
Gunawan B, von Heydebreck A, Sander B, Schulten HJ, Haller F, Langer C, Armbrust T, Bollmann M, *Gašparov S, et al. An oncogenetic tree model in gastrointestinal stromal tumours (GISTs) identifies different pathways of cytogenetic evolution with prognostic implications. *J Pathol.* 2007;211:463-70.

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To model the cytogenetic evolution in gastrointestinal stromal tumour (GIST), an oncogenetic tree model was reconstructed using comparative genomic hybridization data from 203 primary GISTs (116 gastric and 87 intestinal GISTs, including 151 newly analysed cases), with follow-up available in 173 cases (mean 40 months; maximum 133 months). The oncogenetic tree model identified three major cytogenetic pathways: one initiated by -14q, one by -1p, and another by -22q. The -14q pathway mainly characterized gastric tumours with predominantly stable karyotypes and more favourable clinical course. On the other hand, the -1p pathway was more characteristic of intestinal GISTs, with an increased capacity for cytogenetic complexity and more aggressive clinical course. Loss of 22q, more closely associated with -1p than -14q, appeared to initiate the critical transition to an unfavourable cytogenetic subpathway. This -22q pathway included accumulation of +8q, -9p, and -9q, which could all predict disease-free survival in addition to tumour site. Thus, insights into the cytogenetic evolution obtained from oncogenetic tree models may eventually help to gain a better understanding of the heterogeneous site-dependent biological behaviour of GISTs.

Kovačić N, Lukić IK, Grčević D, Katavić V, Croucher P, Marušić A. The fas/fas ligand system inhibits differentiation of murine osteoblasts but has a limited role in osteoblast and osteoclast apoptosis. *J Immunol.* 2007;178:3379-89.

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The authors systematically analyzed: 1) the expression of Fas/FasL during osteoblastogenesis and osteoclastogenesis in vitro, 2) the effect of FasL on apoptosis and osteoblastic/osteoclastic differentiation, and 3) osteoblastogenesis and osteoclastogenesis in mice deficient in Fas or FasL. The expression of Fas increased with osteoblastic differentiation. Addition of FasL weakly increased the proportion of apoptotic cells in both osteoclastogenic and osteoblastogenic cultures. In a CFU assay, FasL decreased the proportion of osteoblast colonies but did not affect the total number of colonies, indicating specific inhibitory effect of Fas/FasL on osteoblastic differentiation. The effect depended on the activation of caspase 8 and was specific, as addition of FasL to osteoblastogenic cultures significantly decreased gene expression for runt-related transcription factor 2 (Runx2) required for osteoblastic differentiation. Bone marrow from mice without functional Fas or FasL had similar osteoclastogenic potential as bone marrow from wild-type mice, but generated more osteoblast colonies ex vivo. These colonies had increased expression of the osteoblast genes Runx2, osteopontin, alkaline phosphatase, bone sialoprotein, osteocalcin, and osteoprotegerin. The results of this study indicate that Fas/FasL system primarily controls osteoblastic differentiation by inhibiting progenitor differentiation and not by inducing apoptosis. During osteoclastogenesis, the Fas/FasL system may have a limited effect on osteoclast pro-

genitor apoptosis. The study suggests that Fas/FasL system plays a key role in osteoblastic differentiation and provides novel insight into the interactions between the immune system and bone.

Mahmutefendić H, Blagojević G, Kučić N, Lučin P. Constitutive internalization of murine MHC class I molecules. *J Cell Physiol.* 2007;210:445-55.

