МІЖНАРОДНІ ПУБЛІКАЦІЇ УКРАЇНСЬКИХ АВТОРІВ*

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Standards of Birth Weight According to Gestational Age in the Northwestern Regions of Ukraine

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An analysis of the neonatal registry for 2001-2010 years in Rivne and Volyn regions of Ukraine as well as 2006-2011 years of Khmelnytsky region was carried out. General information was available about body weight of 366 607 newborns, among which 188 687 were boys and 177 920 girls. Based on the analysis we developed local standards of birth body weight in relation to gestational age separately for boys and girls. Procedure for processing local standards met international standards that have been developed by the WHO. Availability of processed local standards depending on gestational age will enable neonatologists, pediatricians and researchers to clearly identify anomalies in the health of newborns in the northwestern regions of Ukraine. Therefore, identification of newborns with low or high birth weight will enable adequate and timely steps to improve their health.

Keywords: *standards; birth weight; gestational age; the northwestern region of Ukraine*

Vassetzky, Y., Gout, I., Kuznicki, J.

Ukrainian science needs elixir of youth

Nature (Impact Factor: 44.78), 2015, 522(7554), 34-34.

Ukraine's science system stands to benefit from its association with the European Union (EU) Horizon 2020 flagship research programme (Nature http://doi.org/4kq; 2015). But it has problems beyond funding: the re-election of Boris Paton as president of Ukraine's National Academy of Sciences at the age of 96 is symptomatic. We are involved in an initiative to boost cooperation between the EU and Ukraine in biomedicine (COMBIOM). In our view, this will be difficult as long as young scientists feel that they are being held back by the rigid Soviet-style system run by scientists of the old school. Early-career researchers want to gain experience abroad and have little incentive to return. Ukraine's

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science system must be made more competitive. It should reward young scientists who have international expertise and enable them to lead research teams. It should encourage job flexibility and contracts for academy researchers, and identify strategies and research areas to optimize scientific development. It should create institutions that specialize in those areas, and appoint an independent body of EU researchers and Ukrainian scientists abroad to evaluate internal funding applications. Such measures would create a healthy scientific community and promote Ukraine's integration with the European Research Area.

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Cost-Effective HIT Diagnosis: Utilizing IgG-Specific PF4 Immunoassays Reduces the Number of Confirmatory Serotonin Release Assays without Missing True HIT

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In the United States, the most commonly employed screening assay for heparin-induced thrombocytopenia (HIT) is the PF4 ELISA, of which both polyclonal (poly-ELISA) and IgG-specific (IgG-ELISA) assays are commercially available. We compared the IgG-ELISA versus the poly-ELISA to determine whether the IgG-ELISA is more sensitive and specific for the diagnosis of HIT. 453 HIT work-ups were reviewed. Patients with poly-ELISA optical density (OD) values greater than or equal to 0.40 (n=49) were selected for further analysis, including serotonin-release assays (SRAs), IgG-ELISAs, and pre-test probability scoring (4T's score). Both the poly-ELISA and IgG-ELISA identified PF4/heparin antibodies in all true HIT patients (n=8). IgG-ELISA reduced the number of "borderline" cases by 75%. IgG-ELISA is more specific than poly-ELISA and can reduce number of confirmatory SRA required.

Key words: *HIT; IgG-ELISA; PF4 ELISA; Poly-ELISA; Serotonin Release assay (SRA); False positive*

Tomin A, Dumych T, Tolstyak Y, Kril I, Mahorivska I, Bila E, Stoika R, Herrmann M, Kit Y, Bilyy R.

Desialylation of dying cells with catalytically active antibodies possessing sialidase activity facilitate their clearance by human macrophages

Clin Exp Immunol 2015; 179:17-23.

Recently, we reported the first known incidence of antibodies possessing catalytic sialidase activity (sialidase abzymes) in the serum of patients with multiple myeloma and systemic lupus erythematosus (SLE). These antibodies desialylate biomolecules,

such as glycoproteins, gangliosides and red blood cells. Desialylation of dying cells was demonstrated to facilitate apoptotic cell clearance.

Here we assessed the possibility of facilitating dying cell clearance with the use of F(ab)2 fragments of sialidase abzymes. Two sources of sialidase abzymes were used: 1) those isolated from the sera of patients with SLE after preliminary screening of a cohort of patients for sialidase activity; 2) by creating an induced sialidase abzyme through immunization of a rabbit with a synthetic hapten consisting of a non-hydrolysable analogue of the sialidase reaction conjugated with BSA or KLH. Antibodies were purified by ammonium sulphate precipitation, protein-G affinity chromatography and HPLC-SEC. The effect of desialylation on efferocytosis was studied using human polymorphonuclear leukocytes, both viable and aged, as prey, and human monocyte-derived macrophages.

Treatment of apoptotic and viable prey with both disease-associated (purified from the blood serum of SLE patients) and immunization-induced (obtained by rabbit immunization) sialidase abzymes, their F(ab)2 fragments and bacterial neuraminidase (as positive control) significantly enhanced the clearance of prey by macrophages. We conclude that a sialidase abzyme can serve as a protective agent in autoimmune patients and that artificial abzymes may be of potential therapeutic value.

Key words: *abzyme, sialidase, efferocytosis, desialylation, apoptosis*

Kit Y, Bilyy R, Korniy N, Tomin A, Chop'yak V, Tolstyak Y, Antonyuk V, Stoika R.

Two-step chromatography purification of IgGs possessing sialidase activity from human blood serum

Biomed Chromatogr 2015; 29:328-332.

Sialation of cell surface is known to be tightly connected with tumorigenicity, invasiveness, metastatic potential and clearance of aged cells, while sialation of immunoglobulin G (IgG) molecules determines their anti-inflammatory properties. Recently, we have found for the first time IgG-antibodies possessing sialidase-like activity (sialylic abzyme) in blood serum of multiple myeloma and systemic lupus erythematosis patients. This abzyme was detected in a pool of IgGs purified by a typical procedure including immunoglobulin's precipitation with ammonium sulfate and following chromatography on protein G–Sepharose column. Here we describe a novel matrix for affinity purification of sialylic abzyme that is based on using bovine submandibular gland mucin conjugated to Sepharose matrix (mucin–Sepharose). This matrix preferentially binds sialidase-like IgGs from a pool of sialidase-active fraction of proteins precipitated with 50% ammonium sulfate from blood serum of the systemic lupus erythematosis patients. That allowed us to develop a new scheme of double-step chromatography purification of sialidase-like IgGs from human blood serum.

