# XV CONGRESS OF THE CATALAN SOCIETY OF IMMUNOLOGY (SCI)

SOCIETAT CATALANA D'IMMUNOLOGIA
L'Acadèmia

## ADVANCED IMMUNOTHERAPIES

*Barcelona, November 25 and 26th, 2021*
*on-line meeting*

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# *Organization Committee (SCI Board)*

Welcome to the congress,

On behalf of the organizing committee, we would like to warmly welcome you to the XV Societat Catalana d'Immunologia Congress (SCI Congress). We believe that our meeting will present high level scientific knowledge with the contribution of immunologists and different specialists in areas related to the **Advanced Immunotherapies**.

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## Content



**Awards to the best communication and to the best poster at the XV Congress SCI 2021, sponsored by SCI**

This year SCI sponsors the awards for the best communication (200 €) and for the best poster (100 €) of this congress. The Chairpersons of the different sessions of the congress and the board members of the SCI will select the best oral communications presented, taking into account its scientific value and the aspects related to the presentation. The poster awarded will be chosen by the congress attendees. The results will be announced at the end of the congress.

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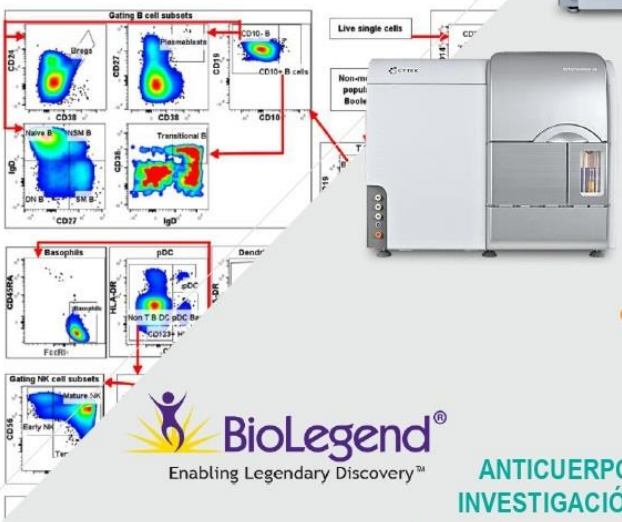

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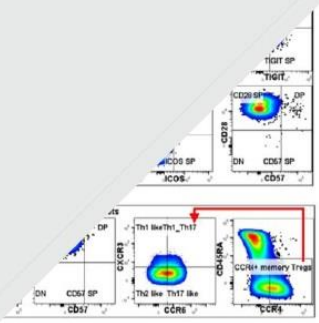


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# Scheme first day

| THURSDAY, November 25th | |
|---|---|
| 16:00h – 16:15h | **Welcome to the XVth CONGRESS of the SCI**<br>***Pablo Engel*** President of the SCI. |
| 16:15h – 17:00h | Opening Lecture<br>**Nanobodies and Nanobody-Based Human Heavy Chain Antibodies**<br>Speaker: ***Friedrich Koch-Nolte*** University Medical Center Hamburg-Eppendorf, Germany.<br>Chair: ***Pablo Engel*** University of Barcelona. |
| 17:00h – 17:30h | Company sponsored session ***Becton Dickinson***<br>**Flow Cytometric Monitoring of Anti-CD20 Therapies**<br>Speaker: ***Bruno Brando*** Haematology Laboratory and Transfusion Center, Western Milan Area Hospital Consortium, Legnano (Milano), Italy. |
| 17:30h – 18:00h | Plenary Session<br>**Cord blood as a starting material for advanced therapies**<br>Speaker: ***Sergi Querol*** Blood and Tissue Bank, Vall d'Hebron Research Institute, Barcelona.<br>Chair: ***Ramón Gimeno*** Institut de Recerca Hospital del Mar (IMIM), Barcelona. |
| 18:00h – 20:00h | Oral Communications I: Basic & Experimental Immunology<br>Chairs: ***Francisco Lozano*** Hospital Clínic/University of Barcelona and ***Jose Aramburu*** University Pompeu Fabra.<br><br>**OC1: IRF1 is required for MDA5 (IFIH1) induction by IFN-a, LPS and poly(I:C) in murine macrophages. *Carlos Batlle* *et al.***<br><br>**OC2: NK cells eliminate Epstein-Barr virus bound to B cells through a specific antibody-mediated uptake. *Elisenda Alari* *et al.***<br><br>**OC3: Enforced sialyl-Lewis-X (sLeX) display in E-selectin ligands by exofucosylation is dispensable for CD19-CAR T-cell activity and bone marrow homing. *Diego Sánchez* *et al.***<br><br>**OC4: HEK293F cell line shows different antigen presentation features than HEK293. *Alba Pastor* *et al.***<br><br>**OC5: CDK11 induces beta cell apoptosis during the inflammatory insult in autoimmune diabetes (T1D). *Conchi Mora* *et al.***<br><br>19:30h –20:00h **Discussion** |

# *Scheme second day*

| FRIDAY, November 26th | |
|---|---|
| 09:00h – 09:30h | Plenary Session<br>**Advanced immunotherapies for the management of complications post-hematopoietic stem cell transplant – Multiple uses of mesenquimal cells**<br>Speaker: ***Joaquim Vives Armengol*** Blood and Tissue Bank, Vall d'Hebron Research Institute, Barcelona<br>Chair: ***Francesc Rudilla*** Blood and Tissue Bank, Vall d'Hebron Research Institute, Barcelona. |
| 09:30h – 11:30h | Oral Communications II: Autoimmunity and Clinical Immunology<br>Chairs: ***Odette Viñas*** Hospital Clínic Barcelona and ***Clara Franco*** Vall d'Hebron Hospital<br><br>**OC6: Association of HLA-B*35 and severe hypersensitivity reactions secondary to benznidazole treatment in chronic Chagas disease patients. *Pau Bosch* *et al.***<br><br>**OC7: Limitations of commercial assays as diagnostic tests of autoimmune encephalitis. *Guillermo Muñoz* *et al.***<br><br>**OC8: Dacmecitos study: Influence of the type of donation on the inflammatory pattern in lung transplantation. *Alberto Sandiumenge* *et al.***<br><br>**OC9: Anti-Th/To auto-antibodies in patients with SSc: are the commercial assays good enough? *Janire Perurena* *et al.***<br><br>**OC10: Interaction between humoral and cutaneous immune response to Candida albicans in plaque psoriasis. *Lidia Sans* *et al.***<br><br>**OC11: Peripheral Blood Lymphocyte Subsets at diagnosis of Arthritis in the Elderly: differences between elderly-onset rheumatoid arthritis and polymyalgia rheumatic. *Aina Teniente* *et al.***<br><br>10:55h – 11:30h **Discussion** |
| 11:30h – 12:00h | Plenary Session<br>**Cellular Therapy in Transplantation**<br>Speaker: ***James Hutchinson*** University Hospital Regensburg, Germany.<br>Chair: ***Carles Serra*** Hospital Clinic Barcelona, University of Barcelona. |

| FRIDAY, November 26th | |
|---|---|
| 12:00h – 12:45h | Company sponsored lunch session I ***Beckman Coulter***<br>**Unmasked Targets, Retired Pipettes, Uncharged Sorting And Other Beckman Coulter Innovations In Flow Cytometry**<br>Speaker: ***Michael Kapinsky*** Beckman Coulter. Regensburg. Germany. |
| 12:45h – 13:15h | Company sponsored lunch session II ***Miltenyi Biotec***<br>**Identification of CAR target candidates against pancreatic adenocarcinoma using ultra-high content imaging**<br>Speaker: ***Daniel Schäfer*** Team Coordinator R&D, Miltenyi Biotec. |
| 13:15h – 14:15h | Ordinary General Meeting- Societat Catalana d'Immunologia |
| 14:15h – 16:30h | Oral Communications III: Tumor Immunology & Immunotherapy<br>Chairs: ***Sonia Guedan*** Institut d'Investigacions Biomèdiques Agusti Pi i Sunyer, IDIBAPS Barcelona and ***Alena Gros*** Vall d'Hebron Institute of Oncology Barcelona.<br><br>**OC12: MYC inhibition by an Omomyc-based therapy abrogates tumor progression and induces immune cell recruitment in models of NSCLC.** ***Sílvia Casacuberta*** *et al.*<br><br>**OC13: ARI0001, autorització sota exempció Hospitalària: com emprar productes d'immunoteràpia autoritzats després d'un assaig clínic exitòs.** ***Manel Juan*** *et al.*<br><br>**OC14: Optimizing a FAP-CAR T cell for clinical trials.** ***Estela Ortega*** *et al.*<br><br>**OC15: Pre-leukemic CD34+CD19-CD22+ early B-cell progenitors might underlie phenotypic escape in patients treated with CD19-directed immunotherapies.** ***Clara Bueno*** *et al.*<br><br>**OC16: A novel and efficient tandem CD19- and CD22-directed CAR for B-cell ALL.** ***Talia Velasco*** *et al.*<br><br>**OC17: DIF peptides, a new approach to cancer immunotherapy. Preliminary studies.** ***Marta Corral*** *et al.*<br><br>**OC18: CD137 costimulation counteracts TGF-B inhibition of NK cell anti-tumor function.** ***Aura Muntasell*** *et al.*<br><br>15:55h – 16:30h **Discussion** |

# FRIDAY, November 26th

| | |
|---|---|
| 16:45h – 19:00h | Oral Communications IV: COVID-19<br>Chairs: ***Gemma Moncunill*** ISGlobal, Barcelona and ***Jorge Carrillo*** IrsiCaixa, Badalona.<br><br>**OC19: SARS-CoV-2 sculpts the immune system to induce sustained virus-specific naïve-like and memory B-cell responses. *Giuliana Magri* *et al.***<br><br>**OC20: Clinical course impacts early kinetics and long-term magnitude and amplitude of SARS-CoV-2 neutralizing antibodies beyond one year after infection. *Edwar Pradenas* *et al.***<br><br>**OC21: Determinants of early antibody responses to COVID-19 mRNA vaccines in exposed and naive healthcare workers. *Gemma Moncunill* *et al.***<br><br>**OC22: A new flow cytometry cell-based assay to efficiently determine RBD-specific neutralization of SARS-CoV-2 emerging variants. *Pablo Hernández* *et al.***<br><br>**OC23: Analysis of Clinical and Laboratory Markers Based on the First COVID-19 Wave in Barcelona: Limitations of the Current Clinicopathological Tests Guides the Identification of Effective Biomarkers. *Ricardo Pujol* *et al.***<br><br>**OC24: High-dose intravenous immunoglobulins might modulate inflammation in COVID-19 patients. *Erola Ainsua* *et al.***<br><br>**OC25: SARS-CoV-2 antibody kinetics in healthcare workers in northern metropolitan Barcelona. *Marc Boigues* *et al.***<br><br>18:55h – 19:00h **Discussion** |
| 19:00h – 19:30h | Plenary Session<br>**Regulatory T cells in Autoimmune diseases**<br>Speaker: ***Piotr Trzonzowski*** Medical University of Gdansk, Poland.<br>Chair: ***Eva Martínez-Cáceres*** Autonomous University of Barcelona. |
| 19:30h – 19:45h | **Prize to the best communication and poster**<br>**Closing of the Congress**<br>***Eva Martínez-Cáceres*** Vice-President of SCI. |

# 1 IRF1 is required for MDA5 (IFIH1) induction by IFN-?, LPS and poly(I:C) in murine macrophages

Carlos Batlle1; Iris Aparici-Herraiz1; Guillem Sánchez-Sànchez1; Pere Rehues1; Martí López-Serrat1; Lorena Valverde-Estrella1; Antonio Celada1; Jorge Lloberas1

*1Macrophage Biology Group, Department of Cellular Biology, Physiology and Immunology, Universitat de*

Melanoma differentiation-associated protein 5 (MDA5) induces type I interferons after the recognition of viral RNA. In addition, gain-of-function mutations in the interferon induced with helicase C domain 1 (IFIH1) gene, which encodes MDA5, lead to type I interferonopathies. Here, we show that Mda5 is highly expressed in murine macrophages and is regulated by pro-inflammatory stimuli such as the cytokines IFN-α and IFN-γ, the TLR ligand LPS, and a mimic of dsRNA, polyinosinic:polycytidylic acid (poly(I:C)). Mda5 induction is mediated through the production of reactive oxygen species (ROS). The induction by IFN-α or LPS occurs at the transcriptional level since the Mda5 mRNA half-life before and after induction is very stable. Interestingly, STAT1 is required for Mda5 induction by IFN-α, LPS or poly(I:C). The time course of induction of at least 3 hours and the need for protein synthesis indicate that Mda5 requires an intermediate protein for transcription. In transient transfection experiments using the Mda5 promoter, we found that a 105-bp fragment of this gene, falling between -1153 and -1258 bps relative to the transcription start site, is required for transcription. In this specific region, we observed an interferon regulatory factor (IRF) 1 binding sequence, which, when mutated, abolishes the induction of Mda5. Chromatin immunoprecipitation assays and gene silencing experiments revealed that IRF1 is essential for Mda5 expression. Therefore, our results indicate that IFN-α, LPS or poly(I:C) activates MDA5 expression through the production of IRF1.

## 2 NK cells eliminate Epstein-Barr virus bound to B cells through a specific antibody-mediated uptake

Elisenda Alari-Pahissa 1; Michelle Ataya 1; Ilias Moraitis 2; Miriam Campos-Ruiz 1; Mireia Altadill 1; Aura Muntasell 3,4; Anna Moles 5; Miguel López-Botet 1,4,6

*1 University Pompeu Fabra, Barcelona, Spain, 2 University of Ioannina, Ioannina, Greece, 3 Autonomous University of Barcelona, Barcelona, Spain, 4 Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain, 5 Department of Experimental Pathology, IIBB-CSIC, IDIBAPS, Barcelona, Spain, 6 Immunology laboratory, Dpt. of Pathology, Hospital del Mar, Barcelona, Spain*

Epstein Barr virus (EBV) causes a highly prevalent and lifelong infection contributing to the development of some malignancies. In addition to the key role played by T cells in controlling this pathogen, NK cells mediate cytotoxicity and IFNγ production in response to EBV-infected B cells in lytic cycle, both directly and through antibody (Ab)-dependent activation. We recently described that EBV-specific Ab-dependent NK cell interaction with viral particles (VP) bound to B cells triggered degranulation and TNFα secretion but not B cell lysis nor IFNγ production. In this report we show that NK cell activation under these conditions reduced B cell transformation by EBV. NK cells eliminated VP from the surface of B cells through a specific and active process which required tyrosine kinase activation, actin polymerization and Ca2+, being independent of proteolysis and perforin. VP were displayed at the NK cell surface before being internalized and partially shuttled to early endosomes and lysosomes. VP transfer was encompassed by a trogocytosis process including the EBV receptor CD21, together with CD19 and CD20. Our study reveals a novel facet of the antibody-dependent NK cell mediated response to this viral infection.

