1. Pidotimod: a reappraisal

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Pidotimod (Polimod ®) is a synthetic dipeptide molecule with biological and immunological activity on both the adaptive and the innate immune responses. In vitro studies, both from animal and human specimens, have documented a good activity on innate and adaptive immune responses and have been confirmed by in vivo studies. These activities have been applied in clinical studies demonstrating the efficacy of pidotimod in reducing the rate of recurrent infections of the upper respiratory and urinary tracts in children. The same results were obtained in recurrent respiratory tract infections in adults. Interestingly, these effects are more evident in the setting of immune defects such as senescence, Down’s syndrome, and cancer. Int J Immunopathol Pharmacol 2009;22:255-262

2. Herpesviruses and periodontal disease: a cautionary tale

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Periodontitis is an inflammatory disease of bacterial origin, characterized by an inconstant progression of lesions affecting the tooth supporting tissues. In spite of more than half a century of research efforts, the clinician still lacks any specific molecular or microbial diagnostic tool to predict the progression of periodontal lesions. Recently, several reports have proposed a role for some herpesviruses in the etiology of destructive phases of periodontitis. This paper critically analyzes these data in the light of consolidated knowledge that was developed in the characterization of virus-bacteria cooperative interactions, and proposes new topics of investigation to clarify the role of herpesviral infections in periodontitis and their potential predictive role as markers of progression. Int J Immunopathol Pharmacol 2009;22:263-268.

3. Strategies for successful vaccination against hepatocellular carcinoma

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Current therapies against hepatocellular carcinoma (HCC) are not curative in the majority of patients. In the past, immunotherapy approaches aimed to non-specifically stimulate immune response were quite ineffective. New treatments based on stimulation of specific anti-tumor immune response are currently
proposed and appear more promising. Tumor-specific antigens identified in HCC demonstrated immunogenicity both in preclinical and clinical trials. Effectiveness in animal studies raised interest in the clinical applicability of non-specific adoptive immunotherapy that prevented disease recurrence after tumor resection. Dendritic cell (DC)-based tumor vaccines achieved encouraging results, and cellular vaccines based on DCs have already entered clinical trials. Preventive and therapeutic DNA vaccination have been proposed, all based on tumor-associated antigens (TAAs), either modified or not, an example being alpha-fetoprotein (AFP). The concomitant expression of co-stimulatory molecules and cytokines was used to increase tumor immunogenicity. Syngeneic or nude mice models indicated that immunotherapy for HCC could stimulate an anti-tumor T-cell response leading to clinical benefit devoid of significant toxicity. The use of DNA-based vaccination raises exciting possibilities in preventing HCC in high-risk individuals such as those with cirrhosis. Novel immunotherapy strategies may contribute in the future to prevention and treatment of HCC. Int J Immunopathol Pharmacol 2009;22:269-277.

4. Chronic lymphocytic leukemia-associated pure red cell aplasia

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Pure red cell aplasia (PRCA) is a well-known marrow failure which may be acquired or constitutional/congenital, as the Diamond-Blackfan syndrome. Acquired PRCA may show as a primary hematological disorder or secondary to an associated disease, infection or drug. PRCA rarely complicates chronic lymphocytic leukemia (CLL), may occur anytime in the course of the disease and, in this context, it is a minority of total PRCA. Anemia due to PRCA in CLL patients must be carefully evaluated and differentiated from other causes (autoimmune hemolytic anemia, neoplastic lymphocyte infiltration of bone marrow, chemotherapy) that require a different therapeutic approach. PRCA is thought to be an immunologically mediated disorder, but there is no uniformity in the setting of the management. Immunosuppressive therapy is frequently given, such as steroids and cyclosporin-A. Recently, anecdotal cases have been published on the effectiveness of monoclonal antibodies rituximab and alemtuzumab. Int J Immunopathol Pharmacol 2009;22:279-286.

5. Pulmonary exposure to soluble cell wall β-(1, 3)-glucan of *Aspergillus* induces proinflammatory response in mice


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Compared to the significant immunomodulation of cell wall component(s) of bacterium such as lipopolysaccharide (*E. Coli*), that of pathogenic fungi has not been well elucidated, especially in *vivo*. Furthermore, although it has been implied that β-(1, 3)-glucan of fungi possesses various biological activities, the impacts of the component have not been properly clarified, possibly due to its insolubility in water and alkali solutions. Previously, we isolated a soluble type of β-(1, 3)-glucan from *Aspergillus* (referred to as ASBG). The present study investigated the effects of a single pulmonary exposure to ASBG on the immune (proinflammatory) responses in naïve mice. ASBG (12.5-100μg/animal) exposure
Induced neutrophilic lung inflammation with an enhanced local expression of proinflammatory cytokines such as interleukin (IL)-1β and chemokines such as macrophage inflammatory protein -1α, and keratinocyte-derived chemotactrant in a dose-dependent fashion with overall trends. On the other hand, ASBG at relatively lower doses significantly amplified the lung expression of IL-2, IL-6, and IL-12 as compared with vehicle. ASBG significantly induced pulmonary edema. Furthermore, ASBG augmented the nuclear translocation of nuclear factor (NF)-κB and its binding capacity to the promoter site of DNA in the lung homogenate. These results suggest that pulmonary exposure to ASBG confers lung inflammation, at least partly, via the enhanced local expression of proinflammatory cytokines, likely through NF-κB-dependent pathway. *Int J Immunopathol Pharmacol* 2009;22:287-297.