Key words: *antibody; sialidase activity; blood serum; mucin; protein G; affinity chromatography*

Yan X, Sivignon A, Alcouffe P, Burdin B, Favre-Bonte S, Bilyy R, Barnich N, Fleury E, Ganachaud F, Bernard J.

Brilliant glyconanocapsules for trapping of bacteria

Chem Commun (Camb, 6.83 Impact Factor) 2015; 51:13193-13196.

Nanoprecipitation of miglyol into droplets surrounded by a functional glycopolymer generates nanocapsules of biointerest. Bright fluorophores are trapped in situ or post-grafted onto the crosslinked polymer shell for efficient imaging. The heptyl-mannose decorated colloids induce aggregation of bacteria through strong specific interactions and promote their facile removal.

Greulich, T., Averyanov, A., Borsa, L., Rozborilová, E., Vaicius, D., Major, T., Chopyak, V., Tudorache, V., Konstantinova, T. and Camprubí, S.

European screening for alpha1-antitrypsin deficiency in subjects with lung disease

The Clinical Respiratory Journal, 2015, doi: 10.1111/crj.12310

Background. Alpha1-antitrypsin deficiency (AATD) predisposes individuals to early-onset emphysema. Despite its prevalence, especially among patients with chronic obstructive pulmonary disease, AATD is still underdiagnosed. The aim of this study is to identify individuals with lung disease and severe AATD in central-eastern Europe.

Methods. Subjects with respiratory symptoms that could be indicative of AATD provided blood samples as dried blood spot. The alpha1-antitrypsin (AAT) concentration was determined by nephelometry and, if lower than 1.70 mg/dL in dried blood spot (equivalent to 1.04 g/L in serum), polymerase chain reaction was used to detect the PiS and PiZ alleles. Isoelectric focusing was used for confirmation of doubtful genotype results.

Results. From 13 countries, 11 648 subjects were included. Genotyping of 1404 samples with AAT levels <1.70 mg/dL revealed 71 (5.06%) PiS, 151 (10.8%) PiZ, 1 (0.071%) PiSS, 8 (0.57%) PiSZ and 32 (2.28%) PiZZ. Phenotyping of 1363 samples negative for the S and Z alleles or with PiS and PiZ genotype showed two (0.147%) PiZ(rare) and two (0.147%) Pi(null)(null). The countries with the highest rate of severe AATD were Croatia, Russia and Slovakia. By regions, the Baltic countries area showed the highest rate of both PiZ and severe AATD (2.45% and 1.20%, respectively) while the lowest rates were observed in the Balkan Peninsula (0.48% and 0.31%, respectively).

Conclusion. This study confirms the need for targeted testing of symptomatic patients and provides AATD genotype data from countries for which only some estimates of prevalence were available until now.

Slaba O., Zukow W.

Peculiarities of bronchial asthma with obesity

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In order to define the peculiarities of bronchial asthma with obesity there was carried out the analysis of the examination of 90 patients suffering from BA. The

patients were divided in 3 groups: the first one consisted of 33 patients with normal body mass, the second one consisted of 29 patients with excessive body mass and the third one consisted of 28 patients with obesity. Bronchial asthma of the patients with obesity significantly more often was complicated by lung tissue pneumosclerosis and these patients more often were diagnosed the comorbid states - hypertensive heart disease and type 2 diabetes. The patients from group with obesity significantly rarely were diagnosed allergic rhinitis and eosinophilia. Within analysis of the respiratory functions it was detected that the patients with obesity and excessive body mass had more expressive restrictive obstructions than the patients with normal body mass. Group with obesity included more women whose disease in comparison to man part was significantly more often complicated by pulmonary insufficiency of the third degree and pulmonary emphysema. In comparison to women men with obesity more often were suffering from type 2 diabetes mellitus.

Key words: *bronchial asthma, phenotype, obesity.*

Berezin A.E., Kremzer A.A.

Impaired phenotype of circulating endothelial microparticles in chronic heart failure patients: Relevance to body mass index

Diabetes Metab. Syndr. 2015 Apr 24. pii: S1871-4021(15)00031-4. doi: 10.1016/j. dsx.2015.04.003. [Epub ahead of print]

AIMS: The objective of the study was to investigate the relationship of circulating endothelial-derived microparticls (EMP) pattern with body mass index (BMI) in CHF patients.

METHODS: The study retrospectively evolved 153 patients (86 males) who were underwent multispiral contrast-enhanced computed tomography angiography or conventional angiographic examination of coronary arteries. Flowcytometry analysis for quantifying the number of EMPs was used at baseline.

RESULTS: Using C-statistics for models with CHF, BMI, and circulating biomarkers (NT-pro-BNP, OPG and adiponectin) as continuous variables we found that adding of BMI to the based model (NYHA class of CHF) improved the relative IDI by 12.5% for increased CD31+/annexin V+ EMPs to CD62E+ EMPs ratio. When we used other model constructed on entering variables IDI appears to be improved up to 5.8% for increased EMPs (available for NT-pro-BNP as continuous variable). Three biomarkers (NYHA class of CHF+NT-pro-BNP+OPG) and four biomarkers (NYHA class of CHF+NT-pro-BNP+OPG+adiponectin) could not significantly improve predictive model based on combination of BMI and NYHA class of CHF for increased CD31+/ annexin V+ EMPs to CD62E+ EMPs ratio.

CONCLUSION: We suggested that lower BMI is significant predictor for impaired phenotype of circulating EMPs in CHF patients.

Serhiyenko V.A., Serhiyenko A.A.

Diabetic cardiac autonomic neuropathy: Do we have any treatment perspectives?

World J. Diabetes. 2015 Mar 15;6(2):245-58. doi: 10.4239/wjd.v6.i2.245.

