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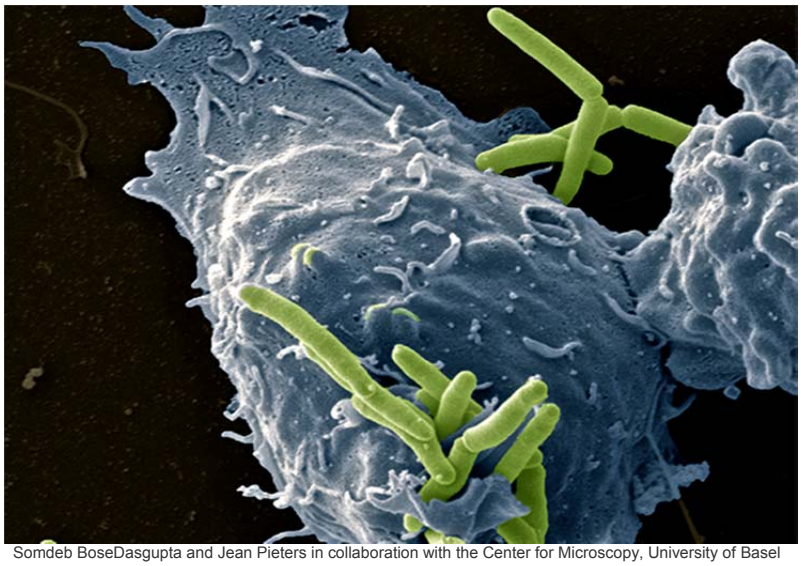
SCI
SOCIETAT CATALANA D'IMMUNOLOGIA

IX CONGRÉS

Societat Catalana d'Immunologia (SCI)

Programa Final

Barcelona, 19 i 20 de Novembre de 2015



Somdeb BoseDasgupta and Jean Pieters in collaboration with the Center for Microscopy, University of Basel

Resposta immunitària contra patògens

Immune response against pathogens

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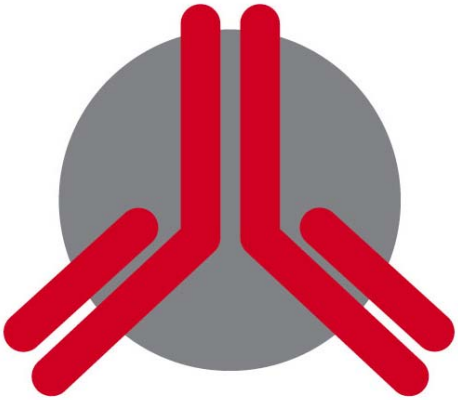

Congress Office:
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Welcome to the Congress,

On behalf of the organising committee, we would like to warmly welcome you to the IXth Societat Catalana d'Immunologia (SCI) Congress. We believe that our meeting will present high level scientific knowledge with the contribution of immunologists and specialists who are experts in this field.

Dr. Cándido Juárez
SCI President

IXth Congress of the Catalan Society of Immunology: Immune response against pathogens, has been accredited by the Catalan Lifelong Learning Board of the Healthcare Professions with 0.8 credit (ref 09/014591-MD, 10/09/2015).

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Content

Scheme first day

Thursday, November 19th	
15:30 17:30	Arrival, Registration and Documentation delivery
16:20 16:30	**Welcome to the IXth CONGRESS of SCI** Dr. Cándido Juárez (President of SCI)
16:30 17:30	Chair: Dra. Annabel Valledor (Fac. Biologia, UB) **Dr. HENRY McSORLEY** University of Edinburgh (United Kingdom) ***"Immune modulation by products of helminth parasites"***
17:30 17:45	Poster viewing – Coffee Break *Posters can be viewed on the 4 electronic panels located in the Hall*
17:45 18:45	Chair: Dr. Ramon Gimeno (Dept. d'Immunitat i Infecció, Institut Hospital del Mar d'Investigacions Mèdiques, IMIM) **Dra. MARGARITA DEL VAL** Centro de Biología Molecular Severo Ochoa (CSIC-UAM) Madrid (España) ***"T-lymphocyte immunity to virus infections"***
18:45 19:45	Oral Communications Session I: **Clinical Immunology** Chairs: Dr. Óscar de la Calle and Dra. Maria José Amengual 18.45h Evaluation of IL12/IFN-γ pathway in pediatric patients with severe intracellular infections. **Esteve-Sole A.** et al. (oral presentaton 1). 18.57h Monitoring CD49d Saturation Levels: A method to Optimize and Personalize Natalizumab therapy in Multiple Sclerosis patients. **Puñet-Ortiz J.** et al. (oral presentation 2) 19.09h Gonosomal mosaicism in monogenic autoinflammatory diseases. **Mensa-Vilaró A.** et al. (oral presentation 3). 19.21h Myeloid-restricted somatic NLRP3 mosaicism in a patient with late-onset but otherwise typical cryopyrin-associated periodic syndrome. **Mensa-Vilaró A.** et al. (oral presentation 4). 19.33h Regulation of MDA5 a protein involved in Aicardi-Goutières Syndrome. **López M.** et al. (oral presentation 5).
19:50	**End of session**

Scheme second day

Friday, November 20th	
08:30 08:55	Arrival, Registration and Documentation delivery
09:00 10:00	Chair: Dr. Francisco José Pérez-Cano (Fac. Farmàcia, UB) **Dra. MARIA LUISA GIL** Universitat de Valencia (España). ***"Candida albicans infection modulates hematopoieis: a new role for TLRs in host immune responses"***
10:00 11:00	Oral Communications Session II: **Immunodeficiencies** Chair: Dr. Cándido Juárez (Ser. d'Immunologia, Hosp. Santa Creu I Sant Pau) 10:00h Newborn screening for Severe Combined Immunodeficiency in Catalonia. A moral imperative. **Castillo-Morillo C.** et al. (oral presentation 6). 10:12h Serum protein electrophoresis allows the detection of a case of complement factor I (CFI) deficiency in an adult patient due to a novel homozygous mutation. **Franco-Jarava C.** et al. (oral presentation 7). 10:24h C4 deficiency due to compound heterozygous mutations in C4 gene compromises innate immune response: A challenging case for next generation sequencing technology. **Colobran R.** et al. (oral presentation 8). 10:36h A complex combined immunodeficiency with CMC and autoimmunity in a GOF-STAT1 patient. **Lozano-Rabella M.** et al. (oral presentation 9). 10:48h Extended inmunophenotype in two patients with human immunodeficiency caused by mutations in the PIK3R1 gene "Activated PI3K-delta syndrome 2". **Martínez-Gallo M.** et al. (oral presentation 10).
11:00 11:30	Poster viewing – Coffee Break *Posters can be viewed on the 4 electronic panels located in the Hall*
11:30 12:30	Chair: Dr. Francesc Rudilla (BST) **Dra. CARLOTA DOBAÑO** CRESIB-ISG, Barcelona (España) ***" Immune response to malarial infection"***
12:30 13:30	**Assemblea General Ordinària** **SOCIETAT CATALANA d'IMMUNOLOGIA** (12.30h – First Call) *Us hi esperem a tots: els socis i no-socis!!*

13:30 15:00	Poster viewing – LUNCH *Posters can be viewed on the 4 electronic panels located in the Hall*
15:00 16:00	Chair: Dr. Oscar de La Calle (HSCSP) **Dra. JULIE DÉCHANET-MERVILLE** CNRS, Universitè de Bordeaux (France) ***" Control of CMV and tumors by stress antigen specific gamma-delta T cells "***
16:00 16:55	Oral Communications Session III: **Innate and Adaptative Immunity** Chair: Dr. Ramón Gimeno (IMIM) and Dr. Jordi Bas (HUB) 16:00h Vaccine-induced but not tumor-derived Interleukin-10 dictates the efficacy of Interleukin-10 blockade in therapeutic vaccination. **Llopiz D.** et al. (oral presentation 11). 16:12h Intratumoral delivery of mTORC2-deficient dendritic cells inhibits B16 melanoma growth by promoting CD8+ effector T cell responses. **Raïch-Regué D.** et al. (oral presentation 12). 16:24h Nanoencapsulated Budesonide Efficiently Induce Human Tolerogenic Dendritic Cells. **Flórez-Grau G.** et al (oral presentation 13) 16:36h Mitochondrial fusion protein Mitofusin 1 is essential for macrophage homeostasis and functional activity. **Marín E.** et al. (oral presentation 14) 16:48h Enhanced interaction of LILRB1 with HLA-I molecules is associated to their dimerization. **Pou J.** et al. (oral presentation 15)
16:55 17:20	Poster viewing – Coffee Break *Posters can be viewed on the 4 electronic panels located in the Hall*
17:20 18:15	Chair: Dra. María José Amengual (Parc Tauli, UAB) **Dr. STEFAN KAUFMANN** Max Planck Institute, Berlin (Germany). ***"Tuberculosis research at the interface between basic and applied immunology"***
18:15 18:30	**Prize to the best communication and poster in the Congress, Sponsored by Miltenyi Biotec Dr. Cándido Juárez (President of SCI).** **End of Congress**

Corporative Abbreviations

BST: Banc de Sang i Teixits
CEMCAT: Centre d'Esclerosi Múltiple de Catalunya
CIBER: Centro de Investigación Biomédica en Red
CIBERehd: Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas
CRC: Centre de Recherche des Cordeliers
CSPT: Corporació Sanitaria Parc Taulí
HIVACAT: Institut de Recerca de la Sida IrsiCaixa i el Servei de Malalties Infeccioses i Sida de l'Hospital Clínic de Barcelona
HUGTiP: Hospital Universitari Germans Trias i Pujol
HSCSP: Hospital de la Santa Creu i Sant Pau
HUVH: Hospital Universitari Vall d'Hebron
IDIBAPS: Institut d'Investigacions Biomèdiques August Pi i Sunyer
IIB: Institut d´Investigacions Biomèdiques Sant Pau
IGTP: Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol
IMIM: Institut Hospital del Mar d'Investigacions Mèdiques
INSA: Institut de Recerca en Nutrició i Seguretat Alimentària
IRB Barcelona: Institut de Recerca Biomèdica Barcelona
IRB Lleida: Institut de Recerca Biomèdica Lleida
PCB: Parc Científic de Barcelona
PRBB : Parc de Recerca Biomèdica de Barcelona
SCI: Societat Catalana d'Immunologia
UAB: Universitat Autònoma de Barcelona
UB: Universitat de Barcelona
UPF: Universitat Pompeu Fabra
VHIR: Vall d'Hebron Institut de Recerca

Abstracts

Oral Communications Session I
Clinical Immunology 1 - 5

1 Evaluation of IL12/IFN-γ pathway in pediatric patients with severe intracellular infections.

Esteve-Sole A.[1,2]; Noguera-Julian A.[3]; Martín-Nalda A.[4]; Cobos E.; Deyà A.; Fortuny C.; Soler-Palacín P.; Gonzalez-Granado L.; Gianelli C.; Cordova W.; Lara R.; Piquer M.; Yagüe J.[6]; Plaza A.M.; Juan M.[6]; Alsina L.

[1]Immunoallergy Unit. Hospital Sant Joan de Deu; [2]Functional Unit of Immunology SJD-Clinic; [3]Infectious Diseases Unit, Pediatrics Department; Hospital Sant Joan de Déu, Fundació Sant Joan de Deu; [4]Pediatric Infectious Diseases and Immunodeficies Unit. Hospital Universitari Vall d'Hebron. Institut; [5]Unidad de Inmunología del Hospital Guillermo Almenara Irigoyen, Lima, Perú; [6]Servei d'Immunologia. Hospital Clínic de Barcelona; [7]Instituto de Investigación I+12, Madrid, Spain; [8]Unidad de Inmunodeficiencias, Departamento de Pediatría, Hospital Universitario 12 de Octubre, Madrid; [9]Departamento de Inmunologia. Hospital Universitario Ramón y Cajal, Madrid, Spain.

***Introduction**:* Severe intracellular infections might underlie a primary immunodeficiency (PID), such as T-cell defects, chronic granulomatous disease and Mendelian Susceptibility to Mycobacterial Disease (MSMD). MSMD is a rare syndrome caused by genetic defects in IL12/IFN-γ pathway, which confers susceptibility to intracellular pathogens in otherwise healthy children. Its diagnosis is difficult due to the complexity and variability of recommended techniques. The aim of our study was to evaluate the immune status of pediatric patients with severe intracellular infections to rule out PID.

***Methods**:* T-cell phenotyping, mitogen proliferation, neutrophil oxidation test (DHR) and IFN-γ /IL12 pathway evaluation were performed. The latter included IL12p70, IFN-γ and other cytokines production (in whole blood culture with BCG +/- IFN-γ or IL12 co-stimulation), IFNGR1/2 and IL12RB1 expression, and STAT1 and STAT4 phosphorylation. Targeted genetic studies (*IFNGR1, IFNGR2, IL12B, IL12RB1, STAT1, IRF8, IKBKG, TYK2, ISG15, RORC, IL23R and CYBB*) were performed when appropriate.

***Results**:* We recruited 32 patients (11 males) with visceral leishmaniasis (n=14), extrapulmonary *Mycobacterium tuberculosis* infection (n=17) and recurrent BCG adenitis (n=1). All patients had normal DHR and T-cell function. IL12/IFN-γ pathway was found normal in 23 patients and abnormal in 9: one patient had an IL12RB1 deficiency, and eight patients displayed partialdefects in IFN-γ production (n=5) or in IFN-γ response (n=3). A complete mutational analysis of the known related genes was performed in patients with partial defects and was normal.

