

МІЖНАРОДНІ ПУБЛІКАЦІЇ УКРАЇНСЬКИХ АВТОРІВ

Horbal L., Ostash B., Luzhetskyy A., Walker S., Kalinowski J., Fedorenko V.

A gene cluster for the biosynthesis of moenomycin family antibiotics in the genome of teicoplanin producer *Actinoplanes teichomyceticus*

Applied Microbiology and Biotechnology. 2016, 100 (17): 7629-7638. (IF=3.376)

Moenomycins are phosphoglycolipid antibiotics notable for their extreme potency, unique mode of action, and proven record of use in animal nutrition without selection for resistant microflora. There is a keen interest in manipulation of structures of moenomycins in order to better understand their structure-activity relationships and to generate improved analogs. Only two almost identical moenomycin biosynthetic gene clusters are known, limiting our knowledge of the evolution of moenomycin pathways and our ability to genetically diversify them. Here, we report a novel gene cluster (tchm) that directs production of the phosphoglycolipid teichomycin in *Actinoplanes teichomyceticus*. Its overall genetic architecture is significantly different from that of the moenomycin biosynthesis (moe) gene clusters of *Streptomyces ghanaensis* and *Streptomyces clavuligerus*, featuring multiple gene rearrangements and two novel structural genes. Involvement of the tchm cluster in teichomycin biosynthesis was confirmed via heterologous co-expression of amidotransferase tchmH5 and moe genes. Our work sets the background for further engineering of moenomycins and for deeper inquiries into the evolution of this fascinating biosynthetic pathway.

Key words: *Actinoplanes; Moenomycins; Nosokomycin; Teichomycin*

Sobczak M., Chumak V., Pomorski P., Wojtera E., Majewski L., Nowak J., Yamauchi J., Rędowicz M.J.

Interaction of myosin VI and its binding partner DOCK7 plays an important role in NGF-stimulated protrusion formation in PC12 cells

*Biochimica et Biophysica Acta (BBA).
Molecular Cell Research. 2016, 1863 (7): 1589-1600. (IF = 5, 128)*

DOCK7 (dedicator of cytokinesis 7) is a guanidine nucleotide exchange factor (GEF) for Rac1 GTPase that is involved in neuronal polarity and axon generation as well in Schwann cell differentiation and myelination. Recently, we identified DOCK7 as the binding partner of unconventional myosin VI

(MVI) in neuronal-lineage PC12 cells and postulated that this interaction could be important in vivo [Majewski et al. (2012) *Biochem Cell Biol.*, 90:565-574]. Herein, we found that MVI-DOCK7 interaction takes also place in other cell lines and demonstrated that MVI cargo domain via its RRL motif binds to DOCK7 C-terminal M2 and DHR2 domains. In MVI knockdown cells, lower Rac1 activity and a decrease of DOCK7 phosphorylation on Tyr1118 were observed, indicating that MVI could contribute to DOCK7 activity. MVI and DOCK7 colocalization was maintained during NGF-stimulated PC12 cell differentiation and observed also in the outgrowths. Also, during differentiation an increase in phosphorylation of DOCK7 as well as of its downstream effector JNK kinase was detected. Interestingly, overexpression of GFP-tagged MVI cargo domain (GFP-GT) impaired protrusion formation indicating that full length protein is important for this process. Moreover, a transient increase in Rac activity observed at 5min of NGF-stimulated differentiation of PC12 cells (overexpressing either GFP or GFP-MVI) was not detected in cells overexpressing the cargo domain. These data indicate that MVI-DOCK7 interaction could have functional implications in the protrusion outgrowth, and full length MVI seems to be important for delivery and maintenance of DOCK7 along the protrusions, and exerting its GEF activity.

Key words: *DOCK7; GEF for Rac; Myosin VI; NGF; PC12 cells; Protrusions*

Szunerits S., Zagorodko O., Cogez V., Dumych T., Chalopin T., et al.

Differentiation of Crohn's Disease-Associated Isolates from Other Pathogenic Escherichia coli by Fimbrial Adhesion under Shear Force

Biology (Basel). 2016, 5(2). DOI: 10.3390/biology5020014.

Shear force exerted on uropathogenic Escherichia coli adhering to surfaces makes type-1 fimbriae stretch out like springs to catch on to mannosidic receptors. This mechanism is initiated by a disruption of the quaternary interactions between the lectin and the pilin of the two-domain FimH adhesin and transduces allosterically to the mannose-binding pocket of FimH to increase its affinity. Mannose-specific adhesion of 14 E. coli pathovars was measured under flow, using surface plasmon resonance detection on functionalized graphene-coated gold interfaces. Increasing the shear had important differential consequences on bacterial adhesion. Adherent-invasive E. coli, isolated from the feces and biopsies of Crohn's disease patients, consistently changed their adhesion behavior less under shear and displayed lower SPR signals, compared to E. coli opportunistically infecting the urinary tract, intestines or loci of knee and hip prostheses. We exemplified this further with the extreme behaviors of the reference strains UTI89 and LF82. Whereas their FimA major pilins have identical sequences, FimH of LF82 E. coli is marked by the Thr158Pro mutation. Positioned in the inter-domain region known to carry hot spots of mutations in E. coli pathotypes, residue 158 is indicated to play a

structural role in the allosteric regulation of type-1 fimbriae-mediated bacterial adhesion.

Key words: *d*-mannose; adherent-invasive *Escherichia coli*; graphene; heptyl α -; shear force; surface plasmon resonance

Stepanenko A., Andreieva S., Korets K., Mykytenko D., Baklaushev V., Huleyuk N., Kovalova O., Kotsarenko K., Chekhonin V., Vassetzky Y., Avdieiev S., Dmitrenko V.

Temozolomide promotes genomic and phenotypic changes in glioblastoma cells

Cancer Cell Int. 2016, 16 (36). DOI: 10.1186/s12935-016-0311-8. [IF = 2,884]

BACKGROUND: Temozolomide (TMZ) is a first-line drug for the treatment of glioblastoma. Long-term TMZ-treated tumour cells acquire TMZ resistance by profound reprogramming of the transcriptome, proteome, kinome, metabolism, and demonstrate versatile and opposite changes in proliferation, invasion, in vivo growth, and drug cross-resistance. We hypothesized that chromosomal instability (CIN) may be implicated in the generation of TMZ-driven molecular and phenotype diversity. CIN refers to the rate (cell-to-cell variability) with which whole chromosomes or portions of chromosomes are gained or lost.

METHODS: The long-term TMZ-treated cell lines were established in vitro (U251TMZ1, U251TMZ2, T98GTMZ and C6TMZ) and in vivo (C6R2TMZ). A glioma model was achieved by the intracerebral stereotactic implantation of C6 cells into the striatum region of rats. Genomic and phenotypic changes were analyzed by conventional cytogenetics, array CGH, trypan blue exclusion assay, soft agar colony formation assay, scratch wound healing assay, transwell invasion assay, quantitative polymerase chain reaction, and Western blotting.