## 3 Enforced sialyl-Lewis-X (sLeX) display in E-selectin ligands by exofucosylation is dispensable for CD19-CAR T-cell activity and bone marrow homing

Diego Sánchez-Martínez 1; Francisco Gutiérrez-Agüera 1; Paola Romecin 1; Meritxell Vinyoles 1; Marta Palomo 1; Néstor Tirado 1; Samanta Romina Zanetti 1; Manel Juan 2; Michela Carlet 3,4; Irmela Jeremias 3,4; Pablo Menéndez 5,6,7

*1 Josep Carreras Leukemia Research Institute, 08036, Barcelona, Spain, 2 Servei d?Immunologia, Hospital Clínic de Barcelona, Barcelona, Spain, 3 Department of Apoptosis in Hematopoietic Stem Cells, Helmholtz Center Munich, German Center for Envi, 4 Department of Pediatrics, Dr von Hauner Children?s Hospital, LMU, Munich, Germany, 5 Department of Biomedicine, School of Medicine, University of Barcelona, Barcelona, Spain, 6 Centro de Investigación Biomédica en Red-Oncología (CIBERONC), Instituto de Salud Carlos III, Madrid, 7 Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain*

CD19-directed chimeric antigen receptors (CAR) T cells induce impressive rates of complete response in advanced B-cell malignancies, specially in B-cell acute lymphoblastic leukemia (B-ALL). However, CAR T- cell-treated patients eventually progress due to poor CAR T-cell persistence and/or disease relapse. The bone marrow (BM) is the primary location for acute leukemia. The rapid/efficient colonization of the BM by systemically infused CD19-CAR T cells might enhance CAR T-cell activity and persistence, thus, offering clinical benefits. Circulating cells traffic to BM upon binding of tetrasaccharide sialyl-Lewis X (sLeX)-decorated E-selectin ligands (sialofucosylated) to the E-selectin receptor expressed in the vascular endothelium. sLeX-installation in E-selectin ligands is achieved through an ex vivo fucosylation reaction.
Here, we sought to characterize the basal and cell-autonomous display of sLeX in CAR T-cells activated using different cytokines, and to assess whether exofucosylation of E-selectin ligands improves CD19-CAR T-cell activity and BM homing. We report that cellautonomous sialofucosylation (sLeX display) steadily increases in culture- and in vivo-expanded CAR T cells, and that, the cytokines used during T-cell activation influence both the degree of such endogenous sialofucosylation and the CD19-CAR T-cell efficacy and persistence in vivo. However, glycoengineered enforced sialofucosylation of E-selectin ligands was dispensable for CD19-CAR T-cell activity and BM homing in multiple xenograft models regardless the cytokines employed for T-cell expansion, thus, representing a dispensable strategy for CD19-CAR T-cell therapy.

# 4 HEK293F cell line shows different antigen presentation features than HEK293

Pastor-Moreno, Alba 1; Area-Navarro, María 1; Tirado-Herranz, Adrián 1; Álvarez, Iñaki 1

*1 Institut de Biotecnologia i Biomedicina*

HEK293 is a cell line of human embryonic kidney origin with several variants deriving from these. Cells of one of these variants, known as HEK293F, grow in suspension rather than being adherent cells, which is the case of HEK293 cells. This is an advantage when there is a need of high number of cells in culture. Both cell lines have been used as equivalent. We planned to use HEK293F cells to purify 20S proteasome and to analyze HLA-I immunopeptidomes. The resulting peptidomes showed that there was a lack of HLA-A3 ligands among the peptide ligands from HEK293F cells, while the peptidome from HEK293 cells contained HLA-A3 peptide ligands. Thus, the transcriptional expression of the different HLA-I alleles presented in HEK293 and HEK293F was studied by qPCR. Results showed that mRNAs corresponding to HLA-A3 were detected, but the ratio HLA-A3/HLA-A2 was lower in HEK293F cells. The analysis of the HLA-I allotypes at the cell surface confirmed that there is no expression of HLA-A3 molecules in the cell membrane of HEK293F cells. Thus, HEK293F do not have the same antigen presentation features than the parental HEK293.

## 5 CDK11 induces beta cell apoptosis during the inflammatory insult in autoimmune diabetes (T1D).

Conchi Mora1; Ester Sala1; Celia Vived1; Júlia Luna1; Noemí Alejandra Saavedra-Ávila1; Upasana Sengupta1; Raúl Ángel Castaño2; Sabrina Villar-Pazos3; Laura Haba4; Joan Verdaguer1; Ana Belén Ropero3; Thomas Stratmann5; Javier Pizarro5; Manuel Vázquez-Carrera5; Ángel Nadal3; Jill M. Lahti6

*1Universitat de Lleida; 2Universitat Autònoma de Barcelona; 3Universidad Miguel Hernández; 4IDIBAPS; 5Universidad de Barcelona; 6St. Jude Children's Research Hospital, Memphis, TN, United States*

Pancreatic islets are exposed to severe inflammatory environment during the progression of the autoimmune attack in Type 1 diabetes (T1D). Consequently, the expression profile and physiology of the endocrine pancreas are deeply altered. We found that CDK11, which is a cyclin dependent kinase that is involved in RNA processing, mitosis and apoptosis, is downregulated in the islets during the insult to beta cells in the T1D prone NOD (non-obese diabetic) mouse model. The complete deficiency in CDK11 is embryonically lethal. We explored the role of CDK11 in the pathogenesis of T1D and found that NOD mice which were hemideficient in CDK11were protected against T1D without exhibiting changes in beta cell proliferation. Moreover, when pancreatic islets were exposed to pro-inflammatory cytokines in the presence of increasing glucose concentrations, they exhibited an impaired sensitivity to cytokine-induced apoptosis, regardless of glucose concentration. However, when islets were exposed to Thapsigargin,, an Endoplasmic Reticulum (ER)-stress inducing agent, apoptosis was not altered between genotypes.
We previously reported that Cyclin D3, a natural partner of CDK11, is also targeted in T1D and protects beta cells against inflammation-induced apoptosis. Interestingly, the protection mediated by the CDK11 hemideficiency did not attenuate the exacerbation of T1D caused by cyclin D3 deficiency in NOD mice, which suggests that the mechanism(s) underlying the cyclin D3 protection may be independent of the CDK11 pro-apoptotic signaling cascade. This study is the first to report that CDK11 is a natural target in T1D that is presumably repressed in beta cells as a protection mechanism against inflammation-induced apoptosis. Conclusions: This study is the first to report that CDK11 is repressed in T1D as a protection mechanism against inflammation-induced apoptosis, and suggests that CDK11 lies upstream Cyclin D3 signaling. We unveil the CDK11/Cyclin D3 tandem as a new potential intervention target in T1D.

# 6 Association of HLA-B*35 and severe hypersensitivity reactions secondary to benznidazole treatment in chronic Chagas disease patients.

Pau Bosch-Nicolau 1; Fernando Salvador 1; Adrián Sánchez-Montalvá 1; Clara Franco-Jarava 1; Iria Arrese-Muñoz 1; Elena Sulleiro 1; Silvia Roure 2; Lluis Valerio 2; Inés Oliveira 1; Núria Serre-Delcor 1; Diana Pou 1; Begoña Treviño 1; Maria Luisa Aznar 1; Juan Espinosa-Pereiro 1; Israel Molina 1

*1 Hospital Universitari Vall d'Hebrón, 2 Unitat Salut Internacional Metropolitana Nord*

Background. Benznidazole is the first line treatment for Chagas disease. Adverse events appear in more than 50% of patients, leading to discontinuation in approximately 15% of the patients. Cutaneous hypersensitivity is one of the most frequent adverse events. HLA-genotyping studies previously identified an association between hypersensitivity reactions to benzidazole and carrying the allele HLA-B*35:05. We designed the present study to validate an HLA-genotyping strategy that predicts cutaneous hypersensitivity.

Methods.This is a prospective observational study including Chagas disease patients aged 18 years old or more who accept to receive benznidazole treatment following current guidelines. Allele genotyping of HLA- B was determined in all patients. Clinical and analytical follow-up was performed at days 0, 7, 14, 30 and 60 of treatment.

Results. Two-hundred and seven patients were included. Seventy percent were female with a mean age of
45.1 (SD ±9.86) years mainly from Bolivia (92.8%). In 49.3% of cases a cutaneous reaction was diagnosed. Forty-eight (46.6%) were classified as mild, 37 (35.9%) as moderate and 18 (17.5%) as severe. Thirty-two (15.4%) patients had to definitively interrupt the treatment due to a cutaneous reaction. Female sex (OR 4.49; 95%CI 1.62-12.47), eosinophilia prior to cutaneous symptoms (OR 2.55; 95%CI 1.2-5.43) and carrying HLAB*35 (OR 2.58; 95%CI 1.2-5.51) were all predictors of moderate to severe cutaneous hypersensitivity reactions. No statistical significance was found when allele HLA-B*35:05 was analyzed.

Conclusions.Patients carrying HLA-B*35 are at higher risk of moderate to severe reactions when taking benznidazole treatment.

# 7 Limitations of commercial assays as diagnostic tests of autoimmune encephalitis.

Guillermo Muñoz Sánchez 1; Eugenia Martinez Hernández 2,3; Laura Naranjo 1; Mar Guasp 2,3,4; Lidia Sabater 2; Albert Saiz 2,3; Josep Dalmau 2,3,4,5,6; Francesc Graus 2; Raquel Ruiz García 1,2

*1 Immunology Department, Centre Diagnòstic Biomèdic, Hospital Clínic, Barcelona, Spain, 2 Neuroimmunology Program, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelo, 3 Neurology Department, Hospital Clinic, and University of Barcelona, Barcelona, Spain, 4 Centro de Investigación Biomédica en Red, Enfermedades Raras (CIBERER), Spain., 5 Neurology Department, University of Pennsylvania, Philadelphia, PA, USA, 6 Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain.*

Aim:

Commercial diagnostic kits have improved the accessibility of neuronal surface antibodies (NSab) detection in suspected cases of autoimmune encephalitis. We evaluated the sensitivity of a commercial kit based on antigen-transfected cells (cell-based assay: CBA) for the detection of NSab in samples with positive reactivity on rat brain immunohistochemistry (tissue-based assay: TBA).

Material and methods:

Between 10/2016 and 10/2020, 6213 serum/CSF samples were screened using rat brain immunohistochemistry. Samples showing positive reactivity were tested with commercial IIFA. Samples that were positive on brain immunohistochemistry but negative on commercial IIFA were later studied with in-house IIFA. To further assess the performance of the commercial IIFA, we retrospectively studied 54 consecutive CSF samples from patients with encephalitis and LGI1 (n=12), AMPAR (n=19) or GABABR (n=23) antibodies confirmed by brain immunohistochemistry and in-house IIFA.

Results and discussion:

TBA showed positive reactivity in 404/6213 (6.5%) samples. Of these, 241 (60%) were negative by commercial CBA. Of these 241 negative samples, 21 (8.7%) were positive by in-house CBA to antibodies tested by the kit (1 NMDAR+, 11 LGI1+, 2 AMPAR+ and 7 GABAbR+). Other 21/241 (8.7%) samples were positive for less frequent antibodies not included in the kit (13 IgLON5+, 3 SEZ6L2+, 2 mGluR1+, 1 mGluR2+, 1 mGluR5+, 1 and GABAaR+). In our study the commercial CBA was not able to detect 42 (20.5%) of the 205 samples with NSab. In patients with high suspicion of autoimmune encephalitis and negative results on the kit we recommend to extend the study of NSab using TBA and in-house CBAs.

# 8 Dacmecitos study: Influence of the type of donation on the inflammatory pattern in lung transplantation.

Aroa Gómez Brey 1; Clara Franco Jarava 1; Alberto Sandiumenge Camps 1; Irene Bello Rodríguez 1; Elisabeth Coll Torres 6; Marina Pérez Redondo 4; Silvana Crowley Carrasco 4; Sara Naranjo Gozalo 3; Javier Pérez Vélez 1; Judit Sacanell Lacasa 1; Cristopher Mazo Torre 1; Alberto Jauregui Abularach 1; Fernando Mosteiro Pereira 2; Maria Deu Martín 1; Teresa Pont Castellana 1

*1 Hospital Universitari Vall d'Hebron, 2 Complexo Hospitalario Universitario A Coruña, 3 Hospital Universitario Marqués de Valdecilla, 4 Hospital Universitario Puerta de Hierro Majadahonda, 5 Hospital Universitario Reina Sofía, 6 Organización Nacional de Trasplantes*

INTRODUCTION AND OBJECTIVES:
During the brain death process an inflammatory storm occurs, this fact might have detrimental effects in lung recipients, as opposed to death by the cardiocirculatory criteria process.
The aim of our study is to compare the inflammatory response pattern of transplanted lungs from brain death donors (DBD) and donors after controlled cardiocirculatory death (cDCD).
METHODS
Eighty adult lung recipients, 40 from DBD and 40 from cDCD, paired by lung transplant indication and age, were prospectively enrolled in a Spanish multicenter study from 07/2018 to 07/2019. General data of donors, recipients and surgical procedure was gathered. Blood samples were collected and analyzed from the donor before (E0) and during (E1) the retrieval, and from the recipient before the implant (R-1), after graft reperfusion (R0), 24 (R23), 48 (R48) and 72 (R72) hours after lung transplant. Inflammatory response (IL-6, IL-8, IL-10, TNF-α) was compared between both groups.
RESULTS
No differences were observed in demographic profile of donors and recipients in the two groups (DBD and cDCD). A higher percentage of DBD received corticoid treatment ($p=0.002$) and vasoactive support ($p=0.001$), and more cDCD received blood transfusion ($p=0.043$) during the retrieval. DBD presented higher plasma levels of IL6 and IL10 ($p<0.001$) and no differences were found in the inflammatory pattern in recipients. Fig 1.
CONCLUSIONS
Donation after controlled circulatory death produces a lower inflammatory response compared to donation after brain death.

Donation after controlled circulatory death is a safe alternative in lung transplant.

FUNDING: Project funded by grant of Fundación Mutua Madrileña (MM/XIV/RECERCA/2017)/ AP167192017.

# 9 Anti-Th/To auto-antibodies in patients with SSc: are the commercial assays good enough?

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Background and aims: auto-antibodies specific for SSc are not only useful for diagnosis, but also for predicting the prognosis of the patients, as they have been linked with distinct clinical features. It has been reported that anti-nuclear auto-antibodies (ANA) are detectable in 90-95% of Systemic Sclerosis (SSc) patients. Anyhow, in a group of patients of our cohort no specific auto-antibodies are found by available commercial assays. The aim of this study was to test seronegative SSc patients determined by commercial assays by RNA immunoprecipitation (RNA-IP).

Methods: autoantibodies against Scl-70, CENP-A, CENP-B, RP11, RP155, fibrillarin, NOR-90, Th/To, Pm- Scl100, Pm-Sc75, Ku and PDGFR were assessed by a commercial assay (LIA). ANAs were detected by immunofluorescence (IIF) test performed on Hep-2 cells as substrate. IIF patterns were categorized according to the International Consensus on ANA Patterns (ICAP) classification. Sixty- nine seronegative SSc patients determined by LIA were tested by RNA-IP.

Results: six (8.7%) of the tested patients were anti-Th/To positive by RNA-IP, all with a homogeneous nucleolar pattern (AC-8). Globally, 16 (23.2%) of the SSc seronegative patients showed a nucleolar pattern by IIF (AC-8,9,10) and 37.5% of these patients with nucleolar patterns were positive for anti-Th/To by RNA-IP. All the tested patients were negative for anti-Th/To by LIA.