Conclusion: In our series, 9 out of 32 children (28.1%) with severe intracellular infections were diagnosed with functional defects in IL12/ IFN-γ pathway. This PID should be part of the diagnostic work-up of these patients. There is an ongoing effort for the optimization of the diagnostic protocol for IL12/ IFN-γ pathway evaluation to improve its performance, especially in patientsdisplaying partial defects.

2 Monitoring CD49d saturation levels: A method to optimize and personalize Natalizumab therapy in Multiple Sclerosis patients

Puñet-Ortiz J.[1,5]; Vicente Hervás J.[2]; Teniente-Serra A.[1,5]; Cano-Orgaz A.[3]; Mansilla M.J.[1,5]; Quirant-Sánchez B.[1,5]; Navarro-Barriuso J.[1,5]; Fernández-Sanmartín M.A.[4]; Ramo-Tello C.[2]; Martínez-Cáceres E.M.[1,5]

[1]Immunology Division. University Hospital Germans Trias i Pujol; [2]Multiple Sclerosis Unit, Department of Neuroscience. University Hospital Germans Trias i Pujol; [3]Neurology Service, Consorci Sanitari del Maresme; [4]Cytometry Unit, Germans Trias i Pujol Research Institute; [5]Universitat Autònoma de Barcelona.

Background: In Multiple Sclerosis (MS), the consequences of depriving Central Nervous System (CNS) immune-surveillance with Natalizumab -an α4-integrin subunit (CD49d) blocker- have been highlighted by the apparition of Progressive Multifocal Leukoencephalopathy (PML), thus bringing out the necessity on optimizing Natalizumab therapy. Extending natalizumab interval dose (EID) could represent a successful strategy as, hypothetically, it may lead to an increase in immunesurveillance levels within the CNS. There are some clinical and radiological compiled data supporting this new treatment hypothesis but almost nothing at immunological level.

Objective: To implement a standardized methodology to quantitatively monitor CD49d saturation.

Methods: Quantitative Flow Cytometry (QFCM) has been used to measure CD49d, bound Natalizumab and saturation levels of CD49d on peripheral blood lymphocytes. The implemented protocol was validated in a 6-month monitorization of 19 Relapsing-Remitting MS (RRMS) patients treated with 300 mg of intravenous (iv.) Natalizumab every 4 (standard dose; SD) or 6 (extended interval dosing; EID) weeks.

Results: QFCM methodology allowed to compare measurements over long time periods bymaintaining initial conditions. Different CD49d saturation thresholds were observed between patients under SD or EID of Natalizumab (50-70% and 70-95%, respectively). A saturation threshold for CD49d of 50-70% does not decrease Natalizumab clinical and radiological efficacy.

Conclusions: A standardized methodology has been developed to monitor CD49d saturation levels in MS patients treated with Natalizumab. It can be of great utility to monitor individual saturation patterns in response to therapy.

3 Gonosomal mosaicism in monogenic autoinflammatory diseases.

Mensa-Vilaró A. [1]; Santiago Jimenez-Treviño[2]; Angelica Balderrama[3]; Weng Tarng Cham[4]; Giuliana Magri[5]; Eva González-Roca[1]; Estibaliz Ruiz-Ortiz[1]; Fina Rius1; Susana Plaza[1]; María Carmen Antón[1]; Jordi Sintes[5]; Andrea Cerutti[5]; Jordi Yagüe[1]; Osvaldo M. Mutchinick[3]; Eduardo Ramos[2]; Juan I. Aróstegui[1].

[1]Department of Immunology. Hospital Clínic-IDIBAPS. Barcelona. Spain; [2]Department of Pediatrics. Hospital Central de Asturias. Oviedo. Spain; [3]Department of Genetics. Instituto Nacional de Ciencias Médicas y Nutrición. México; [4]Selayang Hospital. Kuala Lumpur. Malaysia; [5]Institut Municipal d'Investigació Mèdica. Hospital del Mar. Barcelona. Spain.

Introduction: Monogenic autoinflammatory diseases (AID) are clinical disorders characterized by anabnormally increased inflammation as a consequence of inherited or de novo mutations. On the other hand, gene mosaicism describes an individual who has developed from a single zygote and has two or more cell types with distinct genotypes. In the past few years, somatic gene mosaicism has been involved in the pathogenesis of different human genetic diseases including monogenic AIDs. However, studies of gonosomal mosaicism contributing to the vertical transmission of genetic diseases are lacking.

Objective: To evaluate the presence of gonosomal mosaicism in parents of patients with AID carrying an apparently de novo germline mutation.

Methods: Genomic DNA was extracted from peripheral blood. Gonosomal mosaicism analyses were performed by amplicon-based deep sequencing (ADS).

Results: A total of 20 families were assessed for gonosomal mosaicism, being three of them positive. In these families, ADS detected variable degree of somatic mosaicism (2.4-12.9%) in the peripheral blood of one of the patients' parents. Two families were afflicted by cryopyrin-associated periòdic syndrome (CAPS) due to the p.D303N and p.T348M NLRP3 mutations, respectively. In both families, the parent carrying the gonosomal NLRP3 mosaicism was absolutely healthy. The third family suffered from Blau syndrome due to the p.R334Q germline NOD2 mutation. In this family, the father carrying the gonosomal NOD2 mosaicism displayed a mild phenotype of Blau syndrome characterized by late onset, granulomatous skin rash and recurrent bilateral anterior uveitis.

Conclusions: We herein describe three families with monogenic AID in which gonosomal gene mosaicism has been the cause of vertical transmission of the disease to the offspring. Our findings add novel evidences about the critical implications of gene mosaicism in the genetic counselling of famílies with dominantly or X-linked inherited monogenic diseases.

4 Myeloid-restricted somatic NLRP3 mosaicism in a patient with lateonset but otherwise typical cryopyrin-associated periodic syndrome

Mensa-Vilaró A. [1]; María Teresa Bosque Peralta[2]; Giuliana Magri[3]; Eva González-Roca[1]; Marta Casorran Berges[2]; Jordi Sintes[3]; Susana Plaza[1]; María Carmen Antón[1]; Estíbaliz Ruiz-Ortiz[1]; Andrea Cerutti[3]; Jordi Yagüe[1]; Concha Delgado Beltran[2]; Juan I. Aróstegui[1].

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Introduction: Cryopyrin-associated periodic syndromes (CAPS) are monogenic autoinflammatory diseases caused by dominantly inherited gain-of-function NLRP3 mutations. Next generation sequencingbased methods have recently shown the important role of NLRP3 mosaicism in the pathogenesis of CAPS.

Objective: To identify the genetic cause of the disease in a patient with late onset but otherwise typical CAPS.

Methods: DNA was extracted from whole blood and from different isolated hematopoietic and non-hematopoietic cells. Molecular analysis was performed by both Sanger sequencing and by amplicon-based deep sequencing (ADS).

Results: The patient is a 64 year-old Spanish male who started at the age of 56 years with a generalized urticarial rash, a gradually worsening oligoarthritis, bilateral sensorineural deafnees, and marked leucocytosis, neutrophilia and increased inflammatory markers. ADS detected the novel p.Gln636Glu NLRP3 mutation, with an allele frequency of 25.0% (mean coverage: 3004x) in whole blood, suggesting for the presence of a somatic mosaicism. The analyses of different tissues showed variable frequencies for the mutated allele (range 0-31.8%) depending on the cell's origin. The novel NLRP3 mutation was restricted to cells of myeloid lineage (24.6% in neutrophils and 31.8% in monocytes) and was absent in cells of lymphoid lineage (0% in B cells, T CD4+ cells and T CD8+ cells). The analysis of different CD34+ hematopoietic progenitor cells revealed that the somatic mutation arose in a fraction of the common myeloid progenitor cells, being absent in the hematopoietic stem cells and in the common lymphoid progenitor cells. The novel NLRP3 variant was located on a highly evolutionary conserved amino acid residue and was predicted to be possibly damaging by the PolyPhen-2 algorithm.

Conclusions: We herein describe a novel somatic NLRP3 mutation as the cause of the disease in a patient with late onset, but otherwise typical CAPS, which was restricted to cells of myeloid lineage.

5 Regulation of MDA5 a protein involved in Aicardi-Goutières Syndrome

Martí López; Lorena Valverde; Antonio Celada; Jorge Lloberas.

Dept. Fisiologia i Immunologia, Fac. Biologia, Parc Cientific de Barcelona, Universitat de Barcelona.

Aicardi-Goutières Syndrome (AGS) is a rare encephalopathy which mimics a viral intrauterine infection and is characterized by calcifications of the basal ganglia, cerebral atrophy and type I IFN in the cerebrospinal fluid. AGS is a heterogenic disease associated with mutations in several genes including the exonuclease TREX1, in any of the genes codifying for the ribonuclease H2, in the phosphohydrolase SAMHD1, in the deaminase ADAR1 or in the cytoplasmic sensor MDA5. The knowledge of these genes is basic for the comprehension of the beginning of the pathogenesis of AGS. In this study we focused in the mechanism of Mda5 expression. We have found that Mda5 is induced by pro-inflammatory stimuli but neither by anti-inflamatory stimuli nor TNF-α, and that the induction of Mda5 is through STAT1 pathway. It has also been shown that Mda5 is stable and upon IFN-γ activation, Mda5 is translated to protein. We also find a role of different TLRs in increasing the expression of Mda5. Furthermore we started to characterize Mda5 induction of transcription, so we focused on the study of its promoter. We did a construct in a luciferase-reporter vector with 1.865bp of the Mda5 promoter, and we find that this region of the promoter is enough to induce luciferase expression.

6 Newborn screening for Severe Combined Immunodeficiency in Catalonia. A moral imperative

Castillo-Morillo C.[1]; Alsina L.[2]; Martín-Nalda A. [1]; Juan M.[2]; Martínez-Gallo M.[3]; Deyà A.[2]; Díaz de Heredia C.[4]; Badell I. [5]; Colobran R.[3]; Soler-Palacin P.[1]

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Background and aims: Newborn screening (NBS) for Severe Combined Immunodeficiency (SCID) has demonstrated to improve survival by means of early stem cell transplantation (SCT). Several European countries are on the way to establish their national NBS programs. We pretend to describe the main epidemiological and clinical issues of SCID and to demonstrate the usefulness of TRECs assay in dry blood spots to detect SCID patients in Catalonia.

Patients and methods: Patients with typical SCID and Omenn syndrome (OS) born at Catalonia were retrospectively reviewed (January 2010 to December 2014). Demographic, clinical and immunological data were reviewed. Guthrie cards from the metabolic NBS shall retrospectively analysed to quantify TRECs value by quantitative PCR (qPCR) with Taqman probes.

Results: Seven patients (five males) were collected during the study period. Typical SCID (5) and OS (2) incidence was 1/56.000 alive newborns. Five cases were non-Caucasian and consanguinity was present in 4/7 families. Three RAG 1-2 deficiencies, 1 ADA deficiency and 1 HLA-II deficiency were detected. In two cases (T-B-) molecular diagnosis was inconclusive. Severe infections (5) and family history (2) led to the diagnosis. Median lymphocyte count excluding OS patients was 1.200/mm^3. Median time from clinical diagnosis to transplantation was 74 days (56-140). Four patients underwent HSCT transplantation (3 MSD/1 MUD; 2 BM/2 CB). All except one engrafted and are alive and well. Three patients died due to infections pre-transplant. Overall survival was 43%. TRECs quantification is still pending.

Conclusions: typical SCID and OS incidence in Catalonia is comparable to other European countries and was associated to a high mortality rate. Moreover, SCID cases may be underdiagnosed. Autosomal recessive B- SCID accounted for all detected cases and consanguinity was demonstrated in almost half of the cases. NBS for SCID should be immediately implemented in Catalonia

7 Serum protein electrophoresis allows the detection of a case of complement factor I (CFI) deficiency in an adult patient due to a novel homozygous mutation

Franco-Jarava C. [1,3]; Colobran R. [1,2,3]; Mestre-Torres J. [4]; Pujol-Borrell R. [1,2,3]; Hernández-González M. [1,2,3]

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Complement factor I (CFI) deficiency is associated to recurrent infections with encapsulated microorganisms, and other diseases like systemic lupus erythematosus, vasculitis or glomerulonephritis. This study describes a novel mutation in CFI causing complete factor I deficiency that leads to a systemic C3 consumption detectable in serum protein electrophoresis (SPE).

The patient is a 53-year-old male controlled in hepatology for non-alcoholic fatty liver disease (NAFLD), who is derived to the clinical immunologist due to **low C3 detected by routine SPE**. Patient anamnesis describes multiple ear-nose-throat (ENT) infections since infancy –requiring tonsillectomy at age 8- and a septic meningococcal infection at age 20. There is consanguinity, his father died of pancreatic cancer and has no siblings. His son, aged 19, presents allergy.

Patient's SPE presented a flat beta2 zone. C4 level was normal, but C3 was reduced (19.3mg/dL). Classical pathway activation was very low and **factor I was absent (<0.7mg/dL)**. Sequencing of CFI gene showed a homozygous deletion of 5 nucleotides in exon 12, causing a frame shift that leads to a truncated protein. **This mutation (c.1450_1454delCTTCA / p.Leu484Valfs*3) was novel** and both his mother and son were heterozygous.

Conclusion: This clinical case describes a novel mutation causing CFI deficiency. Although our patient suffered from recurrent ORL infections and presented a septic meningococcal disease, he had never been studied for complement deficiencies. Thus, these entities might not be as rare as they are thought. Furthermore, this case highlights the importance of the correct interpretation of SPE to detect primary or secondary defects on C3.

