

## PRESENT STATUS AND NEW PERSPECTIVES IN LASER WELDING OF VASCULAR TISSUES

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The laser welding of biological tissues is a particular use of lasers in surgery. The technique has been proposed since the 1970s for surgical applications, such as repairing blood vessels, nerves, tendons, bronchial fistulae, skin and ocular tissues. In vascular surgery, two procedures have been tested and optimized in animal models, both *ex vivo* and *in vivo*, in order to design different approaches for blood vessels anastomoses and for the repair of vascular lesions: the laser-assisted vascular anastomosis (LAVA) and the laser-assisted vessel repair (LAVR). Sealing tissues by laser may overcome the problems related to the use of conventional closing methods that are generally associated with various degrees of vascular wall damage that can ultimately predispose to vessel thrombosis and occlusion. In fact, the use of a laser welding technique provides several advantages such as simplification of the surgical procedure, reduction of the operative time, suppression of bleeding, and may guarantee an optimal healing process of vascular structures, very similar to *restitutio ad integrum*. Despite the numerous preclinical studies performed by several research groups, the clinical applications of laser-assisted anastomosis or vessel repair are still far off. Substantial breakthrough in the laser welding of biological tissues may come from the advent of nanotechnologies. Herein we describe the present status and the future perspectives in laser welding of vascular structures.

## SKEWED T-CELL RECEPTOR REPERTOIRE: MORE THAN A MARKER OF MALIGNANCY, A TOOL TO DISSECT THE IMMUNOPATHOLOGY OF INFLAMMATORY DISEASES

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The highly diverse heterodimeric surface T cell receptor (TCR) gives the T lymphocyte its specificity for MHC-bound peptides needed to initiate antigen-recognition. In normal peripheral blood, spleen and lymph nodes, the TCR repertoire of the T lymphocytes is usually polyclonal. However, in malignancies such as leukemias, as well as in lymphoproliferative diseases of mature T cells, the TCR is a reflection of the clonality of the malignant cells and is therefore monoclonal. Several clinical conditions (mainly solid tumors and autoimmune diseases) have been described where the TCR repertoire is restricted. The ability to demonstrate clonal TCR usage provides a useful tool to dissect the immunopathology of inflammatory diseases. In this review we discuss these findings and propose to sub-divide diseases with restricted TCR repertoire into a group of conditions in which there is a known TCR ligand, as opposed to diseases in which the restricted TCR repertoire is the result of impaired T-cell development. This classification sheds light on the pathogenesis of several inflammatory diseases.

## PSYCHOLOGICAL STRESS AND VITAMINS

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Conditions of stress and anxiety have complex interactions with insufficient vitamin intake and malnutrition. This study, based on literature research in Medline, analyzes the inter-relationship between vitamins and stress. This report concerns a number of vitamins that have been receiving much attention in earlier reviews of the literature, for their potential to protect against stress-related events, and focus is placed upon recent findings.

## GABA REPRESENTATION IN HYPOXIA SENSING: A VENTILATORY STUDY IN THE RAT

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Phenibut, a nonspecific GABA derivative, is clinically used as an anxiolytic and tranquilizer in psychosomatic conditions. A GABA-ergic inhibitory pathway is engaged in respiratory control at both central and peripheral levels. However, the potential of phenibut to affect the O<sub>2</sub>-related chemoreflexes has not yet been studied. In this study we seek to determine the ventilatory responses to changes in inspired O<sub>2</sub> content in anesthetized, spontaneously-breathing rats. Steady-state 5-min responses to 10% O<sub>2</sub> in N<sub>2</sub> and 100% O<sub>2</sub> were taken in each animal before and 1 h after phenibut administration in a dose 450 mg/kg, i.p. Minute ventilation and its frequency and tidal components were obtained from the respiratory flow signal. We found that after a period of irregular extension of the respiratory cycle, phenibut stabilized resting ventilation at a lower level [20.0±3.3 (SD) vs 31.1±5.2 ml/min before phenibut; P<0.01]. The ventilatory depressant effect of phenibut was not reflected in the hypoxic response. In relative terms, this response was actually accentuated after phenibut; the peak hypoxic ventilation increased by 164% from baseline vs the 100% increase before phenibut. Regarding hyperoxia, its inhibitory effect on breathing was more expressed after phenibut. In conclusion, the GABA-mimetic phenibut did not curtail hypoxic ventilatory responsiveness, despite the presence of GABA-ergic pathways in both central and peripheral, carotid body mechanisms mediating the hypoxic chemoreflex. Thus, GABA-mediated synaptic inhibition may be elaborated in a way to sustain the primarily defensive ventilatory chemoreflex.