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The authors compared spontaneous internalization of murine major histocompatibility complex (MHC) class I molecules (K^d, D^d, full L^d, and empty L^d) after depletion of their egress to the cell surface (Cycloheximide [CHX], brefeldin A [BFA]) and internalization after external binding of monoclonal antibody (mAb). MHC class I alleles differ regarding their cell surface stability, kinetics, and in the way of internalization and degradation. K^d and D^d molecules are more stable at the cell surface than L^d molecules and, thus, constitutively internalized more slowly. Although the binding of mAbs to cell surface MHC class I molecules results in faster internalization than depletion of their egress, it is still slow and, thereby, can serve as a model for tracking of MHC class I endocytosis. Internalization of fully conformed MHC class I molecules (K^d, D^d, and L^d) was neither inhibited by chlorpromazine (CP) (inhibitor of clathrin endocytosis), nor with filipin (inhibitor of lipid raft dependent endocytosis), indicating that fully conformed MHC class I molecules are internalized via the bulk pathway. In contrast, internalization of empty L^d molecules was inhibited by filipin, indicating that non-conformed MHC class I molecules require intact cholesterol-rich membrane microdomains for their constitutive internalization. Thus, conformed and non-conformed MHC class I molecules use different endocytic pathways for constitutive internalization.

Obad A, Palada I, Valić Z, Ivančev V, Baković D, Wisloff U, et al. The effects of acute oral antioxidants on diving-induced alterations in human cardiovascular function. *J Physiol.* 2007;578(Pt 3):859-70.

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The authors tested the effects of acute antioxidants on arterial endothelial function, pulmonary artery pressure (PAP) and heart function before and after a field dive. Vitamins C (2 g) and E (400 IU) were given to subjects 2 h before a second dive (protocol 1) and in a placebo-controlled cross-

over study design (protocol 2). Seven experienced divers performed open sea dives to 30 msw with standard decompression in a non-randomized protocol, and six of them participated in a randomized trial. Before and after the dives ventricular volumes and function and pulmonary and brachial artery function were assessed by ultrasound. The control dive resulted in a significant reduction in flow-mediated dilatation (FMD) and heart function with increased mean PAP. Twenty-four hours after the control dive FMD was still reduced 37% below baseline (8.1 versus 5.1%, $p=0.005$), while right ventricle ejection fraction (RV-EF), left ventricle EF and endocardial fractional shortening were reduced much less (approximately 2-3%). At the same time RV end-systolic volume was increased by 9% and mean PAP by 5%. Acute antioxidants significantly attenuated only the reduction in FMD post-dive ($p<0.001$), while changes in pulmonary artery and heart function were unaffected by antioxidant ingestion. FMD returned to baseline values 72 h after the dive with pre-dive placebo, whereas for most cardiovascular parameters this occurred earlier (24-48 h). Right ventricular dysfunction and increased PAP lasted longer. Acute antioxidants attenuated arterial endothelial dysfunction after diving, while reduction in heart and pulmonary artery function were unchanged. Cardiovascular changes after diving are not fully reversed up to 3 days after a dive, suggesting longer lasting negative effects.

Vlahović-Palčevski V, Dumpis U, Mitt P, Gulbinović J, Struwe J, Palčevski G, et al. Benchmarking antimicrobial drug use at university hospitals in five European countries. *Clin Microbiol Infect.* 2007;13:277-83.

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A point-prevalence survey of five European university hospitals was performed to benchmark antimicrobial drug use in order to identify potential problem areas in prescribing practice and to aid in establishing appropriate and attainable goals. All inpatients at the university hospitals of Rijeka (Croatia), Tartu (Estonia), Riga (Latvia), Vilnius (Lithuania) and Karolinska-Huddinge (Sweden) were surveyed for antimicrobial drug use during a single day. The frequency of antimicrobial drug use was 24% in Rijeka, 30% in Tartu, 26% in Riga, 14% in Vilnius and 32% in Huddinge. Surgical patients were treated with antimicrobial agents more often than medical patients in Riga (53% vs. 31%), Tartu (39% vs. 26%) and Vilnius (54% vs. 25%). Two-thirds of patients in Rijeka, Tartu, Riga and Vilnius, and fewer than half of the patients in Huddinge, received antimicrobial

agents intravenously. Broad-spectrum antimicrobial agents were used most commonly in Rijeka. The prevalence of nosocomial infections treated with antibiotics was 9% at Huddinge, and 3-5% at the other centres. Benchmarking antimicrobial drug use at five university hospitals identified differences and problem areas. The high rates of intravenous administration, poor compliance with guidelines, and prolonged surgical prophylaxis were general problems that deserved specific attention at all centres. A change in prescription practices may reduce unnecessary drug use and decrease antimicrobial resistance.

