

1. Celiac disease in the 21st century: issues of under- and over-diagnosis

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Until the 1960s celiac disease (CD) or sprue was considered a pediatric disease that was rarely diagnosed in adulthood. Thanks to greater awareness of the disease and the availability of improved diagnostic tools (above all, sophisticated endoscopic techniques and the development of reliable serological markers), the prevalence of CD in Western countries has been increasing steadily, and it is now recognized as a common disorder, even in adults. However, many cases of this disease still go undiagnosed, especially among the elderly and in patients with atypical clinical presentations (which are by no means uncommon). On the other hand, the frequency of unfounded diagnoses of CD is also on the rise. This reflects a tendency toward exclusively symptomatic diagnosis as well as the growing use of invalidated tests for CD (e.g., the cytotoxic test, the sublingual or subcutaneous provocation/neutralization test, etc.). As a result, public healthcare spending is being increased in several countries (Italy included) by the growing number of prescriptions for gluten-free diets. This editorial discusses the problems of under- and over-diagnosis of CD and provides an algorithm for management of suspected cases designed to minimize both problems with particular importance to morphologic aspects of small bowel (also in electron microscopy), in basal conditions or in gluten-free diets. *Int J Immunopathol Pharmacol* 2009;22:1-7

2. *Chlamydia pneumoniae* and atherosclerosis: current state and future perspectives

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Chlamydia pneumoniae, an intracellular bacterial pathogen, is known as a leading cause of human respiratory tract infections worldwide. Over the last decade, several reports in the literature have suggested that infection with *C. pneumoniae* may contribute to the pathogenesis of atherosclerosis. In order to play a causative role in chronic disease, *C. pneumoniae* would need to persist within infected tissue for extended periods of time, thereby stimulating a chronic inflammatory response. *C. pneumoniae* has been shown to disseminate systemically from the lungs through infected peripheral blood mononuclear cells and to localize in arteries where it may infect endothelial cells, vascular smooth muscle cells, monocytes/macrophages and promote inflammatory atherogenous process. The involvement of *C. pneumoniae* in atherosclerosis was investigated by seroepidemiological and pathological studies, *in vivo* and *in vitro* studies, and in clinical antibiotic treatment trials. This review will provide an update on the role of *C. pneumoniae* in atherosclerosis focusing on the recent insights and suggesting areas for future research. *Int J Immunopathol Pharmacol* 2009;22:9-14

3. Autism and immunity: revisited study

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Autism spectrum disorder is of interest neurochemically because it represents a relatively homogeneous disorder with regard to disease development, abnormal cognitive development and intellectual development disturbance. A consistent finding in autistic children is a high number of mast cells and a high level of serotonin which is also found at elevated concentrations in the urine of autistic patients. In addition, a dysfunction of clinical conditions, such as gastrointestinal and immunological symptoms, is frequently noted in autistic children, however, IgE does not appear to be prevalent in these children but probably an increase of cytokines/chemokines produced by mast cells at an early age may play an important role. Therefore an immune hypothesis, involving also autoimmunity, is one possible pathogenetic mechanism in autism. In conclusion, mast cell activation could contribute to immune and neuroinflammatory abnormalities that are evident in patients with autism spectrum disorders. *Int J Immunopathol Pharmacol* 2009;22:15-19.

4. N-oleoyl-dopamine decreases muscle rigidity induced by reserpine in rats

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N-oleoyl-dopamine (OLDA), a product of condensation of oleic acid and dopamine (DA), is a bioactive compound that crosses the blood-brain barrier after systemic administration. The possibility arises that OLDA could have a potential role in treating DA-related disorders, such as Parkinson's disease (PD). In the present study we seek to determine whether OLDA would affect muscle tone and akinesia in two rat models of PD: the reserpine-evoked muscle rigidity and the reserpine- and haloperidol-induced catalepsy. We found that OLDA (20 mg/kg) significantly decreased muscle rigidity induced by reserpine (2.5 mg/kg), measured as an increased mechanical muscle resistance (MMG) in response to a passive extension and flexion of a rat hind limb at the ankle joint. Moreover, OLDA potently decreased the reserpine-enhanced tonic and reflex electromyographic (EMG) activities recorded before and during the movement, respectively. A lower dose of OLDA (10 mg/kg) failed to have appreciable effects. The reference compound L-DOPA (25 mg/kg) also attenuated the reserpine-increased MMG and EMG activities; the effects were, however, observed much later and were less prominent than those characteristic of OLDA. In contrast to the effects on muscle tone, OLDA (20 and 40 mg/kg) did not influence catalepsy induced by either reserpine (1.25 mg/kg) or haloperidol (0.5 mg/kg). In conclusion, the study demonstrates a novel biological action of N-oleoyl-dopamine consisting of lowering the reserpine-induced muscle rigidity. However, the lack of influence on akinesia suggests that the compound has myorelaxant rather than anti-Parkinsonian properties. *Int J Immunopathol Pharmacol* 2009;22:21-28.