# CHANGES OF IMMUNOMODULATORY CYTOKINES ASSOCIATED WITH OMALIZUMAB THERAPY FOR SEVERE PERSISTENT ASTHMA

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Omalizumab is an anti-IgE monoclonal antibody that was proven effective for the treatment of severe asthma. IgE plays a central role in allergic asthma, and an anti-allergic effect of omalizumab has been confirmed in terms of its impact on Th2 cytokines. The objective of the present study is to determine the influence of omalizumab on clinical parameters and circulating immunoregulatory cytokines. Patients with severe allergic asthma were enrolled and given four months of omalizumab therapy. Changes of symptoms and other parameters were assessed, including the asthma control test (ACT) score, morning peak expiratory flow (PEF), peripheral eosinophil count, total serum IgE, and pulmonary function tests. The use of corticosteroids and short-acting bronchodilators, as well as the number of unscheduled hospital visits, were monitored. Circulating levels of cytokines were analyzed with a multiplex cytokine immunoassay in patients with or without omalizumab therapy. Asthma symptoms (evaluated by the ACT score and morning PEF) improved with omalizumab treatment, while total IgE was elevated. Use of corticosteroids and short-acting bronchodilators and the number of unscheduled hospital visits for exacerbation of asthma were all reduced by omalizumab treatment. The level of macrophage inflammatory protein 1- $\delta$  (MIP1- $\delta$ ) was significantly reduced after omalizumab therapy and was high in patients without omalizumab. IL-16 also tended to decrease with omalizumab therapy. Both MIP1- $\delta$  and IL-16 decreased as asthma improved over the 4-month period of omalizumab therapy. These findings suggest that omalizumab may act via IgE-mediated immunoregulation of MIP1- $\delta$  and IL-16.

**BENEFICIAL NUTRACEUTICAL MODULATION OF CEREBRAL ERYTHROPOIETIN  
EXPRESSION AND OXIDATIVE STRESS:  
AN EXPERIMENTAL STUDY**

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**The main object of this study is to examine the effect of Klamin<sup>®</sup>, a nutraceutical containing phenylethylamine, phycocyanins, mycosporine-like aminoacids and aphanizomenon flos aquae-phytochrome on the learning and memory ability, the oxidative status and cerebral erythropoietin and its receptor EPO/EPOR system in prematurely senescent (PS) mice. A total of 28 PS mice, selected according to a prior T-maze test, and 26 non-prematurely senescent mice (NPS) mice were chosen. PS animals were divided into 3 groups and followed for 4 weeks: A) normal chow diet; B) added with Klamin<sup>®</sup> at 20 mg/kg/day (low dose); C) added with Klamin<sup>®</sup> at 100mg/kg/day (high dose). A further group of NPS mice given either normal food (group D) or high dose Klamin<sup>®</sup> (group E) was also considered. The behavioral procedures of spatial learning ability (Morris test) showed that PS mice had significantly longer learning time as compared to their NPS counterpart ( $p<0.01$ ), but this effect was prevented especially in mice supplemented with high-dose Klamin<sup>®</sup> ( $p<0.05$ ) which improved performances in NPS mice ( $p<0.05$ ). High-dose Klamin<sup>®</sup> supplementation restored the depleted total thiol concentration in the brain observed in PS mice while normalizing their increased malonildialdehyde level ( $p<0.05$ ). Moreover, the high-dosage only caused a significant upregulation of EPO/EPOR system both in PS and in NPS animals ( $p<0.05$ ). Taken together, these data suggest that this specific alga Klamath extract has considerable antioxidant and adaptogenic properties, also through a stimulatory effect of cerebral EPO/EPO system.**

# IMMUNE RESPONSES TO *PORPHYROMONAS GINGIVALIS* INFECTION SUPPRESS SYSTEMIC INFLAMMATORY RESPONSE IN EXPERIMENTAL MURINE MODEL