RESULTS: Long-term TMZ treatment increased CIN-mediated genomic diversity in U251TMZ1, U251TMZ2 and T98GTMZ cells but reduced it in C6TMZ and C6R2TMZ cells. U251TMZ1 and U251TMZ2 cell lines, established in parallel with a similar treatment procedure with the only difference in the duration of treatment, underwent individual phenotypic changes. U251TMZ1 had a reduced proliferation and invasion but increased migration, whereas U251TMZ2 had an enhanced proliferation and invasion but no changes in migration. U251TMZ1 and U251TMZ2 cells demonstrated individual patterns in expression/activation of signal transduction proteins (e.g., MDM2, p53, ERK, AKT, and ASK). C6TMZ and C6R2TMZ cells had lower proliferation, colony formation efficiency and migration, whereas T98GTMZ cells had increased colony formation efficiency without any changes in proliferation, migration, and invasion. TMZ-treated lines demonstrated a differential response to a reduction in glucose concentration and an increased resistance to TMZ re-challenge but not temsirolimus (mTOR inhibitor) or U0126 (MEK1/2 inhibitor) treatment.

CONCLUSION: Long-term TMZ treatment selected resistant genotype-phenotype variants or generated novel versatile phenotypes by increasing CIN. An increase of resistance to TMZ re-challenge seems to be the only predictable trait intrinsic to all long-term TMZ-treated tumour cells. Changes in genomic diversity may be responsible for heterogeneous phenotypes of TMZ-treated cell lines.

Key words: *Aneuploidy; Chromosome instability; Drug resistance; Glioma; Heterogeneity; Karyotype*

Mahlangu J., Kuliczkowski K., Karim F., Stasyshyn O., Kosinova M., et al.

**Efficacy and safety of rVIII-SingleChain:
results of a phase 1/3 multicenter clinical trial in severe hemophilia A**

Blood. 2016, 128(5): 630-637. (IF = 11,847)

Recombinant VIII (rVIII)-SingleChain is a novel B-domain-truncated recombinant factor VIII (rFVIII), comprised of covalently bonded factor VIII (FVIII) heavy and light chains. It was designed to have a higher binding affinity for von Willebrand factor (VWF). This phase 1/3 study investigated the efficacy and safety of rVIII-SingleChain in the treatment of bleeding episodes, routine prophylaxis, and surgical prophylaxis. Participants were ≥ 12 years of age, with severe hemophilia A (endogenous FVIII $< 1\%$). The participants were allocated by the investigator to receive rVIII-SingleChain in either an on-demand or prophylaxis regimen. Of the 175 patients meeting study eligibility criteria, 173 were treated with rVIII-SingleChain, prophylactically (N = 146) or on-demand (N = 27). The total cumulative exposure was 14306 exposure days (EDs), with 120 participants reaching ≥ 50 EDs and 52 participants having ≥ 100 EDs. Hemostatic efficacy was rated by the investigator as excellent or good in 93.8% of the 835 bleeds treated and assessed. Across all prophylaxis regimens, the median annualized spontaneous bleeding rate was 0.00 (Q1, Q3: 0.0, 2.4) and the median overall annualized bleeding rate (ABR) was 1.14 (Q1, Q3: 0.0, 4.2). Surgical hemostasis was rated as excellent/good in 100% of major surgeries by the investigator. No participant developed FVIII inhibitors. In conclusion, rVIII-SingleChain is a novel rFVIII molecule showing excellent hemostatic efficacy in surgery and in the control of bleeding events, low ABR in patients on prophylaxis, and a favorable safety profile in this large clinical study. This trial was registered at www.clinicaltrials.gov as #NCT01486927.

Maueröder C., Chaurio RA., Dumych T., Podolska M., Lootsik MD, Bilyy R., et al.

A blast without power - cell death induced by the tuberculosis-necrotizing toxin fails to elicit adequate immune responses

Cell Death Differ. 2016, 23 (6): 1016-1025. (IF = 8,218)

In this study, we deploy a doxycycline-dependent suicide switch integrated

in a tumor challenge model. With this experimental setup, we characterized the immunological consequences of cells dying by four distinct cell death stimuli *in vivo*. We observed that apoptotic cell death induced by expression of the truncated form of BH3 interacting-domain death agonist (tBid) and a constitutively active form of caspase 3 (revC3), respectively, showed higher immunogenicity than cell death induced by expression of the tuberculosis-necrotizing toxin (TNT). Our data indicate that the early release of ATP induces the silent clearance of dying cells, whereas the simultaneous presence of 'find me' signals and danger-associated molecular patterns (DAMPs) promotes inflammatory reactions and increased immunogenicity. This proposed model is supported by findings showing that the production and release of high concentrations of IL-27 by bone-marrow-derived macrophages (BMDM) is limited to BMDM exposed to those forms of death that simultaneously released ATP and the DAMPs heat-shock protein 90 (HSP90) and high-mobility group box-1 protein (HMGB1). These results demonstrate that the tissue microenvironment generated by dying cells may determine the subsequent immune response.

*Farooqi A.A., Fayyaz S., Shatynska-Mytsyk I., Javed Z., Jabeen S.,
Yaylim I., Gasparri M.L., Panici P.B.*

Is miR-34a a Well-equipped Swordsman to Conquer Temple of Molecular Oncology?

Chem Biol Drug Des. 2016, 87 (3): 321-334. (IF = 2,802)

Overwhelmingly increasing advancements in miRNA biology have opened new avenues for pharmaceutical companies to initiate studies on designing effective, safe, and therapeutically active candidates using miRNA mimetics and miRNA inhibitors. In accordance with this approach, development of miravirsin and SPC3649, an LNA-based (locked nucleic acid) antisense molecule against miR-122, to treat hepatitis C has sparked interest in identifying most efficient microRNAs for journey from bench-top toward pharmaceutical industry and breakthroughs in delivery technology will pave the way to 'final frontier'. MRX34, a liposome-formulated mimic of miR-34 for treatment of metastatic cancer with liver involvement and unresectable primary liver cancer, has also entered in clinical trial. There is a successive increase in the research work related to miR-34 biology and miRNA regulation of modulators of intracellular signaling cascades. We partition this review into how miR-34a is regulated by different proteins and how Wnt- and TGF-induced intracellular signaling cascades are modulated by miR-34a. In this review, we bring to limelight how miR-34a regulates its target genes to induce apoptosis and inhibit cell proliferation as evidenced by *in vitro* and *in vivo* analysis. We also discuss miR-34 regulation of PDGFR and c-MET and recent advancements in nanotechnologically delivered miR-34a. Spotlight is also set on modulation of chemotherapeutic sensitivity by miR-34a in cancer cells using reconstruction studies. Clinical trial of miR-34 is indicative of its tremendous potential, and continuous cutting research will

prove to be effective in efficiently translating laboratory findings into clinically effective therapeutics.

Key words: *Apoptosis; cancer; miR-34a*

Alvarez D.D., Sivignon A., Chalopin T., Dumych T., Roos G., Bilyy R., et al.

The Antiadhesive Strategy in Crohn's Disease: Orally Active Mannosides to Decolonize Pathogenic Escherichia coli from the Gut

Chembiochem. 2016, 17(10): 936-952. (IF = 2,850)

Blocking the adherence of bacteria to cells is an attractive complementary approach to current antibiotic treatments, which are faced with increasing resistance. This strategy has been particularly studied in the context of urinary tract infections (UTIs), in which the adhesion of pathogenic *Escherichia coli* strains to uroepithelial cells is prevented by blocking the FimH adhesin expressed at the tips of bacteria organelles called fimbriae. Recently, we extended the antiadhesive concept, showing that potent FimH antagonists can block the attachment of adherent-invasive *E. coli* (AIEC) colonizing the intestinal mucosa of patients with Crohn's disease (CD). In this work, we designed a small library of analogues of heptyl mannoside (HM), a previously identified nanomolar FimH inhibitor, but one that displays poor antiadhesive effects *in vivo*. The anomeric oxygen atom was replaced by a sulfur or a methylene group to prevent hydrolysis by intestinal glycosidases, and chemical groups were attached at the end of the alkyl tail. Importantly, a lead compound was shown to reduce AIEC levels in the feces and in the colonic and ileal mucosa after oral administration (10 mg kg⁻¹) in a transgenic mouse model of CD. The compound showed a low bioavailability, preferable in this instance, thus suggesting the possibility of setting up an innovative antiadhesive therapy, based on the water-soluble and non-cytotoxic FimH antagonists developed here, for the CD subpopulation in which AIEC plays a key role.