Cardiac autonomic neuropathy (CAN) is a serious and common complication of diabetes mellitus (DM). Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of CAN has not been fully appreciated. CAN among DM patients is characterized review the latest evidence and own data regarding the treatment and the treatment perspectives for diabetic CAN. Lifestyle modification, intensive glycemic control might prevent development or progression of CAN. Pathogenetic treatment of CAN includes: balanced diet and physical activity; optimization of glycemic control; treatment of dyslipoproteinemia; correction of metabolic abnormalities in myocardium; prevention and treatment of thrombosis; use of aldose reductase inhibitors; dihomo-γ-linolenic acid (DGLA), acetyl-L-carnitine, antioxidants, first of all α-lipoic acid (α-LA), use of long-chain ω-3 and ω-6 polyunsaturated fatty acids (ω-3 and ω-6 PUFAs), vasodilators, fat-soluble vitamin B1, aminoguanidine; substitutive therapy of growth factors, in severe cases-treatment of orthostatic hypotension. The promising methods include research and use of tools that increase blood flow through the vasa vasorum, including prostacyclin analogues, thromboxane A2 blockers and drugs that contribute into strengthening and/or normalization of Na(+), K(+)-ATPase (phosphodiesterase inhibitor), α-LA, DGLA, ω-3 PUFAs, and the simultaneous prescription of α-LA, ω-3 PUFA and DGLA.

Key words: *Cardiac autonomic neuropathy, Diabetes mellitus, Postural hypotension, treatment.*

Bezpalko L., Gavrilyuk O., Zayachkivska O.

Inflammatory response in visceral fat tissue and liver is prenatally programmed: experimental research

J. Physiol Pharmacol. 2015 Feb;66(1):57-64.

To investigate the mechanisms of developmental programming we analyzed the effects of maternal stress and food intake on physiological activity of adipose tissue and hepatocellular organization in the offsprings. The experiments were conducted in nonlinear female rats (n=20) and their male offsprings (n=28). During their pregnancy female rats were exposed to social and emotional stress using Pratt's model, and nutritional insults: high sugar diet (HSD) with chronic access to 30% solution of saccharose in drinking water ad libitum, high fat diet (HFD) containing 45% calories from fat or their combination - high sugar and high fat diet (HSFD). The effects of maternal stress and nutrition on severity of visceral fat and liver changes were then examined in offsprings, along with changes in serum levels of the pro- and anti-inflammatory cytokines: IL-1b, IL-8 (in rats known as GRO/CINC-1), leptin and adiponectin, respectively. Maternal exposure to stress in combination with HSFD resulted in the most prominent changes in the offsprings:

histological changes in the visceral fat tissue and liver with cell reorganization and signs of inflammation, 217% increase in IL-1β level, 99% increase in GRO/CINC-1 level, 79% increase in leptin level and 41% decrease in adiponectin level. The leptin/adiponectin index was elevated in all study groups and reached 158% in HSD group, 138% in HFD group and was two times higher in HSFD group vs control. The rat model used in this study provides novel insight into development of nonalcoholic fatty liver disease. Expressed pro- and anti-inflammatory cytokines may indicate early changes in liver and adipose tissue functioning and leptin/adiponectin index could be a novel non-invasive marker of metabolic-related liver alteration. Healthy nutrition and stress management during prenatal period may serve as a valid strategy to prevent liver and adipose tissue inflammation/alteration and metabolic disorders in adulthood.

Key words: *liver, adipose tissue, inflammatory process, diet, lifestyle, obesity, stress, leptin, adiponectin, inetrleukin-1b, interleukin-8*

Finn R.S., Crown J.P., Lang I., Boer K., Bondarenko I.M., Kulyk S.O., Ettl J., Patel R., Pinter T., Schmidt M., Shparyk Y., Thummala A.R., Voytko N.L., Fowst C., Huang X., Kim S.T., Randolph S., Slamon D.J.

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

The Lancet Oncology (Impact Factor: 24.73). 12/2014; 16(1). DOI: 10.1016/S1470-2045(14)71159-3

Palbociclib (PD-0332991) is an oral, small-molecule inhibitor of cyclin-dependent kinases (CDKs) 4 and 6 with preclinical evidence of growth-inhibitory activity in oestrogen receptor-positive breast cancer cells and synergy with anti-oestrogens. We aimed to assess the safety and efficacy of palbociclib in combination with letrozole as first-line treatment of patients with advanced, oestrogen receptor-positive, HER2-negative breast cancer.

In this open-label, randomised phase 2 study, postmenopausal women with advanced oestrogen receptor-positive and HER2-negative breast cancer who had not received any systemic treatment for their advanced disease were eligible to participate. Patients were enrolled in two separate cohorts that accrued sequentially: in cohort 1, patients were enrolled on the basis of their oestrogen receptor-positive and HER2-negative biomarker status alone, whereas in cohort 2 they were also required to have cancers with amplification of cyclin D1 (CCND1), loss of p16 (INK4A or CDKN2A), or both. In both cohorts, patients were randomly assigned 1:1 via an interactive web-based randomisation system, stratified by disease site and disease-free interval, to receive continuous oral letrozole 2.5 mg daily or continuous oral letrozole 2.5 mg daily plus oral palbociclib 125 mg, given once daily for 3 weeks followed by 1 week off over 28-day cycles. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. Accrual to cohort 2 was stopped after an unplanned interim analysis of cohort 1 and the statistical analysis plan for the primary endpoint was amended to a combined analysis of

cohorts 1 and 2 (instead of cohort 2 alone). The study is ongoing but closed to accrual; these are the results of the final analysis of progression-free survival. The study is registered with the ClinicalTrials.gov, number NCT00721409.