8 C4 deficiency due to compound heterozygous mutations in C4 gene compromises innate immune response: A challenging case for next generation sequencing technology

Roger Colobran [1,4,6,7]; Clara Franco-Jarava [1]; Francesc Rudilla [3,7]; Francisco Vidal [2,7]; Eva Campos [3]; Manuel Hernández [1,6,7]; Ricardo Pujol-Borrell [1,4,6,7]; Andrea Martín-Nalda [5,6,7]; Pere Soler-Palacín [5,6,7]; Mónica Martínez-Gallo [1,4,6,7].

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Complement C4 molecule plays a crucial role in immune complex clearance as well as in defense against pathogens. C4 is highly variable since it is codified by two genes, C4A and C4B (99% sequence homology), and shows frequent inter-individual copy-number-variation (CNV). Complete C4 deficiency is exceptional but partial C4 deficiency is a relatively common immune defect due to the high frequency of the C4 half-null haplotypes (1-2% of C4AQ0 and 3-5% of C4BQ0 in Spanish population). Although many individuals with C4 partial deficiency are healthy, C4A deficiency is more associated to autoimmune manifestations, whereas C4B deficiency presents more often with recurrent pneumococcal infections.

Here we report the case of a female patient that at 6-months is referred to HUVH due to recurrent respiratory infections (*Streptococcus pneumoniae*, *Haemophilus influenza*, *Pseudomonas aeruginosa*) and bacteraemia. Immunological studies were normal and the only unexpected result was the lack of IFN-γ production. This result, together with the type of infections, pointed out to a defect in innate immunity. No mutations were found in MYD88 or IRAK4. Next-generation-sequencing (NGS) revealed an heterozygous novel mutation in C4 locus (Leu1358Val). This result prompted us to evaluate the classical pathway activation, which resulted low. Then, we checked that both CA4 and C4B genes were present by PCR-RFLP. Finally, since this single mutation hardly explained the clinical phenotype, we decided to sequence C4 by Sanger. This revealed another novel mutation consisting in a 3-bp deletion in exon 5 of C4. This mutation did not appear in the initial analysis of NGS due to the low frequency of the mutation. Additionally the software couldn't ascribe the mutations to C4A or C4B genes. We are currently studying in which gene are located the mutations (C4A o C4B) and the exact number of copies of C4A and C4B genes in the patient.

9 A complex combined immunodeficiency with CMC and autoimmunity in a GOF-STAT1 patient

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Introduction: Chronic mucocutaneous candidiadis (CMC) is characterized by recurrent or persistent infections of the nails, skin and mucous membranes with *Candida sp*. This disease is related to impaired IL-17 immunity. Several genetic defects have been associated to CMC, being STAT1 mutations the most frequent. These mutations resulted in an increased phosphorylation and gain of function (GOF), inducing higher responses to IFN-γ and causing a Th17 impairment, preventing fungi clearance.

Methods: We presented a 31-years old-man who suffered from recurrent candidiasis since early childhood, with several complications like esophageal stenosis and severe pulmonary infections, as well as autoinmune disorders, combined with a complex immunodeficiency. A progressive lymphopenia and hipogammaglobulinemia was established, so a hematopoetical transplant was performed. Although primary encouraging results, the implant was lost. Th17 were determined by flow cytometry. AIRE, IL17F, RORγT and STAT1 were sequenced. STAT1 and P-STAT1 were analysed by western blot. Dynamic of dephosphorylation of STAT1 was studied by flow cytometry using IFN-γ stimuli combined with tyrosine-kinase inhibitor staurosporine.

Results: Th17 cells were absent in the patient. Genetic analysis performed showed a de novo heterozygous mutation in the exon 14 of STAT1 (c.1154C>T) corresponding to the DNA binding domain, that led to the replacement of tyrosine 385 for a methionine (p.T385M). This mutation has been previously reported. WB analysis demonstrated not only increased STAT1 phosphorylation in response to IFN-γ stimuli, but also higher amount of total STAT1. Dynamic analysis showed a prolonged P-STAT1 expression over time, indicating an impaired STAT1 dephosphorylation.

Conclusions: Our patient presented a de novo mutation in STAT1 (p.T385M). Analysis performed corroborated that p.T385M is a GOF mutation. It has been previously associated with CMC but only in some cases with autoimmunity, so other factors must be studied to be able to understand the aggressive phenotype found in this patient.

10 Extended inmunophenotype in two patients with human immunodeficiency caused by mutations in the PIK3R1 gene "Activated PI3K-delta syndrome 2"

Mónica Martínez-Gallo [1,2,6,7]; Martina García Prat [1,3]; Andrea Martín-Nalda [3,6,7]; Francesc Rudilla [4,7]; José Luis Dapena [5]; Pere Soler-Palacín [3,6,7]; Ricardo Pujol-Borrell [1,2,6,7]; Roger Colobran [1,6,7].

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Two new primary predominantly antibody deficiencies caused by hyperactivation of the PI3K signaling pathway were described in 2014, one consists in a gain-of-function mutations in PIK3CD encoding for the p110-delta subunit result in "**A**ctivated **P**I3K-**d**elta **S**yndrome 1" (APDS1) and the other in activating heterozygous splice site mutation in PIK3R1 which encodes the p85alpha, p55alpha, and p50alpha regulatory PI3K subunits named "**A**ctivated **P**I3K-**d**elta **S**yndrome 2" (APDS2).

We herein report two new patients diagnosed with APDS2 in our center: P1 is a 12 year-old male with clinical onset at the age of 18-months. The patient suffered viral infections by EBV, CMV, and Molluscum contagioum. He also suffered severe EBV-related lymphoproliferation chronic enteropathy and failure to thrive.

P2 is a 15 year-old male with clinical onset at the age of 9 years with short stature for age who suffered respiratory infections including two episodes of pneumonia with bronchiectasis, acute viral infection (mumps). Lymphoproliferation with persistent submaxilar, axillary and inguinal lymphoadepathy and splenomegaly was also observed.

Advanced immunophenotype study in peripheral blood was performed by flow cytometry following FITMaN protocol (HIPC-Protocol). We observe high numbers of transitional B cells (IgD+CD27-CD38+CD24+) with low levels of pre-switch memory (IgD+CD27+) and switch memory B cells (gD-CD27+). In the T cell compartment both patients showed a skewing of peripheral blood CD8+ T cells toward terminally differentiated effector cells.

PIK3R1 splice site mutation (c.1425+1G>A) causing skipping of exon 11 was detected in both cases. The mutation leads to loss of amino acid residues 434–475 in the inter-SH2 domain. Activating mutations of *PIK3CD and PIK3R1* shares clinical features with common variable immunodeficiency (CVID) and autoimmune lymphoproliferative syndrome (ALPS) as shown in our patients. The emergence of these and othe new entities makes necessary to genetically reassess patients now classified as CVID or ALPS without a definitive molecular diagnosis.

11 Vaccine-induced but not tumor-derived Interleukin-10 dictates the efficacy of Interleukin-10 blockade in therapeutic vaccination.

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Blocking antibodies against immunosuppressive molecules have shown promising results incancer patients. However, there are not enough data to define those conditions dictatingtreatment efficacy. In this scenario, IL-10 is a cytokine with controversial effects on tumor growth.Thus, our aim was to characterize in which setting IL-10 blockade may potentiate the beneficialeffects of a therapeutic vaccine In the IL-10-expressing B16-OVA and TC-1 P3 (A15) tumormodels, therapeutic vaccination with tumor antigens plus the TLR7 ligand Imiquimod increasedIL-10 production. Although blockade of IL-10 signal with anti-IL-10R antibodies did not inhibittumor growth, when combined with vaccination it enhanced tumor rejection, associated withstronger innate and adaptive immune responses. Interestingly, a similar enhancement on immuneresponses was observed after simultaneous vaccination and IL-10 blockade in naive mice. However, when using vaccines containing as adjuvants the TLR3 ligand poly(I:C) or anti-CD40 agonistic antibodies, despite tumor IL-10 expression, anti-IL-10R antibodies did not provide any beneficial effect on tumor growth and antitumor immune responses. Of note, as opposed to Imiquimod, vaccination with this type of adjuvants did not induce IL-10 and correlated with a lack of in vitro IL-10 production by dendritic cells. Finally, in B16-OVA-bearing mice, blockade of IL-10 during therapeutic vaccination with a multiple adjuvant combination with potent immunostimulatory properties but still inducing IL-10 led to superior antitumor immunity and complete tumor rejection. These results suggest that for therapeutic antitumor vaccination, blockade of vaccine-induced IL-10 is more relevant than tumor-associated IL-10.

12 Intratumoral delivery of mTORC2-deficient dendritic cells inhibits B16 melanoma growth by promoting CD8+ effector T cell responses

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Dendritic cells (DC) play a pivotal role in the induction and regulation of immune responses. In cancer, DC-based vaccines have proven to be safe and to elicit protective and therapeutic immunological responses.Recently,we showed that specific mTORC2 (mechanistic target of rapamycin complex 2) deficiency in DC enhances their ability to promote Th1 and Th17 responses after LPS stimulation. In the present study, bone marrow-derived mTORC2-deficient (Rictor-/-) DC were evaluated as a therapeutic modality in the murine B16 melanoma model. Consistent with their pro-inflammatory profile (enhancedIL-12p70 production and low PD-L1 expression versus control DC), intratumoral (i.t.) injection of LPS-activated Rictor-/- DC slowed B16 melanoma growth markedly in WT C57BL/6 recipient mice. This anti-tumor effect was abrogated when Rictor-/- DC were injected i.t. into B16-bearing Rag-/- mice, and also after selective CD8+ T cell depletion in wild-type hosts in vivo, indicating that CD8+ T cells were the principal regulators of tumor growth after Rictor-/- DC injection. I.t. administration of Rictor-/- DC also reduced the frequency of myeloid-derived suppressor cells within tumors, and enhanced numbers of IFN?+ and granzyme-B+ CD8+ T cells both in the spleens and tumors of treated animals. These data suggest that selective inhibition of mTORC2 activity in activated DC augments their pro-inflammatory and T cell stimulatory profile, in association with their enhanced capacity to promote protective CD8+ T cell responses in vivo, leading to slowed B16 melanoma progression. These novel findings may contribute to the design of more effective DC-based vaccines for cancer immunotherapy.

13 Nanoencapsulated Budesonide Efficiently Induce Human Tolerogenic Dendritic Cells

Georgina Flórez-Grau [1]; Pau Rocas [2]; Raquel Cabezón [1]; Carolina España [3]; Josep Rocas [4]; Julián Panés [1,3]; Fernando Albericio [2,5,6,7]; Daniel Benítez-Ribas [8].

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Dendritic cells (DCs) are one of the most important antigen-presenting cells that have a crucial role in linking innate and adaptive immune responses.Generation of tolerogenic DCs (tol-DCs) encompass great potential for immunotherapy applications such as autoimmunity, acquired immune diseases and transplantation Diabetes, RA and Crohn's disease. To date, immunotherapeutic strategies involve ex vivo generation of DCs. Hence, these protocols require individualized autologous cells isolation and preparation and are extensive and costly culture protocols in certified GMP laboratories. An alternative to ex-vivo cell generation is the in vivo targeting of specific cell subset in order to modulate their immune function.

In the present work, we evaluated redox sensitive polyurethane-polyurea nanoparticles (PUUa NPs) as drug delivery system for the encapsulation of budesonide (BDS) and analysed their potential to generate tol-DCs in vitro. PUUa NPs containing different BDS doses were incubated with human monocyte-derived DCs and their toxicity and internalization were measured. Moreover, co-stimulatory molecules were evaluated showing that PUUa NPs-BDS presented better efficacy in down-regulation of CD80, CD83 and also for MHCII than free BDS cultured DCs. Anti-inflammatory cytokine IL-10 was analysed after LPS stimulation. Interestingly, its production was significantly higher in tol-DCs generated with PUUa NPs-BDS. Furthermore T lymphocytes activation by DC-cultured nanoparticles was also analysed.

In conclusion, herein we have reported that PUUa NPs constitute a true alternative to potentiate the effect of corticosteroids in human DCs and specifically subset cell targeting. We provide biological evidences that PUUa NPs-BDS are a suitable delivery system to target drugs selectively to DCs. Nowadays; more research is underway to functionalize PUUa NPs with bioactive motifs, in order to target even more specifically DCs and demonstrate the ability of this system to induce tolerance in pre-clinical in vivo animal models of human diseases like autoimmunity or chronic inflammatory diseases.

14 Mitochondrial fusion protein Mitofusin 1 is essential for macrophage homeostasis and functional activity

Eros Marín; Joan Tur; Antonio Celada; Jorge Lloberas

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Mitochondria are dynamic organelles that play an essential role in macrophages and inflammation. Optimal mitochondrial function depends on quality control system tightly couple to fusion and fission. In the fusion process, two outer mitochondrial membrane proteins are needed, Mitofusin 1 (Mfn1) and 2 (Mfn2) and one inner membrane protein, optic atrophy 1 (Opa1). Here we provide evidences that Mfn1 plays and essential role in the homeostasis of macrophages. Elimination of Mfn1 in these cells, using conditional knock-out mice, leads to an impairment of a number of functional activities. As expected, Mfn1-deficient macrophages have an abnormal mitochondrial network formation. The LPS activation in Mfn1-deficient macrophages induces a reduced pro-inflammatory phenotype characterized by decreased reactive oxygen species (ROS) and reactive nitrogen species (RNS) production, but increased expression of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). Also, the metabolism of these cells is affected, showing a decreased ATP production and an increase of autophagy. Despite Mfn2 is the main coordinator of mitochondria and endoplasmic reticulum (ER) function due to his presence in both organelles, we found that the lack of Mfn1, although not localized in the ER, leads to ER stress. This study describes for the first time the critical role of Mfn1 in macrophage homeostasis that could have important consequences during inflammation.