Key words: *Crohn's disease; FimH; cell adhesion; inhibitors; lectins; mannosides*

Selikhova M., Tripoliti E., Fedoryshyn L., Matvienko Y., Stanetska H., Boychuk M., Komnatska I., Lees A.J., Sanotsky Y.

Analysis of a distinct speech disorder seen in chronic manganese toxicity following Ephedrone abuse

Clin Neurol Neurosurg. 2016, 147:71-77. (IF = 1,198)

INTRODUCTION: In the last fifteen years a new cause of chronic manganese toxicity has been recognized. It follows recreational intravenous injections

of Ephedrone, synthesized from a cold remedies contained pseudoephedrine. Potassium permanganate is used as an oxidant. It presents with severe parkinsonism-dystonia and a characteristic dysarthria.

OBJECTIVES: We performed a focus perceptual study of dysarthria in Ephedrone induced parkinsonism and compared the findings with the speech disorders seen in Parkinson's disease (PD) and Progressive Supranuclear Palsy (PSP).

METHODS: A digital voice recording, perceptual speech analysis (Darley, 1975) [18], serial neurological assessment and Brain Magnetic Resonance (MR) imaging were performed at the Lviv regional Clinical Hospital. The results were analysed at the Institute of Neurology in London.

RESULTS: Dysarthria developed after 8.5 ± 3.2 months of daily intravenous Ephedrone abuse and was an initial symptom in a third of cases. It was characterised by a robotic-flat prosody, whispering or continuous phonation, an inability to regulate pitch and volume, frozen lip articulation, a variable degree of dystonic tightness, difficulties in speech initiation and palladia, There was no nasality and swallowing was normal. In some patients speech deteriorated even after the discontinuation of Ephedrone. MR imaging, performed soon after drug cessation showed T1 signal hyperintensity in striatum and pallidum, especially in the Globus Pallidum interna.

CONCLUSION: Ephedrone induced chronic manganese toxicity can lead to a mixed hypokinetic-dystonic dysarthria with a distinct dystonic pattern. Perceptual speech analysis can be a helpful ancillary investigation in the differential diagnosis of parkinsonism, and may permit the recognition of chronic manganese toxicity.

Key words: *Dysarthria; Globus pallidum; Manganism; Parkinsonism*

*Cherkas A., Eckl P., Gueraud F., Abrahamovych O., Serhiyenko V.,
Yatskevych O., Pliatsko M., Golota S.*

Helicobacter pylori in sedentary men is linked to higher heart rate, sympathetic activity, and insulin resistance but not inflammation or oxidative stress

Croat Med J. 2016, 57(2):141-149. (IF = 1.483)

AIM: To compare anthropometric parameters, body composition, hormonal and inflammatory profiles, oxidative stress indices, and heart rate variability (HRV) in *Helicobacter pylori* (*H.pylori*) positive and negative healthy sedentary participants.

METHODS: Among 30 recruited apparently healthy male participants (age between 20 and 40) enrolled in this cross-sectional study, 18 were *H.pylori* negative and 12 were positive (stool antigen test). Participants underwent routine physical examination and body composition determination. The following

biochemical parameters were determined in blood: fasting whole blood glucose, glycated hemoglobin, insulin, C-peptide, cortisol, aldosterone, testosterone, thyroid stimulating hormone, C-reactive protein, interleukins 6 and 10, tumor necrosis factor- α , and the urinary level of 1,4-dihydroxynonane mercapturic acid. For HRV evaluation, electrocardiogram in supine position and in orthostatic test was performed.

RESULTS: *H.pylori* contamination was not significantly associated with any changes in anthropometric parameters, body composition, blood pressure, fasting glucose, or glycated hemoglobin levels. No significant difference was found for inflammatory markers as well as 1,4-dihydroxynonane mercapturic acid. *H.pylori*-positive participants, however, had significantly higher heart rate ($P=0.009$), sympathetic/parasympathetic balance in orthostatic test ($P=0.029$), fasting insulin level ($P=0.037$), and HOMA-index ($P=0.047$).

CONCLUSIONS: *H.pylori* contamination is linked to a significantly higher heart rate, sympathetic activation, and increased insulin resistance, while inflammatory and oxidative stress markers remain unaffected in healthy sedentary male subjects.

Devinyak O.T., Lesyk R.B.

5-Year Trends in QSAR and its Machine Learning Methods

Curr Comput Aided Drug Des. 2016, [Epub ahead of print] (IF = 1,29)

A bibliometric analysis of articles published in top molecular modeling and medicinal chemistry journals has been carried out in order to highlight recent trends of QSAR in general and trends of machine learning methods in particular. During 5-year span studied, the fraction of QSAR studies underwent a twofold decrease. Top journals of both categories became less likely to publish Multiple Linear Regression models and increased the presence of Random forest and Naïve Bayes methods. 3D-QSAR remains the most popular method of studying structure-activity relationships with a slight decrease of its presence in molecular modeling journals but a relative increase in medicinal chemistry. The progress in machine learning methods being adopted by chem(o)informaticians finally will help QSAR to find its place in drug design and to move to the Plateau of Productivity.

Desai J., Kumar S.V., Mulay S.R., Konrad L., Romoli S., Schauer C., Herrmann M., Bilyy R., Müller S., Popper B., Nakazawa D., Weidenbusch M., Thomasova D., et al.

PMA and crystal-induced neutrophil extracellular trap formation involves RIPK1-RIPK3-MLKL signaling.

Eur J Immunol. 2016, 46(1): 223-229. (IF = 4.179)

Neutrophil extracellular trap (NET) formation contributes to gout, autoimmune vasculitis, thrombosis, and atherosclerosis. The outside-in signaling

pathway triggering NET formation is unknown. Here, we show that the receptor-interacting protein kinase (RIPK)-1-stabilizers necrostatin-1 or necrostatin-1s and the mixed lineage kinase domain-like (MLKL)-inhibitor necrosulfonamide prevent monosodium urate (MSU) crystal- or PMA-induced NET formation in human and mouse neutrophils. These compounds do not affect PMA- or urate crystal-induced production of ROS. Moreover, neutrophils of chronic granulomatous disease patients are shown to lack PMA-induced MLKL phosphorylation. Genetic deficiency of RIPK3 in mice prevents MSU crystal-induced NET formation in vitro and in vivo. Thus, neutrophil death and NET formation may involve the signaling pathway defining necroptosis downstream of ROS production. These data imply that RIPK1, RIPK3, and MLKL could represent molecular targets in gout or other crystallopathies.