Conclusions: anti-Th/To autoantibodies are directed against two macromolecular ribonucleoproteins, RNase P and RNase MRP. Each of these ribonucleoproteins are composed of at least 11 proteins and a catalytic RNA. LIA uses only hPop1, a common protein for both complexes, as antigen for detecting anti- Th/To auto-antibodies. Therefore, auto-antibodies directed against other components of the two ribonucleoproteins are not detected by this assay. In the present study we have shown that a great number of SSc seronegative patients determined by LIA that showed a nucleolar pattern were actually positive for anti- Th/To auto-antibodies by the gold-standard technique RNA-IP.

## 10 Interaction between humoral and cutaneous immune response to Candida albicans in plaque psoriasis

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Plaque psoriasis (PP) is a chronic inflammatory skin disease resulting from the interaction between epidermal cells and the T-cell mediated IL-17 response. Human circulating memory CLA+ T cells reflect the cutaneous immune abnormalities in the T cell-mediated skin diseases due to its capacity to recirculate between skin and blood. Although the Candida albicans(CA) infections are associated with PP, the immune response against this fungus has not been deeply explored. In our study, plasma from untreated psoriasis patients (cohort 1, n=52) and healthy controls (HC) (n=17) were analysed for the presence of CA-specific immunoglobulins, as well as CLA+/- T cells response to CA when cocultured with autologous epidermal cells. Also, a proteomic profile in non-treated PP patients (cohort 2, n=114) was evaluated regarding their anti-CA IgA levels. PP patients showed increased plasmatic CA-specific IgA and IgG levels compared to guttate psoriasis (GP) and HC. CA induced Th17 (IL-17F, IL-17A) and Th9 (IL-9) response mainly in the CLA+ T-cell subset. Interestingly, CLA+/- Th17 response correlated with CA-specific IgA in PP, but no association with anti-CA IgG was found. When separating cohort 2 into high and low anti-CA IgA, 27 proteins differed significantly between both subgroups and some of them were selected for further validation in cohort 1. CCL18, CHI3L1 and AZU1 were heightened in plasma from PP compared to GP, and they positively correlated with severity, age of onset and negatively correlated with disease duration in PP respectively. The presence of anti-CA IgA in PP without clinical sign of infection identifies subjects exposed to this microbe, a potent driver of IL-17 response. Thus, assessing anti-CA IgA may be useful to better evaluate and stratify psoriasis patients.

## 11 Peripheral Blood Lymphocyte Subsets at diagnosis of Arthritis in the Elderly: differences between elderly-onset rheumatoid arthritis and polymyalgia rheumatica

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**Introduction:** Elderly-onset rheumatoid arthritis (EORA) and Polymyalgia rheumatica (PMR) are common rheumatic diseases in the elderly. EORA is a de novo illness that develops after 60 years old and has different characteristics form young-onset rheumatoid arthritis. Diagnostic differentiation between seronegative EORA and other rheumatologic diseases as PMR is difficult. Previous studies in PMR have speculated the role of CD8 T cells assessment as biomarker of disease although posterior studies did not confirm this. We hypothesize that peripheral lymphocyte subpopulations will show a specific profile in EORA and PMR, being able to define lymphocyte subsets involved in the pathogenesisof these diseases.
**Material and methods**: In this work we analyze,using flow cytometry,T-cell subsets (naïve, central memory, effector memory, TEMRA, Tregs and Th17) and B-cell (naïve, unswitched and switched memory, immature and transitional) subpopulations in whole blood of EORA and PMR patients at the onset of disease and were compared with control individuals of same age and gender. **Results**: Twenty-nine patients and 18 controls (HC) were analyzed (19 RA and 10 PMR). In patients with EORA, we found an increase in the percentages of late effector memory (EM) and EMRA T CD4 subpopulations (p=0.037 and p=0.001 respectively) and a decrease of early EM CD8 T cells (p=0.040) when compared to HC. In contrast, PMR patients at onset of the disease showed higher percentages of naïve B cells (p=0.022) as well as of percentages and absolute counts of central memory CD8 T cells (p=0.039 and p=0.037), whereas percentages of Th17 were decreased (p=0.016) compared to HC. **Conclusions**: EORA and PMR show a different B and T-cell profile in peripheral blood at diagnosis of the disease suggesting a putative role to be used in the differential diagnosis and a role in their pathogenesis.

## 12 MYC inhibition by an Omomyc-based therapy abrogates tumor progression and induces immune cell recruitment in models of NSCLC

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Lung cancer is the leading cause of cancer mortality worldwide. Despite the promise of targeted therapies and immunotherapy, many lung cancer patients do not respond to treatment and are still in need of effective therapeutic options. We propose a distinct and innovative strategy based on the inhibition of MYC, a central molecule that drives multiple aspects of tumor progression and immune evasion. Despite the fact that, for many years, MYC remained considered an undruggable target, we have demonstrated the safety and dramatic therapeutic potential of its inhibition using a MYC dominant negative, termed Omomyc.

Recently, we demonstrated that intranasal administration of the Omomyc mini-protein abrogates tumor progression in a KRAS-driven Non-Small Cell Lung Cancer (NSCLC) mouse model, modulates chemokine/cytokine profiles and recruits T cells to the tumor site. Here we show for the first time that these T cells are CD4+T cells expressing PD-1 and Tim-3, suggesting that Omomyc induces the expansion of this tumor-reactive cell population. Interestingly, Omomyc-treated mice display higher proportions of Th17 cells, specifically of Th1-Th17 hybrid population, and of effector memory T cells. This immune stimulatory effect is not limited to this type of tumor or route of administration because it is also observed upon systemic administration in a p53/KRAS-mutated NSCLC mouse model. In fact, we confirmed that Omomyc treatment also induces CD4+and/or CD8 +T cell recruitment in PBMC-humanized lung cancer mouse models, independently of their driving mutation.

Importantly, the Omomyc mini-protein is now in clinical trials to assess its safety and tolerability in patients with solid tumors. Our findings indicate that Omomyc treatment represents a new opportunity to pharmacologically inhibit MYC in NSCLC and induce an antitumor immune response. In addition, they suggest that combination of our anti-MYC therapy with immunotherapies could overcome immunotherapeutic resistance, thus changing a relevant paradigm of cancer treatment.

## 13 ARI0001, autorització sotta exempció Hospitalària: com emprar productes d'immunoteràpia autoritzats després d'un assaig clínic exitòs.

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The Hospital Exemption (HE) allows for the use of advanced therapy medicinal products (ATMP) next to marketing authorization (MA), but under special conditions. The HE is only applicable to individual patients treated in the hospital setting and it is limited to member states of the European Union (EU); HE is mainly conceded to the academic centers that developed the ATMP, being granted by the national competent authority (NCA), which, in the case of Spain, is the Spanish Agency of Medicines and Medical Devices (AEMPS). The HE follows strict standards of traceability, pharmacovigilance, and quality. In February 2021, our ATMP ARI-0001, a new autologous chimeric antigen receptor (CAR) targeting CD19, was approved by AEMPS under HE for patients older than 25 years with relapsed or refractory CD19+ acute lymphoblastic leukemia. This authorization was a first step in the development of, and access to, academic CAR T-cell products in the EU. The fact that HE is limited to a specific country and hospital, the need of continuous evaluation by the NCA, and the potential future overlap with other centrally approved ATMPs, suggest that the HE could be used as an intermediate step before obtaining a centralized MA by the European Medicines Agency.

# 14 Optimizing a FAP-CAR T cell for clinical trials

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Cancer-associated fibroblasts (CAFs) support tumor growth and metastasis of virtually all solid tumors, making them a potential “universal therapeutic target”. Moreover, Fibroblast Activation Protein (FAP) is selectively over-expressed on tumor-promoting CAFs and deleting FAP+cells inhibits tumor growth in preclinical models. Prior studies in preclinical models suggest, that selective elimination of FAPhigh cells while sparing normal FAP+cells that typically express lower levels of FAP, may be necessary to avoid toxicity due to on-target off-tumor effects. Thus, the aim of this study was to generate a FAP-chimeric antigen receptor (CAR) that selectively targets FAPhighcells but that exhibits minimal activity against FAPlow cells for use in clinical trials.

We generated a FAP-CAR containing an scFv based on a monoclonal antibody that reacts with human, canine and mouse FAP. We show that primary human T cells transduced with this novel FAP-CAR exhibit strong reactivity against cells expressing high levels of human, canine or mouse FAP but not FAPlowor FAP- negative cells in vitro. Moreover, these FAP-CART cells inhibited the growth of human FAP-negative A549 tumor xenografts infiltrated by FAP+murine CAFs in NSG mice. However, expected bone marrow toxicities were observed. In order to find a therapeutic window in which there is significant reduction of tumor burden and minimal toxicity, we are testing a series of modified constructs in which we are varying the strength of the promoter driving the CAR (to reduce the number of CAR’s per T cells), modifying the length of the hinge region, testing alternative cytoplasmic activation domains or adding domains to improve CAR trafficking into the tumors. Once we have tuned the FAP-CAR construct to avoid on-target off-tumor toxicity, we plan to begin clinical trials in tumors expressing high levels of FAP such as pancreas, lung squamous cell, and head neck cancers.

## 15 Pre-leukemic CD34+CD19-CD22+ early B-cell progenitors might underlie phenotypic escape in patients treated with CD19-directed immunotherapies

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BACKGROUND:CD19-directed immunotherapies have revolutionized the treatment of advanced B-ALL. However, despite initial impressive rates of complete remission (CR), many patients ultimately relapse as CD19+or CD19 -B-ALL. The fact that B-ALL patients in CR after successful anti-CD19-directed T-cell therapy eventually relapse coupled with the early onset of CD22 expression during B-cell development suggest that pre-existing CD22+CD19-(pre)-leukemic cells represent an “early/immature progenitor origin- related” mechanism underlying phenotypic escape to CD19-directed immunotherapies.

METHODS: We have used bulk and single-cell RNAseq on multiple cell populations across human fetal B- cell development and flow-cytometry characterization of healthy fetal, cord blood and adult bone marrow (BM)-derived CD34+progenitors. The presence of CD34 +CD19-CD22+cells was assayed by flow-cytometry in 237 non-matched primary B-ALL samples obtained at diagnosis(n=159), CR(n=63) and relapse(n=15). FISH studies in flow-sorted populations together with xenograft modeling were employed to assess the (pre)-leukemic nature of CD34+CD19-CD22+ cells.

RESULTS: We demonstrate that CD22 expression precedes CD19 expression during B-cell development. Similarly, CD34+CD19-CD22+cells are found in BM samples of ~70% B-ALL patients at diagnosis(n=159) and relapse(n=15). The frequency of CD34+CD19-CD22+cells increased two-fold in B-ALL patients in CR after CD19-CART-cell therapy. FISH studies in flow-sorted populations together with xenograft modeling revealed that CD34 +CD19-CD22+cells harbor the genetic abnormalities present at diagnosis and initiate leukemogenesis in NSG mice.

## 15 Pre-leukemic CD34+CD19-CD22+ early B-cell progenitors might underlie phenotypic escape in patients treated with CD19-directed immunotherapies

CONCLUSIONS: Pre-leukemic CD34+CD19-CD22+immature progenitors might underlie phenotypic escape in patients treated with CD19-directed immunotherapies. This approach may help to identify B-ALL patients at risk of relapse after CD19-directed immunotherapy. We encourage its rapid implementation in flow diagnostic labs for initial diagnosis and subsequent monitoring of B-ALL patients during treatment.

## 16 A novel and efficient tandem CD19- and CD22-directed CAR for B-cell ALL

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CD19-directed chimeric antigen receptor (CAR) T-cells have yielded impressive response rates in refractory/relapse B-cell acute lymphoblastic leukemia (B-ALL);however, most patients ultimately relapse due to poor CAR T-cell persistence or resistance of either CD19+or CD19 –B-ALL clones.CD22 is a pan-B marker whose expression is maintained in both CD19+and CD19 – relapses. Indeed, CD22-CAR T-cells have been clinically used in B-ALL patients, although relapse also occurs. Tcells engineered with a tandem CAR (Tan-CAR) containing in a single contruct both CD19 and CD22 scFvs, might be advantageus in achieving higher remission rates and/or preventing antigen loss. We have generated and functionally validated using cutting-edge assays a 4-1BB-based CD22/CD19 Tan-CAR using in-house-developed novel CD19 and CD22 scFvs. Tan-CAR-expressing T-cells showed similar in vitroexpansion than CD19-CAR T-cells with no increased of tonic signaling.CRISPR/Cas9-edited B-ALL cells confirmed the bispecificity of the Tan-CAR. Tan-CAR was as efficient as CD19-CAR in vitroand in vivousing B-ALL cell lines, patient samples and patient-derived xenografts (PDXs). Strikingly, the robust anti-leukemic activity of the Tan-CAR was slightly more effective in controling the disease in long-term follow-up PDX models. This Tan-CAR construct warrants a clinical appraisal to test whether simultaneous targeting of CD19 and CD22 enhances leukemia eradication and reduces/delays relapse rates and antigen loss.

## 17 DIF peptides, a new approach to cancer immunotherapy. Preliminary studies

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Peripherin is an intermediate filament (IF) that is commonly expressed in the cytoskeleton of cells of the peripheral nervous system. All IF proteins share a common structural organization that consists in a central α- helical rod domain flanked by the head and tail domains at both ends. The main differences between IF proteins are found in the head and tail domains, which vary in size, sequence, and secondary structure, while the central part is much more conserved. In our lab, we identified a Peripherin derived peptide (hereinafter, DIF-P) that was able to stimulate the production of proinflammatory cytokines by monocytes as well as to induce the death of various cell types (both murine and human). In addition, these functional properties were altered when the peptide was modified with a 3-lysine (DIF-P3K) or 8-arginine (DIF-P8R) tail. Thus, although proinflammatory cytokine production was lower, DIF-P3K and DIF-P8R peptides induced greater cell death, probably because these amino acid tails turn them into Cell Penetrating Peptides (CPPs) allowing for better internalization. Given the cytotoxic and immunostimulatory properties of DIF-P, DIF-P3K, and DIF-P8R, we decided to make a leap into in vivostudies to study their potential as immunotherapeutic agents against cancer. The different in vivostudies performed so far demonstrate the antitumor activity of DIF peptides in the models of melanoma and mastocytoma, indicating their potential use in the treatment of human cancer, either as cytostatic and/or immunotherapeutic agents. Therefore, DIF peptides could become part of the cancer therapeutic arsenal.

## 18 CD137 costimulation counteracts TGF-? inhibition of NK cell anti-tumor function

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Enhancing NK cell-based cancer immunotherapy by overcoming immunosuppression is an unmet goal. Here, we demonstrate the ability of the anti-CD137 agonist urelumab for overcoming TGF-β-mediated inhibition of human NK cell proliferation and anti-tumor function. Transcriptomic, immunophenotypic and functional analyses evidenced that CD137 costimulation modified the transcriptional program induced by TGF-β on human NK cells by rescuing their proliferation in response to IL-2, preserving the expression of activating receptors (NKG2D) and effector molecules (granzyme B, IFN-γ), in addition to maintaining the acquisition of tumor-retention features (CXCR3, CD103). Activated NK cells cultured in the presence of TGF-β1 and CD137 agonist recovered CCL5 and IFN-γ secretion and showed enhanced direct and antibody- dependent cytotoxicity upon restimulation with cancer cells. Remarkably, trastuzumab treatment of fresh breast carcinoma-derived multicellular cultures induced CD137 expression in tumor-infiltrating CD16+ NK cells, enabling the action of urelumab, which fostered tumor-infiltrating NK cell proportions and recapitulated the enhancement of CCL5 and IFN-γ production. Bioinformatic analysis pointed to IFNGas the molecule driving the association between NK cells and clinical response to trastuzumab in HER2-positive primary breast cancer patients, highlighting the translational relevance of costimulatory axis enhancing IFN-γ production. Our data reveals CD137 as a targetable checkpoint for overturning TGF-β constrains on NK cell antitumor responses.