Hundrić-Hašpl Z, Pečina M, Hašpl M, Tomičić M, Jukić I. Plasma cytokines as markers of aseptic prosthesis loosening. Clin Orthop Relat Res. 2006;453:299-304.

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The proinflammatory cytokines IL-1beta, IL-8, and TNF-alpha play a major role in the process of bone resorption during aseptic loosening of large joint prostheses. These cytokines secreted locally during bone resorption in aseptic loosening may enter peripheral circulation. Increased concentration of IL-1gamma, IL-8, and TNF-alpha in peripheral circulation may indicate aseptic loosening. We determined whether bone resorption could be verified by cytokine presence in plasma. We recruited 50 patients with aseptic prosthesis loosening, 50 with stable prostheses, 50 with osteoarthritis, and 50 healthy individuals. Cytokine levels were determined in plasma by ELISA tests. Patients with prosthesis loosening had higher plasma levels (IL-10, 3.7 ± 5.5 pg/mL; IL-8, 14.7 ± 9 pg/mL; TNF-alpha, 32.7 ± 32.4 pg/mL) than patients with stable prostheses (IL-1beta, 1.5 ± 2 pg/mL; IL-8, 8.1 ± 4.7 pg/mL; TNF-alpha, 22.9 ± 18.7 pg/mL), patients with osteoarthritis (IL-1beta, 0.7 ± 1.1 pg/mL; IL-8, 5.8 ± 3.8 pg/mL; TNF-alpha, 9.8 ± 7.7 pg/mL) and healthy individuals (IL-1beta, 0.7 ± 1.1 pg/mL; IL-8, 4.2 ± 1.3 pg/mL; TNF-alpha, 3.9 ± 3.9 pg/mL). These data suggest elevated plasma levels of proinflammatory cytokines may be useful as markers of bone resorption in the laboratory diagnosis of prosthesis loosening.

Peričić D, Švob-Štrac D. The role of 5-HT(7) receptors in the control of seizures. Brain Res. 2007;1141C:48-55.

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To evaluate the possible role of 5-HT(7) receptors in the control of brain excitability, the authors treated mice with

antagonists and agonists of these receptors prior to exposure to swim stress and the intravenous infusion of picrotoxin, a non-competitive GABA(A) receptor antagonist. In accordance with the previous studies, swim stress increased the doses of picrotoxin producing two convulsant signs (running/bouncing clonus, tonic hindlimb extension) and death, i.e., swim stress increased the seizure threshold for picrotoxin. SB-269970 (10-30 mg/kg ip), a selective antagonist of 5-HT(7) receptors, and ritanserin (1 mg/kg ip), a nonselective 5-HT (2/7) antagonist, failed to affect, while 5-carboxamidotryptamine (5-CT), a potent 5-HT (1/7) receptor agonist, increased in unstressed and swim-stressed mice the doses of picrotoxin producing convulsions and death. The anticonvulsant effect obtained with 5-CT 0.5 mg/kg was not greater than that obtained with 0.1 mg/kg. The 5-CT (0.1 mg/kg ip)-induced increase of the seizure threshold for picrotoxin in stressed mice was abolished with SB-269970 (10 mg/kg), but not with WAY-100635 (0.3 mg/kg), a selective antagonist of 5-HT(1A) receptors, suggesting that the anticonvulsant effect of 5-CT against convulsions produced by picrotoxin was achieved via 5-HT(7) receptors. The results suggest a positive role of 5-HT(7) receptors in the control of seizures.