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Periodontitis is localized infectious disease caused by periodontopathic bacteria such as *Porphyromonas gingivalis* (*P. gingivalis*), and the severity correlates to significance of immune responses. Recently, it has been reported that periodontitis is associated with the development of systemic disease such as diabetes and atherosclerosis because of increasing invasion of oral pathogens to the circulation. However, the association between local and systemic infectious responses is still unclear. In the present study, we examined the differences of biological responses in animals with or without bacterial infection. After Balb/c mice were infected subcutaneously with live *P. gingivalis* W83, serum, skin and liver were collected according to experimental protocol. The skin and liver tissues were observed pathologically by haematoxylin-eosin staining, and serum IL-6 levels were measured using ELISA method. Throughout the experimental period, conditions of the mice were observed continuously. As expected, severe infiltration of leukocytes were observed at inflamed skin corresponding to the number of bacterial challenges. Although no inflammatory appearance of skin was observed, serum IL-6 levels were increased dramatically ( $P < 0.01$ , Student's *t*-test) and liver tissues were injured in the mice without bacterial challenge. Interestingly, although severe inflammatory appearance of the skin was observed, serum IL-6 levels were not increased and no inflammatory responses were observed in the liver of the 3-times bacterially challenged group. Importantly, immunoglobulin G against *P. gingivalis* W83 was detected in the blood of mice with 3-times bacterial challenge corresponding to improvement of weight loss and survival. In conclusion, although multiple infections develop severe localized inflammation, the immune system should be sufficient to protect the systemic inflammatory responses.

# THE EFFECT OF THE PLASTICIZER DIETHYLHEXYL PHTHALATE ON TRANSPORT ACTIVITY AND EXPRESSION OF P-GLYCOPROTEIN IN PARENTAL AND DOXO-RESISTANT HUMAN SARCOMA CELL LINES

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Multidrug resistance (MDR) to cancer therapy is frequently associated with the over-expression of the multidrug transporter MDR1 gene product P-glycoprotein (Pgp) in several types of human tumours. Various chemosensitizers have been used to inhibit Pgp activity but toxicity limits their clinical application. Di(2-ethylhexyl)phthalate (DEHP) is a plasticizer that is released from polyvinyl chloride (PVC) medical devices. Therefore, cancer patients undertaking chemotherapy are exposed to a clinically important amount of DEHP through blood and blood component transfusions, apheresis products, intravenous chemotherapy, parenteral nutrition and other medical treatments. The present study was designed to investigate the effects of DEHP on transport activity and expression of Pgp in order to evaluate its potential use as a chemosensitizer in cancer therapy. Human doxorubicin (doxo) resistant sarcoma cells (MES-SA/Dx5) that over-express Pgp were treated with different doses of doxo (2, 4 and 8  $\mu$ M) in the presence or absence of various concentrations of DEHP (3, 6 and 12  $\mu$ M) that were clinically achievable *in vivo*. Our results show that co-treatment with 2, 4 and 8  $\mu$ M doxo in the presence of the lowest concentration of DEHP (3  $\mu$ M) enhanced significantly doxo accumulation in MES-SA/Dx5 cells and, consistently increased the sensitivity to doxo, when compared to controls receiving only doxo. In contrast, higher DEHP concentrations (6 and 12  $\mu$ M) induced MES-SA/Dx5 to extrude doxo decreasing doxo cytotoxicity toward resistant cells below control values. These results are consistent with the increase in Pgp expression levels in parental MES-SA cells treated with 3, 6 and 12  $\mu$ M DEHP for 24 h and compared to untreated controls. All in all, these findings suggest a potential clinical application of DEHP as a chemosensitizer to improve effectiveness of the antineoplastic drugs in MDR human tumours.

# HIGH PREVALENCE OF LATENT TUBERCULOSIS INFECTION IN AUTOIMMUNE DISORDERS SUCH AS PSORIASIS AND IN CHRONIC RESPIRATORY DISEASES, INCLUDING LUNG CANCER

