Kujundžić M, Vogl TJ, Štimac D, Rustemović N, Hsi RA, Roh M, et al. A Phase II safety and effect on time to tumor progression study of intratumoral light infusion technology using talaporfin sodium in patients with metastatic colorectal cancer. J Surg Oncol. 2007;96:518-24.

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Twenty-seven patients with refractory liver metastases from colorectal cancer took part in a Phase II study of the light infusion technologytrade mark (Litxtrade mark) light-activated drug/device system to assess safety and evaluate time to tumor progression (TTP). Litxtrade mark consists of the light-activated drug, talaporfin sodium (LS11), activated intratumorally by a catheter-like array of light-emitting diodes (LEDs). After placement of the array via ultrasound or computed tomography (CT) guidance, LS11 was administered intravenously, followed 15-60 min later by light infusion for 2.8 hr. Patients were assessed for adverse events and tumor response using physical examination, laboratory values, and CT scan evaluation over a period of 60 days. The observed occurrence of Litxtrade mark treatment-related adverse events was minimal and cumulative toxicity did not occur when combined with chemotherapy. Assessment of TTP and tumor response rate, although statistically non-robust, suggest potential improvement. The Litxtrade mark system was shown to be safe for treating liver metastases from colorectal cancer and there was no cumulative toxicity when combined with standard systemic therapy. Preliminary assessments of TTP and tumor response rate justify further evaluation in a Phase III follow-up study.

Vuger-Kovačić D, Gregurek R, Kovačić D, Vuger T, Kalenić B. Relation between anxiety, depression and locus of control of patients with multiple sclerosis. Mult Scler. 2007;13:1065-7.

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This study was concerned with examining relation between anxiety, depression and locus of control (LC) in Croatian multiple sclerosis (MS) patients in order to determine an indication for psychotherapeutic intervention. The participants were 457 MS patients attending central state medical rehabilitation program at Varaždinske Toplice, asked to fill in the locus of control inventory and Crown-Crisp Experiential Index (CCEI) questioner of personality in the clinical setting. In order to determine whether locus of control changes along natural course of MS, patients were grouped according to the duration of the disease: less than five years, five to 10 years and more than 10 years. The results demonstrated that 405 (88.6%) MS patients exhibited external locus of control while 52 (11.4%) had internal locus of control. Moreover, as the disease progressed, locus of control shifted more to externality. Analysis of gathered data confirms connectivity of external locus of control with anxiety and depression. Results of anxiety and depression level on CCEI questionnaire show continuously increased values regardless on duration of illness. Croatian MS patients like other chronically ill externally oriented patients' show more maladaptive behaviour, which has been strongly linked to anxiety and depression and this, is indication for psychotherapeutic support.

Raguz J, Wagner S, Dikic I, Hoeller D. Suppressor of T-cell receptor signalling 1 and 2 differentially regulate endocytosis and signalling of receptor tyrosine kinases. FEBS Lett. 2007;581:4767-72.

Mediterranean Institute for Life Sciences, Split, Croatia

Suppressor of T-cell receptor signalling 1 and 2 (Sts-1 and 2) negatively regulate the endocytosis of receptor tyrosine kinases. The UBA domain of Sts-2 and SH3-dependent Cbl-binding are required for this function. Sts-1 and -2 also possess a PGM domain, which was recently reported to exhibit tyrosine phosphatase activity. In this paper, the authors demonstrate that the PGM of Sts-1, but not of Sts-2, dephosphorylates the EGFR at multiple tyrosines thereby terminating its signalling and endocytosis. In contrast to Sts-2 the UBA of Sts-1 did not contribute significantly to receptor stabilization. Thus, although Sts-1 and Sts-2 are structurally highly homologous and both inhibit ligand-induced EGFR degradation, their mecha-

nisms of action differ significantly. As a consequence, Sts-1-containing receptor complexes are inactive, whereas Sts-2-containing complexes are signalling competent.