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The most recent guidelines recommend, for otitis externa antibiotic therapy, the use of topical formulations in that they are very safe, have a quicker effect and do not induce bacterial resistance compared to systemic therapy. The choice of the class of antibiotics in empiric therapy of otitis externa must take into consideration the polymicrobial nature of the infection that includes both bacteria (Gram-positive and Gram-negative) and mycetes. For this reason, in this study we evaluated the synergic activity of neomycin in association with polymyxin B against the pathogens commonly responsible for otitis externa, compared to that of a single antibiotic (ciprofloxacin). The polymyxinB/neomycin association shows clear synergic effects with values of both Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) reduced by 3-4 times with respect to the single antibiotic; and in *P. aeruginosa* the synergistic effect of the neomycin/polymyxin B association with respect to neomycin was more evident (5-6 times), with an intrinsic *in vitro* activity constantly higher than that of ciprofloxacin alone or in association with hydrocortisone. From the analysis of the data obtained *in vitro*, we can conclude that the possibility of using a topical formulation containing a synergistic association of antibiotics, such as neomycin-polymyxin B, in such a way as to obtain the maximum effect in the minimum time with an increase in the spectrum of action of non-bacterial pathogens, is an optimal choice for the clinician for the empiric therapy of otitis externa. *Int J Immunopathol Pharmacol* 2009;22:299-302.


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Tonsillectomy and adenoidectomy remain the first choice treatment of chronic or recurrent acute infections of the upper respiratory tract in children. The aim of this study is to investigate the efficacy of the combination of thiamphenicol glycinate acetylcysteinate plus beclometasone, administered as
aerosol, in children awaiting tonsillectomy and/or adenoidectomy. The study comprised 204 children, aged 1 to 12 years, with chronic adenotonsillitis who had been listed for surgery due to obstructive symptoms and recurrent acute infections. Patients were randomized to treatment with thiamphenicol glycinate acetylcysteinate, dosage 250 mg/day in 2 administrations plus beclomethasone with a dosage of 400 μg/day in 2 administrations, or no treatment, control group, unless required. The drugs were administered by aerosol for 10 days/month over a period of 6 months. Clinical visits were at 4, 7 and 12 months after the start of treatment. The primary efficacy outcome was the reduction in the number of patients requiring surgery. Secondary efficacy measures were the reduction of nasal obstruction, the decrease in the number of infectious episodes and the tolerability of the treatment. Aerosol treatment with thiamphenicol glycinate acetylcysteinate plus beclomethasone resulted in a significantly lower proportion of patients requiring surgery (29 of 101; 29%) compared to patients in the control group (100 of 103; 97%) (p < 0.0001). Treatment was also associated with a reduction of nasal obstruction and a decrease in the number of infectious episodes. No treatment-related adverse events were reported and the aerosol therapy proved easy to administer to children. The aerosol therapy with the combination of thiamphenicol glycinate acetylcysteinate plus beclomethasone was able to prevent or postpone surgery in a substantial percentage of patients, without adverse events. These preliminary results suggest that this novel approach could play a role in the antibiotic prophylaxis of chronic infectious diseases of the upper airways. Int J Immunopathol Pharmacol 2009;22:303-310.

8. Inflammasomes are differentially expressed in cardiovascular and other tissues


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To determine the expression of components in Toll-like receptors (TLRs)/Nod-like receptors (NLRs)/inflammasome/caspase-1/interleukin (IL-1)-β pathway, we examined the expression profiles of those genes by analyzing the data from expression sequence tag cDNA cloning and sequencing. We made several important findings: firstly, among 11 tissues examined, vascular tissues and heart express fewer types of TLRs and NLRs than immune and defense tissues including blood, lymph nodes, thymus and trachea; secondly, brain, lymph nodes and thymus do not express proinflammatory cytokines IL-1β and IL-18 constitutively, suggesting that these two cytokines need to be upregulated in the tissues; and thirdly, based on the expression data of three characterized inflammasomes (NALP1, NALP3 and IPAF inflammasome), the examined tissues can be classified into three tiers: the first tier tissues including brain, placenta, blood and thymus express inflammasome(s) in constitutive status; the second tier tissues have inflammasome(s) in nearly-ready expression status (with the requirement of upregulation of one component); the third tier tissues, like heart and bone marrow, require upregulation of at least two components in order to assemble functional inflammasomes. Our original model of three-tier expression of inflammasomes would suggest a new concept of tissue inflammation privilege, and provides an insight to the differences among tissues in initiating acute inflammation in response to stimuli. Int J Immunopathol Pharmacol 2009;22:311-322.

9. Effects of rich-in-fat diets and highly selective COX-2 Inhibitors on 7,12-dimethylbenz-(A)-anthracene -induced tumor growth

Pp 323-332
The effects of diet, of non-steroidal anti-inflammatory drugs, or of their combination on carcinogenesis continue to be a case for controversy. Diets that are high in fat have been linked to increased risk of various tumors. At the same time there is substantial, but not conclusive, evidence that the risk of breast and colon cancer correlates with total fat intake rather than a specific type of fat. On the other hand, non-steroidal anti-inflammatory drugs (NSAIDs) have been studied extensively because they appear to delay or inhibit the development of malignant and pre-malignant lesions. 7,12-Dimethylbenz-(a)-anthracene (DMBA) has been used for a long time to induce carcinogenesis in a number of rat animal models. The present study attempts to identify the effects on DMBA-induced tumor growth (a) of diets rich in fat and (b) of the highly selective COX-2 inhibitor Celecoxib, which has been claimed to offer substantial protection against carcinogenesis.