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The early diagnosis and treatment of individuals harboring *M. tuberculosis* is key to ensuring the effectiveness of health programs aimed at the elimination of tuberculosis (TB). Monitoring for TB also has other important health care implications for the related immune pathology caused by the chronic inflammatory response to *M. tuberculosis*. Moreover, the recent introduction of biologic therapies for the treatment of several immune-mediated inflammatory diseases has shown unexpected high frequencies of reactivation of latent TB. The present cross-sectional study is aimed at estimating the prevalence of latent tuberculosis infection (LTBI) in different groups of subjects, either undergoing a routine program of screening for TB or a clinical monitoring of autoimmune or lung disorders, by analyzing their immune response *in vitro* to a pool of different *M. tuberculosis* antigens through an IFN- $\gamma$ -release assay (IGRA). We consecutively tested 1,644 subjects including health care workers (931), healthy immigrants from different countries (93), patients with a diagnosis of psoriasis (405), patients with lung inflammatory disease (60) or lung neoplasia (32) and a group of HIV-1 infected Italian subjects (120). The prevalence of IGRAs positive responses among health care workers was 8.9%. In comparison, significantly higher frequencies were found in healthy immigrant subjects (33.3%), similar to those found in inflammatory broncho-pneumopathies (34.5%) or lung cancer (29.6%). Interestingly, an unexpected high prevalence was also found in patients affected by psoriasis (18.0%), while HIV-infected subjects had values comparable to those of health care workers (10.8%). An age cut-off was determined and applied for each group by receiver operating characteristic (ROC) curves in order to perform the statistical analysis among age-comparable groups. Multivariate analysis showed that the age and clinical conditions such as having a diagnosis of psoriasis or a lung inflammatory disease were independent risk factors for developing an IGRA positive response. This study highlights an unprecedented high prevalence of IGRA positive responses among patients affected by psoriasis and emphasizes the need for a preliminary assessment of LTBI before the administration of any biologic therapy based on cytokine antagonists such as anti-TNF- $\alpha$ . Moreover, screening for LTBI should be routinely performed in the presence of a chronic pulmonary disease.

# REDOX BALANCE SIGNALLING IN OCCUPATIONAL STRESS: MODIFICATION BY NUTRACEUTICAL INTERVENTION

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There is increasing evidence that psychosocial stress can be viewed as a system-wide derangement of cellular homeostasis, with heightened oxidative stress and triggered proinflammatory mechanisms. The aim of this study is twofold: a) to replicate findings that psychological stress increases oxidative damage and b) to determine whether a fermented papaya preparation known to exert significant protective antioxidant properties could buffer such increases in nuclear DNA damage while also inducing epigenetic protective mechanisms. Twenty-eight sedentary men and women (age range: 28-52), who reported living a stressful lifestyle but with an overall positive attitude, were recruited for this study. Chronic diseases as well as severe burnout and use of drugs for anxiety constituted exclusion criteria. Subjects were supplemented for 1 month with 9g/day (4.5g twice a day) of a certified fermented papaya preparation. All subjects were given a stress and sleep quality questionnaire together with a diet and life style assessment. Blood was collected at 2 and 4 week, erythrocyte and leukocyte were separated to assess redox balance and heme oxygenase-1 (HO-1) gene expression while bilirubin oxidized metabolites (BOMs) were tested in the urine. Stressed individuals showed a significant abnormality of redox status with increased MDA of erythrocyte and increased level of 8-OHdG in leukocyte and BOMs excretion ( $p<0.05$ ). Nutraceutical supplementation brought about a normalization of such values already at the 2 week observation ( $p<0.05$ ) together with a significant upregulation of HO-1 ( $p<0.01$ ). Taken together, the results of this study confirm that stressful occupational life per se, without any overt psychiatric illness, may be associated to increased oxidative stress. Supplementation with functional food affecting redox regulation may be part of the therapeutic armamentarium to be considered in this clinical setting.