15 Enhanced interaction of LILRB1 with HLA-I molecules is associated to their dimerization

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The Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1), also termed ILT2, LIR-1 or CD85j, is an inhibitory receptor specific for HLA class I (HLA-I) molecules expressed by different leukocyte lineages, i.e. monocytes, macrophages, myeloid dendritic cells (DC), B cells, NK and T cell subsets. LILRB1 has been reported to interact with a wide spectrum of HLA class I (HLA-I) molecules, whose different affinities are determined by allelic polymorphisms as well as by conformational features. HLA-G dimerization and the presence of intracellular Cys residues in HLA-B7 have been shown to be critical for their recognition by LILRB1. We hypothesized that dimerization of classical HLA class Ia molecules, previously detected in exosomes, might enhance their interaction with LILRB1. Based on the use of soluble LILRB1-Fc fusion protein and a cellular reporter system expressing a LILRB1-ζ chimera, we provide evidence that specific intracellular Cys residues and dimer formation in HLA class Ia molecules, transfected in 721.221 cell line, are related to their interaction with LILRB1. In primary monocytic cells poor binding of LILRB1-Fc was observed, independently of high HLA-I surface levels. Interestingly, human cytomegalovirus (HCMV) infection of M2 macrophages promotes LILRB1-Fc binding in non-infected population, and we demonstrated that fusion protein engagement was markedly enhanced upon treatment with type-I Interferon (IFN). This effect appeared disproportionate to the cytokine-induced increase of surface HLA-I expression and was accompanied by the detection of HLA class Ia dimers. Our results support the notion that the regulated assembly of these non-canonical HLA-I conformers during the immune response may enhance the engagement of LILRB1, which could be a relevant feature under pathological conditions, as in the case of HCMV infection.

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The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

1 Baseline differences in minor lymphocyte subpopulations may predict response to fingolimod in relapsing-remitting multiple sclerosis patients

Aina Teniente-Serra [1,2]; José Vicente Hervás [3]; Bibiana Quirant-Sánchez [1,2]; María José Mansilla [1]; Laia Grau-López [3]; Cristina Ramo-Tello [3]; Eva María Martínez-Cáceres [1,2].

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Background: Fingolimod, oral treatment for relapsing-remitting multiple sclerosis (RRMS), is an agonist of sphingosine and its metabolite S1P that binds their receptors, blocking the egress of lymphocytes from lymph nodes.
Objective: Our aim was immunomonitoring of minor peripheral lymphocyte subpopulations in RRMS patients under treatment with fingolimod and correlation with treatment response.
Methods: Prospective study. T- and B-cell subpopulations were analysed using multiparametric flow cytometry in peripheral blood from 14 RRMS patients under treatment with fingolimod at baseline, +1, +3, +6, +9 and +12 months of follow-up.
Results: Most changes in minor lymphocyte subpopulations occurred in the first month of treatment and were maintained until the end of follow-up. The basal percentage of recent thymic emigrants (RTEs) and transitional B cells were lower in responder patients than in nonresponders. After 1 month of follow-up, the percentages of late effector memory $CD4^+$ T cells were higher in responder patients than in non-responders.
Conclusion: Analysis of percentages of RTEs, transitional B cells and late effector memory $CD4^+$ T cells in peripheral blood prior and after +1 month of treatment may predict clinical response to fingolimod.

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The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

2 Marcadores de activacion linfocitaria en pacientes con alcoholismo crónico

Paola Zuluaga [1]; Aina Teniente-Serra [2]; Arantza Sanvisens [1]; Bibiana Quirant-Sánchez [2]; Daniel Fuster [1]; Inmaculada Rivas [3]; Ferran Bolao [4]; Eva María Martínez-Cáceres [2]; Jordi Tor [1]; Roberto Muga [1].

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Los pacientes con trastorno por uso de alcohol (AUD) presentan clínica de inmunodeficiencia secundaria. El efecto del alcoholismo sobre los LT no está bien definido. Estudios in vitro han demostrado que el consumo crónico de alcohol es capaz de disminuir la activación de los LTCD4$^+$ y comprometer la capacidad de LTCD8$^+$ de liberar gránulos citotóxicos y neutralizar antígenos.

Objetivos: Analizar los marcadores de activación CD38 y HLA-DR en pacientes con AUD.

Material y métodos: Pacientes que ingresan para desintoxicación de alcohol en el HUGTiP. Criterios de exclusión: VIH$^+$, cáncer, autoinmunidad, tratamiento inmunosupresor. Al ingreso se realizó el inmunofenotipado en sangre periférica de LTCD4$^+$ y LTCD8$^+$ según la expresión de CD38 y HLADR: (I) dobles negativos: HLA-DR$^-$ CD38$^-$, (II) activación temprana: HLA-DR$^-$CD38$^+$, (III) activación tardía: HLA-DR$^+$CD38$^-$ y (IV) doblemente activados: HLA-DR$^+$CD38$^+$. Las subpoblaciones descritas se compararon con las de 50 individuos sanos.

Resultados: Se incluyeron 54 pacientes (88% H). Edad al ingreso: 48 años (RIQ: 34-54 años). Consumo de alcohol: 145g/día (RIQ: 87-202g).

La media (±DE) de LT, LTCD4$^+$ y LTCD8$^+$ fue de 1.370±674x10^9/L, 845±466x10^9/L y 451±240x10^9/L. Los LTCD4$^+$ se distribuyeron, según su estado de activación, de la siguiente forma, (I): 546±291x10^9/L, (II): 244±213x10^9/L, (III): 43±30x10^9/L y (IV): 15±10x10^9/L

Y los LTCD8$^+$: (I): 315 ±178 x10^9/L, (II): 51 ±52 x10^9/L, (III): 59±61x10^9/L y (IV): 20±16x10^9/L

En comparación con individuos sanos, los LTCD4$^+$ de pacientes con AUD presentaron menor activación temprana (p=0.092) y mayor activación tardía (p=0.076). En cuanto a LTCD8$^+$ los casos con alcoholismo presentaron mayor número de linfocitos activados HLA-DR$^-$CD38$^+$ (p=0.037), HLA-DR$^+$CD38$^-$ (p=0.000) y HLA-DR$^+$CD38$^+$ (p=0.082).

Conclusiones: El fenotipo activado en los pacientes con AUD, sugestivo de inflamación crónica, puede explicar en parte la clínica de inmunodeficiencia secundaria observada.

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The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

3 Hemophagocytic syndrome: the challenge of mono-allelic variants

Laura Viñas-Giménez [1]; Roger Colobran [1]; Aina Aguiló [1]; Andrea Martín-Nalda [1]; Pere Soler-Palacín [1]; Laia Alsina [2]; Jose Luís Dapena [1]; Mónica Martínez-Gallo [1].

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Introduction: Familial hemophagocytic lymphohistiocytosis (FHL) is a life-treating autosomal recessive disease caused by an impaired cytotoxicity. Recently, the synergistic effect of heterozygous and dominant negative mutations in cytotoxic pathway has been described as new inherited forms of this condition.
Materials and methods: Functional assays (cytotoxic activity and CTL/NK degranulation), viral-DNA detection and mutation analysis of FHL genes were performed.
Results: We reviewed clinical and laboratory data of three unrelated patients who fulfilled HLH2009 diagnostic criteria. Low cytotoxicity and impaired NK-degranulation were seen in all at disease onset. Heterozygous UNC13D gene mutation (R1075Q) was present in P1 and heterozygous STXBP2 gene mutation (R190C) in P2. In P3 we identified two SNPs in heterozygosity in the UNC13D gene with likely predicted deleterious effect. Virological tests revealed parvovirus infection in P1 and EBV in P2 and P3. All patients relapsed at different times after treatment. In P3 it should be noted the subcutaneous paniculitis T-cell lymphoma development concomitant with HLH reactivation.
Conclusions: Mono-allelic mutations in FHL genes may cause a homeostatic imbalance of cytotoxic cells leading a frank HLH in a context of viral infection. Syndrome reactivation was mainly seen as an FLH flare but in P3, relapse and evidence of T-cell lymphoma matched in time. These observations suggest that individuals with mono-allelic variants could relapse with a FHL phenotype but also with other associated complications as lymphoma.

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The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

4 Different behaviour of the free and total antibodies against TNF-α blockers (Infliximab and Adalimumab)

María Teresa Sanz-Martínez; Noelia Benítez; Anais Mariscal-Rodríguez; Cándido Juárez; Esther Moga.

Hospital de la Santa Creu i Sant Pau.

Objective: The overproduction of TNF-α in a variety of chronic inflammatory diseases can be inhibited by TNF-α-blockers (anti-TNF-α antibodies) like Infliximab and Adalimumab. The long term effectiveness of TNF-α-blockers is strongly influenced by bioavailability, pharmacokinetics and immunogenicity of the agents. An important tool to assess therapy efficiency is the determination of antibodies against TNF-α-blockers serum levels (anti-drug-antibodies, ADA). It is thought that ADA functionally neutralizes the therapeutic antibodies or induces their rapid elimination. We investigated if there are some differences between the presence of free or total ADA with the available drug level in serum.
Methods: A total of 83 samples were included in this study. Forty-one samples from patients treated with Adalimumab were analysed by Promonitor®-ADL, Promonitor®anti-ADL and Gegan TNF-α-blocker (ADA) ELISA Adalimumab Immundiagnostik and forty-two samples from patients treated with Infliximab were analysed by Promonitor®-IFX, Promonitor®anti-IFX and Gegan TNF-α-blocker (ADA) ELISA Infliximab Immundiagnostik.
Results: In the adalimumab group a total of 9 patients with drug levels <0.024µg/ml showed free and total antibodies; 25 patients, with levels from 1.97-12µg/ml (mean 6.88), had no antibodies and 7 patients, with level from 0.33-2µg/ml (mean 1.11) except for one patient (level<0.024µg/ml), had total antibodies without free antibodies. In the Infliximab group 19 patients not showed antibodies, 3 patients had antibodies and 20 patients had total but not free antibodies but unrelated to drug levels.
Conclusions: A subgroup of samples treated with Adalimumab in subtherapeutic range (indeterminate-2µg/ml) has total ADA but no free ADA. We postulate that this subgroup belongs to an earlier stage to present free ADA. Current algorithms propose that patients with subtherapeutic range without presence of free ADA are candidates for increase dose/frequency. We propose that this subgroup would be candidates for drug change. This effect would not happen with patients treated with Infliximab.

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The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

5 Characterization of tumor cells and their interactions with the immune system in malignant pleural effusions

Juan C. Nieto [1]; Carlos Zamora [1]; Iñigo Espinosa [2]; Monica Pascual [2]; Cristina Bertolo [2]; Eulalia Esteva [2]; Virginia Pajares [3]; Ana M. Muñoz [3]; Jaime Prat [2]; Cándido Juárez [1]; Silvia Vidal [1].

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Malignant pleural effusions (MPEs) are mostly caused by carcinomas in the lung, breast, or ovary, or by lymphomas. To study the phenotype of tumor cells and their interactions with the immune system in the pleural compartment, we applied multicolor flow cytometry to 16 MPEs and 6 non-malignant pleural effusions. Tumor cells were gated as $EpCAM^{+}CD45^{-}$ and each $CD45^{+}$ leukocyte subset was identified based on the characteristic morphology (size and granularity) and the expression of specific lineage markers (CD14, CD3, CD20, CD16). The number of $EpCAM^{+}CD45^{-}$ cells and leukocyte subpopulations in flow cytometry correlated strongly with the results of the cytological block examination ($R=0.933$, $p<0.001$). Lymphocytes and macrophages were the predominant leukocytes in MPEs of lung, breast and ovary tumor origin. A higher number of tumor cells/ml was associated with an increased presence of neutrophils ($R=0.704$, $p=0.003$). In addition, the levels of EpCAM expression on tumor cells correlated with the number of lymphocytes/ml ($R=0.901$, $p<0.001$). Tumor cells in MPEs of breast cancer patients expressed lower carcinoembryogenic antigen (CEA) levels than the homologous cells in lung cancer patients (fluorescence intensity: 6.35±2.5 vs. 55.42±10, $p=0.008$). Using flow cytometry, we were able to establish the primary tumor origin of the MPEs and the association of certain subpopulations of leukocytes with the amount and phenotype of tumor cells in MPEs.

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The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

6 Microarray validation in the search for genomic biomarkers for tolerogenic dendritic cell-based therapies in autoimmune diseases

Juan Navarro-Barriuso [1]; María José Mansilla [1]; Bibiana Quirant-Sánchez [1,2]; Aina Teniente-Serra [1,2]; Joan Puñet-Ortiz [1]; Raian Contreras-Cardone [2]; Cristina Ramo-Tello [2]; Eva María Martínez-Cáceres [1,2].

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Background: In many autoimmune diseases, such as multiple sclerosis or rheumatoid arthritis, a breach of tolerance against determined self-peptides leads to a complex and pathologic disorder of the immune system. Novel tolerogenic dendritic cell (tolDC)-based therapies, generated with several strategies such as vitamin D3, dexamethasone or rapamycin treatment, are currently postulating to become promising therapeutic alternatives to conventional and unspecific treatments for autoimmune diseases by their potential ability to restore tolerance against the peptide they present. In order to guarantee the safety and tolerogenicity of tolDC prior to administration into patients, fast, reliable and robust biomarkers, such as the discovery of Differentially Expressed Genes (DEG), becomes mandatory.

Objective: To select and validate DEG as potential and reliable biomarkers to characterize vitamin D3- (vitDC), dexamethasone- (dexaDC), and rapamycin-induced tolDC (rapaDC).

