-groups differences were statistically calculated.
Higher scores in dysfunctional pelvic floor questionnaires were observed in patients with UUI. The results showed that pelvic floor tone (mean difference -1.06, 95%CI= -2.163, 0.310) and muscle stiffness (mean difference -40.55, 95%CI= -76.283, -4.822) was significantly increased in patients with UUI than controls ($P<0.05$), while lumbar tone was higher in healthy group. Patients with UUI showed reduced lumbar mobility when compared to control groups but without significant differences.
MMPs of PFM and LRM was difference in women with UUI when compared to healthy women, patients with UUI demonstrated higher pelvic floor tone and muscle stiffness and lower lumbar tone than controls, which can be associate to UUI pathophysiology.

PSII.z. Evaluation of the in vitro and in silico interaction of a cationic peptide against colistin-resistant P.aeruginosa membrane models.

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Scientific Program: Infectious and immunological diseases
Keywords: Membrane models, Pseudomonas colistin resistant, Cationic peptides.

Abstract: The prolonged and inappropriate use of antibiotics has generated bacteria resistant to multiple antibiotics causing 700,000 deaths annually worldwide, one of the contributors to this figure being Pseudomonas aeruginosa. To combat this bacterium, polymyxin E (colistin) is administered ultimately due to its toxicity. In addition, strains resistant to this antibiotic have appeared, which has generated the search for alternatives such as vaccines, lysines, bacteriophages, probiotics and antimicrobial peptides (AMPs). Peptides have potential due to their low immunogenicity and wide range of action. In this study, our aim was to evaluate the interaction of a cecropin D-derived CAMP (ΔM2) with model membranes that mimic bacterial biomembranes of wild-type strains of P.aeruginosa (WTPa) and colistin-resistant P. aeruginosa (CRPa), using in vitro and in silico approaches. In vitro interaction was determined by infrared (IR) spectroscopy, while in silico molecular dynamics was performed to predict specific interactions between ΔM2 amino acids and lipids in model membrane systems. In experimental analysis this peptide was found to interact with the bacterium-like model membrane lipids of WTPa and CRPa. Similarly, the DM results demonstrated and confirmed a high activity of the ΔM2 peptide against WTPa and CRPa membrane models. Finally, it was evidenced that the amino acid that most interacted with the two membrane models WTPa and CRPa was ARG.

PSII.aa. The novel multiagonist, GLP1-estrogen, improves the management of non-alcoholic fatty liver disease in lean and obese models of polycystic ovary syndrome.

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Scientific Program: Endocrine and metabolic diseases.
Keywords: Multiagonist, GLP-1, GLP-1/estrogen, PCOS, androgenization.

Abstract: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS patients commonly exhibit hyperandrogenism, gonadal and reproductive dysregulation, as well as metabolic disorders, such as obesity, type-2 diabetes and non-alcoholic fatty liver disease (NAFLD); the most prevalent liver disease. Patients with PCOS have four-times higher risk of developing NAFLD.

NAFLD encompasses a set of clinical manifestations that begin with fat accumulation in the liver (steatosis) that may progress to non-alcoholic steatohepatitis (NASH) and more severe stages of the disease. The most recommended intervention for PCOS-associated NAFLD is weight loss. Yet, obese PCOS patients are often unsuccessful in losing weight through lifestyle modifications and, currently, there are no effective pharmacotherapies for the management of hepatic complications associated with PCOS.

In recent years, a novel unimolecular multiagonist, with the ability of activating the GLP-1 (glucagon-like peptide 1) and the estrogen receptor, two anorexigenic hormones, has been shown to improve the metabolic profile, including NAFLD, in male models of obesity. However, the therapeutic potential of this multiagonist for the management of hepatic complications of PCOS remains unexplored.

In this study, we assessed the therapeutic effect of the GLP1-estrogen conjugate on PCOS-associated NAFLD in two murine models of PCOS. Our results revealed that intervention with GLP1-estrogen reduced body weight, fat mass and circulating insulin levels and improved liver steatosis, hepatic lipid content and liver fibrosis in an obese model of PCOS. Treatment in a lean model of PCOS also improved the metabolic profile and reduced liver steatosis and fibrosis. In both PCOS models, treatment with the multi-agonist altered the expression pattern of certain genes related with lipid metabolism, apoptosis and fibrosis in the liver. Our findings may set the basis for the development of novel pharmacotherapies for the effective management of the hepatic perturbations frequently linked with PCOS.

PSII.bb. Metabolic adaptation of female mice overexpressing CYB5R3 and submitted to a caloric restriction intervention.

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Scientific Program: Active aging and frailty.
Keywords: Calorie restriction, CYB5R3 overexpression, Female mice, Sexual dimorphism, Skeletal muscle.