5 The immunosuppressor st1959, a 3,5-diaryl-s-triazole derivative, inhibits T cell activation by reducing NFAT nuclear residency

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3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole (ST1959) has shown therapeutic effects in several animal models of autoimmune diseases. In this study the effects of ST1959 were further investigated in a murine model of colitis. The evidence obtained indicates that the beneficial effects exerted by ST1959 rely upon a decreased local immunological response. The cellular effects of ST1959 were additionally investigated on human peripheral blood mononuclear cells and Jurkat T cells by measuring cytokine production, cell proliferation and activation of a set of transcription factors. ST1959 decreases human T cell proliferation and inhibits cytokine expression at the transcriptional level. Moreover, at doses inhibiting cytokine production, ST1959 blocks phorbol 12-myristate 13-acetate (PMA) and ionomycin-induced nuclear factor protein of activated T cell (NFAT1) activity, without impairing AP-1- and NF- κ B-dependent transcription. Immunofluorescence data show that ST1959 inhibits the nuclear residency of NFAT1 in both Jurkat and human peripheral blood mononuclear cells activated with PMA/ionomycin. leptomycin B, an inhibitor of CRM1/exportin1 α -dependent nuclear export, reverted the inhibitory effect of ST1959 on NFAT1 nuclear localization. This indicates that ST1959 may increase the nuclear export of NFAT1, downregulating NFAT1 activity via a mechanism different from that of cyclosporin A, since it does not affect NFAT phosphorylation/dephosphorylation steps. These findings provide new insights into the molecular mechanisms underlying the immunomodulatory activity of ST1959. *Int J Immunopathol Pharmacol* 2009;22:29-42

6. CXCR4+FOXP3+CD25+ lymphocytes accumulate in CXCL12-expressing malignant pleural mesothelioma

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CXCL12 is a chemokine that binds to a G-protein-coupled receptor (CXCR4). CXCL12 is expressed in various tumors and is considered as playing an important role in tumor growth and invasion. The aim of this study is to investigate the expression of CXCL12 in human malignant mesothelioma (MM), the chemotactic effect of CXCL12 derived from MM, and the expression of CXCR4 in MM tissues in relation to regulatory T cells. CXCL12 expression was examined by immunostaining of tissue specimens from malignant pleural mesothelioma (MPM) and malignant peritoneal mesothelioma (MPEM). The MM group comprised 6 patients (4 men/2 women, MPM=4, MPEM=2, aged 56.0 ± 12.4 years) and the control (non-mesothelioma) group also had 6 patients (4 men/2 women aged 65.0 ± 6.7 years). CXCL12 mRNA expression was also examined by RT-PCR in MPM cell lines (H28, H2052, and H2058), while CXCR4 mRNA expression was examined by *in situ hybridization* in MPM tissue. CXCL12 was expressed in the cytoplasm of MM cells from all patients, but was not expressed in the control group. H2052 and H2058 cells expressed CXCL12 mRNA, but H28 cells did not. CXCL12 in MM tissue homogenate supernatant had a chemotactic effect on CXCR4-expressing THP-1 cells. CXCR4 mRNA was expressed by a part of LCA+CD3+Foxp3+CD25+ T cells that were located adjacent to the border of CXCL12-expressing epithelioid MPM. These findings suggest that CXCL12 contributed to tumor-related inflammation by inducing the accumulation of CXCR4-expressing cells with regulatory T cell markers around MM. *Int J Immunopathol Pharmacol* 2009;22:43-51.

7. Soluble interleukin-2 receptor as an indicator of immunological disturbance found in silicosis patients.

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Silicosis patients (SILs) possess not only respiratory disorders but also alterations in autoimmunity. To determine an early indicator of immunological disturbance in SILs, the role of serum-soluble interleukin

(IL)-2 receptor (sIL-2R) was analyzed. Of ten SILs, immunological clinical parameters such as immunoglobulin (Ig) G, complements, the titer of autoantibodies including anti-nuclear antibodies (ANA), anti-Scl-70 antibody (Ab) and anti-centromere (CM) Ab, and experimental indicators such as serum-soluble Fas, serum IL-2, CD25+ cells in CD4+ or CD8+ fractions, and sIL-2R were divided from respiratory parameters such as % vital capacity (%VC), percentage of forced expiratory volume in 1 second (FEV1.0%) and v25/Ht (liter/second/m(body height) by a correlation assay. Additionally, a stepwise regression test showed that sIL-2R was correlated with Ig G, ANA and anti-CM Ab. Furthermore, factor analysis revealed that sIL-2R contributed to the subpopulation of SILs with poorer immunological status in the absence of alterations in respiratory status. By defining healthy donors as 1, SILs as 2 and patients with systemic sclerosis as 3 for immunopathological progression status as metric variables, sIL2R and ANA showed a strong positive correlation. This suggests that sIL-2R is a good clinical indicator of immunological disturbance found in SILs without clinical manifestations of any disturbance in autoimmunity. Further analysis using a large-scale number of patients should be performed to confirm these findings. *Int J Immunopathol Pharmacol* 2009;22:53-62.