10. Two weeks of permanence in negatively-charged air conditions causes alteration of natural killer cell function


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The effects of negatively-charged air conditions were analyzed as one of the approaches to improve health and quality of life. We previously reported that the use of a charcoal coating and application of an electric voltage yielded predominantly negatively-charged particles in an experimental room, and that 2.5 hours of living in these conditions caused a slight activation of the immune system (slight elevation of serum interleukin (IL)-2), regulated blood flow, and stabilized the autonomic nervous system when compared with control conditions (no dominance of negatively-charged particles). In this study, we expanded the previous study and placed 15 subjects in negatively-charged air conditions for two weeks during the night and analyzed various biological parameters. Although individual biological reactions differed from subject to subject, natural killer (NK) cell activity increased significantly following living in negatively-charged air conditions. Taken together, the results of the previous investigation and those of this study show that repeated elevation of IL-2 (although it immediately returned to the baseline level) causes chronic and recurrent stimulation to NK cells and results in the steady activation of NK cells. Negatively-charged air particles may be a good tool to improve health and quality of life. Int J Immunopathol Pharmacol 2009;22:333-342.
11. Clinical and immunological correlates of pre-co-seasonal sublingual immunotherapy with birch monomeric allergoid in patients with allergic rhinoconjunctivitis

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Sublingual immunotherapy is safe and efficacious in the treatment of patients with allergic rhinitis. The clinical and biological efficacy of modified allergens (allergoids) has not been fully clarified. We investigated in birch allergic patients the effect of a pre-co-seasonal sublingual immunotherapy regimen with a modified allergen extract on clinical parameters and on T cell proliferation and regulatory cytokine production (IL-10, TGF-beta). We found that during the birch pollen season symptoms and drug usage scores were 30 and 40% improved, respectively, in treated versus control subjects (p<0.0001 for both comparisons) whereas well days were 23.5 (33%) versus 16.9 (23%) (p=0.0024), respectively. Bet v 1 allergen specific proliferation decreased (p = 0.0010), whereas IL-10 transcription increased (p = 0.0010) in treated, but not in control patients. Moreover, TGF-beta transcription was increased, although not significantly (p=0.066), following immunotherapy. Thus, sublingual immunotherapy with modified allergen in birch-allergic subjects was safe, clinically efficacious and associated with the reduction of allergen-specific proliferation and with the increased production of the IL-10 regulatory cytokine. Int J Immunopathol Pharmacol 2009;22:343-352.


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The mechanisms of action of extracorporeal photochemotherapy (ECP) in cutaneous T-cell lymphoma (CTCL) are poorly understood. Recently, ECP has been shown to induce an increase in regulatory T cell (T_{reg}) expression and functional activities in Graft-versus-host-disease (GvHD), whereas no data are available in CTCL patients. The aim of this study is to evaluate whether ECP is able to modulate the expression levels of the circulating CD4+CD25+bright subset in CTCL patients and whether these modifications are related to the disease course. The patient population included 43 CTCL and 15 chronic GvHD patients treated by ECP at our institutions since 1992. The expression of the circulating CD4+CD25+bright subset was analysed at baseline and sequentially during treatment by flow-cytometry. Fifty healthy donors were used as controls. The baseline circulating CD4+CD25+bright percentage values in CTCL (median: 4.3%) were similar to those of healthy donors, whereas GvHD showed significantly lower values (median: 1.5%; p<0.001). During treatment, CTCL patients were characterised by an early decrease (from 4.3% to 2.4% median after 6 months). The CD4+CD25+bright decrease was associated to the disease course, as it occurred in 91.3% of responding but in only 25% of PD patients (p=0.0001). On the other hand, a significant increase of CD4+CD25+bright cells was observed in GvHD. ECP induces
a reciprocal modulation of the circulating CD4+CD25+bright cells in CTCL and GvHD, with a
downregulation in CTCL potentially associated with the response mechanisms. Int J Immunopathol

13. High-dose inhaled flunisolide versus budesonide in the treatment of acute asthma
exacerbations in preschool-age children

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The role of inhaled corticosteroids in asthma exacerbation is debated. We compared high doses of
nebulized budesonide versus high doses of nebulized flunisolide, in association with a short-acting beta-
2-agonist, in the treatment of moderate asthma exacerbation in preschool children. In this randomized,
parallel group, simple blind study, 46 children aged between 3 and 5 years affected by an acute moderate
asthma attack were treated with nebulized flunisolide (Group 1) 40 μg/kg twice daily for 7 days and
then 20 μg/kg twice daily for 14 days, or with nebulized budesonide (Group 2) 0.5 mg twice daily for
7 days then 0.25 mg twice daily for 15 days. Inhaled salbutamol (MDI+ spacer - 200 μg 4 times daily)
was administered during the first 3 days of the study and then as needed. At T0, T7 and T21 days,
airway resistances were evaluated with the forced oscillation technique before and after inhalation of
inhaled salbutamol (200 mcg). Parents recorded symptoms and drug use on a diary card. Forty children
completed the study. Airway resistances were significantly reduced at T7 (p< 0.01 flunisolide; p< 0.05
budesonide) and T21 (p< 0.05 flunisolide; p< 0.05 budesonide) versus T0 in both groups, although at T7
the reduction occurred faster in group 1 than in group 2 (p<0.01). During the first 7 days of treatment,
symptom scores decreased in both groups; however, the decrease was greater in group 1 (p< 0.05).
High doses of inhaled flunisolide and budesonide are both effective in the management of moderate
asthma exacerbations in pre-school-age children, but the flunisolide therapeutic effect was faster than

14. Angiogenesis in psoriatic skin and its modifications after administration of etanercept:
videocapillaroscopic, histological and immunohistochemical evaluation.