Abstract: Calorie restriction without malnutrition (CR) is the most effective nongenetic nor pharmacological intervention that promotes healthy aging and can extend lifespan. The NADH-dehydrogenase CYB5R3, which is upregulated by CR in some tissues, plays a key role in controlling mechanisms that promote healthy aging. Transgenic mice overexpressing CYB5R3 (Tg mice) show improved glucose metabolism and increased survival. However, involved mechanisms may depart from those of CR, and we showed in male mice that some benefits of CR may be hindered by CYB5R3 overexpression. Model organisms exhibit differences between males and females, and the outcome of CR in mice is strongly influenced by variables as strain, degree of restriction, and sex. It is thus necessary to include both sexes to gain a greater relevance of the results derived from antiaging interventions. To elucidate if sex influences the crosstalk between CR and CYB5R3 overexpression, we studied the long-term effects of 4 mo. CR (40% restriction starting at the age of 3 months) in female mice overexpressing or not CYB5R3, in terms of body weight, body composition (fat mass, lean mass and lean-to-fat ratio), liver weight and hepatic levels of mitochondrial complexes and markers of mitochondrial mass, dynamics and biogenesis. We demonstrate here in females that, although several effects of CR can be hindered by CYB5R3 overexpression as also occurs in males, sexual dimorphism exists in the metabolic response to CR and CYB5R3 overexpression and in the crosstalk between diet and genotype. Additional studies focused on females are necessary to ascertain unequivocally the effects of these interventions with antiaging potential.

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PSII.cc. S-nitrosoglutathione reductase deficiency in colorectal cancer confers metabolic vulnerabilities that can be therapeutically exploited.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Metabolic reprogramming; mitochondria; bioenergetic metabolism; colorectal cancer; GSNOR; 2-deoxyglucose.

Abstract:
Background and aims: S-nitrosoglutathione reductase (GSNOR) is an evolutionarily conserved denitrosylase enzyme for which a tumor suppressor role has been suggested. We previously showed that metabolic reprogramming induced by GSNOR deficiency is an important mechanism contributing to colorectal cancer (CRC) progression. Consequently, this study was aimed to deepen into the metabolic alterations and derived therapeutic opportunities in GSNOR-deficient CRC tumors. **Material and Methods:** Real-time cell metabolic analyses in GSNOR gene knockout (KO) CRC cells were performed using an Agilent Seahorse XFe24 Extracellular Flux Analyzer. GSNOR expression in clinical CRC tumors was analysed by immunohistochemistry. In vitro 3D culture of patient-derived tumor organoids (PDOs) and patient-derived tumors engrafted into immunocompromised NSG™ mice (PDXs) were used as relevant preclinical models to test the anti-tumor effects of the glycolysis inhibitor 2-deoxyglucose (2-DG). **Results:** The bioenergetic and mitochondrial function analysis showed that compared with parental cells, GSNOR-KO cells exhibited lower oxidative phosphorylation (OXPHOS) rates, with reduced basal respiration and ATP production, in concordance with our previous reports of a fragmented mitochondrial network in these cells. However, GSNOR-KO cells retained a significant respiratory reserve capacity, suggesting a higher metabolic plasticity, thus enabling their adaption to changing conditions during cancer progression. Besides, GSNOR-KO cells displayed a lower glycolytic reserve capacity, indicating that they are operating close to their maximal glycolytic rate as a compensation for lower OXPHOS levels. Accordingly, GSNO-KO cells were more sensitive to the glycolysis inhibitor 2-DG. Importantly, growth of PDOs from GSNOR-negative tumors was more efficiently reduced by 2DG treatment, compared to those generated from GSNOR-positive tumors. Moreover, 2DG treatment significantly reduced the growth of PDXs from GSNOR-negative tumors, but not of PDXs from GSNOR-positive tumors. **Conclusions:** Attacking the metabolic vulnerabilities associated

with their altered bioenergetic metabolism is a valuable strategy for the treatment of aggressive GSNOR-deficient CRC tumors.

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

PSII.dd. Anti-glomerular basement membrane glomerulonephritis. A study in real life.

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

Abstract:

Introduction: Anti-glomerular basement membrane (anti-GBM) disease is a severe entity with few therapeutic options that include plasma exchange and immunosuppressive agents. The aim of the study was to analyse the clinical and pathological features that predict evolution to end-stage kidney disease (ESKD) and the kidney survival in a cohort of anti-GBM patients with renal involvement in real life. **Methods:** A retrospective multicentre observational study including 72 patients from 18 nephrology departments with biopsy-proven anti-GBM disease from 1999 to 2019 was performed. Progression to ESKD in relation to clinical and histological variables was evaluated. **Results:** Creatinine at admission was 8.6(±4) mg/dL and 61 patients (84.7%) required dialysis. Sixty-five patients (90.3%) underwent plasma exchange. Twenty-two patients (30.6%) presented pulmonary haemorrhage. Kidney survival was worse in patients with creatinine levels >4.7 mg/dL (3% vs. 44% $p < 0.01$) and in patients with >50% crescents (6% vs. 49%; $p = 0.03$). Dialysis dependence at admission and creatinine levels >4.7 mg/dL remained independent significant predictors of ESKD in the multivariable analysis (HR [hazard ratio] 3.13 (1.25-7.84); HR 3 (1.01-9.14; $p < 0.01$). The discrimination value for a creatinine level >4.7 mg/dL and 50.5% crescents had an area under the curve (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%, respectively. Patient survival at 5 years was 81%. **Conclusions:** In real life patients with severe anti-GBM disease (creatinine >4.7 mg/dL and >50% crescents) remained with devastating renal prognosis despite plasma exchange and immunosuppressive treatment. New therapies for the treatment of this rare renal disease are urgently needed.