Methods: A microarray study was performed in order to select five DEG in vitDC, dexaDC and/or rapaDC, compared to both immature (iDC) and mature dendritic cells (mDC). Five monocytederived DC differentiations of iDC, mDC and the three conditions of tolDC were generated and characterized phenotypically and functionally (inhibition of allogeneic peripheral blood mononuclear cells), and RNA was extracted in order to obtain its cDNA and finally analyze the expression of the selected DEG by qPCR.

Results: Two DEG in vitDC (logFC 1.47 ± 0.96 and 0,897 ± 0.57 respectively) and one in rapaDC (logFC 1.19 ± 0.59) were preliminary validated. Statistical significance was reached for the first case ($p < 0.05$). No DEG could be validated in either dexaDC or in the three tolDC conditions at the same time.

Conclusions: The results suggest that it is possible to use DEG as biomarkers to fast and reliably characterize tolDC as safe and tolerogenic cellular products. Nevertheless, sample size should be incremented first in order to confirm these results

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7 HLA-DRB5 CNVs (copy number variations) in patients with Multiple Sclerosis

E. Azucena González Navarro [1,2]; Begoña Fernández [2]; Mireia Antón [1]; Diego Archila [3]; Carles Serra-Pagés [1,2,3]; Pablo Villoslada [1,2]; Manel Juan [1,2,3].

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Structural variations are recognized as a rich source of genetic heterogeneity in the human genome, being copy number variations (CNVs) a major element of polymorphism. Therefore CNVs across the genome are increasingly involved in the disease susceptibility: thus far, variation in gene copy number (CN) has been associated with a number of complex inflammatory and infectious disorders.

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system. Both genetic and environmental factors likely affect the pathophysiology of MS. Genome-wide association studies of multiple sclerosis have confirmed the HLA-DRB1*15:01 allele as the major MS risk allele. Several independent groups have successfully identified patterns of gene expression that are altered in subjects with MS compared to healthy control subjects. CNVs can directly influence gene expression through dosage effects where more copies of the gene produce greater expression. HLA-DRB5 is present only in the HLA-DRB1*15 and HLA-DRB1*16 genetic haplotypes.

We hypothesized differences in CNVs of HLA-DRB5 amongst MS patients and healthy controls defining a possible relation with an increase in MS incidence.

In this study, we determined HLA-DRB5 CNVs in genomic DNA by using Real Time PCR of a mix of unlabeled PCR primers and a TaqMan probe in 96 Multiple Sclerosis (MS) patients and 66 controls. From a control gene coding RNAseP, another TaqMan assay was used, following the supplier's recommendations. Data were analyzed to establish statistically significant differences between groups.

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8 Presence of anti-GSTT1 antibodies and graft rejection in liver and kidney transplantation

Marta Español-Rego [1]; Milagros García-Ormaechea [1,2]; Jaume Martorell [1]; Eduard Palou [1]; Guadalupe Ercilla [1]; Odette Viñas [1,2].

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Introduction: Theta 1 Glutathione S-transferase (GSTT1) is an enzyme involved in cellular detoxification, catalyzing the conjugation of toxic elements, highly expressed in liver, kidney and erythrocytes and to a lesser extent in other tissues. It is encoded by a single gene that could be expressed or not (*null allele*). Approximately 20% of Caucasian population has this *null allele*, lacking GSTT1 enzyme. A GSTT1 mismatch between a positive donor and a null receptor occurs in about 16% of transplants. In these cases, GSTT1 can act like a minor histocompatibility antigen and induce the production of anti-GSTT1 antibodies, whose presence may influence graft dysfunction in liver (mainly *de novo* immune hepatitis) and kidney transplantation.
Aim: The aim of our study was to identify, retrospectively, whether the presence of anti-GSTT1 antibodies was associated to a higher risk of developing greater graft dysfunction and or rejection, compared to controls.
Methods: We included 26 (10 kidney and 16 liver) transplanted patients from Hospital Clínic, Barcelona, from 2010 until 2015, with no donor anti-HLA specific antibodies (DSA). Ten patients (4 kidney and 6 liver transplant) had a positive indirect immunofluorescence (IFI) characteristic pattern of anti-GSTT1 antibodies. We analysed biochemical parameters (liver function, renal function) and clinical features.
Results: Preliminary results showed that 1/4 (25%) of anti-GSTT1 positive kidney transplant and 4/6 (66.6%) of GSTT1 positive liver transplanted patients experimented graft rejection vs 2/6 (33.3%) of kidney and 4/6 (66.6%) liver control patients (p=0.6514 and p=0.0216 respectively).
Conclusion: Although the study group is small, the results confirm previous studies showing a higher risk of graft rejection in liver transplant patients with anti-GSTT1 antibodies and suggest that monitoringthe presence of anti-GSTT1 antibodies in recipients of GSTT1 mismatch liver transplant could help to predict liver graft rejection.

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9 A novel antigen in autoimmune encephalitis

Anaís Mariscal-Rodríguez [1]; M. Ángeles Martínez-Carretero [1]; Elena Cortés [2]; Fidel Nuñez [3]; Carmen Hernández [1]; Elisabet Moltó [1]; Luis Querol [2]; Cándido Juárez [1]; Laura Martínez-Martínez [1].

[1]Immunology-Hospital de la Santa Creu i Sant Pau; [2]Neurology-Hospital de la Santa Creu i Sant Pau; [3]Radiology-Hospital de la Santa Creu i Sant Pau.

Introduction: Autoimmune encephalitis includes diverse syndromes that usually present with subacute memory impairment, psychiatric symptoms, cognitive disturbances, movement disorders and seizures. They associate with the presence of paraneoplastic onconeuronal antibodies or against neuron surface antigens, such as NMDA-R.
Methods: A 48 year-old male was admitted in intensive care unit with decreased level of consciousness. Complete microbiology of cerebrospinal fluid (CSF), toxic-metabolic study, electroencephalogram (EEG) and magnetic resonance imaging (MRI) were performed. Immunologic study was also performed to detect autoantibodies targeting brain structures: indirect immunofluorescence (IIF) on monkey brain and cerebellum, immunoblot against purified antigens and guinea pig cerebellum, human brain, fetal rat cerebellum and HeLa cells extracts, followed by immunoprecipitation and mass spectrophotometry.
Results: Diagnostic work-up did not detect infectious or metabolic causes of altered mental status. EEG did not show epileptiform activity. MRI showed hyper intense bilateral hippocampal lesions in T2-weighted and DWI sequences. In the immunological study the IIF revealed an anticytoplasmic perinuclear pattern in brain and cerebellum that did not correspond to any antigen described before. The search for specificity resulted negative for Yo, Hu, Ri, Ma2/Ta, amphiphysin, CV2, recoverin, Sox1, Titin, NMDA-R, AMPA, GABA or LGI1 and Caspr2 antigens, both in CSF and serum. Immunoblotting demonstrated a band of about 80 kDa only in the cerebrum and cerebellum extracts. Immunoprecipitation and mass spectrometry analysis indicated that it could be corresponded to the ?-adducin protein.
Conclusions: Our patient presents limbic encephalitis of likely autoimmune origin that correlates with an IIF on monkey brain and cerebellum specific pattern. Characterization studies performed to date, point to the protein β-adducin as candidate antigen. Further studies must confirm this information.

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10 Utilitat de la determinació dels autoanticossos anti subunitats E2 de les deshidrogenases mitocondrials en el diagnòstic de cirrosi biliar primària

Joan Climent; Francisco Morandeira; Virginia Mas; Jordi Bas.

Hospital Universitari de Bellvitge

Introducció: La cirrosi biliar primària (CBP) és una malaltia autoimmunitària hepàtica caracteritzada per la presència d'autoanticossos anti mitocondrials. Els principals autoantígens descrits corresponen a les subunitats E2 dels complexes 2-oxo-àcid-deshidrogenasa: anti piruvat deshidrogenasa (PDH), oxoàcid deshidrogenasa de cadena ramificada (BCOADC) i 2-oxoglutarat deshidrogenasa (OGDC). L'objectiu del present estudi és avaluar la utilitat clínica de la determinació de les diferents especificitats.
Material i mètodes: S'han inclòs retrospectivament 96 pacients amb anticossos antimitocondrials positius entre 2013 i 2014: 78 dones i 18 homes, promig d'edat de 62 anys. Se'ls ha realitzat estudi d'anticossos antimitocondrials per tècnica estàndard d'IFI en triple teixit i determinació de la especificitat deshidrogenasa mitjançant dot blot. S'ha estudiat la relació entre el tipus d'autoanticòs i diverses variables clíniques, immunològiques i bioquímiques de funció hepática dels pacients.
Resultats: Dels 96 pacients, 77 han presentat autoanticossos front PDH-E2, 45 front BCOAD-E2 i 19 per a la OGDC-E2. Quaranta-vuit pacients tenen diagnòstic de CBP confirmat en el moment de l'estudi. S'han distribuït els pacients en tres grups: presència d'anticossos front una sola especificitat (N=58), dues (N=31) o les tres (N=7). Les CBP diagnosticades en cada grup són 19 (33%), 22 (71%) i 7 (100%) respectivament (σ^2, p=0,0165). S'ha observat la presència de trastorns tiroïdals autoimmunitaris concomitants en 15 pacients, presentant tots autoanticossos front PDH-E2, en 9 casos com a únic autoanticòs i en 6 associats amb un altra especificitat (5 amb BCOAD-E2 i 1 amb OAGD-E2). No s'ha trobat associació entre resposta a una deshidrogenasa en particular i funció hepàtica.
Conclusions:
La presència d'un resultat positiu per a les tres subunitats és indicativa d'una major probabilitat de diagnòstic de CBP i podria indicar tendència a un desenvolupament més ràpid de la malaltia. L'anàlisi preliminar mostra una associació entre la presència de l'anticòs anti PDH-E2 i el desenvolupament de patologia autoimmunitària tiroïdal.

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11 Monoclonal antibodies used for Multiple Myeloma treatment can interfere in serum immunofixation results

Mireia Fonolleda Ramboux [1]; Cristina Motlló Borrella [2]; Jorge Carrascal Sánchez [1]; Montserrat García Caro [2]; Eva M. Martínez-Cáceres [1]; Albert Oriol Rocafiguera [2]; Aina Teniente-Serra [1].

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Introduction: Daratumumab is a novel human IgG1 kappa subclass moAb against CD38, a transmembrane protein highly expressed on Multiple Myeloma (MM) malignant plasma cells. Due to its antibody structure, we hypothesize that Daratumumab could interfere the follow up by immunofixation of MM patients.

Objectives: To analyse by immunofixation, serum samples from MM patients under treatment with Daratumumab and assess if an IgG MC attributable to the moAb is present. Compare these results with the immunofixations done at the time of diagnosis.

Materials and methods: Serum samples from 6 MM patients under treatment with Daratumumab and in suspected clinical complete remission were analysed by immunofixation using Easy Mask Immunofixation Kit and G26 analyzer from Interlab. These results were compared with the immunofixation done at the moment of diagnosis.

Results: 2 patients with an original IgG kappa MC showed 2 different monoclonal band migration patterns when evaluated at the time of suspected clinical complete remission. The bands corresponded to the initial MC and probably to Daratumumab. 4 patients with an original MC different from IgG kappa presented a small IgG kappa MC in the immunofixation done during Daratumumab treatment. One of those who had to stop moAb therapy due to MM progression, showed a disappearance of the IgG kappa MC at the following control immunofixation (with original MC reappearance).

Conclusions: Patients under Daratumumab treatment may have small IgG kappa monoclonal bands which can interfere in patient's assessment of residual MC. For this reason, patient's treatment should be taken into account to make a correct interpretation of the results, especially in those who originally had an IgG kappa MC. The pattern of migration of the MC should be compared with the pattern of migration of the MC at the moment of diagnosis to avoid a wrong interpretation of the results.

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12 Primary membranous nephropathy: anti-phospholipase A2 receptor (PLA2R) antibodies and clinical follow up

A. Llobell [1]; A. Mensa-Vilaró [1]; L. Rodas [2]; N. Martin [3]; X. Barros [3]; L. Rubio [1]; N. Pérez [2]; J.M. Campistol [2]; L. Quintana [2]; M. Blasco [2]; M. García-Ormaechea [1,4]; O. Viñas [1,4].

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Introduction: Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in adults. It is characterized by the presence of immune complexes, considered to be formed in situ, with circulatingantibodies binding to antigens expressed on glomerular podocytes in the subepithelial space of the glomerular filtration barrier. Approximately 25% of MN patients present an underlying disease such as systemic lupus erythematosus, malignant tumors, exposure to certain drugs or infections, if not, the disease is classified as primary. Different podocyte proteins have been reported as target for the immune response in MN, among them, anti-PLA2R antibodies seem to play a major role, being present in 52-78% of primary MN cases.

Methods: Anti-PLA2R IgG antibodies were measured in 82 serum samples from a cohort of 55 patients from Hospital Clínic (Barcelona) and Hospital Universitario Josep Trueta (Girona) with primary MN (confirmed by biopsy) by an ELISA test (EUROIMMUNE, Luebeck, Germany), and were analysed together with their clinical features.

Results: Anti-PLA2R antibodies were considered positive in 23 patients (41,81%) with a mean value of 119,2 ±165,05 U/mL. 7 out of the 23 positive patients had follow up antibody tests, 2 of which remained positive. Mean proteinuria level at the first test was 7,65 ±1,20 g/24h vs 1,20 ± 0,40 g/24h at the time of the second test (p=0,015).

Conclusions: PLA2R IgG ELISA test shows to be a promising tool for evaluating disease activity and response to treatment in MN although further prospective studies in bigger series are still needed.