# A METHOD TO EVALUATE DYNAMICS AND PERIODICITY OF HORMONE SECRETION

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Spontaneous hormone secretory dynamics include tonic and pulsatile components and a number of periodic processes. Circadian variations are usually found for melatonin, TSH and GH, with peak secretions at night, and in cortisol secretion, which peaks in the morning. Free thyroxine (FT4) and insulin-like growth factor (IGF)1 levels do not always change with circadian rhythmicity or show only minor fluctuations. Fractional variations explore the dynamics of secretion related to time intervals, and the rate of change in serum levels represents a signal for the receptorial system and the target organ. We evaluated time-related variations and change dynamics for melatonin, cortisol, TSH, FT4, GH and IGF1 levels in blood samples obtained every 4 h for 24 h from eleven healthy males, ages 35-53 years (mean±SE 43.6±1.7). Nyctohemeral (i.e., day-night) patterns of hormone secretion levels and the fractional rate of variation between consecutive 4-hourly time-qualified hormone serum levels (calculated as % change from time 1 to time 2) were evaluated for circadian periodicity using a 24 and 12-h cosine model. A circadian rhythm was validated for serum level changes in cortisol with peaks of the 24-h cosine model at 07:48h, and melatonin, TSH and GH, with phases at 01:35h, 23:32h, and 00:00h, respectively. A weak, but significant, 12-h periodicity was found for FT4 serum levels, with minor peaks in the morning (10:00h) and evening (22:00h), and for IGF1, with minor peaks in the morning (07:40h) and evening (19:40h). Circadian rhythmicity was found in the 4-hourly fractional variations with phases of increase or surge at 02:00h for cortisol, 22:29h for melatonin, 05:14h for FT4, and 21:19h for GH. A significant 12-h periodicity was found for the 4-hourly fractional variations of TSH with two peaks in the morning (decrease or drop at 04:42h) and afternoon (surge at 16:28h), whereas IGF1 fractional variation changes did not show a significant rhythmic pattern. In conclusion, the calculation of the time-qualified fractional rate of variation allows evaluation of the dynamics of secretion and the specification of the timepoint(s) of maximal change of secretion, not only for hormones whose secretion is characterized by a circadian pattern of variation, but also for hormones that show no circadian or only weak ultradian (12 h) variations (i.e., FT4).

## MOLECULAR CHARACTERIZATION OF NOVEL MELANOMA CELL LINES

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We isolated two novel cell lines from different types of sporadic human malignant melanoma: the *hmel1* line was obtained from a melanoma skin metastasis and the *hmel9* cell line from a primary superficial spreading melanoma. The karyotype and pigmentation parameters were assessed in these cell lines. Cytogenetic analysis in early stages of culture revealed that both cell lines had chromosome instability and simultaneous growth of heteroploid subpopulations. The molecular analysis of some genes involved in melanoma showed that both cell lines harbor BRAF mutations. The unpigmented *hmel1* and the pigmented *hmel9* lines were found to express the tyrosinase gene. The tyrosine hydroxylase activity was detectable only in *hmel9* cells and practically absent in the *hmel1* cell line. This activity was found to be correlated with the relative tyrosinase protein amount in both melanoma cell lines. The biological behaviour in the two melanoma cell lines, derived from two different types of melanoma lesions displaying distinct clinical and histopathological features, confirms the heterogeneous characteristics of sporadic melanoma. Similarities and/or differences between cell lines extracted from different melanoma cases could be useful in the future for diagnostic, prognostic and therapeutic purposes.

# NEURO-ENDOCRINE CORRELATIONS OF HYPOTHALAMIC-PITUITARY-THYROID AXIS IN HEALTHY HUMANS

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Neuro-endocrine hormone secretion is characterized by circadian rhythmicity. Melatonin, GRH and GH are secreted during the night, CRH and ACTH secretion peak in the morning, determining the circadian rhythm of cortisol secretion, TRH and TSH show circadian variations with higher levels at night. Thyroxine levels do not change with clear circadian rhythmicity. In this paper we have considered a possible influence of cortisol and melatonin on hypothalamic-pituitary-thyroid axis function in humans. Melatonin, cortisol, TRH, TSH and FT4 serum levels were determined in blood samples obtained every four hours for 24 hours from ten healthy males, aged 36-51 years. We correlated hormone serum levels at each sampling time and evaluated the presence of circadian rhythmicity of hormone secretion. In the activity phase (06:00h-10:00h-14:00h) cortisol correlated negatively with FT4, TSH correlated positively with TRH, TRH correlated positively with FT4 and melatonin correlated positively with TSH. In the resting phase (18:00h-22:00h-02:00h) TRH correlated positively with FT4, melatonin correlated negatively with FT4, TSH correlated negatively with FT4, cortisol correlated positively with FT4 and TSH correlated positively with TRH. A clear circadian rhythm was validated for the time-qualified changes of melatonin and TSH secretion (with acrophase during the night), for cortisol serum levels (with acrophase in the morning), but not for TRH and FT4 serum level changes. In conclusion, the hypothalamic-pituitary-thyroid axis function may be modulated by cortisol and melatonin serum levels and by their circadian rhythmicity of variation.