PSII.ee. Could the primary cilium predict progression from actinic keratosis to squamous cell carcinoma?

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Primary cilium, squamous cell carcinoma, actinic keratoses, electron microscopy.

Abstract:

Introduction: The primary cilium (PC) is a cell surface organelle that plays part in the initiation of mitosis and has a rol in celular signaling, the absence of a proper signaling or its aberrant activation are related to an uncontrolled cell division. By electron microscopy, we characterized it in relation to squamous cell carcinoma (SCC) of the skin and actinic keratoses (AK). **M&M:** We obtained samples from dermatology patients and from autopsy corpses, consisting it in a punch (3-6 mm) of adult human skin with suspicion of AK and/or SCC. We used part of the skin for diagnosis and the other half for ultrastructural study: fixing in 2.5% glutaraldehyde for up to 4 days, and then stored in PBS. The sample sections were cut with ultramicrotome and examined under electron microscope (EM). **Results:** We got from each sample an hematoxylin and eosin (H&E) histological slice and inmunohistochemistry: CD31, beta-catenin, ki67, vimentin, PTEN, p63, e-cadherin and p53. As to EM, we collected almost 20 images of each sample. We observed a decreased of CP in the cells of SCC and a gradually lost in AK in their different grades of displasia. **Conclusions:** We have shown that PC participates in the malignancy process of AK up to SCC. The decreased expression of the PC appears to be directly proportional to the AK grade, which could help predicting the progression to SCC.

PSII.ff. Comparative Study of a Sjögren's Syndrome Cohort (Primary and Secondary).

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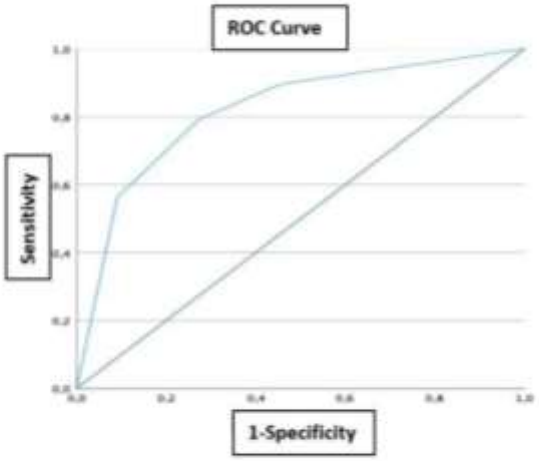
Scientific Program: Chronic and inflammatory diseases.
Keywords: Sjogren's Syndrome, Autoimmunity, Organ disease.

Abstract:

Introduction: Sjögren's syndrome (SS) is characterized by oral and ocular dryness together with anti-nuclear antibodies (ANA), with strong prevalence in females. It is classified as primary (pSS) or secondary (sSS). Hereby the characteristics of a Sjögren's syndrome cohort are analyzed. **Methods**: an observational, cross-sectional, descriptive study was done. Serological characteristics, complementary tests, systemic involvement and death causes of SS patients were analyzed. Comparisons were made using chi-square test. Using univariate and multiple logistic regression analyses, Odds Ratios (OR) were calculated. Discriminative capacity of the multiple model obtained was evaluated by calculating a ROC curve (Image 1) and significance under the curve according to Wald test. All contrasts were bilateral and significant when p< 0.05. **Results:** 576 patients (64,2±13.5 years) were evaluated, 327 pSS and 115 sSS (with Rheumatoid Arthritis in 11.6%). 24 died (5.4%). Mainly of cardiovascular issues (n=9) and lung disease (n=4). Five of malignancies. There is a higher prevalence on female sex (96.3% p:0.014), ANA (81.3% p< 0.001), Anti Ro (59.9% p: 0.002) Anti La (27.8% p:0.005) and Hyper IgG (17.7% p: 0.005) in pSS (Table 1). Rheumatoid factor (RF) was more prevalent among SSs (58.3%, p:0.016). Positive salivary biopsy was frequent in pSS (66.7% p:0.037). There was a higher prevalence of interstitial pneumopathy in sSS (p< 0.05). ORs quantified the association of female sex, ANA, Anti-Ro, Anti-La, IgG and salivary biopsy positivity with pSS. Six lymphoma cases occurred only in pSS. In multivariate analysis only RF showed a protective association (OR 0.13, p: 0.009) with pSS, positive salivary biopsy became a confounding factor. **Conclusion:** pSS was associated with female sex, ANA, Anti Ro, La, Hyper IgG and salivary biopsy positivity; Rheumatoid Factor and interstitial pneumopathy were more frequent in sSS. Only RF positivity was associated with pSS. Only lymphomas or other haematological malignancies were observed in pSS.