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13 NK cell antibody-mediated response against Epstein-Barr virus: role of the NKG2Cbright NK cell subset

Maria López-Montañes [1]; Jordi Sintes [1]; Marcel Costa-García [1]; Miguel López-Botet [1,2]; Aura Muntasell [2].

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Epstein-Barr virus (EBV) is a γ-herpesvirus highly prevalent worldwide. EBV infection is generally asymptomatic although it has been associated to the development of B cell and epitelial malignancies. Among the herpesviruses commonly co-infecting human population, cytomegalovirus (HCMV) can stably reshape the individual NK cell repertoire promoting the expansion of mature NKG2C+ NK-cells displaying enhanced antibody-dependent activation.

In the present study, we have evaluated the interplay between specific serum antibodies and the NKG2C+ NK cell subset in the NK cell response against Epstein-Barr virus (EBV)-transformed B cells.

Upon co-culture with EBV-infected B cells in lytic cycle, the frequency of NK cells degranulating was low and dominated by NKG2A+ NK cell subset, despite the allogeneic nature of the experimental system. Under these conditions, a greater NK cell activation (degranulation, TNF-α and IFN-γ production) was detected in the presence of serum from EBV(+) individuals. Evaluation of ADCC responses against latently infected cells was hampered by the dominant recognition of gp350 adsorbed on the surface of EBV-transformed B cells in vitro. The NKG2Cbright NK-cell subset participated in EBV-specific ADCC responses, displaying comparable degranulation but enhanced TNF-α secretion as compared to NKG2C- NK cells, despite HLA class I surface expression in EBV(+) B cells .

These results highlight the susceptibility of EBV-infected cells to antibody-mediated NK cell recognition. Further studies are required to evaluate the putative influence of HCMV co-infection in the NK cell-mediated responses to EBV.

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14 Antibody-mediated response of NKG2Cbright NK cells against human cytomegalovirus

Marcel Costa-García [1]; Andrea Vera [1]; Manuela Moraru [2]; Carlos Vilches [2]; Miguel López-Botet [1,3]; Aura Muntasell [3].

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Human CMV (HCMV) infection promotes a variable and persistent expansion of functionally mature NKG2Cbright NK cells. We analyzed NKG2Cbright NK cell responses triggered by Abs from HCMV(+) sera against HCMV-infected MRC5 fibroblasts. Specific Abs promoted the degranulation (i.e., CD107a expression) and the production of cytokines (TNF-α and IFN-γ) by a significant fraction of NK cells, exceeding the low natural cytotoxicity against HCMV-infected targets. NK cell-mediated Ab-dependent cell-mediated cytotoxicity was limited by viral Ag availability and HLA class I expression on infected cells early postinfection and increased at late stages, overcoming viral immunoevasion strategies. Moreover, the presence of specific IgG triggered the activation of NK cells against Ab-opsonized cell-free HCMV virions. As compared with NKG2A(+) NK cells, a significant proportion of NKG2Cbright NK cells was FcεRγ-chain defective and highly responsive to Ab-driven activation, being particularly efficient in producing antiviral cytokines, mainly TNF-α. Remarkably, the expansion of NKG2Cbright NK cells in HCMV(+) subjects was related to the overall magnitude of TNF-α and IFN-γ secretion upon Abdependent and -independent activation. We show the power and sensitivity of the anti-HCMV response resulting from the cooperation between specific Abs and the NKG2Cbright NK-cell subset. Furthermore, we disclose the proinflammatory potential of NKG2Cbright NK cells, which could influence the individual responses to other pathogens and tumors.

Work was supported by The Plan Estatal de Investigación Científica, the European Regional Development Fund, the Fundació La Marató TV3, the Red Española de Esclerosis Múltiple, the European Regional Development Fund and the Fundación Asociación Española Contra el Cáncer.

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15 Generation of human myeloid-derived suppressor cells from monocytes and hematopoietic progenitors for their potential clinical application

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Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate in pathological situations and inhibit adaptive immune responses. MDSCs are both a therapeutic target (i.e. in cancer) and a therapeutic tool (i.e. in autoimmunity). This project was aimed at developing efficient methods to generate MDSCs from peripheral blood (PB) monocytes and hematopoietic progenitors for potential clinical applications. To this end, monocytes were isolated from PB samples of healthy donors and $CD34^+$ cells were purified from aphaeresis products. Cells were cultivated for 7 days (monocytes) or 9, 14 and 20 days ($CD34^+$ cells) in the presence of different combinations of cytokines (GM-CSF, IL-6, TGF-β and PGE_2 for monocytes; or GM-CSF, IL-3, IL-6, TPO, SCF and Flt-3 ligand for the $CD34_+$ progenitors). At the end of the cultures the cells were characterizedphenotypically and functionally. At day seven of culture, monocytes efficiently differentiated into monocytic (M)-MDSCs ($CD33^+HLA\text{-}DR^{-/low}CD14^+CD15^-$) which strongly suppressed T-cell proliferation induced by phytohemagglutinin A (PHA). On the other hand, $CD34^+$ cells differentiated into both M-MDSCs and granulocytic (G)-MDSCs ($CD33^+HLA\text{-}DR^{-/low}CD14^-CD15^+$) and the total percentages of MDSCs increased along with the length of culture (31.2±14.3%, 43.1±9.9% and 73.7±9.2% at days 9, 14 and 20, respectively). These MDSCs were immunosuppressive and expressed PD-L1. Finally, in suppression assays using allogeneic PBMCs stimulated with PHA, MDSCs derived from $CD34^+$ cells and those derived from monocytes resulted in different patterns of cytokine secretion. In conclusion, we have established efficient methods to generate human MDSCs under conditions suitable for their potential therapeutic application.

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16 Impaired innate immune response of leukocytes from ascitic fluids of patients with spontaneous bacterial peritonitis

Lídia Perea [1]; Juan Camilo Nieto [1]; Elisabet Sánchez [1,2]; Cristina Romero [2]; Eva Román [1,2]; Maria Poca [2]; Carlos Guarner [1,2,3]; Cándido Juárez [1]; Germán Soriano [1,2,3]; Silvia Vidal [1].

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An ascitic microenvironment can condition the immune response of cells from cirrhotic patients with spontaneous bacterial peritonitis. To characterize this response, we determined the cytokine concentrations in ascitic fluid and analyzed the phenotype and function of ascitic leukocytes at diagnosis and after antibiotic-induced resolution in sterile ascites and ascitic fluid of 2 spontaneous bacterial peritonitis variants: positive and negative bacteriological culture. At diagnosis, a high concentration was found of IL-6 and IL-10 in the ascitic fluid from negative and positive bacteriological culture. The IL-6 concentration correlated with the percentage of neutrophils (R = 0.686, P = 0.001). In this context, positive and negative culture neutrophils had an impaired oxidative burst, and, after the antibiotic, the negative culture spontaneous bacterial peritonitis burst was fully recovered. Higher concentrations of IL-6 and IL-10 correlated with the presence of low granular CD 14low macrophages (R = 20.436, P = 0.005 and R = 0.414, P = 0.007, respectively). Positive culture spontaneous bacterial peritonitis macrophages expressed the lowest levels of CD16, CD86, CD11b and CD206, and HLA-DR, suggesting an impaired global function. Treatment increased all markers on the positive culture macrophages and CD11b and CD86 on negative culture macrophages. In negative culture spontaneous bacterial peritonitis, this increase was accompanied by phagocytic function recovery. The antibiotics then reverted the marker levels on positive and negative culture macrophages to the levels on sterile ascitis macrophages and restored ascitic negative culture cell function.

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17 Clinical application of frozen vitamin D3-tolerogenic dendritic cells

Maria Jose Mansilla [1]; Raian E. Contreras [1]; Juan Navarro-Barriuso [1]; Aina Teniente-Serra [1]; Bibiana Quirant-Sánchez [1]; José Vicente Hervás-García [2]; Sílvia Presas [2]; Cristina Ramo-Tello [2]; Eva M. Martínez-Cáceres [1].

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Background: Tolerogenic dendritic cells (tolDC) loaded with autoantigens is a promising specific cell therapy for the attenuation of pathogenic T cells in autoimmune diseases such as multiple sclerosis (MS). The use of frozen tolDC is an attractive strategy to increase the feasibility of the translation of these cells to the clinics. However, some tolDC products have shown to lose their function after cryopreservation.
Objective: To analyze the *in vivo* functionality of frozen vitamin D3 (VitD3)-tolDC in EAE, the animal model of MS.
Methods: Bone marrow (BM) cells from C57BL/6 mice donors were cultured in presence of GMCSF, LPS and vitamin D3 (VitD3) as tolerogenic agent- for 8 days, and pulsed with (MOG)40-55. Finally, VitD3-tolDC were cryopreserved in medium with 50% FBS+10% DMSO. A total of 1·10^6 thawed tolDC-MOG cells or PBS (sham control) were administrated therapeutically (after the onset of clinical signs) on EAE-C57BL/6 induced mice. Mice were monitored daily for clinical signs. Characterization of immune response was determined in splenic cells at the end of the experiments.
Results: The treatment of EAE-mice with frozen VitD3-tolDC was able to abrogate clinical progression of the disease ($p<0.001$) and reduced MOG-specific response ($p=0.004$) compared to control mice at the same extend than fresh VitD3-tolDC treatment. Furthermore, it was observed that long term treatment with frozen VitD-tolDC (until 74 days of follow-up) was well tolerated and, interestingly, the therapeutic effect of the cells after each administration was progressively increased, extending the interval dosing required. This improvement could be mediated, in part, by an increase of regulatory B cells (Breg, $p=0.015$) and a reduction of NK cells ($p<0.05$).
Conclusion: Our results show that frozen VitD3-tolDC cells could be a feasible therapy for the treatment for MS patients.

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The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

18 The membrane receptor MerTK localizes in the nucleus of human dendritic cells upon *in vitro* tolerogenic treatment

Kyra J. E. Borgman [1]; Daniel Benítez-Ribas [2,4]; Maria F. García-Parajo [3].

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The tyrosine kinase receptor MerTK is a membrane receptor involved in phagocytosis of apoptotic cells, without generating an immune response. However, recent results have showed that *in vitro* generated tolerogenic dendritic cells (tolDCs), used to clinically temper the immune response in cases of autoimmunity, significantly upregulate MerTK gene expression compared to immunogenic DCs. Highly increased levels of the protein were subsequently found on the cell membrane of tolDCs as well as intracellularly. When MerTK on the membrane was blocked, tolDCs regained their ability to generate a strong immune response by stimulating T cell growth and activity. This further indicates a new function for the membrane receptor in inducing tolerance.
Our study aims to elucidate the role of the surprisingly large, around 40% of the total fraction, intracellular pool of membrane receptor MerTK found in tolerogenic DCs.
Using confocal microscopy, we show that the intracellular pool of MerTK almost entirely resides inside the nucleus (Figure 1AB). A significant increase in the levels of nuclear MerTK is observed when comparing tolerogenic to immunogenic DCs (Figure 1C), suggesting a tolerogenic function for not only membranal but also nuclear MerTK. We further show for the first time that a receptor tyrosine kinase resides in the nucleus of healthy primary immune cells, contributing to the hypothesis that these membrane receptors can play a physiological role inside the nucleus.

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19 Heat-killed probiotic bacteria promote IL-10 production in THP-1 non polarized macrophages.

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[1]Institut de Recerca Biomedica Sant Pau; [2]Hospital de la Santa Creu i Sant Pau.

The aim of this study is to evaluate and compare the production of inflammatory mediators by macrophages stimulated with two different TLR ligands or three different heat-killed bacteria.

THP-1 cells were incubated with Vitamin D or macrophage-differentiated with PMA during 72 hours. They were then restimulated during 6, 20 or 40 hours with LTA, LPS, and with *Escherichia coli* ATCC 25922 (E.coli), *Bacteroides fragilis* ATCC 25285 (B.fragilis) and a probiotic mixture (BLS) composed by *Bifidobacterium breve, B.longum, B.infantis, Lactobacillus acidophilus, L.plantarum, L.paracasei, L.bulgaricus and Streptococcus thermophilus*. After incubation with vitamin D, with non-polarizing PMA and after restimulation, the expressions of TLRs and CD14 were analyzed on THP1 cells by flow cytometry. The quantification of TNF-α And IL-10 in the culture supernatant was assessed by ELISA.

Our results showed that PMA- and vitamin D- incubated THP1 produced lower amounts of TNF and IL-10 in the presence of TLR ligands than in the presence of heat-killed bacteria. LTA induced higher TNF-α levels than LPS. Moreover, the restimulation of vitamin D-incubated THP-1 cells with BLS induced a higher and maintained TNF-α and IL-10 production than *E. coli* and *B. fragilis*. Finally, probiotic mixture restimulation induced higher levels of IL-10 in PMA-non polarized THP-1 macrophages than *E.coli* or *B.fragilis*.

In conclusion, the combination of different components in the probiotic bacteria increases the production of anti-inflammatory mediators by macrophages. This observation could explain the beneficial actions of probiotic bacteria in the intestinal immune response.

Posters
Mucosal and Adaptative Immunity 20 - 25

The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

20 Anti-tumoral effects of soluble CD5 in a melanoma mouse model

Inês T. Simões [1]; Fernando Aranda [1]; Esther Carreras [1]; Vanesa G. Martínez [1]; Francisco Lozano [1,2,3].

[1]Grup d'Immunoreceptors del Sistema Innat i Adaptatiu, Institut d'Investigacions Biomèdiques August; [2]Servei d'Immunologia, Centre de Diagnòstic Biomèdic, Hospital Clínic de Barcelona, Barcelona; [3]Departament de Biologia Cel·lular, Immunologia i Neurociències, Universitat de Barcelona, Barcelona.

