# 1st Joint Meeting of European National Societies of Immunology

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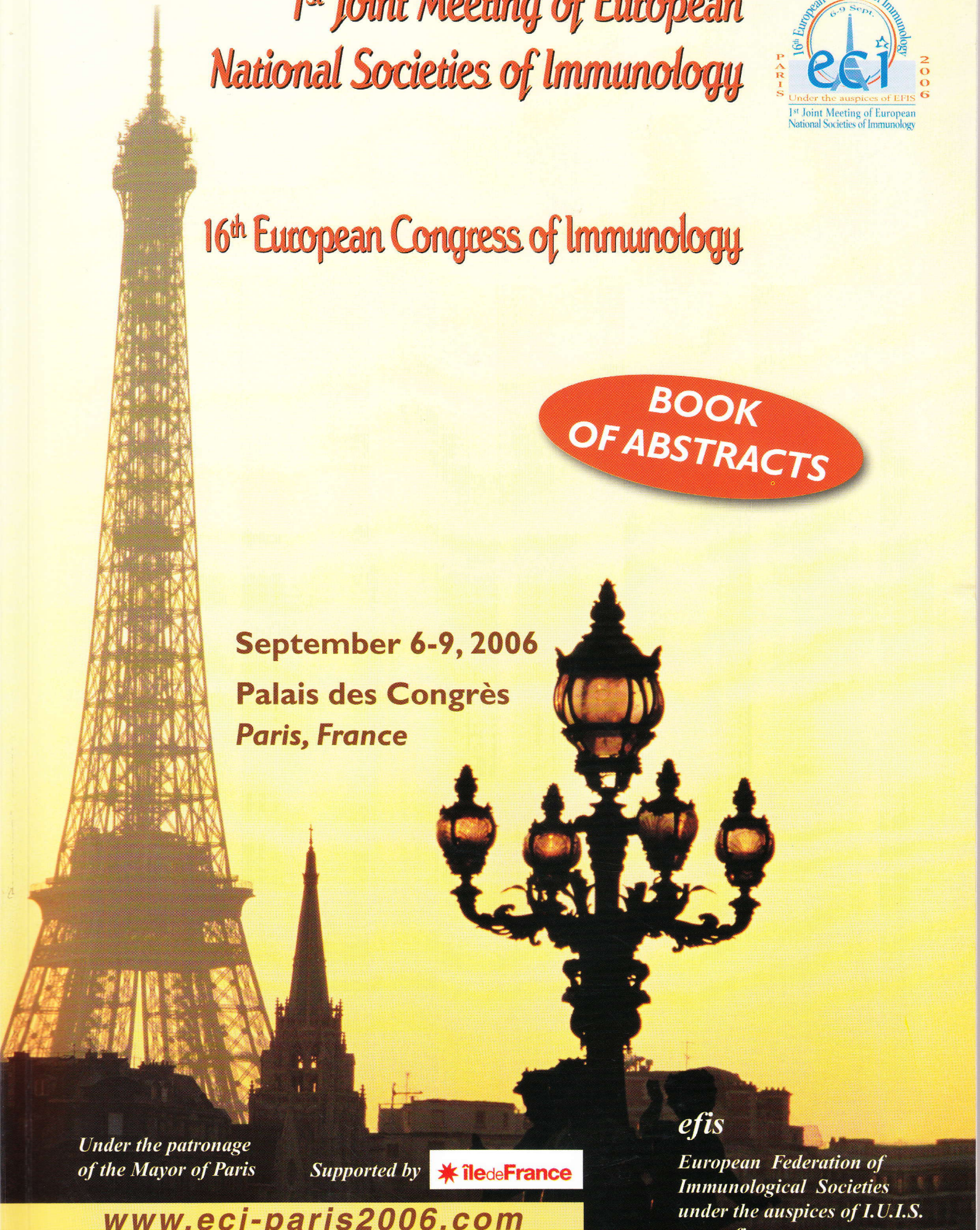
1st Joint Meeting of European National Societies of Immunology

## 16th European Congress of Immunology

**BOOK OF ABSTRACTS**



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### ANTI-ERYTHROCYTE SPECTRIN ANTIBODIES IN MALARIA GABONESES PATIENTS