Image 1:



- *Area under the ROC curve (0.819 (95%CI:0.680-0.958), p:0.001*
- *Sensitivity: 89.6%, Specificity: 54.5%, Accuracy: 83.1%.*
- *Goodness of fit (lozmar-lemeshow test p:0.956)*

PSII.gg. Analysis of the potential role of hepatic kisspeptin in energy and metabolic homeostasis.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: kisspeptin, liver, energy balance, fasting, LiKKO.

Abstract: Energy balance is a dynamic process that integrates energy intake and expenditure. The metabolic state of an organism determines the physiological adaptations needed to ensure survival. As reproduction is one of the most energy-demanding processes, it is tightly bound to the magnitude of body energy reserves and metabolic state. Reproduction is controlled by different factors, including hypothalamic Kiss1 neurons. Kiss1 neurons not only have a prominent role in the control of the reproductive axis but are sensitive also to alterations in metabolic and nutritional status. In addition, expression of Kiss1 and its receptor, Gpr54, has been described in different peripheral metabolic tissues, including the liver, suggesting an additional role of the Kiss1/Gpr54 system in energy homeostasis and peripheral metabolism. However, the actual physiological relevance of kisspeptins in the liver remains largely unknown. We report herein that Kiss1 and Gpr54 are expressed in the mouse liver in a sexuallydifferent manner, with higher levels in females. Hepatic Kiss1 expression is modulated by the nutritional state, with upregulation at >15 hours of fasting in both sexes, while Gpr54 expression was significantly increased by fasting only in male mice. Fasting responses were fully reversed by re-feeding for 24-h. Liver Kiss1 and Gpr54 expression was also modulated by metabolic hormones, with up-regulation by glucagon. To explore the physiological role of hepatic kisspeptin in the control of metabolism, we have generated a novel mouse line with liver-specific ablation of Kiss1 (LiKKO). Our initial studies have confirmed selective elimination of Kiss1 expression from the liver of LiKKO mice and detected alterations in hepatic gene expression of lipid/glucose metabolicpathways and hepatokine production. Our results document a sexually-different and nutritional-dependent pattern of hepatic Kiss1/Gpr54 expression in mice, suggesting a role of liver Kiss1 in the peripheral control of metabolism, which is being currently investigated in the LiKKO mouse.

PSII.hh. Oxidative environment and redox homeostasis in a rare malignant disease: Pseudomyxoma peritonei.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Pseudomyxoma peritonei.

Abstract:

Introduction: Pseudomyxoma peritonei (PMP) is a rare malignant tumour whose molecular mechanisms are unknown. It's characterized by the progressive accumulation of mucin and secreting tumour cells within the abdomen and pelvis. Cytoreductive Surgery combined with Hyperthermic Intraperitoneal Chemotherapy is the only therapeutic option. In addition, recurrence with a fatal end is common. The lack of information about molecular mechanisms is mainly due to the physicochemical characteristics of mucin, which has been designed to protect the epithelial cells. **Objective:** This job aims to test the in vivo oxygen levels in healthy and tumoral tissue for the first time and to correlate it with the redox status of PMP. **Methods:** The intraoperative measurement of the partial pressure of arterial O2 (pO2) in mucin, solid tumour and healthy tissue was carried out using the OxyLite™ single channel dissolved oxygen (pO2) and temperature monitor. Then, to improve the knowledge about the mechanisms implicated in the tumour growing in these O2 conditions, several redox status biomarkers (Hypoxia Inducible Factor-HIF1a, catalase activity and PRDX 6, etc.) were analyzed. **Results and conclusions:** The intraoperative pO2 levels were drastically lower in mucin and solid tumour than in control tissues (blood and healthy peritoneal areas). On the other hand, the HIF1a levels increased, likely due to rapid cell proliferation in low oxygen conditions. Finally, oxidative stress biomarkers showed a significant decrease mainly due to the dramatic drop in oxygen concentration. These results show the first evidence that PMP grows in hypoxia conditions. Furthermore, the correlation between pO2, HIF1a and oxidative stress biomarkers in PMP tumour tissue makes it interesting to improve the knowledge about the mechanisms implicated in the tumour development.

PSII.ii. Ferroptosis is involved in acute kidney injury associated to massive intravascular hemolysis.

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Scientific Program: Chronic and Inflammatory diseases.
Keywords: Ferroptosis, AKI, intravascular hemolysis, cell death.