Kalac M, Quintas-Cardama A, Vrhovac R, Kantarjian H, Verstovšek S. A critical appraisal of conventional and investigational drug therapy in patients with hypereosinophilic syndrome and clonal eosinophilia. Cancer. 2007;110:955-64.

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Hypereosinophilic syndrome (HES) is a rare disorder characterized by persistent and marked eosinophilia, leading to end-organ damage. Over the last decade, great progress has been made in unraveling the molecular basis of HES that has resulted in the characterization of specific genetic alterations linked to clonal eosinophilia. The most frequently encountered genetic aberrancy is the cryptic FIP1-like 1/platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA) fusion transcript, which results in an eosinophilic, myeloproliferative disorder. In addition, in a subset of patients with HES, a population of aberrant T cells that secretes interleukin-5 can be identified, indicating the existence of lymphocyte-mediated hypereosinophilia. These new insights have led to both a genetically based (re)classification of eosinophilic blood disorders and to effective therapies with targeted agents, such as small-molecule tyrosine kinase inhibitors (eg, imatinib, nilotinib, PKC412) and, more recently, monoclonal antibodies (eg, mepolizumab, alemtuzumab). These targeted therapies hold great promise for improving the clinical outcomes of patients with HES and clonal eosinophilia, and they have exhibited relatively safe toxicity profiles.

Telisman S, Čolak B, Pizent A, Jurasović J, Cvitković P. Reproductive toxicity of low-level lead exposure in men. Environ Res. 2007;105:256-66.

Institute for Medical Research and Occupational Health, Zagreb, Croatia

Parameters of semen quality, seminal plasma indicators of secretory function of the prostate and seminal vesicles, sex hormones in serum, and biomarkers of lead, cadmium, copper, zinc, and selenium body burden were measured in 240 Croatian men 19-52 years of age. The subjects had no occupational exposure to metals and no known other reasons suspected of influencing male reproductive function or metal metabolism. After adjusting for age, smoking, alcohol, blood cadmium, and serum copper, zinc, and selenium by multiple regression, significant ($p<0.05$) associations of blood lead (BPb), delta-aminolevulinic acid dehydratase (ALAD), and/or erythrocyte protoporphyrin (EP) with reproductive parameters indicated a lead-related increase in immature sperm concentration, in percentages of pathologic sperm, wide sperm, round sperm, and short sperm, in serum levels of testosterone and estradiol, and a decrease in seminal plasma zinc and in serum prolactin. These reproductive effects were observed at low-level lead exposure (BPb median 49μg/L, range 11-149 μg/L in the 240 subjects) common for general populations worldwide. The observed significant synergistic effect of BPb and blood cadmium on increasing serum testosterone, and additive effect of a decrease in serum selenium on increasing serum testosterone, may have implications on the initiation and development of prostate cancer because testosterone augments the progress of prostate cancer in its early stages.

Tkalčević VI, Čuzić S, Brajša K, Mildner B, Bokulić A, Šitum K, et al. Enhancement by PL 14736 of granulation and collagen organization in healing wounds and the potential role of egr-1 expression. Eur J Pharmacol. 2007;570:212-21.

PLIVA Research Institute Ltd, Zagreb, Croatia

Apart from becaplermin (recombinant human platelet-derived growth factor homodimer of B chains, PDGF-BB), for the treatment of lower extremity diabetic ulcers, few agents are available for pharmacological stimulation of wound healing. The authors compared the mechanism of action of the potential wound healing agent, PL 14736 (G E P P P G K P A D D A G L V), with that of PDGF-BB on granulation tissue formation following sponge implantation in the normoglycemic rat and in healing full-thickness excisional wounds in db/db genetically diabetic mice. Expression of the immediate response gene, early growth response gene-1 (egr-1) was studied in Caco-2 cells *in vitro*. While PDGF-BB and PL 14736 had similar selectivity for stimulation of granulation tissue in both sponge granuloma and in healing wounds in db/db mice, PL 14736 was more active in stimulating early collagen organization. It also stimulated expression of egr-1 and its repressor nerve growth factor 1-A binding protein-2 (nab2) in non-differentiated Caco-2 cells more rapidly than PDGF-BB. EGR-1 induces cytokine and growth factor generation and early extracellular matrix (collagen) formation, offering an explanation for the beneficial effects of PL 14736 on wound healing.