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Several studies suggest that microangiopathy plays a crucial role in the pathogenesis of psoriasis.
TNFalpha up-regulates the genetic transcription of VEGF, a pro-angiogenetic cytokine over-expressed in
psoriatic skin, which promotes micrangiopathic modifications in psoriatic plaque. Etanercept is a
chimeric protein used in the treatment of psoriasis and other immunomediated disorders, which blocks
inflammatory response by interfering in the binding of TNF-alpha to its receptors. Starting from this
data, we retain that Etanercept can improve microangiopathy in psoriatic skin by reducing the synthesis of pro-angiogenic chemokine VEGF. The aims of the study are: to verify the effect of Etanercept on cutaneous en plaque capillaries in vivo using intra-vital videocapillaroscopy analysis, to evaluate the relation between the en plaque videocapillaroscopic pattern and the immunohistochemical cutaneous expression of VEGF in psoriasis, and finally to correlate all these in data with clinical disease activity. Eighteen patients (10 male and 8 female, mean age 51, range 21-60) suffering from stable, eN plaque type psoriasis, involving at least 10% of body surface area (BSA), and not responsive to conventional therapy were included in the study. All the enrolled patients received Etanercept 50mg/twice/week, subcutaneously, for 12 weeks, and were carefully followed up for clinical response with PASI score and DLQI index both before (T0) and after 12 weeks (T12) of treatment with Etanercept. A well-demarcated psoriatic plaque of the extensor surface of upper extremities was chosen to perform an intra-vital videocapillaroscopy analysis (IVCP), and a skin biopsy for immunohistochemical study both at T0 and T12 in all the included patients, in order to evaluate the presence of microangiopathy and its modification after therapy. All the patients experienced a clinical improvement of cutaneous disease with a significant decrease of PASI score (p<0.0001) and DLQI level (p<0.0001), throughout the twelve weeks of treatment. On IVCP analysis, microangiopathy dramatically decreased (p<0.0001), this modification being significantly related with PASI and DLQI decrease at T12. Immunohistochemical expression of VEGF decreased significantly from T0 to T12 (p<0.0001), and was related with a reduction of psoriatic microangiopathy at T12. The results of our videocapillaroscopic and immunohistochemical investigation confirm that the therapeutic potentiality of Etanercept is based also on its capability to promote the regression of psoriatic microangiopathy. Moreover, according to these considerations, videocapillaroscopic evaluation of psoriatic plaque, both before and after treatment with Etanercept, may be a useful tool to objectively demonstrate its effect on microcirculation. Int J Immunopathol Pharmacol 2009;22:371-377.

15. Quantity, distribution and immunophenotypical modification of dendritic cells upon biological treatments in psoriasis.

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Psoriasis is an immune-mediated disease which affects a large world population. It has long been considered a dermatological disorder in which keratinocytes and lymphocytes play a relevant pathogenic role. The aim of our study is to more closely observe and better define the role of dendritic cells (DCs) in psoriasis. We made a comparative analysis of the antigenic profile and the number, by immunohistochemical and electron microscopical study, of skin biopsy samples from psoriatic patients before and 4 months after biological treatments. Our results demonstrate an abundant distribution of activated DCs in lesional skin of psoriatic plaques and a marked decrease after biological therapies [a decrease of 70% for Langerhans cells (LCs) and mature myeloid dendritic cells (mDCs) and of 50% for plasmocytoid dendritic cells (pDCs)]. Both previous reports and the results of the present study support an underlying persistent immune response involving DCs in the onset and persistence of psoriasis. As DCs play a pivotal role in pathogenesis of psoriasis by presenting antigens via major histocompatibility complex class (MHC) II molecules, the present study supports the view that biological therapies are also effective in clearing psoriatic lesions as well as in reducing the number of DCs. Int J Immunopathol Pharmacol 2009;22:379-387.

16. Placenta growth factor is a survival factor for human malignant mesothelioma cells.
Placenta growth factor (PlGF) is a key regulator of pathological angiogenesis and its overexpression has been linked to neoplastic progression. To assess whether PlGF could have a role in malignant mesothelioma (MM), we analyzed the expression of PlGF, VEGF, and their cognate receptors (VEGF-R1 and VEGF-R2) and co-receptors (neuropilin-1 and neuropilin-2) in MM cell lines as well as in resected MM tissues, hyperplastic/reactive mesothelium and normal mesothelium. MM cell cultures expressed both ligands and the associated receptors to a variable extent and released different amounts of PlGF. As assessed by immunohistochemistry, PlGF expression was switched on in hyperplastic/reactive compared to normal mesothelium. Moreover, 74 and 94% of MM tissues overexpressed PlGF and VEGF-R1, respectively ($p<0.05$ MM vs normal mesothelium). Administration of recombinant PlGF-2 did not elicit a significant stimulation of MM cell growth, while it was associated with a transient phosphorylation of Akt, suggesting that PlGF-2 could activate downstream effectors of proliferative and cytoprotective signals via VEGF-R1 in MM cells. Indeed, the administration of an anti-PlGF antibody was found to cause a significant reduction of MM cell survival. In conclusion, our data demonstrate that, by acting as a survival factor, PlGF can play a role which goes beyond the stimulation of angiogenesis in MM. This evidence could help the rational design of new therapeutic interventions for this aggressive tumor. **Int J Immunopathol Pharmacol 2009;22:389-401.**

17. Clinical data and inflammation parameters in patients with cypress allergy treated with sublingual swallow therapy and subcutaneous immunotherapy.