Abstract: Massive intravascular hemolysis is characterized by the rupture of erythrocytes within the blood vessel, causing the release of hemoglobin and its heme-derivatives into the circulation. These hemoproteins can accumulate in the kidney, promoting acute kidney injury (AKI). The accumulation of hemoglobin induces oxidative stress and inflammation, leading to renal cell death and consequent loss of renal function. Traditionally, apoptosis and necrosis have been related to AKI. However, new types of cell death, such as necroptosis and ferroptosis, have been recently identified. In this study, we fully characterized what type of cell death was responsible of the renal injury associated to intravascular hemolysis. We performed a pre-clinical model of intravascular hemolysis-associated AKI by the intraperitoneal injection of 200mg/kg of phenylhydrazine in C57BL/6J mice. To characterize the type of cell death involved in this pathological setting, mice were injected with ferrostatin-1 (5 mg/Kg, a ferroptosis inhibitor), necrostatin-1s (1.65 mg/Kg, necroptosis inhibitor) and Z-Val-Ala-DL-Asp-(OMe)-fluoromethylketone (zVAD, 10 mg/Kg, a pan-caspase inhibitor), 30 minutes before administration of phenylhydrazine. Mice were sacrificed 24 hours after induction of hemolysis. Blood, urine and renal tissue were collected to determine renal function and TUNEL staining. We also performed studies in cultured murine tubular cells (MCTs) to analyze the molecular mechanisms and intracellular pathways involved in hemoglobin-mediated cell death by flow cytometry, western blot and real-time PCR. Induction of intravascular hemolysis increased serum creatinine levels and induced the renal gene expression of the tubular injury markers NGAL and KIM-1, as well as tubular cell death. Pre-treatment with Fer-1 and zVAD ameliorated all these alterations. Data obtained from cells in culture showed that exposure to heme and iron decreased cell viability. Since oxidative stress and lipid peroxidation are important hallmarks of ferroptosis-mediated cell death we analyzed these parameters in MCTs exposed to haemoglobin. Our results showed that haemoglobin induced oxidative stress and lipid peroxidation and Fer-1 treatment reduced these pathological effects. In conclusion, our data suggests that cell death associated to ferroptosis and apoptosis may play a major role in early stages of intravascular hemolysis-AKI, therefore

therapeutic measures aimed at inhibiting both types of death could be of great interest to decrease renal damage in this pathological context.

PSII.jj. Prognostic value of RAS mutation status changes in circulating tumor DNA of metastatic colorectal cancer patients.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Colorectal cancer; liquid biopsy; circulating tumor DNA; RAS mutation; monitoring.

Abstract:

Introduction and objectives: The evolution of metastatic colorectal cancer (mCRC) is a dynamic process. During the course of the disease the mutational status of RAS can change. Liquid biopsy is an accessible and minimal invasive tool to study molecular alterations of the tumor that has emerged as a promising alternative to primary tumor analysis. Concordance between liquid biopsy and tissue RAS mutation analysis is 96%. The main objective of this study was to determine the prognostic role of mutational changes in circulating RAS mutation status during the evolution of the disease by liquid biopsy in mCRC. **Methods:** We retrospectively selected 75 mCRC patients with RAS mutation analysis using BEAMing technique in circulating cell-free DNA (cfDNA) prior to initiation of treatment of metastatic disease and at disease progression and/or retreatment. We next performed a descriptive statistical analysis of clinicopathological variables and evaluated the association of changes in RAS mutational status during disease evolution with overall survival (OS). **Results:** RAS mutational status determination in cfDNA at baseline (87% concordance with tissue analysis) showed that 55 patients were RAS-WT and 20 were RAS-mutated. During disease monitoring 33 of 55 RAS-WT patients maintained RAS-WT status and the other 22 patients acquired a RAS mutation. RAS-mutated patients at baseline and those who acquired RAS mutation during the evolution of the disease showed significant lower OS than those patients who were WT at baseline and during disease monitoring (25 months(m) vs. 41m vs. 82m; Log Rank p=0.042). Moreover, this was also a significant prognostic factor in the multivariate analysis (HR 0.29; 95%CI 0.12-0.71; p=0.007). **Conclusions:** The acquisition of secondary mutations in RAS is associated with lower OS in mCRC patients. Our results support the value of liquid biopsies to monitor dynamic changes in RAS mutational status that may help in personalized clinical-decision-making.

PSII.kk. Gut microbial composition as a diagnostic tool for colorectal cancer.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: gut microbiota, colorectal cancer, diagnostic tool, polyp, colonoscopy.

Abstract:

Introduction: Colorectal cancer (CRC) is one of the most common cancers in developed countries. The composition of the gut microbiota affects the environment of the colon, where it participates in the digestion, regulates the tract and protects the intestinal mucosa, and interacts with the immune system. Our objective was to develop a microbiota-based method for improving the classification of the positive patients for fecal occult blood test, during CRC screening programs. **Methodology:** In this study, we included 152 patients, positive for fecal occult blood test, during the screening program that included people over 50 years of age. Among these patients, 123 presented polyps, 6 presented adenocarcinomas, and in 23 no pathological findings were observed. Gut microbiota composition was analyzed by 16S rRNA gene sequencing on the Illumina MiSeq platform. **Results:** Our results showed a differential profile of gut microbiota associated with the presence of polyps or adenocarcinomas. The mathematical model built using Random Forest combining the microbiome data with nutritional habits obtained an area under the curve (AUC) of 0.77. However, independently, the model that included the microbiome data obtained an AUC of 0.76, and the one that included nutritional habits obtained an AUC of 0.73. **Conclusions:** Our results suggest that using data from the gut microbiome and nutritional habits, it is possible to improve the diagnosis of CRC.