Grubić Z, Žunec R, Peroš-Golubičić T, Tekavec-Trkanjec J, Martinez N, Alilović M, et al. HLA class I and class II frequencies in patients with sarcoidosis from Croatia: role of HLA-B8, -DRB1*0301, and -DQB1*0201 haplotype in clinical variations of the disease. Tissue Antigens. 2007;70:301-6.

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Sarcoidosis is an immune-mediated, multiorgan, granulomatous disease triggered by a combination of environmental and genetic factors. Numerous studies have reported about an association of human leukocyte antigen (HLA) alleles with sarcoidosis, with variation of alleles in different ethnic groups. Therefore, the authors investigated 142 Croatian sarcoidosis patients treated at the University Hospital for Lung Diseases Jordanovac, Zagreb, Croatia. Diagnosis was based on the presence of typical clinical features, chest X-ray findings and biopsy evidence of granuloma. Patients and control subjects (n=190) were typed for HLA class I antigens by serology, while for HLA class II, they were tested by the polymerase chain reaction-sequence specific primers (PCR-SSP) method. Results indicated that HLA-B8, -DRB1*0301, and -DQB1*0201 positive patients have a significantly higher risk of acute onset of the disease (AOD), radiological stage I erythema nodosum (EN), no-medicament therapy, and pulmonary sarcoidosis. On the other hand, the group of non-treated patients (corticosteroids and/or immunosuppressive) showed a significantly lower presence of HLA-B15 antigen in comparison to controls and treated patients (p=0.0490 and p=0.0379, respectively) and for DRB1*04 specificity (p=0.0078 and p=0.0065, respectively). In the group of patients with AOD, those who were positive for DRB1*16 specificity have a statistically significant chance to develop EN, as opposed to those who are positive for DRB1*15 specificity.

Fučić A, Znaor A, Strnad M, van der Hel O, Aleksandrov A, Miškov S, et al. Chromosome damage and cancer risk in the workplace: the example of cytogenetic surveillance in Croatia. Toxicol Lett. 2007;172:4-11.

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The use of cytogenetic assays in the surveillance of populations occupationally exposed to genotoxic carcinogens originates from the assumption that chromosomal alterations might be causally involved in early stages of carcinogenesis. Historical cohort studies have since 1990s consistently reported an association between the level of chromosomal aberrations (CA) in peripheral lymphocytes of healthy subjects and the risk of cancer. Only in few cases, have these results been transformed into a regulatory tool for improving occupational safety. The cytogenetic surveillance program adopted for more than two decades in the Republic of Croatia is one of these few examples. Croatian workers exposed to genotoxic agents were systematically screened for CA, to identify occupational settings needing a priority intervention. Significant increases of mean CA frequency were observed in groups exposed to ionizing radiation, chemical agents, and mixed exposures when compared with a group of unexposed referents. CA data on 736 men and 584 women, monitored between 1987 and 2000, have been associated with cancer incidence. Although the small size of the cohort did not allow for reaching statistical significance, the medium tertile of the CA frequency distribution was associated with a doubling of cancer incidence rate ratio (IRR=2.40; 95% CI 0.85-6.77) when compared with the lowest tertile. For chromosome-type CA, IRR was non-significantly increased for both the medium (IRR 1.53, 95% CI 0.58-3.99) and high categories (IRR 1.69; 95% CI 0.61-4.72). Recommendations for future strategies comprise the inclusion of predictive biomarkers in surveillance programs, the definition of a regulatory framework, and thir possible use for the identification of individual risk profiles.