Between Dec 22, 2009, and May 12, 2012, we randomly assigned 165 patients, 84 to palbociclib plus letrozole and 81 to letrozole alone. At the time of the final analysis for progression-free survival (median follow-up 29·6 months [95% CI 27·9-36·0] for the palbociclib plus letrozole group and 27·9 months [25·5-31·1] for the letrozole group), 41 progression-free survival events had occurred in the palbociclib plus letrozole group and 59 in the letrozole group. Median progression-free survival was 10·2 months (95% CI 5·7-12·6) for the letrozole group and 20·2 months (13·8-27·5) for the palbociclib plus letrozole group (HR 0·488, 95% CI 0·319-0·748; one-sided p=0.0004). In cohort 1 (n=66), median progression-free survival was 5·7 months (2·6-10·5) for the letrozole group and 26·1 months (11·2-not estimable) for the palbociclib plus letrozole group (HR 0·299, 0·156-0·572; one-sided p<0.0001); in cohort 2 (n=99), median progression-free survival was 11·1 months (7·1-16·4) for the letrozole group and 18·1 months (13·1-27·5) for the palbociclib plus letrozole group (HR 0·508, 0·303-0·853; one-sided p=0.0046). Grade 3-4 neutropenia was reported in 45 (54%) of 83 patients in the palbociclib plus letrozole group versus one (1%) of 77 patients in the letrozole group, leucopenia in 16 (19%) versus none, and fatigue in four (4%) versus one (1%). Serious adverse events that occurred in more than one patient in the palbociclib plus letrozole group were pulmonary embolism (three [4%] patients), back pain (two [2%]), and diarrhoea (two [2%]). No cases of febrile neutropenia or neutropenia-related infections were reported during the study. 11 (13%) patients in the palbociclib plus letrozole group and two (2%) in the letrozole group discontinued the study because of adverse events.

The addition of palbociclib to letrozole in this phase 2 study significantly improved progression-free survival in women with advanced oestrogen receptor-positive and HER2-negative breast cancer. A phase 3 trial is currently underway.

Radchenko E., Filipyuk A., Zukow W.

Survival of patients with chronic ischemic heart disease depending on the type of adaptational reaction

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The aim of investigations was to study survival of patients with chronic ischemic heart disease (IHD) depending of the type of adaptational reaction. It was studied correlations between the type of adaptational reactions and the clinical course of chronic IHD in 121 male patients in long-term prospective observation. The diagnosis of IHD was based on clinical examinations, laboratory investigations, electrocardiography, echocardiography, exercise testing, coronary angiography. It was revealed, that distress-reactions (stress, over-activation and defective adaptation) are significant predictors of an unfavorable chronic IHD prognosis. They were associated with acute cardiovascular events onset, functional class III of chronic heart failure, prothrombotic disorders of coagulation haemostasis (high levels of fibrinogen, fibrin-monomer and D-dimer), and dyslipidemia (lower HDL-

cholesterol values). Decreasing of lymphocyte/neutrophil ratio (index of adaptation) is an informative parameter of distress-reactions and a significant predictor of an unfavorable chronic IHD course.

Key words: *adaptational reactions, stress, ischemic heart disease prognosis, fibrin-monomers, lymphocyte/neutrophil ratio.*

Arora A., Chander P., Kacerovsky M., Balazs Z., Ertl T., Ceausu Iu., Rusnak I., Shurpyak S., Sandhu M., Hobel C. J., Dumesic D. A.

Disparities and relative risk ratio of preterm birth in six Central and Eastern European centers

Croatian medical journal. Vol. 56, no. 2 (2015): 119-127.

Aim To identify characteristic risk factors of preterm birth in Central and Eastern Europe and explore the differences from other developed countries. Method Data on 33 794 term and 3867 preterm births (<37 wks.) were extracted in a retrospective study between January 1, 2007 and December 31, 2009. The study took place in 6 centers in 5 countries: Czech Republic, Hungary (two centers), Romania, Slovakia, and Ukraine. Data on historical risk factors, pregnancy complications, and special testing were gathered. Preterm birth frequencies and relevant risk factors were analyzed using Statistical Analysis System (SAS) software. Results All the factors selected for study (history of smoking, diabetes, chronic hypertension, current diabetes, preeclampsia, progesterone use, current smoking, body mass index, iron use and anemia during pregnancy), except the history of diabetes were predictive of preterm birth across all participating European centers. Preterm birth was at least 2.4 times more likely with smoking (history or current), three times more likely with preeclampsia, 2.9 times more likely with hypertension after adjusting for other covariates. It had inverse relationship with the significant predictor body mass index, with adjusted risk ratio of 0.8 to 1.0 in three sites. Iron use and anemia, though significant predictors of preterm birth, indicated mixed patterns for relative risk ratio. Conclusion Smoking, preeclampsia, hypertension and body mass index seem to be the foremost risk factors of preterm birth. Implications of these factors could be beneficial for design and implementation of interventions and improve the birth outcome.

Mateshuk-Vatseba L, Diskovskyi I.

The influence of an opioid on the course of reparative processes

Current Issues in Pharmacy and Medical Sciences 2015; 9(10): 218 – 232.

Objective is to examine the influence of prolonged administration of opioid on the course of the reparative process of multiple post-injection wound of white rat's skin using light microscopy. Studies has been carried out on 24 mature white male rats, aged 4,5-7,5 months, with weight of 130-150 g. For histological examination the skin sections were stained with hematoxylin and eosin. The preparations were studied and photographed at

the magnification: ob.x8, ey.x15 and ob.x40, ey.x10. The computer system «Aver Media» was used for photography of micropreparations. Studying at the level of light microscopy shows that the administration of opioid for 2 weeks does not affect the reparative process of multiple post-injection wound. In most wound canals the formation of a complete regenerate occurs. After 4 weeks of Nalbufin administration the processes of wound healing slow and are complicated by forming of microabscesses. After opioid administration to rats during 6 weeks, destructive changes in the skin have been detected, which in turn leads to the inability of complete regenerate formation of multiple post-injection wound. The experimental results show the negative effect of prolonged administration of opioid on the reparative processes in the skin.

Key words: *skin, animal model, reparative process, opioid.*

Zayachkivska O., Bula N., Khyrivska D., Gavrilyuk E., Wallace J.L.

Exposure to non-steroid anti-inflammatory drugs (NSAIDs) and suppressing hydrogen sulfide synthesis leads to altered structure and impaired function of the oesophagus and oesophagogastric junction

Inflammopharmacology. 2015 Jun;23(2-3):91-9. doi: 10.1007/s10787-015-0230-7. Epub 2015 Feb 25.

INTRODUCTION: The non-steroid anti-inflammatory drugs (NSAIDs) are among the drugs that can commonly cause injury in the esophagus, such as non-reflux oesophagitis, with important clinical consequences. This injury may be 'silent' and therefore often overlooked. Recently, we established that hydrogen sulfide (H_2S) is a critical mediator of esophageal mucosal protection and repair. The aim of the study was to determine the effect of naproxen, the most commonly used NSAIDs, on the oesophagus and oesophagogastric junction and its relation with suppression or stimulation of endogenous H_2S synthesis during naproxen-induced oesophageal injury.