## ENDOTHELIAL ACTIVATION AND INJURY BY CIGARETTE SMOKE EXPOSURE

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Endothelial activation/injury following exposure to cigarette smoke may explain incidence of atherosclerosis and cardiovascular disease in smokers. We investigated cigarette smoke extract (CSE) effects relative to activation, injury, and survival of human umbilical vein endothelial cells (HUVEC) and compared circulating levels of specific endothelial activation markers between smokers and healthy non-smokers before and after smoking cessation. Viability and toxicity of HUVEC were tested by MTT and LDH assay. Release (by endothelial cells) and circulating levels (in smokers) of von Willebrand Factor (vWF), thrombomodulin (TM), was evaluated by ELISA. Incubation with increasing concentrations of CSE reduced the percentage of viable cells, being 33.9%, 23.9% after CSE 4%, 6% respectively. Dose- and time-dependent release of LDH was observed after incubation with CSE. vWF, TM release were assayed after CSE 2% HUVEC stimulation. Significant 42%, 61%, 76% increase in vWF concentration was detected respectively at 30', 60', 120'. Reduction in circulating levels of vWF, from a median value of 144.0% to 123.7%, was observed in the quitters group after smoking cessation. Exposure to cigarette smoke is cytotoxic and induces activation/injury of endothelium *in vitro* and *in vivo*. These findings may provide pathogenetic basis by which smoking can predispose to development of atherothrombosis and cardiovascular disease.

## A SYSTEMS BIOLOGY APPROACH: NEW INSIGHTS INTO FETAL GROWTH RESTRICTION USING BAYESIAN NETWORKS

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IL-6, IGF-II and IGFBP-2 concentrations in placental lysates were previously shown to be associated with foetal growth. This study aimed to apply a Bayesian Network (BN) model in order to investigate complex dependencies among biochemical and clinical factors and fetal growth outcome. Twenty-one Intra-Uterine Growth Restricted (IUGR) and 25 Appropriate for Gestational Age (AGA) pregnancies were followed throughout pregnancy. Information was collected on maternal and gestational age, neonatal gender, previous gynaecological history. Total protein content, IGF-II, IGFBP-1, IGFBP-2, IL-6, and TNF- $\alpha$  concentrations in placental lysates were measured, and IGF-I, IGF-II, IGFBP-1, IGFBP-2 and IL-6 relative gene expression in placenta assessed. A BN and a hybrid forecasting system were implemented: BN revealed a key role of maternal age and TNF- $\alpha$  on IUGR and confirmed a close relationship among IGF-II, IL-6 and foetal growth. A relationship between duration of gestation, appropriateness for gestational age, and placental IL-6 concentration was also confirmed. Compared with other techniques, BN showed a better accuracy. Findings confirmed a major role of maternal age in addition to IGF-II, IL-6 and TNF- $\alpha$  in IUGR. A direct role of IGFBP-2 was not shown. BN confirmed to be useful in understanding the system's biology and graphically representing variable relationships and hierarchy, particularly where, as in IUGR, many interactions among predictors exist.

## STATISTICAL ANALYSIS OF DIFFERENTIAL GENE EXPRESSION IN COLORECTAL CANCER USING CLEAR-TEST

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CLEAR test provides a novel method of analysis by combining inference for differential expression and variability. Frozen tumor specimens from 14 (3 coded Stage I, 5 Stage II, 2 Stage III and 4 Stage IV) colon cancer patients were obtained. Archived primary tumor samples were collected at the time of surgery and normal colon mucosae (controls specimens) were also collected. The studied transcriptomes were clustered using hierarchical agglomeration with Ward's method and Tchebychev distance. The separable groups of transcriptomes were classified as high clinical stage of adenocarcinoma (HCS; stages II-IV), low clinical stage of adenocarcinoma (LCS; stages I and 3 controls), and two normal colon mucosae (controls N1 and N2). The results of the CLEAR-test algorithm in normal colon specimens and adenocarcinoma specimens with low and high clinical stage showed 50 most and 50 least significant genes. The list of differential genes ( $p < 0.01$ ) in normal colon specimens and adenocarcinoma specimens with low and high clinical stage presented 58 genes.