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The clinical efficacy of immunotherapy, either by high dose sublingual-swallow therapy (SLIT) or subcutaneous immunotherapy (SCIT), has been demonstrated in patients with pollinosis but few studies have been carried out analysing differences in these treatments in terms of an improvement of clinical and allergic phlogosis parameters. The aim of this double-blind placebo-controlled study is to investigate the efficacy of high dose SLIT and SCIT using a purified standardized *Juniperus ashei* extract in a population of allergic patients monosensitized to cypress. Forty patients with cypress-allergic rhino conjunctivitis were administered therapeutic or placebo SLIT or SCIT for 12 months. Laboratory parameters were studied, namely the eosinophil cationic protein (ECP) level in nasal lavage and in serum, as well as the number of eosinophils (EOS) in peripheral blood and in nasal lavage and the level of eosinophil chemotactic activity (ECA). These parameters were correlated with clinical symptoms, evaluated by means of the clinical symptoms score (CSS). After SCIT and SLIT the levels of ECP and ECA were reduced in nasal lavage. We also observed a significant reduction in the values of ECP in serum in the patients treated with SLIT. EOS were unchanged in peripheral blood, but significantly reduced in nasal lavage. These data were in accordance with the improvement of clinical symptoms, supported by the close correlation between CSS and laboratory parameters. Our data confirm a clinical improvement correlated with a decline in inflammation parameters after one year of immunotherapy,
supporting the hypothesis that treatment with a major allergen of cypress is able to change the course of allergic rhinitis. *Int J Immunopathol Pharmacol* 2009;22:403-413.

18. The safety of anti-TNF agents in the elderly

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Rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis are commonly thought of as inflammatory diseases that affect younger individuals. Although the initial presentation of these diseases is common in a patient’s twenties or thirties, they usually persist for the duration of the patient’s life. In addition, up to one-third of patients with RA have disease onset after 60 years of age. Anti-TNF-a therapies now have well-recognized safety profiles that have been demonstrated in the usual clinical trial populations for these diseases, but such populations under-represent patients > or =65 years of age. This retrospective study aims to determine the safety profiles for etanercept, infliximab and adalimumab in patients of 65 years or more, undergoing anti-TNF treatment for an active inflammatory disease such as rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis, or skin disease like psoriasis. Our data show that admitting elderly patients into anti-TNF therapeutic regimens is a safe option and that it grants these patients access to the best current therapeutic option, possibly leading to better disease outcome. Quality of life in elderly patients affected by arthritis or psoriasis, often reduced by comorbidities, is as important as quality of life in younger patients. Applying the recommended screening before using biological treatment helps to reduce adverse events related to the therapy, and the application of the same screening in elderly patients seems to lead to comparable results. *Int J Immunopathol Pharmacol* 2009;22:415-426.

19. Functional characterization of muscle fibres from patients with chronic fatigue syndrome: case-control study

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Chronic fatigue syndrome (CFS) is a disabling condition characterized by unexplained chronic fatigue that impairs normal activities. Although immunological and psychological aspects are present, symptoms related to skeletal muscles, such as muscle soreness, fatigability and increased lactate accumulation, are prominent in CFS patients. In this case-control study, the phenotype of the same biopsy samples was analyzed by determining i) fibre-type proportion using myosin isoforms as fibre type molecular marker and gel electrophoresis as a tool to separate and quantify myosin isoforms, and ii) contractile properties of manually dissected, chemically made permeable and calcium-activated single muscle fibres. The results showed that fibre-type proportion was significantly altered in CSF samples, which showed a shift from the slow- to the fast-twitch phenotype. Cross sectional area, force, maximum shortening velocity and calcium sensitivity were not significantly changed in single muscle fibres from CSF samples. Thus, the contractile properties of muscle fibres were preserved but their proportion was changed, with an increase in the more fatigue-prone, energetically expensive fast fibre type. Taken together, these results support the view that muscle tissue is directly involved in the pathogenesis of CSF and it might contribute to the early onset of fatigue typical of the skeletal muscles of CFS patients. Int J Immunopathol Pharmacol 2009;22:427-436.

20. Antibodies to ganglioside complexes in Guillain-Barré syndrome: clinical correlates, fine specificity and complement activation

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In the Schwann cells and neuronal plasma membranes the gangliosides are organized in clusters forming complexes of gangliosides in the microdomains termed lipid rafts. We investigated frequency, clinical correlates, fine specificity and pro-inflammatory properties of antibodies to ganglioside complexes (GSCs) in a Guillain Barré syndrome (GBS) population. In 63 patients with different GBS variants we performed an ELISA for antibodies to Campylobacter Jejuni (C. jejuni), gangliosides and GSCs. We studied the fine specificity of antibodies to GSCs by immunoabsorption study and performed a complement activation assay. Twenty-seven percent of patients had antibodies to GSCs and 71% had antibodies either to single gangliosides or to GSCs. Patients with antibodies to GSCs had more frequent involvement of cranial nerves but did not present more frequent antecedent respiratory, gastrointestinal or C. jejuni infection, did not have a preferential demyelinating or primary axonal GBS variant and did not develop greater disability at six months. The absorption study showed in 2 sera that antibodies to the complex GD1a/GD1b did not react with the gangliosides forming the complex or other single gangliosides, suggesting that antibodies to GSCs are targeted to new conformational glycoepitopes different from the ones displayed by the single gangliosides. Antibody anti-GSCs activated the complement more frequently than antibodies to single gangliosides. Complement activation indicates that antibodies to GSCs have high avidity, pro-inflammatory properties and may exert a pathogenic role in GBS. Int J Immunopathol Pharmacol 2009;22:437-445.