METHODS: Rats were treated with vehicle (control) or naproxen, with or without being subjected to water immersion restricted stress (Takagi et al. Chem Pharm Bul 12:465-472, 1964). Subgroups of rats were pre-treated with an inhibitor of H2S synthesis cystathionine γ-lyase (CSE) or cystathionine β-synthase (CBS), or with the Sodium sulphide (NaHS), which spontaneously generates H_2S in solution. Damage of the oesophageal mucosa and oesophagogastric junction was estimated and scored using a histological damage index.

RESULTS: Treatment with naproxen increased the thickness of the corneal and epithelial layers of the oesophagus, as well as producing disorganization of the muscle plate and irregular submucosal oedema. Both injury factors, stress and suppression of H_2S synthesis resulted in the development of severe esophagitis and damage to the oesophagogastric junction. The damage was exacerbated by inhibitors of H2S biosynthesis, and attenuated by treatment with NaHS.

CONCLUSIONS: Inhibition of endogenous H_2S synthesis provides a novel experimental model that can be useful in preclinical studies NSAID-related non-reflux oesophagitis. H_2S contributes significantly to mucosal defence in the oesophagus.

Key words: *Oesophagus, Oesophagogastric junction, Hydrogen sulfide, Cystathionine* ***c*** *–lyase, Cystathionine* ***b*** *–synthase, NSAID, Mucosal defence*

Waller C.F., Vynnychenko I., Bondarenko I., Shparyk Y., Hodge J.P., Freeman A., Huber B., Lieberman R., Shelton M.J., Dave H.

An open-label, multicenter, randomized phase Ib/II study of eribulin mesylate administered in combination with pemetrexed versus pemetrexed alone as second-line therapy in patients with advanced nonsquamous non-small-cell lung cancer

Clin Lung Cancer. 2015 Mar;16(2):92-9. doi: 10.1016/j.cllc.2014.10.001. Epub 2014 Oct 15.

INTRODUCTION: New treatment options are needed for second-line therapy in patients with NSCLC.

PATIENTS AND METHODS: This was a phase Ib/II study in patients with nonsquamous NSCLC in whom 1 previous platinum-based chemotherapy regimen had failed. Fifteen patients were enrolled in a dose escalation of eribulin mesylate in combination with pemetrexed (E+P). In phase II (n = 80), E+P at the maximum tolerated dose was compared with P.

RESULTS: In phase Ib, the maximum tolerated dose of E+P was defined as eribulin 0.9 mg/m(2) with pemetrexed (500 mg/m(2)) each on day 1 of a 21-day cycle. In phase II, adverse events were comparable between groups. PFS and OS were similar between treatment groups. Median PFS was 21.4 weeks for E+P (n = 26; 95% confidence interval [CI], 12.7-39.6) and 23.4 weeks for P (n = 29; 95% CI, 17.1-29.9), with a hazard ratio of 1.0 (95% CI, 0.6-1.7).

CONCLUSION: During phase Ib, E+P was tolerated only at a markedly lower dosing intensity relative to the eribulin monotherapy regimen approved for breast cancer and used in phase II studies of NSCLC. At the selected phase II dosing regimen, E+P was generally safe and well tolerated but provided no therapeutic advantage for the second-line treatment of locally advanced or metastatic nonsquamous NSCLC.

Mytsyk Y., Borys Y., Komnatska I., Dutka I., Shatynska-Mytsyk I.

Value of the Diffusion-Weighted MRI in the Differential Diagnostics of Malignant and Benign Kidney Neoplasms – Our Clinical Experience

Polish Journal of Radiology 09/2014; DOI: 10.12659/PJR.890604(79):290-295. DOI: 10.12659/PJR.890604

Diffusion-weighted imaging (DWI) is an MRI modality using strong bipolar gradients to create a sensitivity of the signal to the thermally-induced Brownian motions of water molecules and in vivo measurement of molecular diffusion. The apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DWI images which is used as a measure of diffusion. DWI allows to obtain comprehensive information on morphological and functional state of the kidney during a single examination without contrast medium administration. The purpose of the study was to evaluate the value of

DWI in differentiating benign and malignant solid kidney tumors based on the initial stage of the study.

MATERIAL AND METHODS. The study included 19 adult patients with pathologically verified renal tumors: 9 patients with clear cell subtype of the renal cell carcinoma, 5 patients with oncocytoma and 5 patients with angiomyolipoma (AML). In addition, 5 healthy volunteers with completely normal findings according to kidney ultrasound were included into this study and set as reference. All patients underwent renal MR imaging which included DWI with subsequent ADC measurement. MR imaging was performed with a 1.5 T body scanner using an eight-channel phased-array body coil.

RESULTS. The mean ADC value of ccRCC was significantly lower than that of normal renal parenchyma (2.11±0.25×10−3 mm2/s vs. 3.36±0.41×10−3 mm2/s, $p<0.01$). There was a significant difference in ADC between the malignant and benign renal lesions: in patients with angiomyolipoma the ADC value was 2.36±0.32×10−3 mm2/s vs. 2.11±0.25×10−3 mm2/s; $p<0.05$ and in patients with oncocytoma – 2.75±0.27×10−3 mm2/s vs. 2.11±0.25×10−3 mm2/s; $p<0.05$. The difference in ADC values in patients with high and low ccRCC grades was observed.

CONCLUSIONS. DWI can be used to characterize renal lesions; the ADC of a renal lesion can be potentially used as an additional parameter to help determine the appropriate clinical management.

Feuchtner, G., Plank, F., Chevtchik, O., Pedrini, M., Mair, J.

A baby in the heart: ALCAPA with aortic arch fistula

European Heart Journal-Cardiovascular Imaging, 2014 15(9), 1056-1056.