## 19 SARS-CoV-2 sculpts the immune system to induce sustained virus-specific naïve-like and memory B-cell responses

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SARS-CoV-2 infection induces virus-reactive memory B cells expressing unmutated antibodies, which hints at their emergence from naive B cells. Yet, the dynamics of virus-specific naive B cells and their impact on immunity and immunopathology remain unclear. Here, we longitudinally studied moderate-to-severe COVID-19 patients to dissect SARS-CoV-2-specific B cell response over time. We found a broad virus- specific antibody response during acute infection, which evolved into an IgG1-dominated response during convalescence. Acute infection was associated with increased mature B-cell progenitors in the circulation and the unexpected expansion of virus-targeting naive-like B cells. The latter further augmented during convalescence together with virus-specific memory B cells. In addition to a transitory increase in tissue- homing CXCR3+ plasmablasts and extrafollicular memory B cells, most COVID-19 patients showed persisten activation of CD4+ and CD8+ T cells along with transient or long-lasting changes of key innate immune cells. Remarkably, virus-specific antibodies and the frequency of naive B cells were among the major variables defining distinct immune signatures associated with disease severity and inflammation. Aside from providing new insights into the complexity of the immune response to SARS-CoV-2, our finidings indicate that de novo recruitment of mature B cell precursors into the periphery may be central to the induction of antiviral immunity.

## 20 Clinical course impacts early kinetics and long-term magnitude and amplitude of SARS-CoV-2 neutralizing

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Background:Understanding the determinants of long-term immune responses to SARS-CoV-2 and the concurrent impact of vaccination and emerging variants of concern will guide optimal strategies to achieve global protection against the COVID-19 pandemic.

Methods:A prospective cohort of 332 COVID-19 patients was followed beyond one year. Plasma neutralizing activity was evaluated using HIV-based reporter pseudoviruses expressing different SARS- CoV-2 spikes and was longitudinally analyzed using mixed-effects models.

Findings:Long-term neutralizing activity was stable beyond one year after infection in mild/asymptomatic and hospitalized participants. However, longitudinal models suggest that hospitalized individuals generate both short- and long-lived memory B cells, while outpatient responses were dominated by long-lived B cells. In both groups, vaccination boosted responses to natural infection, although viral variants, mainly B.1.351, reduced the efficacy of neutralization. Importantly, despite showing higher neutralization titers, hospitalized patients showed lower cross-neutralization of B.1.351 variant compared to outpatients. Multivariate analysis identified severity of primary infection as the factor that independently determines both the magnitude and the inferior cross-neutralization activity of long-term neutralizing responses.

Conclusions:Neutralizing response induced by SARS-CoV-2 is heterogeneous in magnitude but stable beyond one year after infection. Vaccination boosts these long-lasting natural neutralizing responses, counteracting the significant resistance to neutralization of new viral variants. Severity of primary infection determines higher magnitude but poorer quality of long-term neutralizing responses.

## 21 Determinants of early antibody responses to COVID-19 mRNA vaccines in exposed and naive healthcare workers

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Background
Two doses of mRNA vaccination have shown >94% efficacy at preventing COVID-19 mostly in naive adults, but it is not clear if the second dose is needed to maximize effectiveness in those previously exposed to SARS-CoV-2 and what other factors affect responsiveness.
Methods
We measured IgA, IgG and IgM levels against SARS-CoV-2 spike (S) and nucleocapsid (N) antigens from the wild-type and S from the Alpha, Beta and Gamma variants of concern, after BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) vaccination in a cohort of health care workers (N=578). Neutralizing capacity and antibody avidity were evaluated. Data were analyzed in relation to COVID-19 history, comorbidities, vaccine doses, brand and adverse events.
Findings
Vaccination induced robust IgA and IgG levels against all S antigens. Neutralization capacity and S IgA and IgG levels were higher in mRNA-1273 vaccinees, previously SARS-CoV-2 exposed, particularly if symptomatic, and in those experiencing systemic adverse effects. A second dose in pre-exposed did not increase antibody levels. Smoking and comorbidities were associated with lower neutralization and antibody levels. Among fully vaccinated, 6.3% breakthroughs were detected up to 189 days post-vaccination. Among pre-exposed non-vaccinated, 90% were IgG seropositive more than 300 days post-infection.
Conclusions
Our data support administering a single-dose in pre-exposed healthy individuals. However, heterogeneity of responses suggests that personalized recommendations may be necessary depending on COVID-19 history and life-style. Higher mRNA-1273 immunogenicity would be beneficial for those expected to respond worse to vaccination. Persistence of antibody levels in pre-exposed unvaccinated indicates maintenance of immunity up to one year.

## 22 A new flow cytometry cell-based assay to efficiently determine RBD-specific neutralization of SARS-CoV-2 emerging variants

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Aim: The rapid spreading of SARS-CoV-2 variants raises concerns regarding their capacity to evade immune protection provided by natural infection or vaccination. The receptor- binding domain (RBD) of the viral spike protein is the primary target of neutralizing antibodies, and viral variants accumulate mutations in this region. The aim of this study is to develop a simple method to rapidly determine antibody neutralization against SARS- CoV-2 RBD variants for the quick evaluation of the potential threat of the variants and update effective interventions.

Material and Methods: A non-adherent 300.19 stable cell line expressing the human ACE2 receptor was incubated with RBD-Fc-fusion proteins from several viral variants previously exposed to the plasma samples of 36 COVID-19 convalescent subjects and 67 vaccinated individuals. Cells were stained with anti-mouse IgG-PE and plasma neutralizing capacity was determined by flow cytometry as RBD-ACE2 binding inhibition.

Results: We have established a simple and efficient flow cytometry assay to measure antibody-mediated neutralization against RBD of several variants: Alpha (B1.1.7), Delta (B.1.617.2), Gamma (P.1), Epsilon (B.1.427), and Kappa (B.1.617). These RBD variants showed augmented binding to ACE2 compared to the original Wuhan strain. Variants containing mutations E484Q/K (Gamma, Kappa) with K417T and N501Y (Gamma) or L452R (Kappa), and variants encompassing only L452R (Epsilon), or L452R and T478K (Delta) mutations showed increased resistance to antibody neutralization in comparison to the Wuhan strain or the Alpha variant encompassing N501Y.

Discussion: Our assay, which can be easily adapted to newly emerging variants, should be extremely valuable to assess the ability of these variants to escape immune protection from vaccination.

## 23 Analysis of Clinical and Laboratory Markers Based on the First COVID-19 Wave in Barcelona: Limitations of the Current Clinicopathological Tests Guides the Identification of Effective Biomarkers

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Almost two years after the onset of COVID-19) pandemic, the precise value of the clinical laboratory tests that are currently used at disease onset in assessing the stage and prognosis of COVID-19 patients is not yet clear. An analysis of the performance of these assessment tests in 2,600 patients from three large cohorts of COVID-19 first wave confirmed the association of poor prognosis with neutrophilia, marked lymphopenia, and the changes in acute-phase reactants (APRs) and coagulation factors. However, the reduction in kidney function and an elevated aspartate alanine transaminase showed similar predictive power than that of changes in the APRs and blood cell counts. Statistical modelling to disentangle the contributions of each of the laboratory, demographic and clinical data to outcome, indicates that while the intensity of inflammatory response to the SARS-CoV2 infection is captured by the current clinical laboratory tests, they do not discriminate between an efficient and a dysregulated immune response. Furthermore, as APRs and blood cell count measure the same central inflammatory process and its repercussions, they suffer a level of redundancy that explains their relatively modest increase in performance when used in combination. Furthermore, these clinical laboratory variables correlated with and are dependent on age and comorbidities, which explains their only partially additive effect to the age and comorbidity as predictors. Therefore, there is an urgent need for better, independent predictive biomarkers of the COVID-19 outcome that can discern between efficient and dysregulated immune response to SARS-CoV2, early in the course of the disease. Pilot studies that measure cytokine levels and cell immunophenotype changes using techniques with transferability to clinical laboratories produced good receiver operating characteristics curves that highlight their predictive potential. Additional robust immunological tests in combination with organ and tissue damage indices could provide better guidance on COVID-19 management.

## 24 High-dose intravenous immunoglobulins might modulate inflammation in COVID-19 patients

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The use of high-dose of Intravenous Immunoglobulins (IVIG) as immunomodulators for the treatment of COVID-19 affected individuals have shown promising results. IVIG reduced inflammation in these patients, who progressively restored respiratory function. However, little is known about how they may modulate immune responses in COVID-19 individuals. Here, we have analyzed the levels of 41 inflammatory biomarkers in plasma samples by Luminex and ELISA. Plasma samples were obtained at day 0 (pretreatment initiation), 3, 7 and 14 from five hospitalized COVID-19 patients treated with a 5-day course of 400 mg/kg/day of IVIG. The plasmatic levels of several cytokines (Tumor Necrosis Factor, Interleukin (IL)-10, IL-5, and IL-7), chemokines (Macrophage Inflammatory Proteins-1α ), growth/tissue repairing factors (Hepatic Growth Factor), complement activation (C5a) and intestinal damage such as Fatty acid- binding protein 2 and LPS-binding protein showed a progressive decreasing trend during the next two weeks after treatment initiation. This trend was not observed in IVIG-untreated COVID-19 patients. Interestingly, high levels of some of these molecules had beenassociated with severity and mortality in SARS-CoV-2 infected individuals. Taken together these data suggest that the administration of high-dose of IVIG to hospitalized COVID-19 patients may improve their clinical evolution by modulating their hyperinflammatory and immunosuppressive status.

## 25 SARS-CoV-2 antibody kinetics in healthcare workers in northern metropolitan Barcelona

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Background:
Understanding humoral responses and seroprevalence in SARS-CoV-2 infection is essential for guiding vaccination strategies in both infected and uninfected individuals.
Methods:
We determine the kinetics of IgM against the nucleocapsid (N) and IgG against the spike (S) and N proteins of SARS-CoV-2 in a cohort of 860 health professionals (healthy and infected) in northern Barcelona. We model the kinetics of IgG and IgM at nine time points over 13.5 months from infection, using non-linear mixed models by sex and clinical disease severity.
Results:
Of the 781 participants who were followed up, 478 (61.2%) became infected with
SARS-CoV-2. Significant differences were found for the three antibodies by disease severity and sex. At day 270 after diagnosis, median IgM(N) levels were already below the positivity threshold in patients with asymptomatic and mild-moderate disease, while IgG(N, S) levels remained positive to days 360 and 270, respectively. Kinetic modelling showed a general rise in both IgM(N) and IgG(N) levels up to day 30, followed by a decay whose rate depended on disease severity. IgG(S) levels increased at day 15 and remained relatively constant over time.
Conclusions:
We describe kinetic models of IgM(N) and IgG(N, S) SARS-CoV-2 antibodies at 13.5 months from infection and disease spectrum. Our analyses delineate differences in the kinetics of IgM and IgG over a year and differences in the levels of IgM and IgG as early as 15 days from symptoms onset in severe cases. These results can inform public health policies around vaccination criteria.
Key-words:
COVID-19; Antibodies, IgG, IgM, Seroprevalence, Kinetics, Humoral immunity, Disease spectrum, Sex, Health Care Workers

# Abstracts
# Posters

## 1.1 Immunological status of bladder cancer patients based on urine leukocyte composition at radical cystectomy

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Bladder cancer (BC) is the ninth most common malignancy worldwide, with high rates of recurrence. The use of urine leukocyte composition at the time of radical cystectomy (RC) as a marker for the study of patients' immunological status and to predict the recurrence of muscle-invasive bladder cancer (MIBC) has received little attention. Methods: Urine and matched peripheral blood samples were collected from MIBC patients at the time of RC. Leukocyte composition and expression of PD-L1 and PD-1 in each subpopulation were determined by flow cytometry. Results: All MIBC patients had leukocytes in urine. There were different proportions of leukocyte subpopulations. The expression of PD-L1 and PD-1 on each subpopulation differed between patients. Neoadjuvant chemotherapy (NAC), smoking status, and the affectation of lymph nodes influenced urine composition. We observed a link between leukocytes in urine and blood circulation. Recurrent patients without NAC and with no affectation of lymph nodes had a higher proportion of lymphocytes, macrophages, and PD-L1+ neutrophils in urine than non-recurrent patients. Conclusions: Urine leukocyte composition may be a useful tool for analyzing the immunological status of MIBC patients. Urine cellular composition allowed us to identify a new subgroup of LN- patients with a higher risk of recurrence.

## 2.3 Phenotypic and Functional Consequences of Platelet Binding to Monocytes and Its Association with Clinical Features in SLE

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Platelets (PLTs) can modulate the immune system through the release of soluble mediators or through interaction with immune cells. Monocytes are the main immune cells that bind with PLTs, and this interaction is increased in several inflammatory and autoimmune conditions, including systemic lupus erythematosus (SLE). We aimed to characterize the phenotypic and functional consequences of PLT binding to monocytes in healthy donors (HD) and SLE and to relate it to the pathogenesis of SLE. We analyzed the phenotypic and functional features of monocytes with non-activated and activated bound PLTs by flow cytometry. We observed that monocytes with bound PLTs and especially those with activated PLTs have an up-regulated HLA-DR, CD86, CD54, CD16, and CD64 expression. Monocytes with bound PLTs also have an increased capacity for phagocytosis, though not for efferocytosis. In addition, monocytes with bound PLTs have increased IL-10, but not TNF-α, secretion. The altered phenotypic and functional features are comparable in SLE and HD monocytes with bound PLTs. However, the percentages of monocytes with bound PLTs are significantly higher in SLE patients and are associated with undetectable levels of anti- dsDNA antibodies and hematuria, and with normal C3 and albumin/creatinine levels. Our results suggest that PLTs have a modulatory influence on monocytes and that this effect may be highlighted by increased binding of PLTs to monocytes in autoimmune conditions.

## 3.4 IN-SILICO LYNCH SYNDROME-RELATED NEOANTIGENS PREDICTION FOR A DENDRITIC-CELL BASED CANCER

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BACKGROUND: Lynch syndrome (LS), caused by germline mutations on DNA mismatch-repair genes (MLH1,MSH2, MSH6,PMS2) predisposes patients to colorectal and endometrial cancers (CRC, EC) amongst other tumors. Although CRC prevention methods are effective, no preventive strategies exist for the majority of LS-related tumors. Ex-vivo generated and tumor-antigen-loaded dendritic cell (DC) vaccines are one of the recently featured antitumoral immunotherapies. However, their full therapeutic potential would likely be as a preventive approachin high-risk cancer patients. LS is a paradigmatic model for its limited and predictive mutational spectrum in repetitive DNA sequences termed microsatellites (MS). This study aims to identify the main frame-shift derived neopeptides(FSDN) that are shared among cancers from LS patients to develop a preventive DC-based neoepitope vaccine.