**Y CHANSEAUD[1], V GUIYEDI[1], C FESEL[2], PA CAZENAVE[1], M KOMBILA[3], S PIED[1] - (1) Institut Pasteur, Paris, France. (2) Instituto Gulbenkian de Ciência, Oeiras, Portugal. (3) Faculté de Médecine, Libreville, Gabon.**

We previously shown in a study done on 146 Gaboneses children infected with *Plasmodium falciparum* [64 uncomplicated malaria (UM), 36 severe non-cerebral malaria (SNCM), 21 cerebral malaria (CM)] and 25 uninfected individuals (UI) that CM is associated with an increase of the diversity of circulating IgG recognising brain antigens. Particularly, 90% of the CM patients exhibit reactivity against a brain protein of 147 kDa. In addition, this reactivity was correlated with high TNFa plasmatic concentrations. The identification of the protein recognised was done by mass spectrometry and allows defining the non-erythroid alpha-spectrin (fodrin) as a candidate brain antigen. The non-erythroid alpha-spectrin shares 60% of amino acid sequences identity with the human red blood cell protein. As autoantibodies recognising red blood cells are frequently reported during *Plasmodium* infection, we quantified the production of anti-spectrin IgG antibodies in the plasma of the cohorts of *P. falciparum* infected children. High levels of IgG to erythroid spectrin was found in UM (mean of the ratio per group-standard deviation: 1,016±0,679) when compared to SNCM (0,874±0,433), CM (0,788±0,526) and UI (0,643±0,285). As shown by Mann-Whitney U tests, differences between group were significant when comparing UM vs UI, UM vs CM and CM vs non-cerebral malaria (SNCM and UM).

### MULTIPLE SCLEROSIS RETROVIRAL ENVELOPE CAUSES INFLAMMATION BY MONOCYTE, DC AND T CELL ACTIVATION

**C LOMPARSKI[1], HL DOUGIER[1], A ROLLAND[1], C BERNARD[2], C VIRET[1], E JOUVIN-MARCHE[1], H PERRON[2], PN MARCHE[1] - (1) Laboratoire d'Immunochimie, INSERM U548, CEA/DRDC, Grenoble, France. (2) Geneuro, Genève, Switzerland.**

The Multiple Sclerosis RetroViral element (MSRV) isolated from MS patients cerebrospinal fluid belongs to the Human Endogenous RetroVirus (HERV) W family which comprises about 2% of the human genome. MSRV envelope protein (ENV) may contribute to initiate and/or exacerbate MS. 1) ENV stimulates Peripheral Blood Mononuclear Cells (PBMC) which display polyclonal expansions of TCR Vb16 T cells supporting a possible superantigen activity. 2) ENV activates PBMC from MS patients blood to produce inflammatory cytokines IFN-g, IL-12p40 and IL-6, in relation with disease severity score. 3) ENV induces human monocytes and dendritic cells to produce inflammatory cytokines through engagement of CD14 and TLR4. In this study, anti-CD14, anti-TLR4 and anti-ENV antibodies block the activation by ENV. For *in vivo* validation in the Experimental Allergic Encephalitis (EAE) model, mice are injected with antigenic myelin peptide and adjuvant (Complete Freund) or ENV protein. Clinical score shows significant EAE symptoms both in mice injected with ENV or adjuvant, and no symptoms in control mice. Anti-ENV antibodies block encephalitis when given together with ENV. Cultures of splenocytes from either ENV or adjuvant treated mice with the myelin antigen lead to IFN-g production, suggesting a T lymphocyte reactivity towards the myelin antigen. In conclusion, ENV can promote *in vivo* inflammation leading to disease similar to EAE. Evaluation of myelin damage in brain and of immune responses from ENV injected mice will provide clue to validate if disease promoted by ENV is similar to conventional EAE.

### ANTI-BETA2-GP-I AND ANTIPHOSPHOLIPIDE ANTIBODIES DURING THE COURSE OF TETANUS TOXOID IMMUNIZATIONS

**L DIMITRIJEVIC[1], I ZIVKOVIC[1], M STOJANOVIC[1], A INIC-KANADA[1], S ZIVANCEVIC-SIMONOVIC[2] - (1) Institute of Immunology and Virology, Belgrade, Serbia and Montenegro. (2) Faculty of Medicine, Kragujevac, Serbia and Montenegro.**