Key words: *Necroptosis; Necrosis; Neutrophil; Neutrophil extracellular trap formation; Receptor-interacting protein kinase*

*Gerasimov S.V., Ivantsiv V.A., Bobryk L.M., Tsitsura O.O.,
Dedyshin L.P., Guta N.V., Yandyo B.V.*

Role of short-term use of *L. acidophilus* DDS-1 and *B. lactis* UABLA-12 in acute respiratory infections in children: a randomized controlled trial

Eur J Clin Nutr. 2016, (4):463-9. (IF = 2.935)

BACKGROUND/OBJECTIVES: Evidence suggests that the long-term consumption of probiotics may help in reducing the incidence of or modifying acute respiratory infection (ARI). We assessed the role of the short-term use of probiotics in ARI in children.

SUBJECTS/METHODS: This was a randomized, double-blind, controlled study that enrolled 315 children with 90 dropouts. On the first day of appearance of a sick household member, otherwise healthy children of both sexes aged 3-12 years were allocated to receive *Lactobacillus acidophilus* DDS-1 and *Bifidobacterium lactis* UABLA-12 (Up4-Junior) in a dose of 5 billion colony-forming units daily with 50 mg of fructooligosaccharide (the probiotic group) or rice maltodextrin (the control group). Test supplementation and follow-up lasted for 2 weeks or until the end of the secondary ARI in a child. The primary outcome measure was the incidence of ARI. Time to resolution and the severity of ARI served the secondary outcome measures.

RESULTS: In all, 64 of 113 children in the probiotic group (57%) and 73 of 112 children in the control group (65%) developed ARI ($P=0.261$). Time to resolution of the secondary ARI was shorter in the probiotic group (5.0 (interquartile range (IQR): 4.0-6.0) vs 7.0 (IQR: 6.0-8.0) days, $P<0.001$). The median severity of ARI was 240 (IQR: 163-350) score-days in the probiotic vs 525 (IQR: 364-736) score-days in the control group ($P<0.001$).

CONCLUSIONS: The short-term use of probiotics does not reduce the incidence, but shortens ARI in preschool and elementary school children.

Senkiv J., Finiuk N., Kaminsky D., Havrylyuk D., Wojtyra M., Kril I., Gzella A., Stoika R., Lesyk R.

5-Ene-4-thiazolidinones induce apoptosis in mammalian leukemia cells

Eur J Med Chem. 2016, 117:33-46. (IF = 3,902)

The article presents the synthesis of 5-ene-4-thiazolidinone derivatives with pyrazole core linked by enamine group. The structure and purity of compounds were confirmed by analytical and spectral data including X-ray analysis. Target compounds were screened for their anticancer activity and selective antileukemic action was confirmed. 5-[5-(2-Hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-ylmethylene]-3-(3-acetoxyphenyl)-2-thioxothiazolidin-4-one (compound 1) was selected as most active agent against HL-60 and HL-60/ADR cell lines; IC₅₀ = 118 nM/HL-60 with low toxicity towards pseudonormal cells. The mitochondria-dependent apoptosis was identified as the main mode of 1 action. Moreover compound's effect induces G₀/G₁ arrest of the treated cells and causes inhibition of cell division and is related with activation of ROS production.

Key words: *5-Ene-4-thiazolidinones; Anticancer activity; Apoptosis; Leukemia; ROS*

Bilynsky B.T., Shparyk Y.V., Mryglotsky M.M., Lukavetsky N.O., Volod'ko N.A., Litvinyak R.I.

70th anniversary of the Lviv scientific school of oncology

Exp Oncol. 2016, 38(1):60-2. (IF = 1,25)

Contemporary development of scientific thought is fostered not by separate people but is a purposeful activity of a group of like-minded people armed with progressive ideas and modern technical equipment. Such schools appeared and work actively in the majority of research and educational establishments, clinics, and universities. The Lviv school established in 1945 by Professor H.P. Kovtunovych and developed by Professor A.I. Hnatyshak and his disciples can serve as an example of a successful school of oncology that continues its activity and yields scientific results. This school appeared not out of the thin air. Medieval Lviv could boast of the first university on the territory of the present-day Ukraine. Many discoveries and endeavors that made a beneficial impact on the development of medicine in Eastern Europe were made in this city. For historical reasons, the city of Lviv used to belong to different state formations (Austria-Hungary, Poland, the USSR; now it is a part of Ukraine), which could not but reflect on the staffing of doctor-researchers. This process acquired a special intensity in 1939-1945 when the research staff of the

university changed substantially. Then, in 1945, H.P. Kovtunovych, the disciple of the prominent oncologist N.N. Petrov, came to Lviv and brought the ideas of St.-Petersburg oncology to the Lviv ground. The Lviv school was influenced by the two times Nobel Prize winner Marie Skłodowska Curie, who facilitated the initiation of oncological radiology in Lviv. The article contains data on research done by the disciples of Professors H.P. Kovtunovych and A.I. Hnatyshak. The first ever teaching chair of oncology in the USSR was founded in Lviv (1966), as well as the first Ukrainian hospice--an institution for palliative care for the oncological patients. The Lviv oncology center is one of the biggest and best-equipped oncology centers in Ukraine. An organic combination of theory and clinical practice has always been the guiding principle of the Lviv school of oncology. Presently, the Lviv school of oncology unites six doctors of sciences, a large collective of educators and researchers, as well as practitioners of the center of oncology. The school maintains close scientific and practical ties with oncologists of Ukraine as well as with leading oncological centers of Europe and America.

Tsyplik O., Yushchuk O., Zaburannyi N., Flärth K., Walker S., Fedorenko V., Ostash B.

Transcriptional regulators of GntR family in *Streptomyces coelicolor* A3(2): analysis in silico and in vivo of YtrA subfamily

Folia Microbiol (Praha). 2016, 61(3):209-20. (IF = 1,335)

Transcriptional factors of the GntR family regulate numerous physiological and morphological processes in response to the nutrient state of bacterial cells. The number of GntR transcriptional factors in genomes of soil-dwelling actinomycetes is one of the highest among bacteria, reflecting both the large size of their chromosomes and the complex ecological niche that they occupy. However, very little is known about the roles of GntRs in actinomycete biology. Here, we analyzed the genome of model actinomycete, *Streptomyces coelicolor* A3(2), in an attempt to gain new insights into the function of GntR family. All 56 GntR proteins of M145 strain were classified into FadR, HutC, MocR, YtrA, and DevA subfamilies according to their secondary structure. We then checked for the presence of GntR orthologs in six other sequenced *Streptomyces* and one *Kitasatospora* genomes, revealing that 12 GntRs were conserved in all analyzed strains. Genomic analysis of the less studied YtrA type regulators revealed 160 sequences present in 88 members of Coriobacteridae, Rubrobacteridae, and Actinobacteridae subclasses. These proteins form seven dense clusters on the consensus phylogenetic tree and their genes are usually co-located with the genes for transport proteins. Probable operator sites were identified for orthologous groups of Sco0823 and Sco3812 proteins. All *S. coelicolor* YtrA-like regulatory genes (SCO0823, SCO1728, SCO3812) were analyzed at transcriptional level, knocked out, and introduced on moderate copy number plasmid in M145 strain. Also, gene SCO0824, a part of putative SCO0823 operon, was studied. Results of these experiments are discussed here.