METHODS: Systematic search of coding MS (cMS) and FSDN in LS tumors published in literature and in public databases (Seltar Database; The Cancer Genome Atlas, TCGA). Application of epitope prediction pipelines to prioritize those FSDN with high coverage on the most frequent HLA-I and HLA-II haplotypes (pVACbind). In-silicoFSDN validation in colorectal adenomas (CrAD) and EC samples by sequencing through a cMS-targeted InDel panel and analysis of epitope prevalence through prediction pipelines (pVACseq).

RESULTS: 531 frame-shift peptide sequences derived from 269 cMS were selected and computed through the pVACbind pipeline with a labile HLA-binding affinity threshold (IC50=<5000nM). We prioritized 98 epitopes, 53 HLA-I and 45 HLA-II restricted. CrAD and EC sample analysis through the pVACseq software determined that virtually A) our FSDN bind to 36 HLA-II and 60 HLA-I alleles, and B) up to 26 of the analyzed FSDN are presented in these samples.

CONCLUSIONS: Our predicted FSDN have an optimal coverage among LS patients in terms of HLA alleles, associated cancers and prevalence. These results are key to the following step involving in-vitro functional analysis to determine FSDN immunogenicity.

## 4.5 Non-invasive vagus nerve stimulation as an alternative treatment to immunomodulatory drugs in rheumatoid arthritis: a proof-of-concept study

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Aim To investigate the safety and efficacy of non-invasive stimulation of the auricular branch of the vagus nerve for the treatment of rheumatoid arthritis (RA) patients and its effect on inflammatory response.
Methods This prospective, multicenter, open-label, single-arm proof-of-concept study enrolled adult patients with active RA who had an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (DMARDs) and up to one biological DMARD. Biological DMARDs were stopped at least 4 weeks before enrolment and concomitant use was not allowed during the study. All eligible participants were assigned to use a non-invasive, wearable vagus nerve stimulation device for up to 30 min per day, which delivered pulses of 20 kHz.
The primary endpoint was the mean change in Disease Activity Score of 28 joints with C-reactive protein (DAS28-CRP) at week 12. Circulating cytokine concentrations (IL-6, IL-10, IL-1b, IFNg, TNFa, IL-2Ra and IL12p70) were measured through microfluidic-based immunofluorescence assay (ELLA, Protein Simple) collected at all assessments.

## 4.5 Non-invasive vagus nerve stimulation as an alternative treatment to immunomodulatory drugs in rheumatoid arthritis: a proof-of-concept study

Findings 30 patients were enrolled at six centers in Spain between Dec 2018-Oct 2019, of whom 27 (90%) completed the week 12 visit. The mean change in DAS28-CRP at 12 weeks was –1.4 (95% CI –1.9 to –0.9; p<0.0001). 37% of patients reached DAS28-CRP of 3.2 or less, and 23% of patients reached DAS28-CRP of less than 2.6. Four adverse events were reported, none of which were serious and all resolved spontaneously. Among the changes in serum cytokine concentrations a significant median reduction in TNF (Δ-0.9 pg/mL ,p=0.032) and in IL10 levels (Δ-0.4 pg/ml, p=0.013) was found.

InterpretationThe device was well tolerated, without safety concerns, and patients had meaningful reductions in DAS28-CRP. This was an uncontrolled, open-label study, and the results must be interpreted in this context. Further evaluation is needed to confirm whether this non-invasive approach might offer an alternative treatment for RA

## 5.9 Influence of the maternal diet during pregnancy and lactation on the development of the immune system in suckling rats.

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The development of the immune system occurs during gestation, lactation, and early life. These periods are crucial for a proper infant immune system maturation and they are highly dependent on the maternal environment. In this regard, maternal diet during gestation and lactation has been suggested to modulate milk composition which in turn impacts neonate's immune system.

In the present study the impact of two different dietary patterns to dams during gestation and lactation on the descendants has been evaluated. Lewis rats were divided into two groups (D1 and D2) depending on the diet they followed. Diet 1 was composed of vegetal proteins and a higher proportion of fiber, while Diet 2 was formulated with higher animal protein and lower fiber content. A reference group following a regular diet was included (REF). To evaluate the effect of the maternal diet on pups, different morphometric variables were evaluated from birth to the end of the suckling period. Additionally, for characterization of the stage of development of the immune system, mucosal (mesenteric lymph nodes, MLN) and systemic (spleen) lymphocyte phenotype and immunoglobulin levels were evaluated. Results from D1 group animals showed a positive effect in the small intestine growth, changes in the phenotypical pattern of immune cells in both the MLN and the spleen, and also the promotion of the Th1-associated immunoglobulin acquisition which leads to a more mature infant's immunity.

In conclusion, the study showed that a maternal dietary pattern based on vegetal protein and fiber during gestation and lactation has a positive effect on neonates due to its effects during gestation on the development of the neonate's systems and to the passive transfer of bioactive components through the milk. Further studies are needed to ascertain which period has a higher impact on the immune system development.

## 6.10 Staphylococcus epidermidis' overload during suckling impacts the immune development in rats

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Mastitis is an inflammation of the mammary gland occurring in 3 - 33% of the breastfeeding mothers, that can be accompanied or not by infection. Infectious mastitis involves breast milk' microbiota dysbiosis. In these cases, the concentration of the causal bacteria, generally Staphylococci,increases and that of the rest of the bacterial groups is drastically reduced.

Our hypothesis is that during a mastitis involving an overgrowth of Staphylococcus epidermidis, an overload of this bacterium is transferred via human milk to the baby which may have an impact on the body growth and immune system development. The aim of this study was to analyze the impact of a high and a low overload of S. epidermidis during sucklingin neonatal rats.

From day 2 to day 21 of life, suckling rats were daily supplemented with low (Ls group) or high (Hs group) dose of S. epidermidis or vehicle(REF group). Body weights and fecal humidity were periodically recorded. On day 21 and 42 of life, morphometry, intestinal gene expression, immunoglobulin profile and spleen cells' phenotype by immunofluorescence staining, were assessed.

The S. epidermidis administration during suckling had some impact on the pups, even at day 42, after 3 weeks without receiving the bacteria. Although no differences were found in body weight, Ls and Hs groups showed higher naso-anal length and lower fecal humidity compared to REF animals. The expression of the intestinal immaturity biomarker FcRn was higher in Hs group than in the REF group. Both interventions modified the plasma immunoglobulin profile suggesting a delay in Th1 maturation and induced small changes in the proportion of some lymphocyte subpopulations, and their activation (CD25) and homing (CD62L/αE) phenotypes.

In conclusion, the overload with both low and high doses of S. epidermidis during suckling affects the immune development of rats in early life.

## 7.12 T-cell response as a correlate of COVID-19 vaccination. A pilot study in Health Care Workers.

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Background:
It is crucial to assess the levels of protection generated by natural infection or SARS-CoV-2 vaccines, mainly in individuals professionally exposed and in vulnerable groups. Measuring Tcell responses may complement antibody tests currently in use as correlates of protection. Our aim was to assess the feasibility of a validated assay of T-cell responses.
Methods:
Twenty health-care-workers (HCW) were included. Antibody test to SARS-CoV-2 N and S proteins in parallel with a commercially available whole-blood-interferon-gamma-releaseassay (IGRA) to S-peptides and two detection methods, CLIA and ELISA were determined.
Results:
IGRA test detected T-cell responses in naturally exposed and vaccinated HCW already after first vaccination dose. The correlation by the two detection methods was very high (R>0.8) and sensitivity and specificity ranged between 100 and 86% and 100-73% respectively. Even though there was a very high concordance between specific antibody levels and the IGRA assay in the ability to detect immune response to SARS- CoV-2, there was a relatively low quantitative correlation. In the small group primed by natural infection, one vaccine dose was sufficient to reach immune response plateau. IGRA was positive in one, with Ig(S) antibody negative vaccinated immunosuppressed HCW illustrating another advantage of the IGRA-test.

## 7.12 T-cell response as a correlate of COVID-19 vaccination. A pilot study in Health Care Workers.

Conclusion:

Whole-blood-IGRA-tests amenable to automation and constitutes a promising additional tool for measuring the state of the immune response to SARS-CoV-2; they are applicable to large number of samples and may become a valuable correlate of protection to COVID-19, particularly for vulnerable groups at risk of being re-exposed to infection, as are health-careworkers.

## 8.13 Effect of cocoa and orange polyphenols on cytotoxic and phagocytic activities of rats following an intensive training and exhausting exercise

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High intensity exercise may alter immune system functionality thus increasing the risk of infection. The function of neutrophils, monocytes and natural killer (NK) cells may be impaired by intensive exercise (1). Polyphenols have shown to enhance NK cytotoxicity (2) and modulate blood monocyte and neutrophil proportion and their phagocytic function (3). We aimed to assess the influence of cocoa and orange polyphenols on splenic NK cytotoxic activity and blood phagocytes proportion and activity after a model of intensive exercise. For this purpose, Lewis rats were fed either a standard diet, a diet containing 10% cocoa (C10) or a diet containing 10% cocoa plus 0.5% hesperidin (CH) for 6 weeks. In this period, animals were submitted to a high-intensity running on a treadmill, involving three trainings per week and two exhaustion tests. A sedentary control group per each dietary condition was included. At the end, runner rats were distributed into two groups: trained (samples obtained 24 h after a regular training) and exhausted (samples obtained immediately after a final exhaustion test). Cytotoxic and phagocytic activity were immediately assessed. The final exhaustion induced a higher spleen NK cytotoxic activity, which was prevented by the intake of CH diet. However, the C10 diet did not prevent this change and, on the contrary, it promoted an increase in NK cytotoxicity. Concerning blood phagocytes, intensive exercise decreased the proportion of phagocytic monocytes without modifying that of neutrophils. On the other hand, the final exhaustion decreased the phagocytic monocyte activity whereas tended to increase that of neutrophils. Neither the C10 diet or the CH diet prevented these changes, in fact C10 intake also reduced the phagocytic monocyte proportion. Overall, intensive running exercise affects the functionality of NK cells and blood phagocytes, some of which could be attenuated by a diet rich in cocoa and hesperidin.

# 9.14 Natural Killer receptors variants role in the predisposition and evolution of Myelodysplastic Syndromes patients

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Myelodysplastic Syndromes (MDS), a complex group of hematological malignancies, are characterized by ineffective hematopoiesis, bone marrow dysplasia, cytopenia and risk of progression to secondary Acute Myeloid Leukemia (sAML).
This retrospective study aimed to decipher the role of different activating and inhibiting KIR genes as well as the activating NKG2D receptor presents mainly in NK cells, and also their respective ligands, HLA-A, -B, -C, -G, -F, MICA and MICB, in the evolution of the disease. To achieve this goal, 89 MDS patients (of which 18 progressed to sAML) were recruited. As control samples, healthy donors (n=445) from the Barcelona Blood Bank and a group of patients with AMLdenovo (n=76) were analyzed.
When compared genotypes from MDS patients with healthy controls, we found out that MICA129met, which enhances a stronger binding with the NKG2D activating receptor, was statistically associated with protection against MDS [(n=37, 41,57%) vs (n=57, 59,38%), p-value = 0.023]. On the other hand, MICA*004, was assessed as a risk factor to develop MDS [(n=33, 37,08%) vs (n=21, 21,88%) p- value=0.034]. KIR2DL3/HLA-C1 was the most common combination of KIR-ligand in the MDS sample (n=70, 78.65%) in contrast with the donors (n=283, 63.59%), being associated with MDS (p- value=0.0089). Regarding the risk to develop AML, activating haplotype gene KIR2DL2 was associated with protection against AMLdenovo in comparison to healthy donors [(n=35, 45,9%) vs (n=26, 59,8%), p-value=0.02]. Moreover, the combination KIR2DL1HLA-C2 was present in a higher proportion in MDS(sAML) and AMLdenovo (n= 13, 72.22% and n= 54, 71.56%) than in controls (n= 248, 55.73%) (p- value=0.14 and p-value=0.0049 respectively). No significant statistical differences were found between the MDS(sAML) group and the AMLdenovo cohort.

In summary, our results showed that activating NK receptor phenotypes might protect against MDS, as well as the progression from MDS to sAML, probably by increasing the NK activity.

## 10.16 Supplementation of gestating and lactating mothers with extra virgin olive oil influences the offspring immune system

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The immune system in neonates is immature and makes them vulnerable to infections. Breast milk plays a key role in the development of the immune system of newborns and protects them against many diseases. Diet can influence the microbiota and the immune system of the lactating mothers and also the composition of the breast milk thus influencing the infant´s health. Extra virgin olive oil (EVOO) is the main source of fat from the Mediterranean diet and it is known for its antioxidant and anti-inflammatory benefits that come from its high content in monounsaturated fatty acids and the presence of polyphenols.

The aim of this study was to establish if a supplementation with EVOO to gestating and lactating mothers have an impact on the development of the descendants' immune system.

For this 10 mL/Kg of EVOO or water (reference group) were administered orally once a day to rats during gestation and lactation periods. A refined oil was also used as a control oil. On day 21, immunoglobulin (Ig) concentrations in plasma and mesenteric lymph node (MLN) tissue samples were quantified by a ProcartaPlex® multiplex immunoassay. The expression of genes related to immune system and intestinal barrier function was also quantified by RT-PCR.

EVOO pups had higher plasma levels of IgG2b and IgG2c -isotypes related to a Th1 response- than the rest of the groups, without affecting the Ig profile in MLN. However, the oil decreased the gene expression of Toll-like receptors (TLR)3 and TLR5, MUC-2 and MUC-3 and tight junction proteins ZO-1, occludin and claudin-4. Additionally, it increased the expression of neonatal Fc receptor.

Overall, supplementation with EVOO to rats during the gestation and lactation periods had an impact on the descendants, however further studies are needed to clarify its role in the development of the immune system.

## 11.17 IgA autoantibodies in Systemic Sclerosis

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Introduction

Systemic Sclerosis (SSc) is an autoimmune disease characterized by excessive fibrosis and vasculopathy. It usually affects the skin and, variably, other organs. Interstitial lung disease (ILD) is the most important causes of mortality.

Different autoantibodies (Abs) against nuclear proteins are present in >95% of patients. IgG-anti-Scl70, associated with diffuse-cutaneous (dcSSc) phenotype with lung involvement; IgG-anti-CENP-B, with limited- cutaneous (lcSSc) involvement and lower-risk of ILD and IgG-anti-RNA-polymerase-III, with an aggressive diffuse-skin involvement, and scleroderma-renal crisis, are included in the SSc-ACR/EULAR classification criteria. The detection of additional Abs is of interest when those are negative. Currently, the study of IgA isotype is limited to a few Abs but it is possible that it plays some role in ILD. Thus, the aim of this study was to analyse the IgA-Scl70 and IgA-CENP-B Abs in a SSc cohort.

Methods

Ninety-seven patients, including 48.5% lcSSc, 15.5% dcSSc, 32.0% sine-SSc and 4.0% preSSc, were tested for IgG/IgA-Scl70 and IgG/IgA-CENP-B by EliATM(Thermo Fisher Scientific). Manufacturer reference values for IgG were used and 50 healthy individuals were tested to establish the analytical conditions to evaluate the IgA-Scl70 and IgA-CENP-B Abs as well as a cut-off value. Anti-RNA-Polymerase-III Abs were no systematically analyzed.