PSII.II. The role of physical activity on psychological well-being in children and adolescent with type 1 diabetes: preliminary data of a cross-sectional study.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: type 1 diabetes; chronic diseases; psychosocial variables; physical activity; psychological well-being.

Abstract:

Background: Psychosocial and motivational variables play an important role in the emotional and psychological well-being of patients with chronic diseases. Purpose: The present study aims to analyze the role of physical activity on psychological well-being in children and adolescents' patients with type 1 diabetes. Specifically, we evaluated the relationship between physical activity with perceived social support, self-efficacy, subjective well-being and emotional stability. **Methods:** To do so, we carried out a crosssectional study including 133 patients (44.4% women; Mage = 13.4, SDage = 3.51) with a type 1 diabetes diagnosis from the endocrinology and nutrition unit of the Reina Sofia University Hospital. After signing informed consent, all participants completed the evaluation including the information related to Physical Activity (APALQ), Positive and Negative Affect (PANAS), Perceived Social Support (MSPSS), Emotional stability (BFI) and Diabetes-specific Self-Efficacy (SED). **Results:** A Pearson correlation coefficient was performed to assess the linear relationship between physical activity and the psychosocial variables evaluated. Significant and positive correlations were found between physical activity and perceived social support, diabetes-specific self-efficacy, and positive affect. **Conclusions:** These results support the previous literature that highlight the importance of physical activity for the emotional regulation and well-being of pediatric patients with type 1 diabetes and underline the importance of the design and development of awareness programs and psychoeducational interventions to promote physical activity as a healthy habit in this clinical population.

PSII.mm. Adipokines and hepatokines as potential biomarkers of hepatocellular carcinoma.

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Scientific Program: Cancer (Oncology and Oncohematology).
Keywords: Hepatocellular carcinoma, adipokines, hepatokines.

Abstract:

Objective: To assess the role of hepatokines and adipokines as potential biomarkers in hepatocelullar carcinoma (HCC). **Material and methods:** The expression of hepatokines and adipokines was assessed on HCC tumoral and peritumoral –cirrhotic- liver tissue, which was obtained from liver resection or transplantation specimens. We used polymerase chain reaction (PCR) for quantitative measurement of mRNA of 57 hepatokines and adipokines. Clinical data was also collected. We performed uni- and multivariate logistic regression analyses to indentify proteins differentially expressed in tumoral vs peritumoral tissue. The discrimination capacity was evaluated by the c-statistic, which mirrors the area under the receiver operating characteristics (ROC) curve. **Results:** Eighty-seven patients were included. There were 84% men with a mean age of 60 years (standard deviation (SD) 9.33). The most common aetiologies of liver disease were hepatitis C (46%) and alcoholic liver disease (36%). Twenty-three patients (26.4%) had undergone locoregional treatment prior to surgery. The histopathological analysis revealed poor differentiated tumors in 10.3% of patients. Those hepatokines/adipokines obtaining p<0.2 in the univariate analysis entered the initial multivariate analysis. After excluding non-significant covariates and potential interactions, the final model included five hepatokines and two adipokines, which are potentially involved in key oncogenic and metabolic processes such as antioxidant, inflammation, carcinogenesis, oncogene suppressor: adropin (OR=0.963; 95%CI 0.932-0.995; p=0.022), alfa-1-microglobuline (OR=0.932; 95%CI 0.884-0.983; p=0.009), dipeptidyl-peptidase 4 (OR=1.038; 95%CI 1.003-1.074; p=0.032), hepassocin (OR=1.002; 95%CI 1-1.005; p=0.099), omentin (OR 0.989; 95%CI 0.976-1.002; p=0.101), sexual hormone liking globulin (OR 1.91; 95%CI 1.054-3.46; p=0.033) y angiopoietin 1 (OR 0.942; 95%CI 0.885-1.002; p=0.059). This model achieved an AUROC of 0.77 to discriminate between tumoral and peritumoral tissue, with an optimal 80% sensitivity and 64% specificity. **Conclusion:** Adipokines and hepatokines are

differently expressed in HCC tumoral and peritumoral liver tissues, thus suggesting their potential role as biomarkers.

SESSION VI.

NUTRITION, ENDOCRINE AND METABOLIC DISEASES II.

VIa. Personalized diagnostic and therapeutic potential of miR-191-5p in the pathophysiological relationship between obesity and prostate cancer.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: miRNAs; obesity; Prostate Cancer; Diagnosis-prognostic biomarker.