21. Imaging progression despite clinical remission in early rheumatoid arthritis patients after etanercept interruption

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The aim of this preliminary study is to evaluate clinical and imaging response in twenty patients with early Rheumatoid Arthritis (eRA) treated with Etanercept (Etn) + Methotrexate (Mtx) and to investigate whether clinical and MRI remission may be maintained after biological therapy interruption. Assessment included: radiography, Visser score and anti-CCP antibodies at baseline; disease activity score in 44 joints (DAS44), rheumatoid factor (RF), Magnetic Resonance Imaging (MRI) of hands and wrists at baseline (T0), 12 (T1), and 24 months (T2). MRI was scored for synovitis, bone oedema and erosions (OMERACT study); patients who reached clinical and imaging remission at T1 were considered eligible for interrupting Etn. At T1 8/20 (40%) patients showed a total remission [DAS44 from 5 (T0) to 1.4 (T1); p<0.02], whereas the other 12/20 (60%) showed an improvement, without complete remission [DAS44 from 4.8 (T0) to 2.8 (T1); p<0.05]. Etn was therefore interrupted in the first group of patients (group A), whereas it was continued in the other group (group B). At T2, group A maintained clinical remission and group B showed further not significant DAS44 reduction from T1. At T1, a significant reduction in synovitis, bone oedema and total score (p<0.01) was observed both in group A and in group B. At T2, group A showed an increase in all the MRI scores that was significant for the synovitis and total score, whereas group B exhibited a further not significant reduction. This preliminary study reports an excellent clinical and imaging response in eRA patients treated with Etn with total remission in 40% of them after a 1-year therapy period. However, it indicates that joint damage may progress, despite a sustained clinical remission, after Etn suspension Int J Immunopathol Pharmacol 2009;22:447-454.

22. Ultrasound-guided hyaluronic acid injection in carpometacarpal osteoarthritis: short-term results

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Carpometacarpal osteoarthritis (CMC-OA) is a disabling condition, characterized by pain and functional impairment. The aim of the present study is to evaluate the efficacy of a single ultrasound-guided injection of hyaluronic acid (HA) in patients suffering from CMC-OA. Eighteen patients with CMC-OA, grade 2-3 Kellgren and Lawrence score, attending the Orthopaedic Department of the University Hospital of Chieti, were enrolled. They underwent clinical evaluation at baseline and after one month follow-up, evaluating: grading of pain (VAS at rest and during activities), function (Dreiser Index), grip and pinch strengths Jamar dynamometer), as well as NSAIDs consumption. Each patient received a single ultrasound-guided injection of HA into the articular CMC joint. The results were that pain at rest and during activities decreased from 1.8 ± 1.07 to 0.5 ± 0.68 (p < 0.001) and from 8.05 ± 0.94 to 4.15 ± 1.42 (p < 0.001), respectively. Dreiser Functional Index showed a significant improvement (+11.59 %; p < 0.004), as well as pulp pinch strength (24.07 %; p < 0.001). The consumption of NSAIDs was also clearly reduced, from 16 to 7 patients (~45%) and from 2.45 ± 1.98 to 1.15 ± 1.30 tablets per week (p < 0.02). Mild local side effects,
lasting less than 3 hours, were observed only in 2 cases. A single ultrasound guided injection of HA is a safe and effective procedure in CMC-OA, with a significant improvement in terms of pain and function. However, studies with larger samples and longer term follow-up are warranted. *Int J Immunopathol Pharmacol* 2009;22:455-460.

23. **Structure and function of the nicotinic arm of acetylcholine regulatory axis in human leukemic T cells.**

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Although acetylcholine (ACh) is widely known as a neurotransmitter, it also functions as a local humoral factor translating environmental stimuli into alterations in T cell development and function. The cholinergic components present in neurons are expressed in T cells where they constitute an independent cholinergic system. Both non-immunologic and immunologic stimulations can alter expression and function of cholinergic elements in T cells. Recent studies have convincingly demonstrated regulation of immune system by auto/paracrine ACh, which provides a basis for development of new immunomodulatory therapies with nicotinic agonists. The purpose of our research is to integrate information about the structure and activity of the ACh regulatory axis with the phenotypic and functional alterations of T cells during their development and commitment. In this study, we used the Ach producing human leukemic T cell line CCRF-CEM (CEM) to investigate auto/paracrine mechanisms of T cell regulation through the nicotinic class of ACh receptors (nAChRs). The intact CEM expressed alpha3, alpha5, alpha6, alpha7, alpha 9, beta2 and beta4 nAChR subunits. Stimulation of CEM with 10 μg/ml of phytohemagglutinin (PHA) for 16 h upregulated expression of the alpha3, alpha5, alpha7, alpha9 and beta2 and downregulated that of alpha6 and beta4 subunits, indicating that TCR activation leads to overexpression of high Ca2+-permeable ACh-gated ion channels. Activation of alpha7- and alpha3 AChRs predominantly abrogated PHA-dependent upregulation of the pro-inflammatory cytokine TNF-alpha and IFN-gamma receptors, respectively, at the mRNA and protein levels. Signaling through alpha7 and alpha3 nAChRs also significantly (p<0.05) altered expression of the cell state regulators p21 and Bcl-2, respectively, suggesting that downregulation of inflammation via nAChRs includes effects on the T cell cycle progression and apoptosis. These findings indicate that constant stimulation of alpha7 and alpha3 nAChRs by endogenously released ACh controls T cell activation and that signaling downstream of distinct nAChR subtypes targets specific inflammatory and cell cycle genes. Learning the cholinergic pharmacology of inflammation should allow to regulate specific types of immune reactions by selectively activating or blocking the types of nAChRs expressed by the immune cells mediating specific immune reactions. *Int J Immunopathol Pharmacol* 2009;22:461-472

24. **Amyloid β peptides trigger CD47-dependent mast cell secretory and phagocytic responses.**