## 11.17 IgA autoantibodies in Systemic Sclerosis

Results

Prevalence of isolated IgG-Scl70 was 3.1% whereas IgG-CENP-B was 17.5%. Moreover, double positive IgG/IgA-Scl70 was 19.6% (being 4/19 IgA-CENP-B positive also) and double positive IgG/IgA-CENP-B was 30.9% (being 3/30 IgA-Scl70 positive too). There were only 2 patients with isolated IgA isotype (1 IgA- Scl70; 1 IgA-CENP-B). Finally, 26.8% patients were IgG-IgA double negative (Scl70 and CENP-B).

Conclusions

This study evaluates for the first time the presence of IgA-Abs against Scl70 and CENP-B. Many of the IgG Abs against Scl70 and CENP-B are actually double positive, IgG and IgA. More studies are necessary to explore the role of IgA isotype in the pathogenesis of SSc.

## 12.19 Mesura d'interleuquina-6 en líquid amniòtic. Ús en pacients amb sospita de corioamnionitis

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OBJECTIUS: Determinar el valor de normalitat d'interleuquina-6 (IL-6) en líquid amniòtic (LA), estudiar factors materns i fetals que poden influir en els seus nivells i determinar-ne la seva utilitat pel diagnòstic de corioamnionitis.

MÉTODES: Estudi prospectiu en el que s'inclouen gestants tributaries d'amniocentesi per estudi genètic o sospita d'infecció intra-amniòtica des d'octubre de 2016 fins setembre de 2019 (n=213). Per la determinació d'IL-6 en LA es va realitzar un immunoassaig de fluorescencia mitjançant tecnología de microfluids (ELLA Protein Simple, Biotechne). Per obtenir la corba de normalitat es van incloure les amniocentesis genètiques (n=140). Les pacients amb sospita de corioamnionitis (n=73) es van categoritzar en 5 grups: amenaça de part preterme (APP), sospita d'infecció per analítica, sospta d'infecció per LA, sospita d'infecció per analítica i LA, i amenaça de part immadur (API).

RESULTATS: IL-6 cruda no segueix una distribució normal però sí al realizar una transformació logarítmica. Els nivells de log(10)-IL-6 no es modifiquen per l'edat gestacional, edat materna, índex de massa corporal, ètnia, tabac, multiparitat o reproducció assistida.

En el grup de gestants amb sospita de corioamnionitis se'n van confirmar 25 per l'estudi anatomopatologic placentari. 27 (37%) gestants tenien IL-6 >p95 i 32 (43,8%) >p90. Les diferències segons el tipus de sospita van ser estadísticament significatives ($p<0.001$). La mediana d'IL-6 en les corioamnionitis confirmades fou de 3046 pg/mL, significativamente més alta que en les no confirmades ($p=0.021$). 14 de les 25 (56%) corioamnionitis confirmades tenien IL-6 >p95. L'AUC de la IL-6 per la detecció de corioamnionitis en aquest brup fou de 0,658 (IC95% 0,508-0,809), no superior al AUC de glucosa, gram ni cultiu.

CONCLUSIONS: IL-6 segueix una distribució normal en LA amb una transformació logarítimica i no es veu modificada pels principals factors materns ni fetals. Està augmentat en casos de corioamnionitis i la seva determinació pot ser útil pel diagnóstic de corioamnionitis subclínica.

## 13.21 Immunogenicity induced by full academic CD19 chimeric antigen receptor (CAR) T cells (ARI0001) in patients with relapsed/refractory B cell malignances

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Background:CART19-BE-01 is the phase 1 multicenter trial of ARI-0001 cell therapy in patients with CD19+ relapsed/refractory (R/R) B- cell malignancies. It has been approved by the Spanish Agency of Medicine in 2021 for the treatment of relapsed/refractory acute lymphoblastic leukemia (ALL) in patients older than 25 years. This fully academic CAR19 consists of the anti-CD19 single-chain variable fragment (scFv), originated from a mouse monoclonal antibody A3B1, conjugated with the intracellular regions 4-1BB and CD3z. Its safety and efficacy have been demonstrated, but no studies have been conducted about the immunogenicity it might trigger.
Methods: Regarding the humoral immunogenicity, anti-CAR T response was assessed by a cell-based fluorescence assay to detect human anti-murine antibodies (HAMA) in patients´ sera. Assessment was carried out at different time points. Subsequently, cytotoxicity assay for positive patients' sera were done to appraise the effect of HAMA. Regarding the cellular immunogenicity, patients included in the clinical trial were HLA typed to predict the binding of the CAR19 peptides to HLA molecules in silico.
Results:Forty-seven patients (37 adults/10 pediatrics) received ARI-0001 cells. Approximately twenty-five per cent (12 out of 47) of the patients tested positive for the presence of anti-CAR antibodies after hundred days (~ 3 months) of the first or second infusion. Even though twenty-five per cent had anti-CAR antibodies, only some of them were diminishing the effectiveness of CAR-T19. In relation to the prediction in silico, a set of 94 priorized immunogenic peptides (62 HLA-I peptides and 32 HLA-II peptides) of CAR19 were selected for assessing the T-cell response.
Conclusions:These data suggest that the assessment of immunogenicity induced by CAR-T19 could be important, specially before considering a second infusion after relapse.

## 14.22 Defective anti-N Antibody response and SARS-CoV-2-specific memory CD4+ T cells in a group of post infected vaccinated healthcare workers.

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Aim
The aim of the study is to compare the antibody response and the activation markers on memory CD4+T lymphocytes from unexposed, post-infected and vaccinated healthcare workers (HCW)induced in vitro with SARS-CoV-2 M, N and S proteins.
Material and methods
Blood samples were collected from unexposed-unvaccinated (n=9), post-infected (n=28),and unexposed- vaccinated (n=9)HCW. Peripheral blood mononuclear cells (PBMCs) were obtained by density gradient, and stimulated during 24h at 37ºC withS M and N SARS-CoV-2 15-mer peptide pools (PepTivator SARS- CoV-2 Prot M, N and S. MiltenyiBiotec) or with PHA-M (phytohemaglutinin, as positive control). The stimulated PBMCs were stained with 7-AAD, anti-CD3, anti-CD4, anti-CD8, anti-CD45RA, anti-CD137 (BD Pharmingen) and anti-CD134 (Cytognos) fluorescent conjugated monoclonal antibodies. Samples were acquired with BD FACSLyric cytometer (BD Biosciences), and analyzed with FlowJo v10.7.2 software. Anti-N total IgG, IgA and IgM (N-Total GAM) antibodies were analyzed by a chemiluminescent immunoassay (cobas801, Roche). Statistical analyses were performed with GraphpadPrism v5.0 software.
Results
During the collection of samples, we identified three groups of post-infected HCW based on their anti SARS-CoV-2 N-Total GAM antibody response: First group (COVID+) those who developed anti-N protein antibodies to SARS-CoV-2(n=12). Second group (COVID+SN) those who did not develop anti-protein N antibodies to SARS-CoV-2(n=7) and the third group (COVID+ SC) those who negativized the antibodies after 6 months from infection (n=9).
The cellular phenotyping showed a significant difference in the % of activated induced memory CD4+ T lymphocytes in response to protein M and N in seropositive (COVID+) compared to seronegative (COVID+SN) post-infected HCW. As well as in response to protein N in seropositive (COVID+) compared to seronegativized (COVID+SC) post-infected HCW.

## 15.29 OPTIMIZATION OF NEXT GENERATION SEQUENCING HLA TYPING FOR THE DETECTION OF HLA LOSS RELAPSE

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HLA loss relapse (HLA-LR) consists on genomic loss of mismatched HLA molecules in re-emerging leukaemic cells. Until now, this frequent mechanism leukemia-immune evasion after HSCT has been reported in retrospective studies and mostly in haplo-HSCT setting.
Prospective HLA-LR detection requires a sensitive and cost-effective technique implemented in routine laboratories. Contrary to HLA-KMR® (GenDx) (assay based on qPCR but with limited gene allele HLA coverage), next-generation sequencing (NGS) HLA typing is a sensitive method with complete HLA gene and allele coverage and nowadays its use is being extensive in many HLA typing laboratories.
Our aim is to optimize our NGS HLA typing strategy in order to apply this method in the first multicentric prospective study to evaluate HLA loss detection capacity and prognostic value during post-HSCT monitoring in patients with myeloid and lymphoid malignancies at high risk of relapse.
As sensitivity is correlated directly to deep coverage and indirectly to noise level, we improve deep coverage by overrepresenting the interest samples in the final pool (x2.4) and adjusting some analysis parameters in order to maximize the number of reads analyzed.
After analyzing two artificial chimerism mixes of haploidentical samples (80%-20%, 90%-10%, 95%-5% and 97%-3%) and relapse samples with known chimerism results (obtained by STR polymorphic markers), we observed that chimerism as well as calculated haplotype representation correlate with deep coverage proportion of the specific allele. Regarding noise level, we detected intergenic and intragenic variation being lower and more homogeneous in class II than in class I HLA genes. HLA-DQB1 gene showed the best correlation with chimerism (R2=0.84) and with calculated haplotype representation (DQB1 R2=0.91) as well as the best capacity to detect 3% of the allele of interest.
In conclusion, NGS HLA typing is a useful tool for HLA-LR detection due to its sensitivity and complete gene and allele HLA coverage.

## 16.33 HLA-A*24:552. Un nuevo alelo identificado en dos donantes voluntarios de médula ósea no relacionados en Tenerife (Islas Canarias).

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Los genes del antígeno leucocitario humano (HLA) son los genes más polimórficos del genoma humano. En concreto, el locus HLA-A es el segundo gen más polimórfico en el sistema HLA, con casi 7000 alelos identificados hasta la fecha.
Cada vez con más frecuencia, se están identificando nuevos alelos de HLA en la población española como resultado de la incorporación en la práctica clínica de los sistemas secuenciación de próxima generación (NGS, Next Generation Sequencing) para el tipaje HLA en trasplantes de células progenitoras hematopoyéticas.
En este trabajo, informamos un nuevo alelo HLA-A*24, oficialmente llamado HLA-A*24:552, que se encontró en dos individuos no relacionados en la isla de Tenerife.
El análisis de secuenciación del nuevo alelo no mostró una coincidencia perfecta con ninguna combinación conocida de alelos HLA-A*24 encontrada, lo que sugiere la presencia de una nueva variante A*24.
Encontramos que A*24: 552 difiere de A*24:02:01:01 por el cambio de un solo nucleótido en la posición 1952 del exón 5 (CCA → TCA, codón 276) lo que da como resultado una mutación con cambio de aminoácido, de Prolina a Serina.
El nombre A*24: 552 fue asignado oficialmente por el Comité de Nomenclatura de la Organización Mundial de la Salud (OMS) en julio de 2021.
Una masiva incorporación de técnicas de NGS para tipaje HLA en los laboratorios producirá un importante incremento en la identificación de nuevos alelos de HLA, quedando por evaluar la repercusión que esto pueda tener en la futura selección de parejas donante-receptor.

## 17.36 Introducing immortalization as useful approach in reproducible and scalable manufacturing of Wharton's Jelly Mesenchymal Stromal cell-derived EV products

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The use of mesenchymal stromal cell-derived extracellular vesicles (MSC-EV) as therapeutic agents has shown to exert beneficial effects on tissue regeneration and immunomodulation. However, issues like large- scale EV productions and cost-effective manufacturing of EV are still important hurdles to use them in the clinics. Furthermore, EV functional and therapeutic variations are observed between donors and GMP manufacturing demands get limited due to lack of reproducibility. Since MSC immortalization could overcome some of these drawbacks to reach EV clinical demands, we immortalized Wharton's Jelly MSC (iWJ-MSC) by hTert and/or SV40 transduction and produced EV from these cells (iWJ-MSC-EV). iWJ- MSC were immunophenotyped, tested for their ability to differentiate into the adipogenic, chondrogenic and osteogenic lineages and analyzed for their immunomodulatory functions. iWJ-MSC kept a constant proliferative rate throughout a high number of passages, maintained the MSC surface markers and were able to differentiate into the three lineages after immortalization. In terms of immunomodulation, iWJ-MSC were able to suppress T cell proliferation like their non-immortalized MSC counterparts. Furthermore, iWJ- MSC-EV retained their functional capabilities. Specifically. iWJ-MSC-EV successfully recruited pro- regenerative and pro-angiogenic cells in an agarose spot migration assay and promoted angiogenesis in human umbilical vein endothelial cells (HUVEC) in a tube formation assay.

## 18.38 Moving forward personalised therapy in Relapsing-Remitting Multiple Sclerosis patients under anti-CD49d biological therapy

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Background.Natalizumab is a humanized monoclonal antibody that binds the α4-integrin (CD49d). It is one of the most effective treatments for Relapsing-Remitting Multiple Sclerosis (RRMS) patients, but its use is associated with risk of developing Progressive Multifocal Leukoencephalopathy. Although there are three risk factors that help to predict this risk, we need more sensitive strategies to establish criteria to better assess the risk or to monitor the treatment, increasing the safety of Natalizumab use. Objective.To identify biomarkers to monitor Natalizumab treatment and to establish a personalised dose. Methods.Ongoing transversal study in 29 RRMS patients under Natalizumab in standard interval dose (SD) of 300mg/4wks or extended interval dose (EID) of 300mg/6wks. Peripheral blood samples were analysed by flow cytometry to determine in parallel CD49d saturation and expression in several T and B lymphocytes subpopulations. Each patient was analysed at two different timepoints separated by 3 Natalizumab administrations. Results.When comparing the two timepoints no significant differences were observed neither for CD49d expression nor for CD49d saturation. SD patients showed saturation levels around 80% and EID patients around 60%. The percentage of CD49d expression was significantly decreased in SD patients compared with EID inactive patients in some minor lymphocyte subsets. Conclusions.CD49d expression and saturation are stable parameters that could be used as a biomarkers in the immunomonitoring of Natalizumab treatment.

## 19.43 Anti-OJ antibody not detected by commercial line immunoassay

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Introduction:
The anti-synthetase syndrome (ASS) is a rare autoimmune disease defined by antibodies directed against an aminoacyl tRNA synthetase along with clinical features that can include interstitial lung disease (ILD), myositis, Raynaud's phenomenon, arthritis, unexplained fever, and mechanic's hands. The anti-synthetase antibodies are particularly useful in the identification of patients with ILD since many times the distinctive muscle weakness is not present.
Clinical case:
We report a 65 years old male who debuted in February 2021 with low exertion dyspnoea, with cough without expectoration that required oxigenotherapy. Radiography was performed showing bilateral infiltrates in the lungs, and it was evaluated as a bilateral pneumonia, highly suspicious of infection by SARS- COV-2. The result of the PCR was negative and the CT scan showed findings consistent with bilateral organized pneumonia.
Treatment with 80 mg prednisone was started but despite that, due to increased O2requirements, he was transferred to the ICU where he required invasive ventilation. In the differential diagnosis of organized pneumonia, antinuclear antibodies (ANA) and commercial myositis profile were tested.
Results:
The ANA testing revealed a 1:640 cytoplasmic dense fine speckled (AC-19) pattern that strongly suggested an anti-synthetase antibody. But the myositis profile turned out to be negative. Because the clinical suspicion matched the ANA pattern, an RNA immunoprecipitation was performed and we observed a pattern compatible with anti-synthetase antibody. Then, we performed a protein immunoprecipitation-western blot. The result revealed that it was an anti-OJ antibody that recognizes conformational epitopes.
Conclusion:
In the case of a negative myositis immunoblot with high clinical suspicion for anti-synthetase syndrome and ANA pattern that supports it, the diagnosis should not be discarded. In these cases, it is recommended to perform an extended analysis including RNA and protein immunoprecipitations.