CD5 is a transmembrane glycoprotein expressed on all T cells and the B1a B-cell subset. CD5 is a signal transducing receptor physically associated to the clonotypic receptor of T (TCR) and B1a (BCR) cells, playing a relevant role in T-cell development and activation by negatively modulating the intracellular signals generated during antigen recognition. To date, the nature of the CD5 ligand/s is a controversial matter, and no human CD5-deficiencies have been reported. In an attempt to further investigate the *in vivo* consequences of blocking CD5 function under physiological and pathological conditions, our group has developed a transgenic mouse line (shCD5Eu.Tg) which expresses a soluble form of human CD5 (shCD5) at pg/mL range. This shCD5 would act as a "decoy receptor" likely blocking the ligand-receptor interactions mediated by membrane-bound CD5 *in vivo* and resulting in a "functional" knock-down. The shCD5Eu.Tg mice showed a decreased frequency of spleen and lymph node Treg cells and peritoneal IL-10^{+}CD5^{+} Breg cells, together with an increased frequency of spleen NKT cells. Accordingly, shCD5Eu.Tg mice showed enhanced immune responses to auto-antigens (collagen, myelin) and cancer cells (B16), a fact that was reproduced in wild-type mice treated with repeated infusions of recombinant shCD5 protein. In this work we further study the mechanism underlying such an enhanced anti-tumoral response in the B16 melanoma model. We found that the decrease in melanoma size/weight in shCD5Eu.Tg mice is associated with increased numbers of tumorinfiltrating lymphocytes and of total and activated CD8^{+} and CD4^{+} cells in tumor draining lymph nodes (TdLN). The decrease in tumor size/weight induced by therapeutic administration of exogenous shCD5 protein to already established melanomas was also accompanied by increased numbers of total and activated T-cells in TdLN. These results suggest that the antitumoral effect of shCD5 is related to its ability to enhance T-cell activation in response to melanoma.

Posters
Mucosal and Adaptative Immunity 20 - 25

The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

21 L'anèrgia de limfòcits B s'associa a respostes T CD4$^+$ Th17 en el model 116C-NOD de Diabetis tipus 1

Leire Egia-Mendikute [1]; Jorge Carrascal [1]; Jorge Carrillo [1]; Berta Arpa [1]; Estela Rosell-Mases [1]; Irma Pujol-Autonell [2]; Raquel Planas [2]; Conchi Mora [1]; Dídac Mauricio [3]; Rosa Maria Ampudia [2]; Marta Vives-Pi [2]; Joan Verdaguer [1].

[1]Departament d'Inmunologia. Universitat de Lleida-IRB de Lleida; [2]Departament d'Inmunologia. Institut d'investigació Germans Trias i Pujol; [3]Departamente d'Endocrinologia. Hospital Germans Trias i Pujol.

El ratolí 116C-NOD és un model de Diabetis tipus 1 espontània que es caracteritza per la producció monoclonal de limfòcits B amb especificitat per un autoantigen encara desconegut present en les cèl·lules beta dels illots pancreàtics. La incidència de Diabetis Autoimmune en aquest model està disminuïda en ambdós sexes en comparació amb ratolins NOD no transgènics. Els estudis inicials van indicar que els limfòcits B dels ratolins 116C-NOD pateixen diversos mecanismes immunes de selecció (incloent supressió clonal i l'anergia) que actuen en el desenvolupament, el fenotip i la funció dels limfòcits B autoreactives, fets tots ells que expliquen el descens de la incidència de la malaltia. Sorprenentment, un anàlisi més precís ha revelat que, malgrat la seva condició anèrgica, els limfòcits B 116C mantenen la capacitat d'expressar algunes molècules coestimulatories després de l'activació i promouen un canvi de fenotip dels limfòcits T cap a Th17. Els resultats també suggereixen que aquest efecte sobre els limfòcits T no es dona només quan els limfòcits T i B interaccionen, si no que sembla que es produeix en les etapes on es dirimeixen els diferents llinatges Th CD4$^+$.

Posters
Mucosal and Adaptative Immunity 20 - 25

The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

22 Changes in intestinal lymphoid tissue by a cocoa diet in rats

Mariona Camps-Bossacoma; Malen Massot-Cladera; Sandra Saldaña-Ruíz; Àngels Franch; Francisco J. Pérez-Cano; Margarida Castell.

Departament de Fisiologia, Facultat de Farmàcia, Universitat de Barcelona, Institut de Recerca en Nutrició i Seguretat Alimentària (INSA-UB), Barcelona.

Background: The interest on how cocoa intake acts on the immune system has recently increased. Previous studies have shown that a 10% cocoa diet has immunomodulatory activity both on intestinal and systemic compartments in rats.
Objective: The aim of the current study was to go into depth on the intestinal effects of cocoa diet byassessing the lymphocyte composition in several immune intestinal compartments.
Methodology: Three-week-old female Lewis rats were fed either a reference diet or an isoenergetic diet containing 10% cocoa for four weeks. Thereafter, lymphocytes from mesenteric lymph nodes (MLN), Peyer's patches (PP) and those from the epithelial compartment (intraepithelial lymphocytes, IEL) were isolated to establish their phenotype by immunofluorescence staining and flow cytometry analysis. Faecal samples were obtained weekly to determine intestinal IgA.
Results: In MLN, the diet with a 10% cocoa significantly increased the percentage of B lymphocytes and TCRγδ$^+$ cells, the latest being due to a higher percentage of CD8αα$^+$ lymphocytes. On the contrary, cocoa diet reduced the TCRαβ$^+$ cell proportion caused by a decrease in the relative percentage of T helper cells. In PP, the cocoa diet also increased the proportion of TCRγδ$^+$ and NKT cells. Moreover, the cocoa intake also induced higher proportion of TCRγδ$^+$ cells into IEL. These changes in intestinal lymphocyte composition were accompanied by a decrease of intestinal IgA concentrations in comparison to the reference group.
Conclusion: These results show that the intake of a 10% cocoa diet for four weeks induces changes in the intestinal lymphocytes profile in young rats. Particularly, it promotes an increase in the proportion of cells involved in innate immunity such as TCRγδ and NKT lymphocytes. Moreover, cocoa diet decreases the Th cell proportion in MLN which could be responsible for the decrease of intestinal IgA concentration previously reported.

Posters
Mucosal and Adaptative Immunity 20 - 25

The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

23 Canvis en la funció de barrera de l'epiteli intestinal, activitat fagocítica i resposta limfoproliferativa en rata durant la lactància

Blanca Grases-Pintó [1,2]; Lidia Marín-Morote [1]; Sandra Saldaña-Ruíz [1,2]; Margarida Castell [1,2]; M. José Rodríguez-Lagunas [1,2]; Francisco J. Pérez-Cano [1,2]; Àngels Franch [1,2].

[1]Departament de Fisiologia, Facultat de Farmàcia, Universitat de Barcelona, Barcelona; [2]Institut de Recerca en Nutrició i Seguretat Alimentària (INSA-UB), Barcelona.

A l'etapa postnatal, la nutrició és un factor crític per a l'establiment de la funció de barrera intestinal i per al desenvolupament i maduració del sistema immunitari (SI) intestinal i sistèmic del nadó. Donada la dificultat de realitzar estudis d'intervenció nutricional en nadons humans, sorgeix la necessitat de disposar de models en animals lactants que permetin la realització d'estudis d'immunonutrició.

L'objectiu d'aquest estudi ha estat aprofundir en el desenvolupament de la resposta immunitària innata -concretament, en la funció de barrera de l'epiteli intestinal i l'activitat fagocítica- i de la resposta immunitària adaptativa -capacitat limfoproliferativa- en rata lactant. S'han utilitzat rates Wistar lactants d'11, 14, 18 i 21 dies d'edat (final de la lactància). Per avaluar la funcionalitat de la barrera de l'epiteli intestinal s'ha mesurat la permeabilitat *in vivo,* mitjançant la quantificació del pas de dextrans per via paracel·lular. L'activitat fagocítica dels leucòcits sanguinis s'ha determinat mitjançant l'assaig Phagotest. Finalment, s'ha quantificat la resposta proliferativa dels limfòcits
esplènics i de ganglis limfàtics mesentèrics (GLM).

Els resultats van demostrar el pas de dextrà de 4 kDa -des de la llum intestinal fins a la sang- en animals d'11 i 14 dies d'edat. Aquest pas ja no es va observar als 21 dies d'edat, fet que indica la presència d'una barrera intestinal més madura. L'activitat fagocítica dels granulòcits en rates lactants (11-21 dies) va ser comparable a la de l'edat adulta. En canvi, els monòcits procedents d'animals d'11 dies van mostrar una activitat fagocítica menor respecte a la resta d'edats estudiades. La resposta proliferativa dels limfòcits esplènics i de GLM va incrementar progressivament durant la lactància, sense assolir els valors propis de l'edat adulta.

Globalment, aquests resultats permeten establir possibles marcadors de maduració de la barrera intestinal i de la funcionalitat del SI intestinal i sistèmic en rata lactant.

Posters
Mucosal and Adaptative Immunity 20 - 25

The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

24 The probiotic strain *B. breve* M-16V promotes rat immunological maturation in early life

Saldaña-Ruíz S. [1,2]; Rigo-Adrover M. [1,2]; Azagra-Boronat I. [1,2]; van Limpt K. [3]; Knipping K. [3]; Garssen J. [3]; Franch A. [1,2]; Castell M. [1,2]; Pérez-Cano F. J. [1,2].

[1]Department of Physiology, Faculty of Pharmacy, University of Barcelona; [2]Institut de Recerca en Nutrició i Seguretat Alimentària (INSA), Barcelona, Spain; [3]Nutricia Research, Utrecht, The Netherlands

Introduction: Probiotics have become a point of interest due to the multiple potential beneficial effects attributed to them. Some probiotic strains have demonstrated their protective role in infectious processes, or even as vaccine adjuvants. *B. breve* M-16V has shown modulatory effects in disorders related with immunity, such as asthma and inflammation.

Objective: The aim of this study was to evaluate the effect of the supplementation with the probiotic strain (*Bifidobacterium breve* M-16V) in the development of the Immune System at intestinal and systemic level during suckling.

Methods: Lewis suckling rats were supplemented p.o. with a daily dose of $4.5x10^8$ CFU *B. breve* M-16V/100 g of body weight since day 6th to day 18th of life. Faecal samples were obtained daily and faecal pH was measured in certain days. On sacrifice day, sample extraction and extemporaneous determinations were performed. Gut wash was obtained for IgA quantification, and intraepithelial lymphocytes (IEL), mesenteric lymph nodes (MLN) and spleen cells were obtained and phenotyped.

Results: The probiotic supplementation of neonatal animals during early life, does not modify their morphological and intestinal variables (body growth, pH or consistency of their faeces); enhances the ability to respond against danger signals (increasing expression of TLR4 in MLN cells) in intestinal and effector intestinal sites, but not at systemic level; promotes the intestinal recruitment and its retention in epithelia (by increasing αEβ7 in MLN cells and IEL); and although does not impact on the immune system at systemic level, it increases the intestinal humoral immune response (by increasing IgA concentration at mucosal sites).

Conclusion: It can be concluded that the probiotic strain *Bifidobacterium breve* M-16Vsupplementation during suckling just during 12 days modulates the development of the mucosal immune response in early life.

Posters
Mucosal and Adaptative Immunity 20 - 25

The authors will attend the poster on **19/11/2015**: 17:30h; **20/11/2015**: 11:00h, 13:30h, 16:55h.

25 Probiotic modulation of immune response in a preclinical model of a double rotavirus infection

Rigo-Adrover M. [1,2]; Saldaña-Ruíz S. [1,2]; van Limpt K. [3]; Knipping K. [3]; Garssen J. [3]; Franch A. [1,2]; Castell M. [1,2]; Pérez-Cano F.J. [1,2].

[1]Department of Physiology, Faculty of Pharmacy, University of Barcelona; [2]Institut de Recerca en Nutrició i Seguretat Alimentària (INSA), Barcelona, Spain; [3]Nutricia Research, Utrecht, The Netherlands

Introduction: Rotaviruses (RV) are the leading cause of severe diarrhoeal disease among infants worldwide. After RV infection, immunity is not complete and less severe re-infections usually occur. This infection can be modulated by nutritional interventions with bioactive compounds, such as probiotics.

Objective: The aim of this study was to evaluate the influence of the probiotic strain *B. breve* M-16V on the immune response developed against a RV first infection and after a second infection.

Methods: Lewis rats were inoculated with SA11 (first RV infection) on 6th day of life and with EDIM (second RV infection) on 17th day of life. Some of them were also orally administered with $4.5x10_8$ CFU *Bifidobacterium breve* M-16V/100 g of body weight/day between d3 and d9. Immunological parameters such as *ex vivo* secreted cytokines (CK) by splenocytes, cytokines concentration in gut wash or colonic gene expression were evaluated after both first and second infections.

Results: The double-infected animals showed a different *ex vivo* ability to secrete CK than the single infected animals (SA11 or EDIM). A dietary intervention with the probiotic enhanced IFN-γ, IL-4, TNF-α and IL-10 production after both first and second infection. IL-4 and IL-10 concentrations in intestinal wash after the first infection were higher in the probiotic supplemented group than in the control groups (infected and non-infected animals receiving vehicle). Infections did not affect any of the studied molecules gene expression in colon, however, the dietary intervention significantly up-regulate TLR2 whereas down-modulate TLR4, occludin and TGF-β gene expression. Mucin and IL-10 gene expression were not modified and IL-4, IFN-γ and foxp3 were very low expressed and therefore undetectable.

Conclusion: *B. breve* M-16V supplementation is able to modulate the immune response against RV infection, and even on a second RV infection, after one week of finishing the supplementation.