Barčot O, Balarin M, Gamulin O, Ježek D, Romac P, Brnjas-Kraljević J. Investigation of spermatozoa and seminal plasma by fourier transform infrared spectroscopy. Appl Spectrosc. 2007;61:309-13.

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Fourier transform infrared (FT-IR) spectra of human spermatozoa and seminal plasma were recorded and analyzed. The procedure that was established for sample preparation enabled acquisition of reproducible spectra. The parameter I_{1087}/I_{966} for controlling spectra reproducibility was defined. The assignment of bands was carried out using an empirical approach and the origin of the "sperm specific doublet", the bands at 968 cm^{-1} and 981 cm^{-1} , was determined. The principal component regression (PCR) algorithm was used to define the specific spectral regions correlating to characteristics of spermatozoa, such as concentration, straight-line velocity (VSL), and beat cross frequency (BCF). Then, simple spectral parameters, such as band intensities and band ratios, were tested to determine which one best correlates to characteristics of spermatozoa. The region of the amide I band, between 1700 cm^{-1} and 1590 cm^{-1} , was defined as a specific spectral region that correlates to the concentration of spermatozoa. The parameter that gave the linear dependence to the concentration of spermatozoa was the intensity of the amide I band. For VSL, the bands between 1119

cm^{-1} and 943 cm^{-1} were defined as the specific spectral region. The relative amount of nucleic acids with respect to proteins showed linear dependence on the straight-line velocity of spermatozoa. BCF showed the best correlation to the bands between 3678 cm^{-1} and 2749 cm^{-1} , which largely represent lipids and proteins. These results suggest that FT-IR spectroscopy can serve as an adjunct to conventional histopathology studies.

Belušić-Gobić M, Car M, Juretić M, Cerović R, Gobić D, Golubović V. Risk factors for wound infection after oral cancer surgery. *Oral Oncol.* 2007;43:77-81.

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The purpose of this study was to identify the most important factors contributing to operative wound infections in patients with oral and oropharyngeal cancer. A retrospective review of complications in 111 patients after oral and oropharynx cancer surgery with an immediate reconstruction is presented. Potential risk factors for infection were categorized based on the patient, the disease, and the treatment. Flap-related complications developed in 73 patients (65.76%). Wound infection occurred in 69 (62.12%), and a fistula in 10 patients (9%). Other complications developed in 41.44% of the patients. The analysis of risk factors for the development of infection showed the following factors to be significant: male sex, T and S tumour stages, reconstruction, tracheostomy, nasogastric tube or gastrostomy feeding and extent of surgery.

Pavić L, Gregurek R, Radoš M, Brkljačić B, Brajković L, Šimetin-Pavić I, et al. Smaller right hippocampus in war veterans with posttraumatic stress disorder. *Psychiatry Res.* 2007;154:191-8.

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Chronic stress can putatively cause damage in the human hippocampus, but evidence of damage has not been consistently shown in studies on hippocampal morphology in posttraumatic stress disorder (PTSD). The authors compared hippocampal volumes in PTSD patients and normal subjects. Using a 3D T1-weighted GRE magnetic resonance imaging sequence, they measured hippocampal volumes in 15 war veterans with combat-related chronic PTSD and 15 case-matched normal controls. Although war veterans, PTSD subjects in this study were not professional soldiers and were mobilized shortly before they were exposed to a very specific combat-related trauma over a 3-day period. The period between traumatic exposure and imaging was considerably shorter, on average, 9 years, compared with at least two decades in previous studies on subjects with combat-related PTSD. Moreover, the subjects in this study were free of any comorbidity, treatment or medication. The right hippocampus was significantly smaller in PTSD subjects than in healthy controls. The left hippocampus was also smaller in PTSD subjects than in controls, but the difference was not significant. In all PTSD subjects, the right hippocampus was smaller than the left (on average, 7.88%). These results show smaller volume of the right hippocampus in PTSD patients than in normal subjects.