8. Immunomodulatory effects of 1,25-dihydroxyvitamin D3 on TH1/TH2 cytokines in inflammatory bowel disease: an *in vitro* study

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Crohn's disease (CD) is associated with a higher type-1-helper T cell (Th1) cytokine expression, whereas ulcerative colitis (UC) appears to express a modified Th2 response. In addition to its classic role in calcium homeostasis, calcitriol, the hormonal active form of vitamin D, exerts immunoregulatory effects such as modulation of Th1/Th2 cytokines. Therefore, calcitriol administration could modify immune dysfunction in CD and UC. Nine patients with UC [M/F: 5/4; mean age 47 years, remission(R)/active(A) disease: 7/2], 8 patients with CD [M/F: 2/6; mean age 36, R/A 5/3] and 6 healthy controls (HC) [M/F: 3/3, mean age 46] were enrolled. Peripheral blood was collected after a drug-washout of 15 days and peripheral blood mononuclear cells were stimulated with mitogens alone or in the presence of physiological concentrations of calcitriol (100 pg/ml). Type 1 (IL-2, TNF- α , IFN- γ) and type 2 (IL-10) cytokine production was assayed on supernatants by ELISA. Compared to HC, TNF- α production was significantly higher both in UC (p=0.0002) and CD (p=0.0001) patients, at baseline and after incubation with calcitriol (UC p=0.0003, CD p=0.0009). The effects of calcitriol incubation were: 1) reduced IFN- γ (p=0.024) and increased IL-10 (p=0.06) production in UC patients; 2) reduced TNF- α production in CD (p=0.032); 3) no significant effects in HC. Calcitriol increased, albeit not significantly, IL-10 production in UC compared to CD patients (p=0.09). These results suggest an important modulatory role of vitamin D in the Th1/Th2 immune response. The observation that the effect of this modulation was different in CD compared to UC patients provides an interesting area of research into the pathogenesis and treatment of these inflammatory conditions. *Int J Immunopathol Pharmacol* 2009;22:63-71.

9. Selection and characterization of a novel agonistic human recombinant anti-TRAIL-R2 minibody with anti-leukemic activity

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Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising natural anticancer therapeutic agent because through its “death receptors”, TRAIL-R1 and TRAIL-R2, it induces apoptosis in many transformed tumor cells, but not in the majority of normal cells. Hence, agonistic compounds directed against TRAIL death receptors have the potential of being excellent cancer therapeutic agents, with minimal cytotoxicity in normal tissues. Here, we report the selection and characterization of a new single-chain fragment variable (scFv) to TRAIL-R2 receptor isolated from a human phage-display library, produced as minibody (MB), and characterized for the *in vitro* anti-leukemic tumoricidal activity. The anti-TRAIL-R2 MB2.23 efficiently and specifically bound to membrane-associated TRAIL-R2 on different leukemic cell lines and could act as a direct agonist *in vitro*, initiating apoptotic signaling as well as complement-dependent cytotoxicity and antibody-dependent cell cytotoxicity, providing a rationale for further investigations of MB2.23 in anticancer therapy. *Int J Immunopathol Pharmacol* 2009;22:73-83.

10. Andolast acts at different cellular levels to inhibit immunoglobulin E synthesis

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The anti-asthmatic agent andolast is thought to inhibit the release of allergic mediators, but its mechanism of action is not fully understood. We investigated whether the compound inhibits immunoglobulin E (IgE) synthesis and tested the hypothesis that andolast affects immunoglobulin class switching. Interleukin (IL)-4 and the interaction of CD40 expressed on B cells with its ligand on T cells are necessary for IgE synthesis. Thus, peripheral blood mononuclear cells (PBMCs) from 40 asthmatic, 16 non-asthmatic allergic, and 9 normal donors were stimulated with IL-4 and/or anti-CD40 antibody. T cells from 9 additional allergic donors were activated with anti-CD3/CD28 antibodies to express IL-4 mRNA. After incubation in the absence or presence of test compounds, immunoglobulin concentrations were measured by enzyme immunoassay, and mRNA levels were analyzed by RT-PCR. Andolast significantly inhibited IgE synthesis by stimulated PBMCs from both asthma patients and combined allergic/normal donors. In mechanistic studies, andolast was found to act at different cellular levels. Firstly, it reduced by about 45% ($p < 0.05$) the levels of IL-4 mRNA in T cells stimulated with anti-CD3/CD28. Secondly, andolast reduced by about 36% ($p < 0.05$) the expression of epsilon (ϵ) germline transcripts in PBMCs stimulated with IL-4/anti-CD40. Thirdly, the effect of andolast on immunoglobulin synthesis was selective in that the production of IgG4 antibodies was not significantly inhibited. Our findings, while supporting the evidence that andolast is effective for the treatment of asthma, provide new insights into its mechanism of action. *Int J Immunopathol Pharmacol* 2009;22:85-94.