2016 Events

Lifelong Learning SCI Program 2016

Data i hora: 5 de febrer de 2016, a les 18:30h.
"New mechanisms that modulate the inflamatory response".
Dra. Cristina López Rodríguez (UPF, Barcelona). Lloc: Auditori Acadèmia de Ciències Mèdiques (Major de Can Caralleu 1-7, Barcelona).

Data i hora: 3 de març de 2016, a les 18:30h.
"Immune and non-immune functions of neutrophils".
Dr. Andrés Hidalgo (Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC, Madrid). Lloc: Parc de Recerca Biomèdica de Barcelona (PRBB), sala Xipre 1ª planta (c/Doctor Aiguader 88, Barcelona).

Data i hora: 7 d'abril de 2016, a les 18:30h.
"Monitorization of memory humoral aloresponse in kidney transplantation".
Dr. Oriol Bestard (Hospital Universitari de Bellvitge. Institut d'Investigació Biomèdica de Bellvitge (IDIBELL). Barcelona). Lloc: Sales Polivalents, Planta 2, de Hospital de la Santa Creu i Sant Pau (c/ Sant Quintí, 89, Barcelona).

Data i hora: 28 d'abril de 2016, dia de la IMMUNOLOGIA, 16h-21h
Tema: Nanotecnologia aplicada a la Immunologia
Una iniciativa de la IUIS (International Union of Immunological Societies) amb la col·laboració directa de la EFIS (European Federation of Immunological Societies). Lloc: Institut d'Estudis Catalans, sala Pere i Joan Coromines. c/del Carme 47. Barcelona.

Data i hora: 5 de maig de 2016, a les 18:30h.
"Detection of immune responses against biological drugs: technical and regulatory aspects".
Dr. Carles Morte (Kymos Pharma Services. Barcelona). Lloc: Hospital Clinic, Sala Farreras Valentí, escales 9-11, (c/Villarroel 170, Barcelona).

Data i hora: 2 de juny de 2016, a les 18:30h.
"Epigenomics and Immune diseases: Mechanisms and Clinical Aplications".
Dr. Esteban Ballestar (Institut d'Investigació Biomèdica de Bellvitge (IDIBELL). Barcelona). Lloc: Sales Polivalents, Planta 2, de Hospital de la Santa Creu i Sant Pau (c/ Sant Quintí, 89, Barcelona).

Data i hora: 7 de juliol de 2016, a les 18:30h.
"Editorial policies and Hot Topics in the European Journal of Immunology".
Dr. Andreas Radbruch (Editor of European Journal of Immunology). Lloc: Auditori Acadèmia de Ciències Mèdiques (Major de Can Caralleu 1-7, Barcelona).

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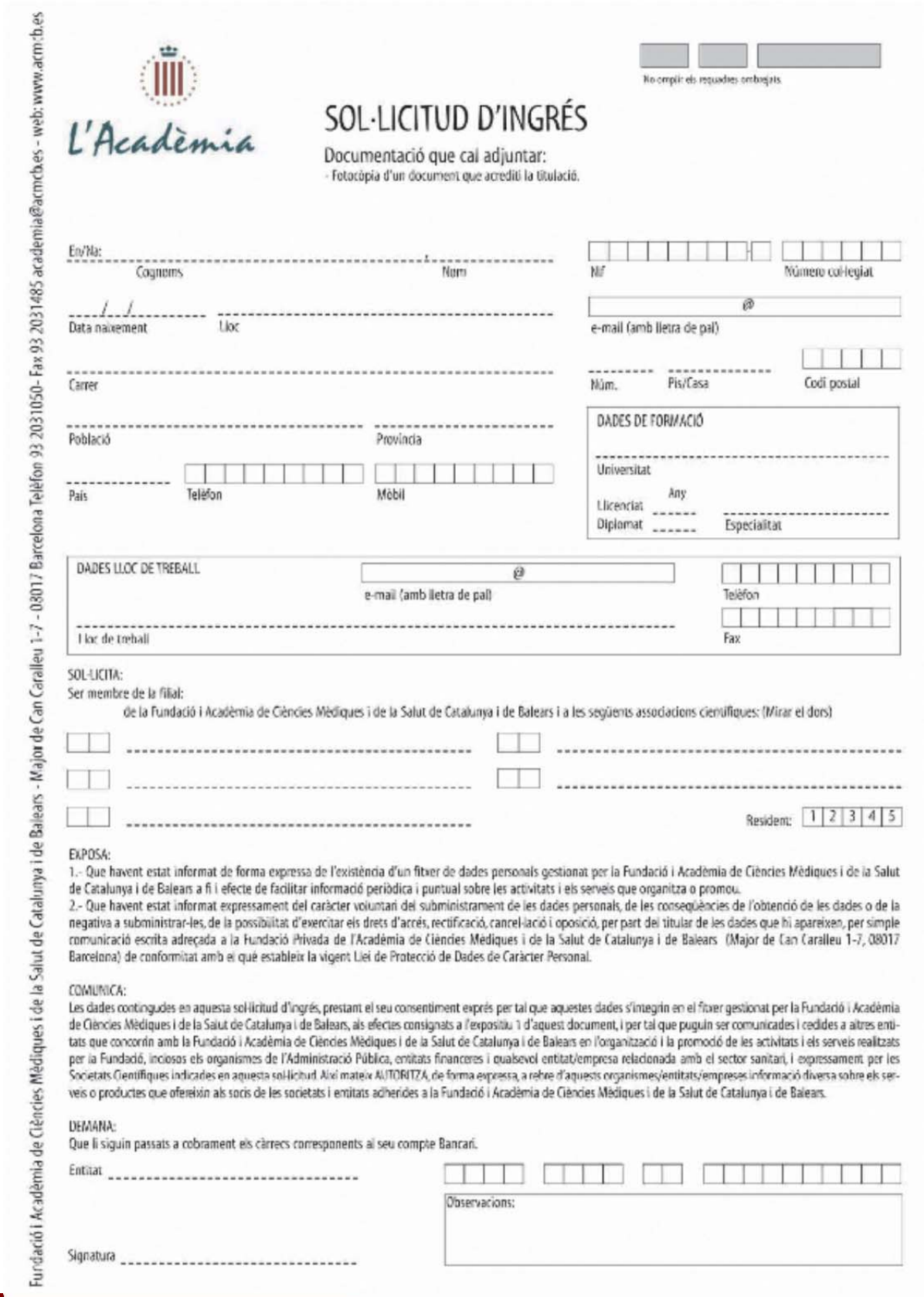

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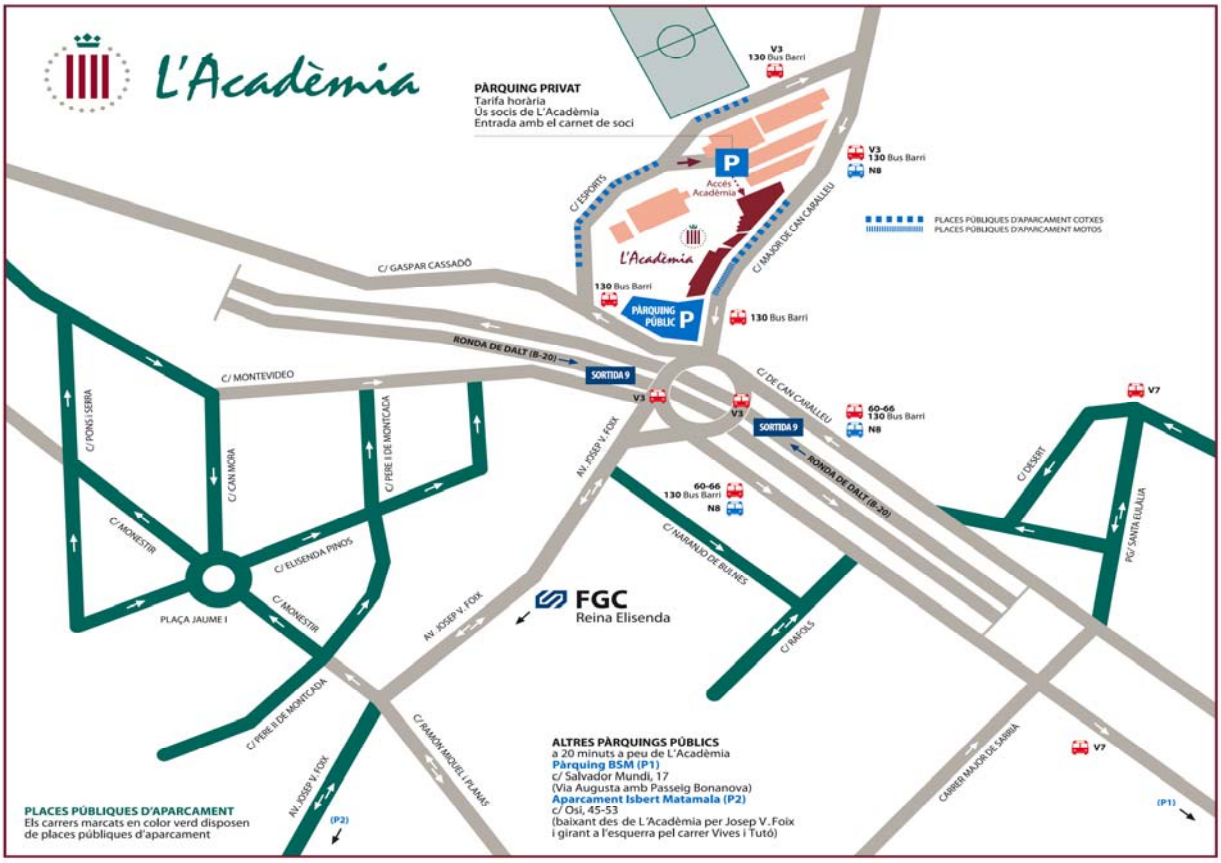

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Transportation:

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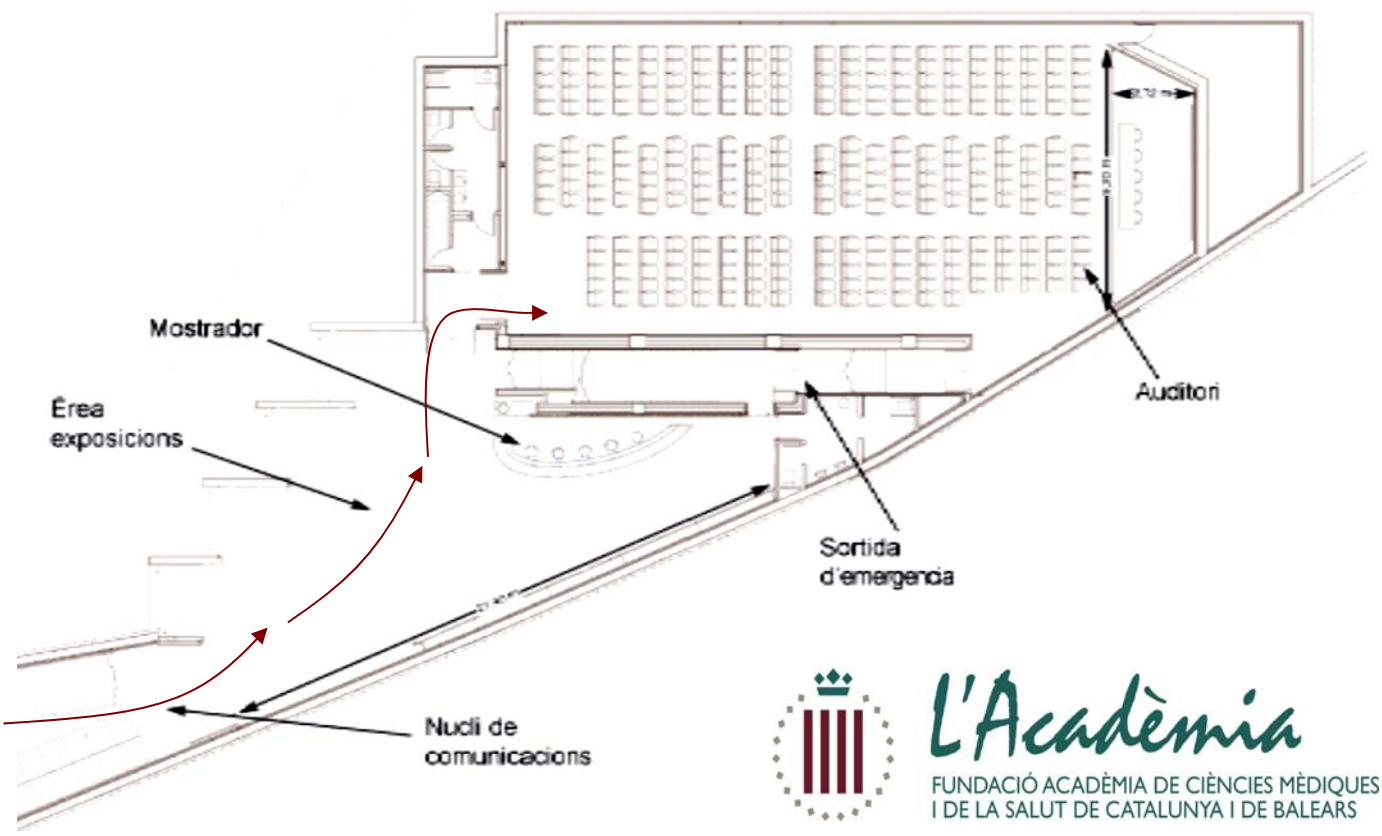
List of participants and authors

Other useful information and notes



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IX CONGRÉS

Societat Catalana d'Immunologia (SCI)

Barcelona, 19 i 20 de novembre 2015

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