## 20.44 Titers of anti-IFN-I antibodies in Health Care Workers with a moderate SARS-CoV2 infection

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We compared the titers of antibodies against IFN-α2 and IFN-ω in the plasma from 232 health care workers (HCWs) that were infected with SARS-CoV2 and 35 HCWs that were not infected (IgG and IgM anti-N seronegative). Two samples from each infected HCW were collected at 1-2 (t=1) and 3-4 months (t=2) after infection.

Antibodies were determined using an inhouseELISA using IFN-α2 and IFN-ωattached to 96-well plates and detection was performed with biotinylated anti-IgG against H chain. To identify positive controls, we previously analyzed the antibody titers of 30 patients diagnosed with severe COVID-19.

Despite the titers of anti-IFN-α2 and IFN-ωcorrelated significantly, we found that the titers of anti-IFN-α2, but not anti-IFN-ω, antibodies were significantly higher in infected than in non-infected HCWs. The titers of anti-IFN-α2 and IFN-ωantibodies were not different in HCWs separated according to sex, smoking habits, or age. Interestingly, the titers of anti-IFN-ωantibodies were lower in those HCWs with positive anti- N IgM at t=1. However, no relationship was found between titers of anti-IFN antibodies and IgG anti-N, S1 and S2 SARS-CoV2 antigens. No differences were found when titers of anti-IFN antibodies were analyzed according to the presence of fever, cough, dyspnea or headache during infection. However, infected HCWs with asthenia had higher levels of anti-IFN-ωantibodies and infected HCWs with diarrhea had lower levels of anti- IFN-α2 and IFN-ω antibodies at t=1. Whereas in 63 HCWs we found a decrease (>10%) of both anti-IFN-α2 and IFN-ω antibodies, only in 6 HCWs we found an increase of titers of both antibodies between t=1 and t=2.

In conclusion, despite most of anti-IFN antibodies decrease in time, similarly to anti-SARS-CoV2 antibodies, no association was found between these two types of antibodies. This finding suggests a different mechanism of induction after SARS-CoV2 infection.

## 21.46 EVALUATION OF ANAS TITRE VARIATION IN THE MONITORIZATION OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS.

I. Arrese-Muñoz1; L.Viñas-Gimenez1; M. Sanz-Martinez1

*1Immunology Division . Vall d'Hebron University Hospital. Barcelona. Spain.*

Introduction:
Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multi-organ involvement. Antinuclear antibodies (ANAs) detected by indirect immunofluorescence (IF) are a hallmark of SLE. The new EULAR/ACR classification for SLE consider ANAs as an entry criterion. Even though it is known the key role of ANAs in SLE diagnosis, the variation of ANAs titre along time is an aspect to consider and nowadays is a controversial subject.
Objective:
Evaluate the variation of ANAs titres during the follow-up of patients controlled in the Lupus unite of the Vall d'Hebron Hospital.
Methods:
We studied 1344 patients who underwent SLE screening between 2019 and 2021, of which 1147 patients have more than one ANA test, corresponding with 4980 samples grouped as: 0-3 (n=1532), 3-6 (n=425), 6-12 months (n=999) and >1 year (n=2024). The variation of ANAs titre was studied comparing the titre at day 0 with the titre observed in the follow-up time.
TheANAs determination was carried out by IF on Hep-2 cells in the Vall d'Hebron immunology laboratory.
Results:
We observed that 75,8% (n=3776) of all samples showed no changes in ANA titres during the monitorization corresponding to 619 patients. A single change was observed in 20% (n=995) of samples, 2, 3 and 4 changes in less than 4% (n=171, 27 and 11 respectively). Finally, the analysis revealed that the 3% (n=134) of samples changed from a positive ANA titre to negative, which is equivalent to the 10,9% (n=125) of the patients.
Conclusion:
Although most patients included (54%, n=619) in this cohort do not vary along time, there are 10,9%
(n=125) of them that seroconverted from positive to negative regarding ANA titre. . So, we conclude that is important to continue following up these patients and carry out more studies to clarify the seroconversion significance.

## 22.47 Influence of testosterone levels on immune responses to COVID-19

Iria Arrese-Muñoz1,2,3; Emily Toscano-Guerra4,5; Sandra Salgado Perandrés1; Jessica Muñoz Nuñez1; Sara Briongos Sebastian1; Manuel Hernández-González1,2,3; Timothy M.Thomson6,7; Rosanna Paciucci4,5; Monica Martinez-Gallo1,2,3

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Infection with SARS-CoV-2 portends a broad range of outcomes, from a majority of asymptomatic cases or mild clinical courses to a lethal disease. Robust correlates of severe COVID-19 include old age, male sex, poverty and co-morbidities such as obesity, diabetes or cardiovascular disease. A precise knowledge is still lacking of the molecular and biological mechanisms that may explain the association of severe disease with male sex. Here, we show that testosterone trajectories are highly accurate individual predictors (AUC of ROC = 0.928, $p < 0.0001$) of survival in male COVID-19 patients. Longitudinal determinations of blood levels of luteinizing hormone (LH) and androstenedione suggest an early modest inhibition of the central LH- androgen biosynthesis axis in a majority of patients, followed by either full recovery in survivors or a peripheral failure in lethal cases. Moreover, failure to reinstate physiological testosterone levels was associated with evidence of impaired T helper differentiation and decrease of non-classical monocytes. The strong association of recovery or failure to reinstate testosterone levels with survival or death from COVID-19 in male patients is suggestive of a significant role of testosterone status in the immune responses to COVID-19.

# 23.50 RITUXIMAB PLASMA AND URINE MONITORIZATION IN A PATIENT AFFECTED BY NEPHROTIC SYNDROME BY ELISA

María Teresa Sanz-Martínez 1; Janire Perurena Prieto 1; Laura Viñas Giménez 1; Mónica Martínez Gallo 1; María Larrosa-García 1; Irene Agraz Pamplona 1; Roxana Paola Yuri Macias 1; Danae Anguita Domingo 1; Jose Bruno Montoro Ronsano 1; Manuel Hernández González 1

*1 Vall d?Hebron University Hospital. Barcelona. Spain.*

Introduction: Rituximab (RTX) is a monoclonal antibody used to treat various conditions including glomerular diseases (GD). There is a high variability in RTX pharmacokinetics (PK) and it has scarcely being studied in case of nephrotic syndrome (NS). One of the causes of this variability could be the RTX excretion in urine, however there are no commercial methods for its quantification.
We report the PK analysis of RTX in a GD case and measured the excretion of RTX in urine by adapting commercial ELISA for plasma samples.
Methods:We present a 72 years old male diagnosed with membranous nephropathy in September2020. In October2020 patient suffered severe NS so RTX was prescribed according to clinical guidelines (KDIGO 2021).
Routine blood and 24h urine samples were collected for clinical monitorization. RTX was measured with Lisa-Tracker®Rituximab (Theradiag®) according to manufacturer's instructions in plasma. Urine RTX was measured with the same ELISA kit using in-house standards and urine samples diluted to 1/100 in Phosphate- Tween-Buffer.
RTX's PK analysis was done using a monocompartimental model and non-lineal regression (Winnolin®).
Results:RTX plasma concentration was 26.38mcg/ml at d7, 7.93mcg/ml and 64.99mcg/ml at d15 (pre- and post-dose respectively) and 3.72mcg/ml at d28. RTX urine concentration was 2.12mcg/ml at d7.
After PK analysis we determined thatby d7 there were 93.2mg of RTX in the body and 17.8mg were eliminated that day. Considering a 1500ml/24hurine production, 3.18mg of RTX were excreted at d7, meaning that urine excretion justified 17.9% of RTX elimination.
Conclusion:RTX may be eliminated in urine in case of NS and this fact partially explain RTX's PKs alteration. Therefore, it is important in the follow-up of these patients not only to monitor RTX plasma levels but also urine. We show that ELISA could be a useful tool for this quantification in patients with elevated proteinuria.

## 24.51 Expression and killing activity of an anti-CD5 chimeric antigen receptor (CAR) in NK cells

Laura Carrillo 1; María Velasco-de Andrés 1; Cristina Català 1; Sergi Casadó-Llombart 1; Alejandra Leyton-Pereira 1; Clara Bueno 4,5; Pablo Menéndez 4,5,6; Francisco Lozano 1,2,3

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The advent of Chimeric Antigen Receptor (CAR)-based adoptive cell transfer technology has revolutionized the therapy of hematological malignancies. While remarkable achievements have been made in the field of B-cell malignancies, similar CAR approaches for T-cell malignancies remain underdeveloped. CD5 is a lymphocyte surface receptor expressed in most T cell acute lymphoblastic leukeamia (T-ALL) and peripheral T cell lymphoma (PTCL). This project aimed at generating a proprietary second-generation CAR directed against CD5 (anti-CD5CAR) for further expression and functional analysis in allogeneic NK cells, which represents a feasible off-the-shelf strategy. To this end, the human NK-cell lines KHYG-1 and NK92 were used as model to overcome the availability and expansion limitations intrinsic to primary NK cells. Results show that the anti-CD5CAR can be successfully expressed by KHYG-1 and NK-92 cells upon lentiviral transduction. Cytotoxicity and INF-γ production assays against CD5+ and CD5-Jurkat 2G5 cells showed the specificity and efficiency of anti-CD5CAR transduced KHYG-1 cells, thus denoting their suitability for future CAR immunotherapy development.

## 25.52 Predicción de la alorespuesta a través de las incompatibilidades HLA a nivel molecular y su implicación al trasplante de progenitores hematopoyéticos de donante no idéntico

Cristina Arnaldos-Pérez 1; Marta Gómez Hernando 2; Juan Torres Canizales 1; Jose Luis Caro 1; Carles Serra 1; Eduard Palou 1; Montserrat Rovira 2; Carmen Martínez Muñoz 2

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Tradicionalmente se ha relacionado la incompatibilidad HLA a nivel alélico con los resultados post- trasplante, pero existe poca información respecto a las diferencias a nivel de epítopos. Actualmente, los métodosin silico predicen los missmatch moleculares (MM) que generan alorreactividad de epítopos HLA reconocibles indirectamente (PIRCHE) ó directamente (HLA-EMMA). Sin embargo, hay poca información sobre cómo los MM influyen en la incidencia de complicaciones en el trasplante de progenitores hematopoyéticos (TPH) de donantes no idénticos.
Objetivo:Analizar la relación entre los MM y la reconstitución linfocitaria temprana con la incidencia de enfermedad injerto contra receptor (EICR) y/o recaída en pacientes que recibieron TPH no idéntico en nuestro centro entre 2018-2020.
Materiales y métodos:37 pacientes receptores de TPH haploidéntico (n=15) o un TPH de donante no emparentado con 1-2 diferencias HLA (n=22) fueron incluídos. Los MM fueron calculados mediante los algoritmos PIRCHE y HLA-EMMA en dirección Graft vs.Hosty Host vs.Graft(HvG). Linfocitos absolutos (ALC) y monocitos fueron recogidos entre los días +15-90 post-TPH.
Resultados:La media de edad fue de 54 años y la del seguimiento post-TPH fue de 692 días [91-1307]. La supervivencia global a 2 años fue de 74,5% (IC95%:0.564-0.859). Un MM-PIRCHE menor de 5 MM en el sentido HvG en clase-I se asoció significativamente a EICRa (p=0,024). Pacientes con mayor MM-PIRCHE clase-I en sentido HvG (>5MM) tenían una menor tasa de recaída (p=0,042) y un incremento de ALC al día
+60 post-TPH (850células/µl) comparado con aquellos con MM-PIRCHE bajo (<5MM) (250células/µl).
Conclusiones:MM en la dirección HvG están relacionados con complicaciones post-TPH como EICH o recaída, y podrían ser útiles para definir estrategias en la selección de donantes ó de tratamientos post-TPH. Sin embargo, es necesario ampliar estudios que permitan confirmar su implicación en el los resultados del trasplante, así como en la reconstitución inmune.

## 26.53 Myeloid activation markers analysis (nCD64 and mCD169) in patients with infectious diseases admitted to the intensive care unit.

Iria Arrese-Muñoz 1; Sandra Salgado Perandrés 1; Jessica Muñoz Nuñez 1; Sara Briongos Sebastian 1; Luis Chiscano-Camón 2; Adolfo Ruiz-Sanmartín 2; Juan Carlos Ruíz 2; Mónica Martínez-Gallo 1

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Innate immune cells use a variety of pattern recognition receptors (PRRs) to inspect their environments and activate myeloid cells as an early response in front of bacteria or viruses. CD64 expression increases on neutrophils during bacterial infections and CD169 increase the expression on monocytes during viral infections.
The study of myeloid activation markers (nCD64 and mCD169) in the first 48h after admission to the ICU and after 10 days may be useful as a biomarker of etiological classification and progression of the immune response to infection.
We studied the expression of mCD169, nCD64 and HLA-DR by flow cytometry in two groups of adult patients: bacterial infection (n=9) and SARS-Cov2 viral infection (n=20). Clinical and analytical variables were collected to classify patients into groups.
Mean Fluorescent Intensity (MFI) of the three different parameters were collected. For mCD169 a cut-off point 0.97 was established (sensitivity (65%) and specificity (88%)). For nCD64 a cut-off point 2.04 was established (sensitivity (88%) and specificity (90%)) and for HLA-DR a cut-off point 6.68 was established (sensitivity (66%) and specificity (75%)).
Sixty percent of patients with SARS-CoV-2 infection showed elevated intensity levels of mCD169. In the group of patients with bacterial infection only one patient was positive. Regarding nCD64, 89% of patients with bacterial infection showed expression levels above the cut-off point, which decreased at 10 days (10%). We found that 2 patients with viral infection were low positive for this marker, becoming negative at 10 days. The expression of HLA-DR in monocytes is decreased in 66.7% of patients with bacterial infection and in 25% of patients with viral infection. Of these, 82% recovered expression.
The study of CD169 expression on monocytes and CD64 on neutrophils confirms the importance of these markers to evaluate a viral and bacterial immune response.

## 27.54 Atypical presentation of cryoglobulinemic vasculitis. Importance of minimal temperature variations and small IgM monoclonal components when testing for cryoglobulins.