11. Osteoblast apoptosis in periodontal disease: role of TNF-related apoptosis-inducing ligand

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Periodontal disease (Pd) is characterized by an increased osteoclast resorption and a decreased osteoblast (OB) bone formation. OBs obtained from alveolar bone of Periodontitis patients (Pp) undergo apoptosis in the presence of TNF-related apoptosis-inducing ligand (TRAIL). We studied the intracellular apoptotic pathway induced by TRAIL; TRAIL death (DR4, DR5) and decoy (DcR1, DcR2) receptors expression in Periodontitis patients' OBs (PpOBs), and we measured the concentration of TRAIL in the serum of Pp. We demonstrated that DNA fragmentation and activation of caspase-8 and caspase-3 in PpOBs, following TRAIL stimulation, occurred in shorter time; moreover, a higher amount of both caspases was activated in order to direct OBs. Down-regulation of DcR2 in PpOBs was demonstrated and high TRAIL levels were detected in the serum of Pp. In conclusion, our data suggest that PpOBs are more sensitive to TRAIL-induced apoptosis when compared to the control group. The down-regulation of DcR2 possibly leads to an imbalanced ratio between death and decoy receptors. Our findings highlight a role of TRAIL in the pathogenesis of Pd. *Int J Immunopathol Pharmacol 2009;22:95-103.*

12. Role of interleukin-15 receptor α polymorphisms in normal weight obese syndrome.

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Previous published studies have identified a class of women, Normal Weight Obese women (NWO) with normal BMI and high fat content. An important role of Interleukin-15 (IL-15) has been documented in facilitating muscle proliferation and promoting fat depletion. Indeed the presence of three types of IL-15 receptor subunits in fat tissue suggests a direct effect on adipose tissue. We studied three single nucleotide polymorphisms (SNP) of IL-15R α receptor gene and investigated their relationship with NWO phenotype. We considered two classes of women according to their BMI and percent fat mass (%FAT), class 1: including 72 overweight-obese women (high BMI-high fat mass) and class 2: including 36 NWO (normal BMI, high fat mass). Three sites of Interleukin-15 receptor subunit α gene were examined, located respectively in exon4, exon5 intron-exon border and exon7. Genotyping of the identified

polymorphisms was performed by restriction fragment length polymorphism. Haplotype frequency estimation was performed by using the Mendel-University of Chicago program. Odds ratio analyses were calculated by EPISTAT program. Highly significant differences were observed for exon 7- exon5 intron-exon border and exon 4-exon 7 haplotype distribution between class 1 and class 2 women. These results strongly support the hypothesis that genetic variability of the IL-15 receptor has an important role in body fat composition. Our data underscore previous findings that suggest a potential role of IL-15 cytokine in NWO syndrome. *Int J Immunopathol Pharmacol* 2009;22:105-113.

13. Allelic frequencies of 3' Ig heavy chain locus enhancer HS1,2-A associated with Ig levels in patients with schizophrenia.

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Infectious and autoimmune pathogenic hypotheses of schizophrenia have been proposed, prompting searches for antibodies against viruses or brain structures, and for altered levels of immunoglobulins. Previous experiments have shown that allele frequencies of the Ig heavy chain 3' enhancer HS1,2*A are associated with several autoimmune diseases, suggesting a possible correlation between HS1,2 alleles and Ig production. To test this, we analyzed levels of serum Igs and HS1,2*A genotypes in two independent cohorts, one of 88 schizophrenic inpatients (24 women) and a second of 133 healthy subjects (59 women). Both groups were similar in the frequency of individuals with altered serum concentration of Ig classes and IgG subclasses (schizophrenia panel-80%; controls-68%). With the possible exception of a stabilizing effect of olanzapine, no psychopharmacological drug consumed during the month prior to serum sampling in the schizophrenia group significantly affected Ig levels. In both patient and control cohorts, an increased frequency of the HS1,2*2A allele corresponded to increased Ig plasma levels, while an increased frequency of the HS1,2*1A allele corresponded to decreased Ig plasma levels. EMSA analysis with nuclear extracts from human B cells showed that the transcription factor SPI bound to the polymorphic region of both HS1,2*1A and HS1,2*2A while NF-κB bound only to the HS1,2*2A. We predict that differences in transcription factor binding sites in the two allelic variants of the 3' IgH enhancer HS1,2 may provide a mechanism by which differences in Ig expression are affected. *Int J Immunopathol Pharmacol* 2009;22:115-123.