*Bilyy R., Fedorov V., Vovk V., Leppkes M., Dumych T.,
Chopyak V., Schett G., Herrmann M.*

Neutrophil Extracellular Traps Form a Barrier between Necrotic and Viable Areas in Acute Abdominal Inflammation

Front Immunol. 2016, Oct 10;7:424. eCollection 2016. (IF = 5,695)

Neutrophils form neutrophil extracellular traps (NETs) of decondensed DNA and histones that trap and immobilize particulate matter and microbial pathogens like bacteria. NET aggregates reportedly surround and isolate large objects like monosodium urate crystals, which cannot be sufficiently cleared from tissues. In the setting of acute necrotizing pancreatitis, massive tissue necrosis occurs, which is organized as pancreatic pseudocysts (1). In contrast to regular cysts, these pseudocysts are not surrounded by epithelial layers. We hypothesize that, instead, the necrotic areas observed in necrotizing pancreatitis are isolated from the surrounding healthy tissues by aggregated NETs. These may form an alternative, putatively transient barrier, separating necrotic areas from viable tissue. To test this hypothesis, we investigated histological samples from the necropsy material of internal organs of two patients with necrotizing pancreatitis and peritonitis accompanied by multiple organ failure. Tissues including the inflammatory zone were stained with hematoxylin and eosin and evaluated for signs of inflammation. Infiltrating neutrophils and NETs were detected by immunohistochemistry for DNA, neutrophil elastase (NE), and citrullinated histone H3. Interestingly, in severely affected areas of pancreatic necrosis or peritonitis, chromatin stained positive for NE and citrullinated histone H3, and may, therefore, be considered NET-derived. These NET structures formed a layer, which separated the necrotic core from the areas of viable tissue remains. A condensed layer of aggregated NETs, thus, spatially shields and isolates the site of necrosis, thereby limiting the spread of necrosis-associated proinflammatory mediators. We propose that necrotic debris may initiate and/or facilitate the formation of the NET-based surrogate barrier.

Key words: *inflammation; neutrophil elastase; neutrophil extracellular traps; neutrophils; sepsis*

Zimba E., Olkhova O.

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S): CLINICAL CASE

Georgian Med News. 2016, (254):43-7. (IF = 0,16)

Granulomatosis with polyangiitis (Wegener's disease) - systemic vasculitis, initial manifestations, the clinical picture may be present in a wide variety. This leads to difficulties in establishing a timely diagnosis. The prognosis in untreated generalized granulomatosis with polyangiitis is extremely poor. The present case

report illustrates a late diagnosis of granulomatosis with polyangiitis. A 53-year-old woman was diagnosed with granulomatosis with polyangiitis only after ten months of onset of disease. Wrong diagnosis of tuberculosis of ear leads to a lot of delay in the treatment this type of vasculitis. At the time of diagnosis she had generalized form of disease presented with involvement of the eyes, upper and lower respiratory tracts, kidneys, and nervous system. Remission was achieved with methylprednisolone and cyclophosphamide but suffered a relapse shortly afterwards. Further treatment with rituximab achieved a second remission, but the patient continued to suffer from dry conjunctivitis. Symptomatic therapy in this case was ineffective. An effective pathogenic therapy for this condition was instillation of cyclosporine eye drops.

Lukavetskyy O., Boyko N., Fedorov V., Ogurtsov O., Havrysh Y.

Abdominal tuberculosis that masked under the early postoperative septic complications

Int J Surg Case Rep. 2016, 28:4-8. (IF = 0,627)

INTRODUCTION: At the same time even laparoscopic adrenalectomy can become the source or the causing factor of a number of complications. In the following report we present the clinic case of diagnostic complications during postsurgical period of “rapid” development and signs of tuberculosis after laparoscopic adrenalectomy.

PRESENTATION OF CASE: The patient underwent ultrasonography and CT was found out: the tumor of right adrenal gland. Operational treatment: right laparoscopy adrenalectomy. Pathologistological conclusion: clear cell adenoma. On the fourth day there was a high temperature rise noted 38-39°C. On the 10th day the CT, where there were no signs of free liquid abscess formation. Relaparoscopic: small amount of serous-hemorrhagic liquid in small pelvis, hyperemated peritoneum, in both - left and right liver lobes tight knots of white color. After, the patient still had hyperthermia 38°C. Phthisiatrician consulted the patient and diagnosed abdominal tuberculosis. After six-month treatment the patient in satisfactory condition was discharged home.

DISCUSSION: But in case of our patient’s case such visual diagnostic methods, such as CT and ultrasonography of abdominal cavity appeared to be non-informative in lymph system diagnostics due to the number of reasons. The described clinical case and literature data prove the fact, that crucial in abdominal tuberculosis form management treatment is a diagnostic laparoscopy with tissue biopsy.

CONCLUSION: Labors, as well as adrenalectomy are possible factors which decrease the immunity and can cause the activation of tuberculosis process. Diagnostic laparoscopy and intraoperative histological tissue study of abdominal cavity are the main points in prescribing diagnosis of abdominal tuberculosis form.

Key words: *Abdominal tuberculosis; Laparoscopic adrenalectomy; Relaparoscopy; Septic complications*

Ivankiv T., Ogurtsov O., Pokhylevych G.

Organized hematoma mimicking retroperitoneal cystic tumors

Int J Surg Case Rep. 2016, 19:147-9. (IF = 0,627)

INTRODUCTION: Isolated retroperitoneal cysts are uncommon with an estimated incidence of 1/5750-1/250,000. In women they occur about 1.5-2 times more often than in men. The largest numbers of patients are young or middle aged (20-50 years). Lack of knowledge about the causes of these rare entities and asymptomatic clinical picture often leads to diagnostic and tactical mistakes.

METHODS: The medical history of 54-year old male patient B., who has been hospitalized at Surgical Department №1 of Danylo Halytsky Lviv National Medical University (Surgical Department of Lviv Regional Clinical Hospital), was processed retrospectively.

RESULT: Diagnosing of retroperitoneal organized hematoma in the early stages is not always possible, because exploration of retroperitoneal space can be difficult. General tests and tumor markers are usually normal range and not prognostically informative in this case. Decisively important were imaging diagnostic methods-USG and CT. As clinical cases of organized hematoma are quite rare, finding out retroperitoneal formation with irregular contours and infiltrative component indicates for retroperitoneal tumors. Thus, this formation accumulated contrast that says for increased vascularization. Intraoperative: formation with thick walls and heterogeneous structure. Histological diagnosis: hematoma in a phase of deep organization. On our opinion, taking into account location and structure of tumors, laparoscopic intervention was not appropriate, open surgery was reasonable approach. Preoperative biopsy has a crucial role to set preliminary diagnosis.

CONCLUSION: Despite the fact that organized retroperitoneal hematomas are quite rare, their diagnosis requires detailed examination and histological verification.

Key words: *Cystic tumors; Organized hematoma; Retroperitoneal space*

Hecht J.R., Bang Y.J., Qin S.K., Chung H.C., Xu J.M., Park J.O., Jeziorski K., Shparyk Y., Hoff P.M., Sobrero A., Salman P., Protsenko S.A., et al.

Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC--A Randomized Phase III Trial

J Clin Oncol. 2016, 34(5):443-51. (IF = 9,38)

PURPOSE: To evaluate the efficacy of adding lapatinib to capecitabine and oxaliplatin (CapeOx) in patients with previously untreated human epidermal growth

factor receptor 2 (HER2) -amplified advanced gastroesophageal adenocarcinoma.

PATIENTS AND METHODS: Patients with HER2-positive advanced gastroesophageal adenocarcinoma were randomly assigned at a one-to-one ratio to CapeOx plus lapatinib 1,250 mg or placebo daily. Primary end point was overall survival (OS) in patients with centrally confirmed HER2 amplification in the primary efficacy population.