An 83-year-old female was transferred to our emergency department on Christmas Eve evening after a documented asystole and cardiopulmonary resuscitation. She had a history of chronic renal dysfunction stage III, mitral and tricuspid regurgitation grade II, heart failure, and paroxysmal atrial fibrillation. Chest CT revealed anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) with a retropulmonary ostium (*Panel 1A* and *B*; white arrow) and massive hypertrophy and calcification of the left main, left anterior descending artery, and circumflex artery (CX) (up to 2 cm in diameter—*Panel 1A* and *B*) and right coronary artery (*Panel 1D*). The CX was communicating with one aortic arch-feeding vessel (*Panel 1B*; white and black arrow) and forming a huge vessel convolute in the mid-mediastinum. She died on Day 7 in the hospital due to cerebral hypoxia and multi-organ failure. Ao, aorta; P, pulmonary trunk. ALCAPA (or Bland–White–Garland syndrome) is a rare congenital condition (1/300 000 births) which usually manifests during the neonatal period as intractable heart failure and ischaemia. Late clinical manifestation is very rare. Early diagnosis with surgical treatment helps prevent an adverse outcome. Uniquely, our patient developed an extensive fistula of CX to the aortic arch due to chronic ischaemia of the left ventricle and chronic steal phenomenon over her lifetime, and surprisingly survived until the age of 83.

Such a case calls for CT-imaging in adult patients with heart failure of unclear aetiology in order to rule out rare grown-up congenital heart disease.

Zayachkivska O, Havryluk O, Hrycevych N., Bula N., Grushka O., Wallace J.L.

Cytoprotective effects of hydrogen sulfide in novel rat models of non-erosive esophagitis

PLoS One. 2014 Oct 21;9(10): e110688. doi: 10.1371/journal.pone.0110688. eCollection 2014.

Non-erosive esophagitis is a chronic inflammatory condition of the esophagus and is a form of gastroesophageal reflux disease. There are limited treatment options for non-erosive esophagitis, and it often progresses to Barrett's esophagus and esophageal carcinoma. Hydrogen sulfide has been demonstrated to be a critical mediator of gastric and intestinal mucosal protection and repair. However, roles for H2S in esophageal mucosal defence, inflammation and responses to injury have not been reported. We therefore examined the effects of endogenous and exogenous H2S in rat models of non-erosive esophagitis. Mild- and moderate-severity non-erosive esophagitis was induced in rats through supplementation of drinking water with fructose, plus or minus exposure to water-immersion stress. The effects of inhibitors of H2S synthesis or of an H2S donor on severity of esophagitis was then examined, along with changes in serum levels of a pro- and an anti-inflammatory cytokine (IL-17 and IL-10, respectively). Exposure to water-immersion stress after consumption of the fructose-supplemented water for 28 days resulted in submucosal esophageal edema and neutrophil infiltration and the development of lesions in the muscular lamina and basal cell hyperplasia. Inhibition of H2S synthesis resulted in significant exacerbation of inflammation and injury. Serum levels of IL-17 were significantly elevated, while serum IL-10 levels were reduced. Treatment with an H2S donor significantly reduced the severity of esophageal injury and inflammation and normalized the serum cytokine levels. The rat models used in this study provide novel tools for studying non-erosive esophagitis with a range of severity. H2S contributes significantly to mucosal defence in the esophagus, and H2S donors may have therapeutic value in treating esophageal inflammation and injury.

Plank, F., Feuchtner, G., Chevtchik, O., Mair, J.

Unusual late clinical manifestation of Bland–White–Garland syndrome as sudden cardiac death survival

Wiener klinische Wochenschrift, 2014, 127(5-6), 225-226.

Summary. In this report, we present an extremely late clinical manifestation of Bland–White–Garland syndrome in a 53-year old woman who was ttransferred to our hospital after successful cardiopulmonary resuscitation. Coronary angiography revealed a dilated right coronary artery giving rise to multiple dominant septal collaterals to the left coronary artery (LCA) which arose from the pulmonary trunk (left to right shunt 0.15). Cardiac computed tomography identified a retropulmonary course of the LCA. The patient underwent cardiac surgery with LCA occlusion and triple coronary bypass grafting.

Key words: *Anomalous left coronary artery from the pulmonary artery (ALCAPA) · Coronary arteries · Computed tomography · Bland-White-Garland syndrome · Ventricular fibrillation Coronary angiography*

Antonyuk R., Lutsyk A., Antonyuk V.

Lectin purification from fruiting bodies of brown roll-rim fungus, Paxillus involutus (Fr.) Fr., and its application in histochemistry.

Rom J. Morphol Embryol. 2014;55(3):787-96.

A lectin (agglutinin) from fresh fruit bodies of the brown roll-rim fungus [Paxillus involutus (Fr.) Fr.] has been purified with output approx. 60 mg÷kg of raw material. Method of purification included the sedimentation of viscous polysaccharide by ethanol, removal of ethanol by dialysis, ion-exchange chromatography on DEAE-Toyopearl and affinity chromatography on Sepharose 6B column with immobilized mannose-specific Polygonatum multiflorum lectin. The obtained lectin preparation (abbreviated PIFA) is a glycoprotein with 6.5±1% carbohydrates, molecular mass of 64 kDa, consisting of four identical subunits. Lectin interacted only with N-acetyl-lactosamine and glycoproteins that contained Galβ1-4GlcNAc disaccharide moieties; agglutinated erythrocytes of dog, sheep and horse, but not of humans. The specificity of PIFA binding to tissue samples of the rat has been investigated. Lectin selectively reacted with gastric parietal cells, submandibular salivary gland duct cells. In the kidney, PIFA labeled epithelial cells of renal tubules, collecting ducts, nuclei of podocytes and mesangiocytes. It was also revealed selective lectin binding to Purkinje cells of cerebellum. Brush border of absorptive cells in small intestine was also strongly reactive, while goblet cells both in small and large intestine were completely negative. Considering similarities in carbohydrate specificity of Paxillus involutus (PIFA) and Ricinus communis agglutinin (RCA-120), histochemical reactivity of these two lectins was compared. It was similar, yet not identical: differences included absence of PIFA binding to the brush border of renal tubules, higher interaction with absorptive cells of the small intestine, lower background staining of cerebellar cortex and renal corpuscles. A conclusion was made that due to the unique carbohydrate specificity PIFA lectin can cover prospective position in experimental histochemistry and diagnostic histopathology comparable to PNA (Peanut agglutinin) and SNA (Sambucus nigra agglutinin).