14. In vitro evaluation of the efficacy of a new laser surface implant: cellular adhesion and alkaline phosphatase production tests

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Bone tissue reacts in different ways to implant surfaces with different patterns. The aim of this study is to understand which laser generated surface pattern produces the best cell adhesion *in vitro*, evaluating both the activity of the alkaline phosphatase and the cells adhering to titanium samples. Tests were carried out on titanium samples with sandblasted surfaces with laser-produced holes with diameters of 5, 10, and 20 μm , and on sandblasted titanium cylinders without holes as controls. The samples were inserted into culture medium containing SaOS-2 cells for 3, 7 and 10 days. The results showed that at days 3 and 7 the laser surfaces stimulated a higher production of alkaline phosphatase (ALP) compared to the data from the control group. At day 10 there were no significant differences between the test group and the control group. *Int J Immunopathol Pharmacol* 2009;22:125-131.

15. Plant-derived recombinant F1, V, and F1-V fusion antigens of *Yersinia pestis* activate human cells of the innate and adaptive immune system

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Plague is still endemic in different regions of the world. Current vaccines raise concern for their side effects and limited protection, highlighting the need for an efficacious and rapidly producible vaccine. F1 and V antigens of *Yersinia pestis*, and F1-V fusion protein produced in *Nicotiana benthamiana* administered to guinea pigs resulted in immunity and protection against an aerosol challenge of virulent *Y. pestis*. We examined the effects of plant-derived F1, V, and F1-V on human cells of the innate immunity. F1, V, and F1-V proteins engaged TLR2 signalling and activated IL-6 and CXCL-8 production by monocytes, without affecting the expression of TNF- α , IL-12, IL-10, IL-1 β , and CXCL10. Native F1 antigen and recombinant plant-derived F1 (rF1) and rF1-V all induced similar specific T-cell responses, as shown by their recognition by T-cells from subjects who recovered from *Y. pestis* infection. Native F1 and rF1 were equally well recognized by serum antibodies of *Y. pestis*-primed donors, whereas serological reactivity to rF1-V hybrid was lower, and that to rV was virtually absent. In conclusion, plant-derived F1, V, and F1-V antigens are weakly reactogenic for human monocytes and elicit cell-mediated and humoral responses similar to those raised by *Y. pestis* infection. *Int J Immunopathol Pharmacol* 2009;22:133-143.

16 *In vitro* detection of herpes simplex virus -1 and -2 infection with immunospecific GD₃+CL₆-enhanced magnetic resonance imaging

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Herpes simplex virus infections are prevalent viral infections in humans. HSVs are also the most common cause of sporadic viral encephalitis (HSE). Magnetic resonance is the imaging method of choice for HSE because it provides the most sensitive method for detecting early lesions. The objective of this study is to set-up and *in vitro* test an experimental contrast agent specific for antigens present on HSV-infected cells, bound with a paramagnetic agent detectable by MR imaging. A selected anti-HSV HrFab was labelled with Alexa Fluor 488, ¹²⁵I and Gd₃₊Cl₆. In order to assess anti-HSV affinity and specificity, ELISA assays were performed. Vero cells infected with HSV strains were visualized by MRI using anti-HSV HrFab/Gd₃₊Cl₆ complex. Results of the ELISA tests demonstrated that the anti-HSV HrFab labelled with Gd₃₊Cl₆ showed similar affinity for the antigens while the ¹²⁵I immunoconjugate showed reduced affinity. MRI confirmed high affinity and specificity of antibody for the detection of HSV infections. *Int J Immunopathol Pharmacol* 2009;22:145-151.

17. Necrotic cell death in human amniotic cells infected by *Listeria monocytogenes*

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Listeria monocytogenes can cause a placental-foetal infection that results in spontaneous abortion, premature labour, stillbirth, or neonatal sepsis and meningitis. Bacteria cross the maternofetal barrier at the villous syncytiotrophoblast level and subsequently spread from the placenta to the fetus. *L. monocytogenes* is able to induce different kinds of death in a variety of cells. Murine hepatocytes, murine T and human B lymphocytes, and murine dendritic cells die by apoptosis, whereas bacterial infection of murine and human macrophages leads mainly to necrotic cell death. As we previously described the efficient infection and growth of *L. monocytogenes* in a human amniotic cell line, we investigated the fate of these cells in order to analyse the mode of cell death. Our results provide biochemical and morphological evidence of necrotic death induced by *L. monocytogenes* infection. *Int J Immunopathol Pharmacol* 2009;22:153-162.