RESULTS: A total of 545 patients were randomly assigned, and 487 patients comprised the primary efficacy population. Median OS in the lapatinib and placebo arms was 12.2 (95% CI, 10.6 to 14.2) and 10.5 months (95% CI, 9.0 to 11.3), respectively, which was not significantly different (hazard ratio, 0.91; 95% CI, 0.73 to 1.12). Median progression-free survival in the lapatinib and placebo arms was 6.0 (95% CI, 5.6 to 7.0) and 5.4 months (95% CI, 4.4 to 5.7), respectively (hazard ratio, 0.82; 95% CI, 0.68 to 1.00; $P = .0381$). Response rate was significantly higher in the lapatinib arm: 53% (95% CI, 46.4 to 58.8) compared with 39% (95% CI, 32.9 to 45.3) in the placebo arm ($P = .0031$). Preplanned exploratory subgroup analyses showed OS in the lapatinib arm was prolonged in Asian and younger patients. No correlation was observed between HER2 immunohistochemistry status and survival. There were increased toxicities in the lapatinib arm, particularly diarrhea.

CONCLUSION: Addition of lapatinib to CapeOx did not increase OS in patients with HER2-amplified gastroesophageal adenocarcinoma. There were clear differences in the effect of lapatinib depending on region and age. Future studies could examine this correlation.

TRIAL REGISTRATION: *ClinicalTrials.gov* NCT00680901.

Shatynska-Mytsyk I., Rodrigo L., Cioccocioppo R., Petrovic D., Lakusic N., Compostella L., Novak M., Kruzliak P.

The impact of thyroid hormone replacement therapy on left ventricular diastolic function in patients with subclinical hypothyroidism

J Endocrinol Invest. 2016, 39(6):709-13. (IF = 1,994)

OBJECTIVE: Subclinical hypothyroidism (SH) is associated with a moderately elevated risk of heart failure events among older adults. The objective of our prospective study was to assess the impact of thyroid hormone replacement therapy (HRT) with low doses of L-thyroxine (6.25-25 $\mu\text{g}/\text{day}$) on left ventricular diastolic function in patients with SH.

MATERIALS AND METHODS: 33 patients with SH and 25 healthy controls were involved. All participants underwent standard echocardiography and Doppler imaging at baseline and, the patient group, also after a course of HRT.

RESULTS: At baseline, patients with SH showed significantly lower E (0.79 ± 0.22 vs. 0.93 ± 0.19 , $p < 0.001$), E/A ratio (1.19 ± 0.29 vs. 1.31 ± 0.25 , $p < 0.003$),

and higher intraventricular septum thickness (IVST) (0.99 ± 0.14 vs. 0.89 ± 0.18 , $p < 0.001$) in comparison with healthy controls. After 6 months of therapy, the E/A ratio underwent significant increase (1.28 ± 0.21 vs. 1.19 ± 0.29 , $p < 0.001$), while the IVS displayed a robust reduction (0.92 ± 0.16 vs. 0.99 ± 0.14 , $p < 0.001$).

CONCLUSIONS: HRT with low-dosed L-thyroxine may improve left ventricular diastolic function in patients with SH.

Key words: *Echocardiography; Heart failure; Left ventricular diastolic function; Subclinical hypothyroidism*

Siedlarz P., Sroka M., Dylağ M., Nawrot U., Gonchar M., Kus-Liškiewicz M.

Preliminary physiological characteristics of thermotolerant *Saccharomyces cerevisiae* clinical isolates identified by molecular biology techniques

Lett Appl Microbiol. 2016, Mar;62(3):277-82. (IF = 2,156)

The aim of the study was a molecular identification and physiological characteristic of the five *Saccharomyces cerevisiae* strains isolated from patients. The tested isolates were compared with control strains (which are of laboratory or commercial origin). The relation of the isolates to baker's yeast *S. cerevisiae* was studied using species-specific primers in PCR analysis of the ITS-26S region of DNA. Five isolates were genetically identified as the yeast belonging to the genus *S. cerevisiae*. The effects of temperature and carbon sources on the growth of the yeast strains were analysed. A quantitative characterization of growth kinetics approve that some tested isolates are thermotolerant and are able to grow at range 37-39°C. Among them, one representative is characterized by the highest specific growth rate (0.637 h^{-1}). In conclusions, some strains are defined as potential candidates to use in the biotechnology due to a higher growth rate at elevated temperatures. Screening for further evaluation of biotechnological significance of the tested isolates will be done (e.g. ethanol and trehalose production at higher temperatures). The physiological characterization and confirmation of species identification by molecular methods for yeasts important in the context of biotechnology industry were demonstrated.

SIGNIFICANCE AND IMPACT OF THE STUDY: Thermotolerant microbial strains are required in various industrial applications, for improving productivity and for decreasing the risk of undesirable contaminations when higher temperatures are used. It is important to search for such strains in extreme environments or exotic niches. In this paper, new thermotolerant strains were identified belonging to the *Saccharomyces cerevisiae*, but differed from typical bakers' yeast, essentially by their growth rate at higher temperature. The described yeast strains are promising for using in biotechnological industry, especially, for production of ethanol and other products at higher temperatures.

Key words: *Saccharomyces cerevisiae; clinical isolates; growth rate; molecular identification; thermotolerance*

Oliynyk I.

Limits of application of initiated chemiluminescence in monitoring of oncological process of mucous membrane of mouth and larynx

Luminescence. 2016, 31(6):1213-9. (IF = 1,452)

Investigation into the limits of application of chemiluminescence (CL) methods in oncology still attracts the attention of researchers. In the present work we analyze the screening and monitoring of oncological processes (OP) in the mucous membrane of the mouth and larynx by initiated CL (ICL). Chemiluminescence has already been used by stomatologists to define the start of OP, but methods that reflect the metabolic changes in organism under cancer diagnostics still have not found their place. This work presents results of ICL on blood serum (BS) of patients with oncological diseases at different stages of medical treatment compared with those of healthy people. We found an essential metabolic difference only in types of OP that are characterized by two maxima on chemiluminograms. These OP represent only 12.81% of groups of patients with oncological diseases. The possibility to apply ICL methods to monitor operation quality and control medical treatment at different stages when the two ICL maxima are present is established. At present, the chemiluminograms with the two maxima are mostly informative, but this does not exclude the quantitative analysis of other ICL kinetic methods and is encouraging for their investigation. Any OP introduces changes in organism function and these should be reflected in the ICL.

Key words: *blood serum; chemiluminescence; oral cancer; second maximum*

Mulay S.R., Desai J., Kumar S.V., Eberhard J.N., Thomasova D., Romoli S., Grigorescu M., Kulkarni O.P, Bilyy R.

Cytotoxicity of crystals involves RIPK3-MLKL-mediated necroptosis

Nat Commun. 2016, 7:10274. doi: 10.1038/ncomms10274. (IF = 11,329)

Crystals cause injury in numerous disorders, and induce inflammation via the NLRP3 inflammasome, however, it remains unclear how crystals induce cell death. Here we report that crystals of calcium oxalate, monosodium urate, calcium pyrophosphate dihydrate and cystine trigger caspase-independent cell death in five different cell types, which is blocked by necrostatin-1. RNA interference for receptor-interacting protein kinase 3 (RIPK3) or mixed lineage kinase domain like (MLKL), two core proteins of the necroptosis pathway, blocks crystal cytotoxicity. Consistent with this, deficiency of RIPK3 or MLKL prevents oxalate crystal-induced acute kidney injury. The related tissue inflammation drives TNF- α -related necroptosis. Also in human oxalate crystal-related acute kidney injury, dying tubular cells stain positive for phosphorylated MLKL. Furthermore, necrostatin-1 and necrosulfonamide, an inhibitor for human MLKL suppress crystal-induced cell death in human renal progenitor cells. Together, TNF- α /TNFR1, RIPK1, RIPK3 and MLKL are molecular targets to limit crystal-induced cytotoxicity, tissue injury and organ failure.