Gamelli L., Mykychack I., Kushnir A., Driscoll D.N., Fuzaylov G.

Targeting burn prevention in Ukraine: evaluation of base knowledge in burn prevention and first aid treatment.

J. Burn. Care Res. 2015 Jan-Feb;36(1):225-31. doi: 10.1097/BCR.0000000000000103.

Burn prevention has been identified by the World Health Organization (WHO) as a topic in need of further investigation and education throughout the world, with an increased need in low-income countries. It has been noted that implementing educational programs for prevention in high income countries has aided in lowering the rate of burn injuries. The purpose of this study is to evaluate the current education level of knowledge of prevention and first aid treatment of scald burns. A prevention campaign will target these educational needs as a part of an outreach program to improve burn care in Ukraine. The research team evaluated the current health structure in Ukraine and how it could benefit from the increased knowledge of burn prevention and first aid. A test was designed to assess the baseline level of knowledge with regard to first aid and scald prevention in

parents, pregnant woman, and healthcare and daycare providers. A total of 14,456 tests were sent to pediatric clinics, obstetrician clinics, and daycare facilities to test respondents. A total of 6,120 completed tests were returned. Doctors presented with the highest level of knowledge averaging 77.0% on prevention and 67.5% on first aid while daycare workers presented the largest gap in knowledge at 65.0% in prevention and 54.3% in first aid. Interest in further educational materials was reported by 92% of respondents. The results of this study clearly show a lack of knowledge in first aid and prevention of scald burn injury in all the populations tested.

Vynograd N.

Natural foci diseases as a stable biological threat

Arch Immunol Ther Exp (Warsz). 2014 Dec;62(6):445-7.
doi: 10.1007/s00005-014-0316-8. Epub 2014 Oct 19.

The key aspects of the natural foci of especially dangerous diseases as a type of biological threats are presented. Approaches to epidemiological surveillance and control to the spread of the agents of especially dangerous diseases on endemic areas are described for zoonosis that has a medical value. The knowledge of specific design of tools for the implementation of epidemiological surveillance, monitoring and evaluation of natural foci diseases in developing countries is low; accordingly, little is known on the ecology and transmission dynamics for the agents of especially dangerous diseases. Important is to know the effectiveness of serological monitoring of the indigenous population to determine the activity of natural foci of hemorrhagic fever with renal syndrome, tick-borne encephalitis, tularemia, Q-fever, Lyme disease and West Nile disease. The main species of reservoirs and vectors for these agents have been determined in different regions of Ukraine. New tick-borne agents that were unknown for certain regions have been detected. These data indicate the spreading of different pathogens in combination with natural foci.

Mykhalchyshyn G., Kobyliak N., Bodnar P.

Diagnostic accuracy of acyl-ghrelin and it association with non-alcoholic fatty liver disease in type 2 diabetic patients

J. Diabetes Metab Disord. 2015 May 19;14:44.
doi: 10.1186/s40200-015-0170-1. eCollection 2015.

BACKGROUND: Ghrelin is a hormone produced mainly by the cells lining the fundus of the stomach, which is involved in regulation of lipid and glucose metabolism. Two major forms of ghrelin can be found in circulation: an acylated form, and non-acylated form. Serum acyl-ghrelin (AG) concentration is significantly increased in patients with visceral obesity and insulin resistance. This study was conducted to evaluate changes in serum AG levels, its diagnostic accuracy and association with NAFLD in patients with type two diabetes (T2D).

METHODS: In this cross-sectional study, 91 T2D patients, age of 40-80 years, were included. All patients were divided into 3 groups. The control group included 28 T2D patients without NAFLD. The main group included 63 T2D patients with NAFLD,

which was divided in 2 subgroups depending on transaminase levels: normal (n=37) and elevated (n=26) transaminases group. To assess the diagnostic accuracy of AG for NAFLD we used ROC-analysis.

RESULTS: We observed 1.5 (p=0.016) and 2.5 (p<0.001) fold increasing of serum AG levels in patients with NAFLD and normal or elevated transaminases compared to control groups. In multivariate logistic regression analysis high AG level was an independent, from transaminases activity, triglycerides (OR 1.791; 95 % CI 1.162-2.759; p=0.008) and degree of IR (OR 1.599; 95 % CI 1.019-2.508; p=0.044) predictor that associated with NAFLD. When serum AG used as non-invasive marker for NAFLD detection AUROC was 0.835 (95 % CI 0.752-0.918, p<0.001). The cut-off value was >0.52 ng/ml, with sensitivity, specificity, PPV and NPV - 60.3 %, 92.8 %, 95.0 %, 50.9 % respectively. For distinguishing patients with NAFLD and elevated transaminases from patients with NAFLD and normal values AG was less effective.

CONCLUSIONS: Our study has demonstrated that elevated AG level were associated with NAFLD. Patients with elevated transaminases had significantly higher AG levels. An increase of AG over 0.52 ng/ml can be used as a diagnostic marker for NAFLD detection in patients with T2D.

Keywords: *Acyl-ghrelin; Non-alcoholic fatty liver disease; Type 2 diabetes/*

Buznyk O., Pasyechnikova N., Islam M.M., Iakymenko S., Fagerholm P., Griffith M.

Bioengineered Corneas Grafted as Alternatives to Human Donor Corneas in Three High-Risk Patients

Clin Transl Sci. 2015 May 21. doi: 10.1111/cts.12293. [Epub ahead of print]

Corneas with severe pathologies have a high risk of rejection when conventionally grafted with human donor tissues. In this early observational study, we grafted bioengineered corneal implants made from recombinant human collagen and synthetic phosphorylcholine polymer into three patients for whom donor cornea transplantation carried a high risk of transplant failure. These patients suffered from corneal ulcers and recurrent erosions preoperatively. The implants provided relief from pain and discomfort, restored corneal integrity by promoting endogenous regeneration of corneal tissues, and improved vision in two of three patients. Such implants could in the future be alternatives to donor corneas for high-risk patients, and therefore, merits further testing in a clinical trial.

Nyankovskyy S., Dodryanskyy D., Ivakhnenko O., Iatsula M., Javorska M., Shadryn O.