18. Effect of SP3 silencing on cytokeratin expression pattern in HPV-positive cells

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In an attempt to understand the molecular factors underlying squamous cell carcinogenesis in HPV-infected oral and cervical tissues, we examined the Sp3-dependent cytokeratin expression in HPV-positive CaSki cells. Two sets of cytokeratins were examined: the simple epithelial CK 7, 8, 18, 19, and 20, which are generally expressed in simple epithelia and CK4, 10, 13, and 17, which are expressed in squamous epithelia. Two additional CK pairs, i.e. CK6/CK16 and CK4/CK13 were analyzed as controls of the proliferation/differentiation cell status, respectively. We report that Sp3 gene silencing specifically hits CK18 and CK19, which are markers of oral and cervical squamous tumors. These data may be of help in

immunopathological definition of squamous carcinogenesis. *Int J Immunopathol Pharmacol* 2009;22:163-168.

19. Vaccination with *Trichinella spirallis* antigens increases CD8⁺ peripheral T cells and enhances the Th2 immune response in *Leishmania infantum* challenged mice

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In this study we investigate the effect of *Trichinella spiralis* vaccination on immune responses elicited in BALB/c mice challenged subcutaneously with 0.5 x10⁶ of *Leishmania infantum* promastigotes. Secretion of specific anti-*L. infantum* antibodies and changes in the number of CD4⁺, CD8⁺ T cell and CD19⁺ B cells in the peripheral blood were tested for the evaluation of immune responses. Immunization with low amounts of *T. spiralis* antigens induced depression in anti-*Leishmania* specific antibodies of the IgG1 isotype, while no changes in the number of CD4⁺ and CD8⁺ T cell subpopulations or CD19⁺ B cells were observed. In contrast, high amounts of *T. spiralis* antigens induced an enhancement in anti-*Leishmania* specific antibodies of total IgG and IgG1 isotype, increase of CD8⁺ T cell number and activation of CD19⁺ B cells, indicated by the co-expression of CD69 marker. Our results suggest that immunization with a certain dose of *T. spiralis* antigens in experimentally challenged mice with *L. infantum* leads to an increase of peripheral CD8⁺ T cells which are responsible for the control of *L. infantum* infection, although a simultaneous enhancement in Th2-type of immune response is also observed. *Int J Immunopathol Pharmacol* 2009;22:169-174.

20. Exploiting immunotherapy in *Mycobacterium tuberculosis*-infected mice: sphingosine 1-phosphate treatment results in a protective or detrimental effect depending on the stage of infection

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Sphingosine 1-phosphate (S1P) is a natural lysophospholipid able to enhance antimycobacterial innate immune response. In the present study, we address the possible therapeutic role of S1P administered during primary or acute infection in mice aerogenically infected with *Mycobacterium tuberculosis* (MTB). Results show that the administration of S1P during primary infection significantly reduces the presence of MTB-infected cells within pulmonary granulomas and mycobacterial burden in the lung and in the spleen. However, if S1P treatment was started during acute infection, a detrimental effect was observed in terms of pulmonary histopathology and mycobacterial burden in the lung and in the spleen. Taken

together, these results show that S1P can exert a therapeutic effect as a treatment of primary infection only. *Int J Immunopathol Pharmacol* 2009;22:175-181.

21. Expression of internalin A and biofilm formation among *Listeria monocytogenes* clinical isolates

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Internalin A (InlA), a cell wall-bound protein of *Listeria monocytogenes*, is among the major components involved in the adhesion to and invasion of host cells expressing specific forms of E-cadherin. Some *L. monocytogenes* strains secrete truncated non-functional forms of InlA. The purpose of this study is to compare the biofilm-forming abilities of *L. monocytogenes* strains from clinical sources expressing InlA proteins in the different forms. A total of 70 *L. monocytogenes* strains were examined using SDS-PAGE, Western blot, DNA sequencing, and microtitre plate biofilm formation assays. We found that 8 of the 70 strains expressed truncated InlA, and that this group of strains exhibited significantly enhanced biofilm-forming ability compared to the group expressing full-length InlA. Further experiments showed that: (i) *L. monocytogenes* biofilms were detached by treatment with protease K; (ii) protein fragments resulting from proteolysis, rather than intact proteins, are responsible for biofilm enhancement, because biofilm formation was impaired by the protease inhibitor α 2-macroglobulin; (iii) truncated and/or proteolytically cleaved InlA are likely involved in the biofilm enhancement, based on the effects that anti-InlA monoclonal antibodies produced on the biofilm formation of *L. monocytogenes* strains expressing either truncated or full-length InlA. These data provide a basis for further investigation of the molecular structure and composition of *L. monocytogenes* biofilms.