Elionor Lynton Pons 1; Patricia Moya 1; Yolanda Álvaro 1; David Lobo 1; Daniel Albert 1; Esther Roe 1; Ivan Castellví 1; Cándido Juárez 1; Héctor Corominas 1; Esther Moga 1

*1 Hospital de la Santa Creu i Sant Pau*

Introduction.
Cryoglobulinemic vasculitis is a small vessel vasculitis manifesting clinically with the classical triad of purpura, arthralgia and weakness. An atypical symptomatic presentation (livedo reticularis), an undervalued small IgM monoclonal component and false-negative cryoglobulin test result led us to a difficult definitive diagnosis.
Clinical case.
A 79-year-old woman was referred to our hospital with long-evolution low-grade fever, palpable purpura, arthralgia and tickling cough. Regarding the pandemic situation, her first diagnosis was COVID because of a positive SARS-CoV-2 PCR and other parameters supporting that diagnosis. Nevertheless, months later she returned with wrists and shoulders pain and, eventually, livedo reticularis involvement in both lower extremities.
Laboratory test results were: cryoglobulins 71 mg/dL, IgG 282 mg/dL, IgA 90 mg/dL, IgM 285 mg/dL, C3 66.30 mg/dL and C4 1.98 mg/dL. An immunofixation demonstrated the presence of an IgM monoclonal component that could not be detected by capillary electrophoresis. Meanwhile, skin biopsy resulted to be compatible with polyarteritis nodosa. The differential diagnosis was polyarteritis nodosa vs cryoglobulinemic vasculitis.
A second cryoglobulin test result was negative and given the patient's biopsy and clinical presentation the diagnosis was polyarteritis nodosa. Nevertheless, worsening of the patient's health condition, the incongruous results in cryoglobulin tests and regarding the small IgM monoclonal component made us to reconsider the diagnosis. A qualitative cryoglobulin test done strictly at 37-38 ˚C with preheated tubes even at the time of blood collection and immediate sample processing was required to confirm the cryoglobulinemia and the patient was finally diagnosed of cryoglobulinemic vasculitis.
Conclusions.
Cryoglobulinemic vasculitis is a complex disease that, in some cases, should be considered even when clinical manifestations and/or laboratory determinations are not supporting the diagnosis, especially when an IgM monoclonal component is involved regardless of component size.

## 28.55 Anti-Scl-70 antibodies: Comparison of two methods and clinical relevance

Andrés Baucells de la Peña 1; Anaís Mariscal Rodríguez 1; Yolanda Álvaro Gargallo 1; Elisabeth Moltó Lacosta 1; Verónica Calahorro Aguilar 1; Cándido Juárez Rubio 1; José Luis Tandaipán 2; Iván Castellví Barranco 2; Laura Martínez Martínez 1

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Introduction:
Systemic sclerosis (SSc) is an autoimmune disease characterised by fibrosis and vascular abnormalities of the skin, joints and internal organs. Raynaud phenomenon is often the first manifestation of the disease.
There are two major subgroups of SScbased on the extent of skin involvement: limited (lcSSc) and diffuse (dcSSc). In turn, there are defined autoantibody subsets, that have their own clinical associations and prognosis, which make them into useful diagnostic tools.
Anti-Scl-70 autoantibodies are found in 30–40% of SSc, mainly dcSSc. These patients are at increased risk of developing complications, including pulmonar fibrosisand cardiac involvement, thus anti-Scl-70 are considered a poor prognostic sign.
Material and Methods:
32 serum samples from Sant Pau Hospital patients that tested positive for anti-Scl70 between 2015-2021 either by the line-blot EUROLINE Systemic sclerosis/ ANA Profile (EUROIMMUN) or by the chemiluminescence immunoassay (CLIA) QUANTA Flash Scl-70 (INOVA Diagnostics) were retested with the other method.
We recollected the clinical history of these patients, as well as their ANA pattern tested with NOVA Lite Hep-2 ANA Kit (INOVA Diagnostics)
Results:
25/32 patients were anti-Scl70 positive by both methods. All of them had ANAs titre >320 and were SSc.
5/32 were positive by the line-blot but negative by CLIA. None of them were SSc, but 2/5 had Raynaud and were classified as pre-SSc by the clinicians.
2/32 were positive by CLIA but negative by line blot. None of them were SSc.
Conclusion:
As expected, both methods have a good concordance. When both line-blot and CLIA detect anti-Scl70 antibodies, all patients have a definite diagnosis of SSc. However, when anti-Scl70 antibodies are detected only by one of these methods, none of the patients have a SSc diagnosis. So, when anti-Scl70 antibodies are detected and the clinical diagnosis is uncertain, to retest with a different method is recommendable.

## 29.58 Postbiotic and prebiotic mixture modifies intestinal gene expression in rotavirus-infected suckling rats

Carla Morales-Ferre1,2; Ignasi Azagra-Boronat1,2; Malen Massot-Cladera1,2; Angels Franch1,2; Karen Knipping3 ; Johan Garssen3 ; Margarida Castell1,2; Maria J Rodríguez-Lagunas1,2; Francisco J Pérez Cano1,2

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Rotavirus (RV) is a non-enveloped virus of the family Reoviridaethat causes 20% of diarrhea-associated deaths in children under 5 years. The postbiotic LactofidusTMand the prebiotic mixture of short chain galactoligosaccharides(scGOS)/long chain fructoligosaccharides(lcFOS) have previously been shown to reduce the incidence and severity in a preclinical model of RV-induced diarrhea in suckling rats.
This work aims to identify the mechanisms of LactofidusTMand scGOS/lcFOS during the RV infection. Therefore, the changes in the intestinal gene expression during the peak of diarrhea in a preclinical RV- model of a suckling rats were assessed.
On day 5 of life, Lew/OrlRj rats were orally inoculated with the RV, except the control group, which received PBS (REF). Suckling rats were daily supplemented with the prebiotic mixture scGOS/lcFOS (RV+PRE), postbiotic LactofidusTM(RV+POST) or both (RV+P/P). On day 8, at the peak of infection, a central portion of the small intestine was obtained post-mortem and analyzed by a Microarray using SurePrint G3 Rat Gene Expression v2 8x60K Microarray Kit (Agilent). The fold change of the gene expression and the Biological Processes and Gene Ontology pathways were analyzed and the changes in key target genes were confirmed by Real Time PCR.
The RV infection affected the intestinal gene expression, mostly of genes involved in the immune response (e.g. Oas1a, Oas1k, Irf7, Ifi44, Ifi27, Isg15). The supplementation with the scGOS/lcFOS or LactofidusTM modified some of these genes and the supplementation with both products showed specific changes with respect to the other groups, suggesting a complementary action. All supplemented groups evidenced higher intestinal maturity (e.g. Afp).
In conclusion, the postbiotic LactofidusTM, the prebiotic mixture scGOS/lcFOS and the combination modified the intestinal gene expression of host defensive response and the epithelial barrier maturity. This could explain the reduction in the severity of RV infection observed previously in these interventions.

## 30.56 PATIENT WITH BRUTON'S AGAMMAGLOBULINEMIA AND ASIMPTOMATIC COVID

Franco-Leyva, T[1]; Martínez-Martínez, L[1,2,3]; Lynton Pons, E[1]; Albert Jares, D[1]; De la Calle Martín, O[1,2,3]

*[1]Immunology Department, Hospital de la Santa Creu i Sant Pau, [2]Biomedical Research Institute Sant Pau (IIB Sant Pau), [3]Universitat Autònoma de Barcelona*

We present the clinical case of a male born in 1972. Since his first year of life, he suffered from recurrent respiratory tract infections and developed bronchiectasis. At 15y.o., he presented with purulent pericarditis caused by Streptococcus pneumonia. Profound hypogammaglobulinemia affecting all IgG subclasses accompanied by severe B lymphopenia (<0.5%) was then found. The diagnosis of Common Variable Immunodeficiency was established and intravenous immunoglobulin replacement therapy was instituted. In 2009, he moved to Barcelona and consulted with our department. The initial diagnosis was challenged and X- linked agammaglobulinemia (XLA) was suspected. We found low levels of the Btk protein expression. The analysis of the BTK gene showed the missense mutation c.G863A (p.Arg288Gln) in hemizygous. This mutation had been previously associated with XLA.
In September 2020, during the COVID-19 pandemic, he was admitted to our hospital for intense abdominal pain and weight loss, being twice positive for SARS-Cov2 PCR tests. He hadn't suffered from any symptoms related to lower respiratory tract infection nor COVID-19 such as dyspnea, desaturation, ageusia, or anosmia. During his hospitalization, he persistently had low IgG and fever, which was attributed to his underlying disease. Although he never showed positive SARS-Cov-2 antibodies, we detected specific T-cell responses against SARS-Cov-2 antigens being the production of interferon-gamma similar to immunocompetent controls.
Unfortunately, during his hospitalization, he was diagnosed with metastatic gastric carcinoma. Firstly, chemotherapy was ruled out because he was categorized as an immunosuppressed patient. However, the demonstration that his T lymphocytes were functional with our in-house SARS-Cov-2 test, allowed him access to immunotherapy with Nivolumab (anti-PD1).

# Lifelong Learning SCI Program 2021

## Curs Immunologia Avançada 2021-2022

**07-10-2021 | 18:00 - 20:00 | Virtual**
**18:00 - 20:00Dissecting human plasma cell diferentiation routes using single-cell RNA sequencing ( Sessió inaugural )**
Professor/a: Marieke van Ham*. Sanquin Blood Supply Foundation and Faculty of Science, University of Amsterdam. | Prof. dr. S.M., Head dept. of Immunopathology*

**25-11-2021 | 09:00 - 20:00 | Virtual**
**09:00 - 20:00Congrés SCI | Advanced Therapies ( Sessió )**
Professor/a: Piotr Trzonzowski*. Department of Medical Immunology, Medical University of Gdańsk | Head Dept and Full Professor*
Professor/a: James Hutchinson*. Department of Surgery, University Hospital Regensburg | Group Leader*
Professor/a: Friedrich Koch-Nolte*. Laboratory of Molecular Immunology Institute of Immunology University Medical Center Hamburg-Eppendorf | Full Professor*
Regulatory Responses Within Allografts
La sang de cordó com a material de partida de teràpies avançades
Professor/a: Sergi Querol Giner*. Banc de Sang i Teixits, Barcelona. Transfusional Medicine Research Group, Vall d'Hebron Research Institute (VHIR), Barcelona | Head Advanced Therapies BST*
Advanced immunotherapies for the management of complications post-hematopoietic stem cell transplant
Professor/a: Joaquim Vives*. Cell Therapy Service, Blood and Tissue Bank (BST), Barcelona | Head of Development Advanced therapies*

**03-02-2022 | 18:00 - 20:00 | Sala 3**
**18:00 - 20:00Taula Rodona ( Sessió )**
Professor/a: M. Jose Mansilla López*. Division of Immunology, LCMN, Germans Trias i Pujol University Hospital and Research Institute, Barcelona | Sara Borell Post doctoral researcher*
Professor/a: Ruben Lopez Vales*. Facultat Biociències UAB | Full professor UAB*
Professor/a: Lidia Sabater Baudet*. IDIBAPS Centre de Recerca Biomèdica CELLEX Laboratori de Neuroimmunologia Researcher*

**03-03-2022 | 18:00 - 20:00 | Sala 3**
**18:00 - 20:00Trained immunity in transplantation and cancer ( Sessió )**
Professor/a: Jordi Cano Ochando*. Laboratorio de Inmunologia Instituto de Salud Carlos III | Scientist*

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# Lifelong Learning SCI Program 2021

## Curs Immunologia Avançada 2021-2022

**28-04-2022 | 17:00 - 20:00 | Sala 3**
**17:00 - 19:30Dia de la Immunologia "Immunodeficiencies" ( Sessió )**
Professor/a: Peter Olbrich . *Pediatrics Dept , Hospital Infantil Universitario Virgen del Rocío, Sevilla | Staff pediatrician*
Genetic testing and genotype-phenotype correlation in primary immunodeficiencies involving JAK/STAT pathway
Professor/a: Roger Colobran Oriol. *Servei d'Immunologia, Servei de Genètica, H. Universitari Vall d'Hebron (HUVH), VHIR, UAB | Head d'Immunogenètics HUVH, Assistant professor UAB*
Professor/a: Laia Alsina Manrique de Lara. *Ud. Inmunología Clínica e Inmunodeficiencias Primarias, Sec. Alergia e Inmunología Clínica pediátrica, H. Sant Joan de Déu| Head Clinical Immunology and immunodeficiencies, S. Joan Déu, Ass. Prof. UB*
Clinical cases: from genetics to targeted treatments

**05-05-2022 | 18:00 - 20:00 | Sala 3**
**18:00 - 20:00Taula rodona ( Sessió )**
Experimental models in Autoimmunity
Professor/a: Joan Verdaguer Autonell. *Immunology Unit, Department of Experimental Medicine, Faculty of Medicine, IRBLleida, University of Lleida | Full professor UdL*
Experimental models of infection
Professor/a: Pere Joan Cardona Iglesias. *Experimental Tuberculosis Unit, Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Universitat Autònoma de Barcelona, Head Dept Microbiology. Associate Professor UAB*
Experimental models of vaccination
Professor/a: Luís Enjuanes Sánchez. *Consejo Superior de Investigaciones Científicas (CSIC) | Research Professor CSIC*

**17-06-2022 | 10:00 - 18:00 | Sala 3**
**10:00 - 18:00Jornada de Recerca per a Residents i Doctorands ( Sessió )**
Professor/a: Pablo Engel Rocamora. *Titular d'Immunologia | Doctor en Medicina i Cirurgia*
Professor/a: Eva Martínez Cáceres. *Professora Agregada d'Immunologia UAB, Cap del Servei d'Immunologia Hospital Germans Trias i Pujol, Vicepresidenta Societat Catalana d'Immunologia, Vicepresidenta Societat Espanyola d'Immunologia*

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# XV CONGRESS OF THE CATALAN SOCIETY OF IMMUNOLOGY (SCI)

SOCIETAT CATALANA D'IMMUNOLOGIA
L'Acadèmia

## ADVANCED IMMUNOTHERAPIES

*Barcelona, November 25 and 26th, 2021*
*on-line meeting*

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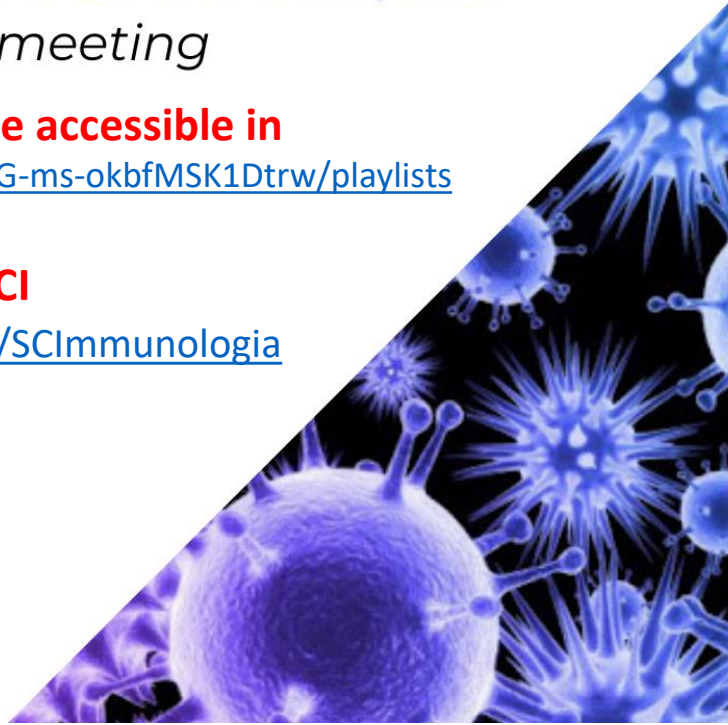

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