## ANTI-TUMOR NECROSIS FACTOR TREATMENT IN OCCULT HEPATITIS B VIRUS INFECTION: A RETROSPECTIVE ANALYSIS OF 62 PATIENTS WITH PSORIATIC DISEASE

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One of the problems possibly related to the use of biological agents targeting tumor necrosis factor (TNF)-alpha is the increased risk of infections, including the activation of hepatitis B virus (HBV). HBV activation can occur in carriers of hepatitis B surface antigen (HBsAg), but the risk may also involve the HBsAg-negative (anti-HBc ± anti-HBs) occult carriers. Precise data on the safety of anti-TNF and/or other immunosuppressive drugs in HBV occult carriers are not available. We performed a retrospective analysis of 62 psoriatic patients with occult HBV infection treated with anti-TNF biological agents over a period of approximately 4 years: 44 subjects were treated with etanercept, 8 with infliximab and 10 with adalimumab. During the observational treatment period, no signs of HBV activation were observed. Only in one patient the reappearance of HBsAg, without detectable HBV-DNA, was noted before retreatment with etanercept and after 10 months from discontinuation of the previous course. In this patient etanercept was re-administered in association with lamivudine without any adverse event. Our results suggest the overall safety of treatment with anti-TNF drugs in HBV occult carriers, although a careful and constant monitoring of virological markers is required in such patients during treatment with anti-TNF drugs in order to have an early recognition of viral reactivation.

# A PILOT STUDY ON THE TRANSCRIPTIONAL RESPONSE OF ANDROGEN- AND INSULIN-RELATED GENES IN PERIPHERAL BLOOD MONONUCLEAR CELLS INDUCED BY TESTOSTERONE ADMINISTRATION IN HYPOGONADAL MEN

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The aim of the present study is to determine whether testosterone (T) administration changes the expression profile of androgen- and insulin-related genes in peripheral blood mononuclear cells (PBMC). To this end, we evaluated the gene expression profile of 19 genes (*AKT2*, *CCND1*, *GSK3ALPHA*, *IGF1*, *GSK3BETA*, *FOXO3*, *IL6*, *IGFBP2*, *UGT2B17*, *ARA55*, *CREBBP*, *CYP11A*, *HSD17B1*, *HSD17B7*, *UGT2B7*, *SELADIN 1*, *CLU*, *PGC1*, *AKR1C1*) selected according their function in the androgen pathways, in a series of 11 hypogonadal men pharmacologically treated with T. We noted that 7 genes were differentially expressed, five of them were up-regulated (*AKT2* FC=2.39, *CREBBP* FC=11.2, *GSK3beta* FC=5.6, *UGT2B7* FC=4.49, *UGT2B17* FC=2.88) and two were down-regulated (*ARA55* FC=-2.0, *CYP11A* FC=-2.47). This experience suggests that androgen- and insulin-related genes can be considered useful blood genomic biomarkers for specific steroid drugs.

## SERUM IL-9 LEVELS AND SUBLINGUAL IMMUNOTHERAPY: PRELIMINARY REPORT

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Th9 is a new T cell subset characterized by IL-9 production. It has been reported that serum IL-9 levels are related with symptom severity in patients with allergic rhinitis (AR). This study is aimed at investigating whether serum IL-9 may be modulated by sublingual immunotherapy (SLIT) in patients with persistent AR due to *Parietaria* allergy. Twenty-one AR patients (9 males, median age 41 years) successfully treated with SLIT and 52 AR patients (25 males, median age 34 years) treated only with drugs were evaluated during the pollen season. Serum IL-9 was dosed in all patients. SLIT-treated patients showed significantly lower serum IL-9 levels than untreated AR patients ( $p < 0.0001$ ). In conclusion, this preliminary study shows that a single pre-seasonal SLIT course might modulate serum IL-9.

## MAY NASAL HYPERREACTIVITY BE A SEQUELA OF RECURRENT COMMON COLD?

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**Respiratory viral infections may worsen bronchial hyperreactivity. However, there is no data on the possible role of recurrent infectious rhinitis in nose hyperreactivity. This study was therefore designed to investigate whether subjects suffering from recurrent common cold have nasal hyperreactivity, assessed by histamine nasal challenge. This study included a group of 40 patients (19 males, mean age 34.1 years) with history of at least five episodes of common cold in the previous year, but without documented allergy, and twenty healthy subjects (8 males, mean age 32.3 years) were enrolled as control group, all of whom were non-allergic. Nasal provocation test with histamine was performed in all subjects. Nasal provocation test with histamine induced a 200% increase in nasal resistance after provocation in 24 (60%) patients suffering from recurrent viral rhinitis. No normal subject had an increase >180% in nasal resistance. There was a significant difference between the patient group and the control group ( $p < 0.05$ ). In conclusion, this study shows that nasal hyperreactivity might be a *sequela* of recurrent common cold. Further studies should be conducted to confirm this preliminary finding.**