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22 Analysis of memory and effector CD8⁺ T cell subsets in chronic graft-versus-host disease

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In humans, the selective depletion of CD8⁺ cells may prevent GVHD after allogeneic transplantation. These cells can infiltrate and damage target tissues. It is of interest to investigate the phenotypical characteristics and cytotoxic properties of the different CD8⁺ subsets in cGVHD patients. In a preliminary study we found that patients with cGVHD had a markedly elevated percentage of peripheral blood CCR7⁺/CD45RA⁺ cells compared to patients without cGVHD; conversely, the CCR7⁻/CD45RA⁺ subsets of CD8⁺ cells was significantly decreased. In this study, we report in depth on the phenotype of effector T cell subsets in cGVHD patients, as well as their proliferative capability, cytotoxic properties and cellular turnover. We confirm a predominance of effector T cell subsets in cGVHD patients and show that a large fraction of these cells down-regulate CCR7 and re-express CD45RA, thus approaching end-stage differentiation. Moreover CD8⁺ cells of cGVHD patients have low CD8 coreceptor expression, reduced proliferative potential and a high content of perforin and granzyme A. They also have a lower cell

turnover and have more propensity to apoptosis, as demonstrated by BrdU incorporation. Taken together, our findings indicate a perturbation of the balance between naive/memory and effector/CD45RA⁺ CD8⁺ T cells, and suggest an involvement of the latter compartment characterized by a high content of cytotoxic equipment, in the pathogenesis of cGVHD. *Int J Immunopathol Pharmacol* 2009;22:195-205.

23. Duodenal intraepithelial lymphocytes of children with cow milk allergy preferentially bind the glycan-binding protein galectin-3

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A breakdown in intestinal homeostasis results in inflammatory bowel diseases including coeliac disease and allergy. Galectins, evolutionarily conserved beta-galactoside-binding proteins, can modulate immune-epithelial cell interactions by influencing immune cell fate and cytokine secretion. In this study we investigated the 'glycosylation signature' as well as the regulated expression of galectin-1 and -3 in human duodenal samples of allergic and non-allergic children. Whereas galectin-1 was predominantly localized in the epithelial compartment (epithelial cells and intraepithelial lymphocytes) and the underlying lamina propria (T cells, macrophages and plasma cells), galectin-3 was mainly expressed by crypt epithelial cells and macrophages in the lamina propria. Remarkably, expression of these galectins was not significantly altered in allergic *versus* non-allergic patients. Investigation of the glyco phenotype of the duodenal inflammatory microenvironment revealed substantial α 2-6-linked sialic acid bound to galactose in lamina propria plasma cells, macrophages and intraepithelial lymphocytes and significant levels of asialo core 1 O-glycans in CD68⁺ macrophages and enterocytes. Galectin-1 preferentially bound to neutrophils, plasma cells and enterocytes, while galectin-3 binding sites were mainly distributed on macrophages and intraepithelial lymphocytes. Notably, galectin-3, but not galectin-1 binding, was substantially increased in intraepithelial gut lymphocytes of allergic patients compared to non-allergic subjects, suggesting a potential role of galectin-3-glycan interactions in shaping epithelial-immune cell connections during allergic inflammatory processes. *Int J Immunopathol Pharmacol* 2009;22:207-217.

24. Influence and variation of the body mass index in patients treated with etanercept for plaque-type psoriasis

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A relationship between psoriasis, pro-inflammatory cytokines and obesity has been demonstrated. Tumour necrosis factor-alpha (TNF- α), that is involved in the pathogenesis of psoriasis, is commonly over-expressed in obese subjects, and seems to be derived from inflammatory cells and adipocytes. The primary aim of this study is to investigate whether the Body Mass Index (BMI) of patients influences the clinical response to etanercept, a competitive inhibitor of TNF- α approved for the treatment of moderate-to-severe plaque-type psoriasis. The secondary aim is to evaluate whether the TNF- α inhibition influences the weight and BMI profile of patients. One hundred patients received 50 mg etanercept twice weekly for 12 weeks, followed by 25 mg. At weeks-12 and 24, treatment efficacy and tolerability were evaluated, as well as body weight and BMI. BMI values did not correlate with etanercept efficacy. Mean PASI score variation did not show significant differences among the BMI groups. A statistically significant weight gain and BMI variation were observed in a consistent rate of patients. Patient BMI does not influence psoriasis efficacy parameters. Although the role of anti TNF- α molecules on weight regulation need to be confirmed, our study shows that etanercept treatment may induce weight gain and a BMI increase. *Int J Immunopathol Pharmacol* 2009;22:219-225.

25 A multicenter open-label experience on the response of psoriasis to Adalimumab and effect of dose escalation in non-responders: the Aphrodite project

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There is much evidence to show the efficacy of adalimumab, a human monoclonal antibody targeting tumour necrosis factor-alpha, in the treatment of plaque psoriasis. In this open-label experience, 147 high-need patients suffering from plaque psoriasis, with a mean Psoriasis Area and Severity Index (PASI) of 18.8, and concomitant psoriatic arthritis (PsA) received subcutaneous injections of 40 mg of adalimumab every other week (EOW). This was actually the dosage regimen recommended for PsA, as the drug had not then been approved for psoriasis at the time of the patients' enrolment. At week 12, an improvement of at least 50% of the PASI (PASI-50) was observed in 111 (77%) patients. Continuation of treatment in responders with adalimumab 40 mg EOW led to a sustained response, with the PASI-50 achieved by 97% of patients in the as-treated analysis at week 24 (PASI-75 in 82% and PASI-90 in 45% out of 109 patients who received EOW injections up to week 24). Thirty subjects who failed to attain the PASI-50 response at week 12 were treated with adalimumab 40 mg every week for a further 12 weeks. At week 24, 80% of these patients obtained a PASI-50 response after dose escalation. Tolerability was good in the majority of patients. Only two patients discontinued treatment because of an adverse event (repeated flu-like episodes

and a pleuropericarditis of unknown origin, respectively). *Int J Immunopathol Pharmacol* 2009;22:227-233.