Cherkas A. et al.

Binding, Antioxidant and Anti-proliferative Properties of Bioactive Compounds of Sweet Paprika (*Capsicum annuum* L.)

Plant Foods Hum Nutr. 2016, 71(2):129-36. (IF =2,276)

The scope of this research was to determine the bioactive composition, antioxidant, binding, and anti-proliferative properties of red sweet paprika growing under artificial light. The amounts of carotenoids, chlorophyll, polyphenols, tannins, and flavonoids in red paprika (RP), cultivated in Korea, before and after light treatments under high pressure sodium (HPS) and lighting emitting plasma (LEP) lamps (RPControl, RPHPS, RPLEP), were analyzed in water (W) and ethanolic extracts (Et). Spectroscopic, radical scavenging assays, fluorescence and cytotoxicity measurements were applied. The results of this study showed that total chlorophyll and carotenes were the highest in RPHPS (10.50 ± 1.02 and 33.90 ± 3.26 $\mu\text{g/g}$ dry weight (DW)). The strongest antioxidant capacity ($\mu\text{M TE/g DW}$) in a 2, 2'-azino-bis (3-ethyl-benzothiazoline-6-sulfonic acid) diammonium salt (ABTS(•+)) assay was in RPControlEt (24.34 ± 2.36), in a ferric-reducing/antioxidant power (FRAP) assay in RPHPSW (27.08 ± 2.4) and in a cupric reducing antioxidant (CUPRAC) in RPLEPW (70.99 ± 7.11). The paprika ethanolic extracts showed lower values in their bioactivity than the water ones. The binding and cytotoxicity abilities of extracted polyphenols correlated with their amounts. LEP treatment is better for plant growth characteristics than other conventional treatments. The investigated paprika samples can be used as a source of antioxidants.

Key words: *Antioxidants; Binding; Cytotoxicity; Fluorescence; Light treatments; Red sweet paprika*

Makukh H. et al.

A European Spectrum of Pharmacogenomic Biomarkers: Implications for Clinical Pharmacogenomics

PLoS One. 2016, 11(9):e0162866. doi: 10.1371/journal.pone.0162866.
eCollection (IF = 3,54)

Pharmacogenomics aims to correlate inter-individual differences of drug efficacy and/or toxicity with the underlying genetic composition, particularly in genes encoding for protein factors and enzymes involved in drug metabolism and transport. In several European populations, particularly in countries with lower income, information related to the prevalence of pharmacogenomic biomarkers is incomplete or lacking. Here, we have implemented the microattribution approach to assess the pharmacogenomic biomarkers allelic spectrum in 18 European populations, mostly from developing European countries, by analyzing 1,931 pharmacogenomics biomarkers in 231 genes. Our data show significant

inter-population pharmacogenomic biomarker allele frequency differences, particularly in 7 clinically actionable pharmacogenomic biomarkers in 7 European populations, affecting drug efficacy and/or toxicity of 51 medication treatment modalities. These data also reflect on the differences observed in the prevalence of high-risk genotypes in these populations, as far as common markers in the CYP2C9, CYP2C19, CYP3A5, VKORC1, SLCO1B1 and TPMT pharmacogenes are concerned. Also, our data demonstrate notable differences in predicted genotype-based warfarin dosing among these populations. Our findings can be exploited not only to develop guidelines for medical prioritization, but most importantly to facilitate integration of pharmacogenomics and to support pre-emptive pharmacogenomic testing. This may subsequently contribute towards significant cost-savings in the overall healthcare expenditure in the participating countries, where pharmacogenomics implementation proves to be cost-effective.

Gerasun B.A.

New Method of Inhibition of Activity of Tumor Necrosis Factor Alpha In Patients with Psoriasis

Recent Pat Endocr Metab Immune Drug Discov.
2016, Apr 26. [Epub ahead of print] (IF = 2,29)

INTRODUCTION: A new method of reduction of tumor necrosis factor alpha activity via intradermal immunization with inactivated autoleukocytes (patent UA97493 (2015) [1]) has been presented in the article. New patents from various countries have been analyzed [2-7].

OBJECTIVE: Patients with psoriasis (24) with high level of tumor necrosis factor alpha in their blood (30pg/ml) were immunized with autoleukocytes.

METHOD: Leukocytes were isolated by centrifuging plasma, obtained after precipitation of a patient's heparinized peripheral venous blood. Precipitate was suspended in 1.0 - 1.5ml of a patient's blood serum and 0.1ml of blood was injected into the skin of the back. For determination of autoleukocyte immunization efficacy, concentration of tumor necrosis factor alpha in a patient's blood was compared prior to immunization and at different periods after immunization.

RESULTS: In 30 days after single immunization, a considerable decrease in cytokine concentration was observed in all patients (100%); it reduced to zero in 16 out of 24 of immunized individuals (66.7%). The degree of reduction and duration of the achieved effect were individual, thus, if necessary the immunization was repeated several times. The procedure was well tolerated, and general condition of patients was improved.

CONCLUSION: The method of reduction of tumor necrosis factor alpha activity is recommended for implementation into clinical practice.

Semen K., Yelisyeyeva O., Jarocka-Karpowicz I., Kaminsky D., Solovey L., Skrzydlewska E., Yavorskyi O.

Sildenafil reduces signs of oxidative stress in pulmonary arterial hypertension: Evaluation by fatty acid composition, level of hydroxynonenal and heart rate variability

Redox Biol. 2016, 7:48-57. (IF = 6,235)

Pulmonary arterial hypertension (PAH) is a rare multifactorial disease with an unfavorable prognosis. Sildenafil therapy can improve functional capacity and pulmonary hemodynamics in PAH patients. Nowadays, it is increasingly recognized that the effects of sildenafil are pleiotropic and may also involve changes of the pro-/antioxidant balance, lipid peroxidation and autonomic control. In present study we aimed to assess the effects of sildenafil on the fatty acids (FAs) status, level of hydroxynonenal (HNE) and heart rate variability (HRV) in PAH patients. Patients with PAH were characterized by an increase in HNE and changes in the FAs composition with elevation of linoleic, oleic, docosahexanoic acids in phospholipids as well as reduced HRV with sympathetic predominance. Sildenafil therapy improved exercise capacity and pulmonary hemodynamics and reduced NT-proBNP level in PAH. Antioxidant and anti-inflammatory effects of sildenafil were noted from the significant lowering of HNE level and reduction of the phospholipid derived oleic, linoleic, docosahexanoic, docosapentanoic FAs. That was also associated with some improvement of HRV on account of the activation of the neurohumoral regulatory component. Incomplete recovery of the functional metabolic disorders in PAH patients may be assumed from the persistent increase in free FAs, reduced HRV with the sympathetic predominance in the spectral structure after treatment comparing to control group. The possibilities to improve PAH treatment efficacy through mild stimulation of free radical reactions and formation of hormetic reaction in the context of improved NO signaling are discussed.

Key words: *Fatty acid composition; Heart rate variability; Hydroxynonenal; Oxidative stress; Pulmonary arterial hypertension; Sildenafil*

Ieremeieva T.V.