Abstract: Prostate cancer (PCa) is one of the most common causes of cancer-related deaths in men worldwide. Therefore, it is highly necessary the identification of non-invasive diagnostic biomarkers and therapeutic targets. As miRNAs have been proposed as promising elements for the identification of novel diagnostic/therapeutic tools for different pathologies, we investigated the miRNA landscape in PCa patients and explored their putative diagnostic/therapeutic utility. Specifically, the miRNome of plasma samples from healthy (n=18) and PCa patients (n=19) was initially determined using an Affymetrix-miRNA array. The main changes were validated [independent cohort (n=295)] by qPCR. Additionally, in silico and in vitro assays in normal and tumor prostate cell-lines were performed. Results from the array revealed that the expression of 104 miRNAs was significantly altered ($p<0.01$) in plasma samples from PCa-patients vs. healthy-controls. Notably, 6 of these miRNAs also exhibited a significant ROC-curve to distinguish between healthy and PCa patients with an AUC=1. The validation using an independent cohort of patients demonstrated that miR-191-5p was one of the most profoundly altered miRNAs in PCa ($p<0.0001$) exhibiting an AUC=0.67, and outperforming the ability of prostate-specific-antigen (PSA) to distinguish between control and PCa patients, especially in the “grey zone”, which represents the range where PSA levels are less accurate to diagnose PCa. Interestingly, the diagnostic capacity of miR-191-5p was even stronger in obese patients (BMI>30). Furthermore, we found that miR-191-5p levels were also dysregulated in PCa-cells vs. non-tumor cells. Moreover, in vitro miR-191-5p overexpression significantly increased proliferation and migration in aggressive PCa cell models (DU145 and PC-3). Finally, these functional effects were associated with the alteration in key cellular elements critical in PCa and obesity pathophysiology. Altogether, we demonstrate that miR-191-5p might represent a novel and useful personalized diagnostic biomarker in PCa, especially in patients with obesity, as well as a potential therapeutic tool in PCa.

VIb. The role of intestinal microbiota in the different prevalence of coronary disease between genders.

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Scientific Program: Nutrition, Endocrine and metabolic diseases.
Keywords: Dimorphism, intestinal microbiota, 16S sequencing , Cordioprev Study.

Abstract: The incidence of cardiovascular diseases (CVD) is influenced by sex and appears with major frequency in men than women. Our objective was to evaluate differences in the alterations in the intestinal microbiota in men and women with coronary disease (CD).
In that study, we have included the population of the CORDIOPREV study, 837 men and 165 women with CD. The composition of the intestinal microbiota was analyzed by 16-gene RNAseq on the Illumina MiSeq platform. The sequences were processed by the Quiime2 program. Additionally, we carried out a Linear Discriminant Analysis (LEfSe). Functional studies were carried out using the PICRUSt tool.
Differences were observed in beta-diversity between men and women with cardiovascular disease, whereas were no differences observed in alpha-biodiversity. Our results showed enrichment in Actinobacteria phylum and Barnesiella, Parabacteroides, and Bilophyla genera in women with CD. On the other hand, we can observe an enrichment in Prevotella, Roseburia, and Clostridiales in men with CD. By PICRUSt analysis, we observed differences between men and women, regarding the functionality associated with the intestinal microbiota.
Our results suggest that differences in the alteration of intestinal microbiota in men and women with CD could determine, at least, the influence of sex in its incidence.

VIc. Impaired metabolic and inflammatory profile in adult patients with a history extra-uterine growth restriction.

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Keywords: Adipokines, metabolism, growth, EUGR.

Abstract: Extra uterine growth restriction (EUGR) refers to the preterm newborn who, although born with a weight and length according to gestational age, presents a very poor growth in the first weeks after birth. It should be noted that this developmental window is essential for the programming of various metabolic tissues such as adipose tissue. Therefore, children with a history EUGR may present alterations in adipose tissue that predispose to metabolic alterations in the future. Previous studies conducted by our group have documented an increased risk for prepubertal children with a history of EUGR to suffer from certain metabolic alterations such as insulin resistance and low-grade inflammation. However, long-term health consequences of EURG remain unexplored. For this purpose, the objective of this study is to determine altered biomarker in adults with a history of EUGR to evaluate the risk of metabolic diseases in these patients.
To this aim, we present herein a case-control study, including a sample of 36 adults with a history of EUGR and a control group of 62 healthy patients of similar age of both sexes. Anthropometric and blood pressure measurements were evaluated, as well as concentrations in blood of adipokines (adiponectin and resistin), insulin and glucose were determined. Interestingly our results document that while adiponectin was increased during prepuberal stages suggesting a proinflammatory state in those children, both adiponectin and resistin were significantly reduced in the EUGR adult patients along with a decrease of fat mass and body weight compared to the controls. However, EUGR adults presented a higher abdominal perimeter, which indicate a different distribution in fats. Additionally, analyses of HOMA index shown a significant increase of insulin resistant state in adult patients with EUGR.
In conclusion, altogether our data suggest that patients with EUGR tend to have an increased risk of metabolic diseases, being more evident during the pubertal stage, but also during adulthood.

VId. Micronutrients and their implications in the incidence of type 2 Diabetes Mellitus. Pieces of evidence from the CORDIOPREV study.

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Keywords: nutrition; zinc; magnesium.