26. Efficacy of cyclosporine in the treatment of a case of infliximab-induced erythrodermic psoriasis

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A clinical case is described of infliximab-induced erythrodermic psoriasis resistant to conventional topical therapy and high-dose corticosteroids. Cyclosporine therapy for some months resolved the severe psoriasis picture. Pathogenetic mechanisms are considered through which anti-TNF agents could induce psoriasis. An activation of T lymphocytes with cutaneous overexpression of a CXCR3 subset and, mainly, an increase in IFN-alpha due to the blockage of TNF-alpha could be the causes for this paradoxical adverse event of biological agents. Cyclosporine can work in psoriasis induced by biological agents thanks to its peculiar suppressive activity on T lymphocytes and the concomitant specific action on keratocytes and angiogenesis. *Int J Immunopathol Pharmacol* 2009;22:235-238.

27 The erythromycin-resistance in *S. pyogenes* does not limit the human polymorphonuclear cell antimicrobial activity

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In order to highlight the potential erythromycin immunomodulatory properties related to different antibiotic resistance patterns in *Streptococcus spp.*, we evaluated the influence of the macrolide on the PMNs primary functions against erythromycin-susceptible (Ery-S) and erythromycin-resistant (Ery-R) *S. pyogenes* strains. A total of 438 *S. pyogenes* were isolated over the period 2005-2007. On the basis of the triple disk testing, 345 out of 438 *S. pyogenes* isolates were Ery-S and 93 were Ery-R; among the resistant strains, 65 displayed the cMLS_B phenotype, 23 had the M phenotype and 5 had iMLS_B phenotype. Concerning antibacterial activity of PMNs, our results showed that erythromycin did not modify bacterial uptake, but significantly increased the phagocyte intracellular killing, compared with controls, for both Ery-S and Ery-R strains. Consequently, this report underlines that in immunocompetent hosts the dichotomy between the *in vitro* resistance and clinical trial data for antimicrobial agents should be thoroughly re-evaluated. *Int J Immunopathol Pharmacol* 2009;22:239-242.

28. Successful cyclosporine treatment in a case of amicrobial pustulosis associated with immunological abnormalities

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Amicrobial pustulosis associated with autoimmune diseases (APAD) is a clinical entity which was described only recently and few cases are reported in the literature. This condition is characterized by recurrent acute onset with pustular lesions predominantly involving skin folds, genitals, scalp and external auditory canals of young women. The etiopathogenesis of APAD is unknown and the most effective therapeutic treatment seems to be systemic corticosteroids. We describe the case of a 16-year old female patient suffering from APAD successfully treated with cyclosporine A.

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29. Specific immunotherapy for allergic rhinitis in Italy: the patients' points of view

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Specific immunotherapy (SIT) is the unique causal treatment for allergy, but its use is quite limited. A perspective, cross-sectional telephone interview survey was carried out in Italy to evaluate the characteristics of 500 patients with allergic rhinitis (250 of whom treated with SIT). Relevant differences were found concerning therapeutic management of allergic rhinitis, mainly regarding the use of drugs and co-morbidities. The allergist is the most important consultant who prescribes SIT. This study therefore provides evidence that the course of allergic rhinitis may depend on the therapy prescribed by and the level of allergy awareness of the physician. *Int J Immunopathol Pharmacol 2009;22:247-250.*

30. Specific immunotherapy for allergic rhinitis in Italy: the doctors' points of view

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Specific immunotherapy (SIT) is the unique causal treatment for allergy, but its prescription is quite restricted. A perspective and cross-sectional survey based on telephone interviews was carried out in Italy to evaluate the profile of doctors prescribing SIT for allergic rhinitis. A total of 540 doctors were interviewed, 200 of whom are GPs, 60 allergists, 60 ENT specialists, 100 familial paediatricians, 60 hospital paediatricians and 60 pulmonologists. Significant differences concern diagnostic and therapeutic management of allergic rhinitis, mainly regarding SIT prescription. The allergist is the most important consultant who prescribes SIT, as opposed to the paediatrician. This study therefore provides the evidence that doctors' behaviour towards SIT depends on the type of graduate studies. *Int J Immunopathol Pharmacol* 2009;22:251-254.