Data which connect vaccinations, with autoantibody production are accumulating nowadays. It is known that tetanus toxin exerts homology with beta2-glycoprotein-I (beta2-GP-I) which is usually citied as target antigen in antiphospholipid syndrome (APS). According to its similarity to cholera toxin, tetanus toxoid could participate in autoimmune status through its potential of polyclonal cell activation. In this report we choose to analyze the effect of exposure to high dose of tetanus toxoid in two different mice strains (Balb/c and C57BL/6) undergone different immunization scheme on generation of anti- beta2-GP-I and antiphospholipide antibodies. Non-treated, CFA-pretreated or glycerol-pretreated mice (females, 10 weeks old) were immunized with high doses of tetanus toxoid (TTd), 3 times in two-weeks intervals, 500 mg/ml, 200 ml/mouse (≈ 30 Lf/dose), subcutaneously mixed with glycerol or alum (Al) as adjuvant. Sera were collected in two-week intervals for twenty-two weeks. Humoral immune response (IgG and IgG subclasses) toward TTd as well as beta2-GP-I, phospholipids and cardiolipin was followed. Tetanus toxoid immunization induced the rise of tetanus toxoid as well as of beta2-GP-I, phospholipids and cardiolipin specific antibodies in all immunized animals. At the level of autoantigen specific antibodies much stronger response was obtained in C57BL/6 mice. Antigen specific secondary response in Balb/c mice was missing in all groups of Al immunized animals. In C57BL/6 mice, antitetanus secondary immune response was omitted only in glycerol pretreated and glycerol immunized animals. Rise and fluctuations in pools of IgG Abs specific for self (beta2-GP-I and phospholipids) were registered in all mice groups. Secondary immune response towards beta2-GP-I and phospholipids was obtained only in C57BL/6 mice in all immunized animals. Highest levels of anti-beta2-GP-I had been achieved in sera of CFA-pretreated Al immunized C57BL/6 mice. Detected fluctuations in the levels of anti-beta2-GP-I and antiphospholipids antibodies presented herein implicate that tetanus toxoid in high doses could be regarded as potential autoantigen which exerts its beta2-GP-I mimicry properties in C57BL/6 mice and its polyclonal cell activator properties in pretreated and Al immunized Balb/c mice. This favors its role in pathological autoimmunity.

### THE ROLE OF G6PD ACTIVATORS ON THE RESISTANCE OF MURINE PERITONEAL MACROPHAGES AGAINST LEISHMANIA MAJOR

**A ZAVARAN HOSSEINI[1], S ZAMANI TAGHIZADEH RABE[2], SAR MESBAH NAMIN[3] - (1) Department of Immunology, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran. (2) Department of Immunology, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran. (3) Department of Biochemistry, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran.**

It has been shown that intracellular NADPH is essential cofactor for cell viability and defence against several infectious agents.Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are susceptible to several infection. Macrophage activation is required to control the intracellular infection include leishmaniasis. In this study,the effect of two G6PD activators (lipopolysaccharide and melatonin) on the nitric oxide (NO) production and the destruction of L.*major in* peritoneal macrophages of *Balb/c* mice was investigated.Cell viability, G6PD activity, amount of nitric oxide production and the rate of amastigotes per macrophages were determined after treatment by G6PD activators. Peritoneal macrophages of BALB/c mice were isolated and treated with lipopolysaccharide (0.25 ng/ml) or melatonin ($10^{-12}$ molar),respectively. The viability of treated macrophages was measured by MTT assay at 540 nm. G6PD activity was measured in the cell suspension were infected with *Leishmania major* amastigotes. After 18 hours NO production was determined by Griess method .This activators were used for study the activation of leishmanicidal activity and changes in number of L. *major* amastigotes in macrophages from day 1 to 7. The results showed that G6PD activators alters G6PD activity, amount of nitric oxide and the rate of amastigotes per macrophage. Treatment by G6PD activators augments destruction of intracellular amastigotes.The number of amastigotes in treated macrophages decreased significantly from day 1 to 7($P<0.05$).