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Mast cells are found in the brain, where they contribute to immune responses. They have been implicated in multiple sclerosis, but their potential role in Alzheimer’s disease (AD), another inflammatory disease of the central nervous system, remains elusive. In the present study, we examined mast cell responses to
amyloid β (Aβ) peptides 1-40 and 1-42, the major components of the Alzheimer amyloid plaques. Rat peritoneal mast cells were used as experimental model for human brain serosal mast cells. Fibrillar Aβ1-40 and Aβ1-42 peptides induced concentration-dependent exocytosis, as assessed by measurement of histamine secretion; exocytosis was reduced by pre-treatment with pertussis toxin and with antibodies against the CD47 receptor and the β₃-integrin subunit. Fibrillar Aβ1-40 and Aβ1-42 peptides coated on heat-inactivated yeast particles and soluble fibrillar Aβ1-40 and Aβ1-42 peptides were also recognized and phagocyted by mast cells. Uptake of the peptides was decreased in the presence of 4N1, a peptide agonist of the CD47 receptor, but remained unchanged in the presence of 4NGG, a peptide derived from 4N1 which does not bind to CD47. Non-fibrillar forms of Aβ1-40 and 1-42 peptides were unable to elicit mast cell responses. These results show that fibrillar Aβ peptides can trigger mast cells and elicit exocytosis and phagocytosis. The Aβ-induced activation of mast cells operates through a CD47/β₃-integrin membrane complex coupled with Gi-protein. The present data support the hypothesis that mast cells, similarly to microglial cells, could play a major role in AD pathogenesis. *Int J Immunopathol Pharmacol* 2009;22:473-483.

25. Enhancement of fibroblast proliferation, collagen biosynthesis and production of growth factors as a result of combining sodium hyaluronate and aminoacids.


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Fibroblasts play a key role in tissue healing by producing the majority of extracellular matrix components, favouring granulation tissue formation, and stimulating re-epithelialization. Hyaluronan is a component of ECM and its anti-inflammatory effects and properties in enhancing wound closure are well known. In this study, we examined the effects of Aminogam® gel, a new pharmacological preparation suggested to improve wound healing, composed of hyaluronic acid, proline, lysine, glycine and leucine, on human fibroblasts. Results show that fibroblasts treated with hyaluronic acid plus aminoacid solution increased their proliferative activity, collagen I and III, and fibronectin synthesis. Moreover, HA plus aminoacid solution increased the expression of transforming growth factor beta, connective tissue growth factor, interleukin-6 and -8, assayed by RT-PCR. These results suggested that Aminogam® gel, involved in several stages of wound healing, as fibroblast proliferation, granulation tissue formation, ECM component deposition, and production of cytokines, may be a useful device to favour and accelerate wound closure. *Int J Immunopathol Pharmacol* 2009;22:485-492.

26. The role of interleukin-6 and transforming growth factor-β1 in predicting restenosis within stented infarct-related artery.


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Despite high efficacy of percutaneous coronary intervention (PCI), in-stent restenosis proves to be a significant problem of therapy. Restenosis concerns around 30% of patients. Studies have suggested that restenosis is initiated by cells which participate in intense inflammatory reaction caused by stent implantation. Atherosclerotic plaque rupture during stent implantation and PCI-associated injury of the vessel wall lead to hemorrhage and release of various cytokines. They are probably responsible for quick recurrence of vascular lumen stenosis (restenosis). Interleukin-6 (IL-6) is known as a main pro-inflammatory cytokine, whereas Transformig Growth Factor-β1 (TGF-β1) has anti-inflammatory properties. The study population comprised 36 patients with myocardial infarction treated with PCI with stent implantation. They underwent control coronary angiography after 12 months. At this time plasma concentration of IL-6 and TGF-β1 was measured in peripheral blood. Serum IL-6 concentration in the analyzed population correlates with lumen loss (p<0.01) and the severity of stenosis (p<0.001). No such correlation was found between serum TGF-β1 concentration and lumen loss (p=NS) or the severity of stenosis (p=NS). The IL-6 plasma concentration may be a marker of in-stent restenosis in patients after PTCA, while the concentration of TGF-β1 is not associated with the occurrence of restenosis at one year of follow-up. Int J Immunopathol Pharmacol 2009;22:493-500.

27. Apicidin, the histone deacetylase inhibitor, suppresses Th1 polarization of murine bone marrow-derived dendritic cells
Pp 501-515


Apicidin is a fungal metabolite shown to exhibit anti-proliferative, anti-invasive, and anti-inflammatory properties by the inhibition of histone deacetylase (HDAC). However, the effects of apicidin on the maturation and immunostimulatory function of dendritic cells (DCs) remain unknown. In this study, we investigated whether apicidin modulates surface molecule expression, cytokine production, endocytosis capacity, and underlying signaling pathways in murine bone marrow-derived DCs. We observed that apicidin significantly attenuated surface molecule expression in LPS-stimulated DCs, suppressed production of interleukin (IL)-12 and proinflammatory cytokines (IL-6 and TNF-α) by DCs, and reduced IFN-γ production by T cells. The apicidin-treated DCs were found to be highly efficient in antigen capture via mannose receptor-mediated endocytosis. Apicidin also inhibited LPS-induced MAPK activation and NF-κB nuclear translocation in DCs. Moreover, the apicidin-treated DCs were incapable of inducing Th1 responses and normal cell-mediated immune responses. These novel findings not only provide new
insights into the immunopharmacological role of apicidin in terms of its effects on DCs, but also broaden current perspectives of the immunopharmacological functions of apicidin, and have implications for the development of therapeutic adjuvants for the treatment of DC-related acute and chronic diseases. *Int J Immunopathol Pharmacol* 2009;22:401-415.

28. **The transplant of the white man’s leg: a novel representation of Cosma and Damian’s miracle**

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The history of the miracle performed by the patron saints of medicine Cosma and Damian is well known: physicians and historians have dealt with this subject on many occasions, giving rise to a large range of literature. The Author brings up the problem again, on the ground of a novel Spanish painting which has never previously been taken into consideration from a medical point of view but which reserves some surprises and offers a possible psychological consideration of the matter. *Int J Immunopathol Pharmacol* 2009;22:517-520.