Sociological research on the population awareness regarding ophthalmological care in Ukraine

Wiad Lek. 2016, 69(3 pt 2):532-536.

INTRODUCTION: nowadays, there are about 45 million blind individuals and, according to the prognosis, their quantity will reach over 76 million in 2020. In such a way, nowadays ophthalmological problems become more widespread, and the market of the ophthalmological services is not studied enough to understand all the tendencies and processes.

AIM: was to study the patients' awareness on eye diseases and choice

peculiarities of the information sources and medical institutions among various population age groups of Lutsk, Rivne and Ternopil cities.

MATERIALS AND METHODS: the research was conducted as an anonymous questionnaire survey of respondents according to a specially designed integrated protocol by means of interviewing people at the streets of Lutsk (n=2000), Rivne (n=1500) and Ternopil (n=1500) cities.

RESULTS: there was conducted a research on the population awareness concerning vision problems, analysis of social factors and peculiarities of the choice of information sources about eye diseases and factors influencing the choice of a medical institution and an ophthalmologist. It was determined that younger population prefers private medical institutions in almost half of the cases (95% confidence interval (CI) of the private institution choice probability: 0,48-0,52), while older population prefers mainly state ones (95% CI of the choice probability: 0,71-0,74).

CONCLUSION: it was determined depending on the age, the range of people having vision problems varied from 22% in the “under 30 years” population group up to 76% in the “over 60 years” group, although at least 21,5% of the whole population realizing their problems do not address an ophthalmologist.

Key words: age groups of respondents; eye diseases; ophthalmological care; sociological survey

Hryhoriy K.

Peculiarities of heart rate in the patients with unstable angina and non-ST elevation myocardial infarction and concomitant diabetes mellitus type 2

Wiad Lek. 2016, 69(3 pt 2):524-526.

INTRODUCTION: type 2 diabetes mellitus is one of the most important medical and social problems in the world. Patients with diabetes are prone to coronary artery disease, in particular acute coronary syndrome, with atypical clinical signs and susceptibility to tachycardia. Elevated heart rate is an important factor of premature mortality in all patients with acute coronary syndrome. The aim of the investigation was to reveal the heart rate peculiarities in unstable angina and non-ST elevation myocardial infarction patients suffering from diabetes mellitus type 2 for more effective treatment of these patients.

MATERIALS AND METHODS: 40 patients with unstable angina and non-ST elevation myocardial infarction were examined in the consecutive way during 2013- 2015 years. The patients were divided in two groups. The main group consisted of 25 patients with UA and NSTEMI with concomitant DM. The control group consisted of 15 patients with UA and NSTEMI but without DM. Basic clinical examinations, electrocardiography and 24 hours electrocardiography monitoring were performed. Carvedilol in the dose from 12.5 to 25 mg daily was also prescribed.

RESULTS: we revealed statistically higher heart rate in the patients with unstable angina, non-ST elevation myocardial infarction and concomitant DM on hospitalization, at the fifth day of treatment and before their discharge from the hospital.

CONCLUSIONS: 1. Patients with unstable angina and non-ST elevation myocardial infarction in associations with diabetes mellitus type 2 are characterized with increased heart rate partly resistant to β -blockers, which indicates worse prognosis of cardiovascular diseases. 2. Prescription of carvedilol in daily dose 12.5 - 25 mg. is inadequate for obtaining HR < 70 bpm. in some patients with acute coronary syndrome and diabetes mellitus. 3. According to heart rate resistance to β -blockers in patients with unstable angina and non-ST elevation myocardial infarction and concomitant diabetes mellitus patients need individual titration of higher doses of carvedilol.

Key words: *diabetes mellitus type 2; elevated heart rate; non-ST elevation myocardial infarction ; unstable angina*

Mishchuk V., Lerchuk O., Dvorakevych A., Khomyak V.

Features of respiratory support during laparoscopic correction of inguinal hernias in children

Wideochir Inne Tech Maloinwazyjne. 2016, 11(2):55-9. (IF = 1,092)

INTRODUCTION: The objectives were to study the changes in the mechanics of respiration in children undergoing surgery depending on the value of intra-abdominal pressure (IAP) during laparoscopic procedures, and to compare the effects of different mechanical ventilation modes - pressure controlled (PCV) and volume controlled (VCV) ventilation - on the mechanics of respiration considering carboxyperitoneum conditions (CP).

AIM: To study the changes in the mechanics of respiration in operated children depending on the value of intra-abdominal pressure during laparoscopic procedures.

MATERIAL AND METHODS: Fifty-two children aged 1-12 years undergoing laparoscopic surgery on inguinal hernias were randomly allocated to receive mechanical ventilation using either VCV (n = 24) or PCV (n = 28) mode. Respiratory mechanics were measured before application of carboxyperitoneum (initial data) and after the gas had been pumped into the abdominal cavity, at the following intra-abdominal pressure values: 6 mm Hg, 8 mm Hg, 10 mm Hg, 12 mm Hg, 14 mm Hg.

RESULTS: Elevation of intra-abdominal pressure due to carboxyperitoneum conditions had a negative effect on the mechanics of respiration. Changes in the respiratory mechanics were restrictive in nature in both groups. The patients who were receiving pressure controlled ventilation showed a decrease in tidal volume, exhaled minute volume, and dynamic lung compliance, which affected the gas

exchange at intra-abdominal pressure values ≥ 12 mm Hg. Patients who were receiving volume controlled ventilation showed an increase in peak inspiratory pressure and mean airway pressure and a decrease in dynamic lung compliance in response to higher intra-abdominal pressure. A significant increase of concentration of exhaled carbon dioxide (etCO₂) was registered at IAP ≥ 12 mm Hg.

CONCLUSIONS: Application of carboxyperitoneum causes increased intra-abdominal pressure and restrictive disorders in respiratory mechanics. Intra-abdominal pressure readings within 8-12 mm Hg allow laparoscopic procedures to be performed without significant gas exchange disorders in children older than 1 year.

Key words: *pneumoperitoneum; respiratory mechanics*

*Yarema R., de Manzoni G., Fetsych T., Ohorchak M.,
Pliatsko M., Bencivenga M.*

On the road to standardization of D2 lymph node dissection in a European population of patients with gastric cancer

World J Gastrointest Oncol. 2016, 8(6):489-97. (IF = 1,72)

The amount of lymph node dissection (LD) required during surgical treatment of gastric cancer surgery has been quite controversial. In the 1970s and 1980s, Japanese surgeons developed a doctrine of aggressive preventive gastric cancer surgery that was based on extended (D2) LD volumes. The West has relatively lower incidence rates of gastric cancer, and in Europe and the United States the most common LD volume was D0-1. This eventually caused a scientific conflict between the Eastern and Western schools of surgical thought: Japanese surgeons determinedly used D2 LD in surgical practice, whereas European surgeons insisted on repetitive clinical trials in the European patient population. Today, however, one can observe the results of this complex evolution of views. The D2 LD is regarded as an unambiguous standard of gastric cancer surgical treatment in specialized European centers. Such a consensus of the Eastern and Western surgical schools became possible due to the longstanding scientific and practical search for methods that would help improve the results of gastric cancer surgeries using evidence-based medicine. Today, we can claim that D2 LD could improve the prognosis in European populations of patients with gastric cancer, but only when the surgical quality of LD execution is adequate.

Key words: *D2 lymph node dissection; European patients; Evidence-based medicine; Gastric cancer; Regional lymph nodes*

*Матеріал міжнародних публікацій
підготувала Уляна ПІДВАЛЬНА*