**Keywords:**Leishmania major, glucose-6-phosphate dehydrogenase, nitric oxide, lipopolysachharide, melatonin

### BACTERICIDAL PERMEABILITY INCREASING PROTEIN (BPI) IN THE AIRWAYS OF CYSTIC FIBROSIS PATIENTS

**D AICHELE[1], M SCHNARE[1], M RÖLLINGHOFF[1], A GESSNER[1] - (1) Institute for clinical Microbiology, Immunology and Hygiene, Erlangen, Germany.**

Cystic fibrosis (CF) is a fatal hereditary metabolic disease caused by the lack of a functional chloride-channel on epithelial membranes. This is a result of the mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. The major cause for morbidity and mortality in CF are chronic airway infections, predominantly with *Pseudomonas aeruginosa (P. aeruginosa)* strains showing a mucoid phenotype and are therefore capable to form biofilms. The majority of CF patients synthesize antineutrophil cytoplasmic antibodies (ANCA) primarily directed against the bactericidal permeability increasing protein (BPI) potentially interfering with antimicrobial effects of BPI.
We have analyzed the expression of BPI in the airways of CF patients using sputum samples as well as broncho-alveolar lavages. BPI mRNA was expressed by nearly all patients on a low level, which was consistent over several months. Furthermore BPI protein was produced mainly by neutrophil granulocytes as shown by intracellular staining and subsequent flow cytometry. Levels of BPI protein showed varying amounts in different patients and quantitatively correlated with IL-8 concentrations in the lung fluid. In vitro analysis revealed that *P. aeruginosa* initiated a rapid release of BPI, occurring independently of protein de novo synthesis.
In addition, purified natural BPI as well as a 27-mer BPI-derived peptide displayed antimicrobial activity even against patient-derived mucoid *P. aeruginosa* strains and bacteria resistant against all antibiotics tested. Thus, BPI is functionally active against mucoid *P. aeruginosa* strains and is expressed in the airways of CF patients. This function might be hampered by autoantibodies directed against BPI resulting in chronic infection.

### NFKBIL1, A PUTATIVE INHIBITOR OF NFKB, IS ASSOCIATED WITH CHRONIC CHAGAS CARDIOMYOPATHY DISEASE

**R RAMASAWMY[1], E CUHNA-NETO[1], KC FAE[1], FG MARTELLO[1], VL CAVALCANTI[1], B IANNI[1], C MADY[1], AC GOLDBERG[1], J KALIL[1] - (1) Laboratory of Immunology, Heart Institute (InCor),University of Sao Paulo, Sao Paulo, Brazil.**

Chagas' disease is a chronic inflammatory disease leading to cardiomyopathy with a complex etiology in which the protozoan parasite *Trypanosoma cruzi* (*T cruzi*) within a genetically susceptible host persists and drives a Th1 immune response. Only a subset of individuals infected by *T cruzi* develops chronic Chagas cardiomyopathy (CCC) and the rest are considered asymptomatics. This has led to the hypothesis of an individual susceptibility to T cruzi infection outcome. CCC patients display high levels of circulating proinflammatory cytokines. Heart infiltrating lymphocytes from CCC patients also express proinflammatory cytokines (TNFalpha and IFNgamma)) detectable in biopsies and surgical heart tissue samples from CCC patients. NFkBIL1 (IKBL) encodes a protein considered to be a putative member of the IkB family of proteins that regulate the NFkB family of transcription factors. NFkBIL1 has been suggested to be a putative inhibitor of NFkB and variant in its promoter region influence transcriptional level. We investigated NFkBIL1 variant in the promoter region at position -62A/T by PCR-RFLP in 340 Chagassic patients. Of these patients, 167 have developed CCC and the remaining 76 are considered asymptomatic (ASY). All ASY patients had normal ECG with normal left ventricular ejection fraction (LVEF) at echocardiography as well as normal chest, oesophagus and colon radiography. CCC patients presented ECG abnormalities. The frequencies of the genotypes among CCC were significantly different from those of ASY. Subjects carrying the AA genotype had a three fold risk of developing CCC compared with those carrying the TT genotype (P = 0.01; OR = 3 [95% CI 1.2 – 7.3]). The heterozygous CT genotype also showed an increased risk for CCC (P = 0.02; OR = 1.8 [1 – 3.2]. The A variants at –62 confers susceptibility to CCC (P= 0.003; OR=1.8 [1.2 – 2.7]. It has been suggested that the A at -62 disrupts the binding site for the transcription factor dEF1 and it is also reported that transcriptional reporter assays showed higher transcriptional activity with IKBL promoters containing the -62T allele. Hence, it can be suggested that the -62A/T may alter the transcriptional promoter activity affecting the immune response in the development of CCC.