29. **Association between familial mediterranean fever and retroperitoneal fibrosis: retroperitoneal fibrosis regression after colchicine therapy.**

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30. **High serum tryptase value in massive acute myocardial infarction with ventricular arrhythmia exortion in a cocaine abuser**

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A 38-year-old cocaine abuser was admitted to the Emergency Department with a one hour history of precordial chest pain associated with shortness of breath and extreme discomfort. On admission his blood pressure was 90/60 mmHg, the resting 12-lead ECG showed ventricular tachycardia at about 300 beats per minute, and oxygen saturation was 86% in room air. After electrical cardioversion, the 12-lead ECG revealed sinus rhythm and a significative ST segment elevation in leads I, aVL and V1-V6, that was about 0.5 mV in leads I and aVL and more than 1 mV in leads V2, V3 and V4. Laboratory determinations showed elevated creatine-chinase MB (CK-MB) and troponin I. An emergency coronary angiogram was normal. Cocaine use is a major cause of acute myocardial infarction in patients with normal epicardial coronary arteries but the exact mechanism still remains unclear. We hypothesize a non-IgE mediated mast-cell activation, with a direct action played by cocaine, and consequent massive expression of several factors affecting the microcirculatory system, including pro-inflammatory cytokines and chemokines. Our hypothesis is supported by an elevated serum tryptase levels in the patient. Int J Immunopathol Pharmacol 2009;22:525-529.

31. Successful lamivudine monotherapy in an elderly patient suffering from HBV-related decompensated cirrhosis associated with widespread leukocytoclastic vasculitis

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Hepatitis B virus (HBV) infection is known to be responsible for both hepatic and extrahepatic manifestations including dermatitis, polyarthralgias and arthritis, pulmonary disease, aplastic anemia, glomerulonephritis and vasculitis. The mechanism of these extrahepatic disorders is thought to be linked to immune complex disease, but their pathogenesis is poorly clarified. Immunosuppressive treatment could promote viral load and impair hepatic disease, also worsening the vasculitis by enhancing viral antigenemia. Lamivudine is a nucleoside analogue approved for treating chronic hepatitis B, that decreases the amount of viral antigens by suppressing HBV replication. Several reports have suggested lamivudine in the treatment of vasculitis associated with HBV infection, but, although significant inhibition of HBV is achieved in the short term, resistance develops in 15-32% annual risk rating. We report an elderly patient whose chronic hepatitis B decompensated cirrhosis with associated refractory hepatic hydrothorax and extensive leukocytoclastic vasculitis was successfully treated with ongoing long-term lamivudine monotherapy. Int J Immunopathol Pharmacol 2009;22:531-535.

32. Detection of different Borrelia burgdorferi genospecies in serum of people with different occupational risks: short report

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This study is aimed at applying a previously described PCR-based method to detect B. burgdorferi
sensu lato and different *Borrelia* genospecies in total DNA preparations of serum samples collected from people with different occupational risks for tick bite and with serological evidence of borreliosis. Among the seropositive samples, the PCR for *B. burgdorferi* confirmed the positivity in 65% of the forestry workers and in 60% of the subjects living in the same area. None of the seronegative subjects belonging to the control group showed the presence of *B. burgdorferi* sensu lato DNA. Results on genospecies distribution show that *B. afzelii* was the predominant species, followed by *B. garinii* and finally by *B. valaisiana*. Int J Immunopathol Pharmacol 2009;22:537-541.

33. Efficacy and safety of anti-TNF-α therapy combined with cyclosporine a in patients with rheumatoid arthritis and concomitant hepatitis C virus infection

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This study further expands our previous observation demonstrating the usefulness of combination therapy of anti-TNF-alpha and Cyclosporine A in the treatment of rheumatoid arthritis and concurrent hepatitis C virus infection, as well its efficacy and safety in controlling HCV viremia and liver toxicity. Seven patients were included in the study; transaminase levels remained unchanged, HCV RNA serum levels decreased significantly and DAS 28 significantly improved after twelve month follow-up. No side effects were registered. *Int J Immunopathol Pharmacol* 2009;22:543-546.

34. Successful treatment with etanercept of a patient with psoriatic arthritis after adalimumab-related hepatotoxicity

Pp 547-549

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Inhibitors of Tumor Necrosis Factor (TNF) alpha (infliximab, etanercept, adalimumab) are nowadays widely used for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), not responding to conventional therapies. Anti-TNF alpha drugs have demonstrated great efficacy in slowing the disease, however, to date, concern still remains regarding acute and long-term toxicity related to TNF block. Increase in liver tests may be observed during treatment with anti-TNF agents, more often related to concomitant drugs (i.e. NSAIDS, methotrexate) or to reactivation of chronic HBV or HCV infections. However, liver damage directly induced by the drug has been described in patients treated with infliximab or adalimumab. To our knowledge, no cases of liver injury closely related to etanercept have been reported so far. We report the case of a patient with PsA who presented liver dysfunction during adalimumab, subsequently successfully treated with etanercept. *Int J Immunopathol Pharmacol* 2009;22:547-549.
Behcet’s disease (BD) is a chronic, relapsing, multi-system inflammatory disorder, clinically characterized by recurrent oral and genital ulcers, skin lesions, and uveitis. Other manifestations include arthritis, a positive pathergy test, thrombophlebitis, central nervous system disease and gastrointestinal ulcerations. The majority of affected individuals do not have life-threatening disease, although mortality can be associated with vascular-thrombotic and neurological manifestations. Currently, treatment of BD is symptomatic and empirical, and is tailored according to the severity of clinical features. In the past few years, isolated reports and case-series have been published on adult BD patients suggesting that inhibition of TNF-α is a promising therapeutic approach for severe ocular and various extra-ocular manifestations, including central nervous system involvement. In this study we present our promising experience with Etanercept therapy in juvenile-onset BD patients, characterized by refractory multiorgan involvement. Int J Immunopathol Pharmacol 2009;22:551-555.