Abstract: Type 2 Diabetes Mellitus (T2DM) is one of the major causes of death in Western countries, and it is increasing since 2014. World Health Organization affirmed that the risk of T2DM development is closely related to obesity and unhealthy diets, thus obtaining dietary quality indexes is mandatory to evaluate the dietary patterns of the population. Some authors proposed that the mineral composition of diet could be considered a parameter of diet quality. The aim of the study was to evaluate the relation between the mineral of a diet (expressed as nutritional density (ND)) conditioned the T2DM incidence after a dietary intervention in patients who were not diabetic at beginning of the CORDIOPREV study.
462 patients who were diagnosed as non T2DM at the beginning of the CORDIOPREV study were evaluated for 5 years, and the incidence of T2DM was realized according to the criteria of American Diabetes Association. During this period of time, the patients were randomly treated with two models of healthy diet: Mediterranean Diet and Low-fat diet. To evaluate the dietary intervention, ND (micrograms/milligrams of each mineral/1000 kcal of diet) were calculated for basal state and 1 year of intervention, and the difference between these states was developed (ΔNRF9.3). To evaluate the possible relationship between T2DM incidence and DNA, a variant test (ANOVA) was developed.
After 5 years of dietary intervention, 107 patients developed T2DM and 355 did not develop it. For all patients, an increase of mineral ND were reported, evidencing the positive effect of the dietary interventions. Moreover, an inverse relationship between magnesium and zinc ND values and the incidence of T2DM were shown.
The present results reported that the monitorization of mineral ND could be a useful tool to evaluate the incidence of T2DM.

VIe. Effect of diet on the expression of microRNAs and its relationship with aging in patients with coronary heart disease: CORDIOPREV study.

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Keywords: microRNAs, aging, low-fat diet, Mediterranean diet, cardiovascular disease.

Abstract:
Introduction and Objective: Recent WHO studies indicate that the mortality rate from aging-related disease (CVD, obesity, T2DM) will increase significantly in the next decade. The role of epigenetic markers (miRNAs, DNA methylation) in disease development has also been demonstrated. Thus, our objective was to study the effect of two healthy diets on microRNA expression profiles and their relationship with aging-related parameters (lipidic and inflammatory) in patients with coronary heart disease. **Material and Methods:** The present study included 240 patients with coronary heart disease who participated in the CORDIOPREV study with a mean age greater than 60 years. Using RT-PCR, the expression of 17 microRNAs was determined in peripheral blood mononuclear cells both at the beginning and after 54 months of dietary intervention. Finally, ANOVA analyzes for repeated measures were carried out using SPSS software. **Results:** After the intervention, it was observed that the low-fat diet induced a decrease in miR-1 and miR-126 expression in patients with decreased total cholesterol and CRP levels, respectively ($p < 0.01$). Finally, the expression of miR-133 decreased in patients whose Lp(a) levels decreased after intervention with the Mediterranean diet ($p = 0.005$). **Conclusion:** Diet could be a key element in the regulation of the expression of microRNAs, which are related to changes in lipid and inflammatory parameters associated with aging in patients with coronary heart disease.

VIf. Novel multiagonist therapy for efficient management of metabolic complications polycystic ovary syndrome.

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Keywords: Multiagonist, GLP-1, GLP-1/estrogen, PCOS, androgenization.

Abstract:
Polycystic ovary syndrome (PCOS) is the most frequent endocrinopathy in pre-menopausal women, characterized by ovulatory dysfunction, cystic ovaries and hyper-androgenism, and frequently bound to metabolic perturbations, as obesity, insulin resistance and type-2 diabetes.
The management of metabolic alterations of PCOS is currently based on the use of insulin sensitizers or weight-lowering therapies. Yet, most of these therapies are not sufficiently effective and safe. Recently, an array of unimolecular multiagonists, with combined actions of related metabolic hormones, has been developed. Chronic treatment with these compounds has been shown to improve the metabolic function in male models of obesity. However, the effects of these multiagonists on the metabolic manifestations of PCOS, as well as their mechanisms of action, have not been explored to date.
We report herein the metabolic efficacy of the treatment with three multiagonists, (i) a glucagon-like peptide-1 (GLP1)/gastric inhibitory peptide (GIP) dual agonist (ii) a GLP1/GIP/glucagon triagonist; or (iii) a GLP1-estrogen conjugate, in an obese mouse model of PCOS with overt metabolic alterations. Intervention with these multiagonists reduced body weight and fat mass, and improved glucose intolerance and insulin resistance. Notably, the effects of the GLP1-estrogen conjugate were more pronounced that those of the rest of the compounds, whereas all multiagonists outperformed the actions of metformin, the fist-line choice for the management of metabolic alterations in PCOS. In addition, the GLP1-estrogen conjugate was more efficient than its individual constituents, GLP1 and estrogen, in improving the metabolic and hormonal profile, and caused substantial proteomic changes in the hypothalamus, the main target of the conjugate, which are being investigated as basis for its mechanism of action.
In sum, our findings suggest that this novel class of drugs, particularly the GLP1-estrogen conjugate, may be considered as novel therapeutic strategy for the efficient management of the metabolic and hormonal complications associated to PCOS.