Dietary habits and nutritional status of children from Ukraine during the first 3 years of life

Pediatria polska 08/2014; DOI: 10.1016/j.pepo.2014.08.003

AIM: The aim of our study was to assess the nutritional status and eating behavior of young children and identify the prevalence of macro- and micronutrient diet deficiencies

in Ukraine. MATERIALS AND METHODS: Three hundred and fifty children aged from 9 months to 3 years from central, eastern and western regions of Ukraine were involved in the cross-sectional study. Basic child's data were collected, health status was assessed by a physician, and parents used a 3-day food diary and a food questionnaire for self-completion. Data from the diaries and questionnaires were analyzed with DietPlan 6 software. Results: The diet composition was mostly adequate for age. Overall average provision with energy (1165.67 [29.67–4951.33] kcal/day), protein (40.53 [0.63–230.37] g/day) and carbohydrates (153.63 [3.53–708.7] g/day) exceeded the corresponding standards. The diet of the majority of children did not comply with the recommended intake of zinc (91%), iron (68%), calcium (61%), iodine (49%), vitamins A (99%), D (97%), B6 (89%), B12 (71%), E (70%) and B1 (61%). Excessive weight was significantly associated with higher levels of energy, protein, carbohydrates and fat consumption. Overweight was reliably correlated with a higher diet's energy and carbohydrates content.

CONCLUSIONS: The contemporary diet of young children in Ukraine, like in many other developed countries, is generally unbalanced, containing an excess of energy and protein as well as inadequate amount of many minerals and vitamins.

Finn R.S., Crown J.P., Lang I., Boer K., Bondarenko I.M., Kulyk S.O., Ettl J., Patel R., Pinter T., Schmidt M., Shparyk Y., Thummala A.R., Voytko N.L., Fowst C., Huang X., Kim S.T., Randolph S., Slamon D.J.

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

The Lancet Oncology (Impact Factor: 24.73). 12/2014; 16(1). DOI: 10.1016/S1470-2045(14)71159-3

Palbociclib (PD-0332991) is an oral, small-molecule inhibitor of cyclin-dependent kinases (CDKs) 4 and 6 with preclinical evidence of growth-inhibitory activity in oestrogen receptor-positive breast cancer cells and synergy with anti-oestrogens. We aimed to assess the safety and efficacy of palbociclib in combination with letrozole as first-line treatment of patients with advanced, oestrogen receptor-positive, HER2-negative breast cancer.

In this open-label, randomised phase 2 study, postmenopausal women with advanced oestrogen receptor-positive and HER2-negative breast cancer who had not received any systemic treatment for their advanced disease were eligible to participate. Patients were enrolled in two separate cohorts that accrued sequentially: in cohort 1, patients were enrolled on the basis of their oestrogen receptor-positive and HER2-negative biomarker status alone, whereas in cohort 2 they were also required to have cancers with amplification of cyclin D1 (CCND1), loss of p16 (INK4A or CDKN2A), or both. In both cohorts, patients were randomly assigned 1:1 via an interactive web-based randomisation system, stratified by disease site and disease-free interval, to receive continuous oral letrozole 2.5 mg daily or continuous oral letrozole 2.5 mg daily plus oral palbociclib 125 mg, given once daily for 3 weeks followed by 1 week off over 28-day cycles. The primary endpoint

was investigator-assessed progression-free survival in the intention-to-treat population. Accrual to cohort 2 was stopped after an unplanned interim analysis of cohort 1 and the statistical analysis plan for the primary endpoint was amended to a combined analysis of cohorts 1 and 2 (instead of cohort 2 alone). The study is ongoing but closed to accrual; these are the results of the final analysis of progression-free survival. The study is registered with the ClinicalTrials.gov, number NCT00721409.

Between Dec 22, 2009, and May 12, 2012, we randomly assigned 165 patients, 84 to palbociclib plus letrozole and 81 to letrozole alone. At the time of the final analysis for progression-free survival (median follow-up 29·6 months [95% CI 27·9-36·0] for the palbociclib plus letrozole group and 27·9 months [25·5-31·1] for the letrozole group), 41 progression-free survival events had occurred in the palbociclib plus letrozole group and 59 in the letrozole group. Median progression-free survival was 10·2 months (95% CI 5·7-12·6) for the letrozole group and 20·2 months (13·8-27·5) for the palbociclib plus letrozole group (HR 0·488, 95% CI 0·319-0·748; one-sided p=0.0004). In cohort 1 (n=66), median progression-free survival was 5·7 months (2·6-10·5) for the letrozole group and 26·1 months (11·2-not estimable) for the palbociclib plus letrozole group (HR 0·299, 0·156-0·572; one-sided p<0.0001); in cohort 2 (n=99), median progression-free survival was 11·1 months (7·1-16·4) for the letrozole group and 18·1 months (13·1-27·5) for the palbociclib plus letrozole group (HR 0·508, 0·303-0·853; one-sided p=0.0046). Grade 3-4 neutropenia was reported in 45 (54%) of 83 patients in the palbociclib plus letrozole group versus one (1%) of 77 patients in the letrozole group, leucopenia in 16 (19%) versus none, and fatigue in four (4%) versus one (1%). Serious adverse events that occurred in more than one patient in the palbociclib plus letrozole group were pulmonary embolism (three [4%] patients), back pain (two [2%]), and diarrhoea (two [2%]). No cases of febrile neutropenia or neutropenia-related infections were reported during the study. 11 (13%) patients in the palbociclib plus letrozole group and two (2%) in the letrozole group discontinued the study because of adverse events.

The addition of palbociclib to letrozole in this phase 2 study significantly improved progression-free survival in women with advanced oestrogen receptor-positive and HER2-negative breast cancer. A phase 3 trial is currently underway.

Kryvko Y., Mateshuk-Vatseba L., Savka I., Luszczewska-Sierakowska I., Wawrzyniak A., Radzikowska E., Maciejewski R.

Ultrastructural hemomicrocircular channel links of rat testicle of Streptozotocin-induced diabetes

Journal of Pre-Clinical and Clinical Research 2014; 8 (2): 86 – 89.

The first changes in rat testicle hemomicrocircular channel links ultrastructural arrangement are noticed already in 2 weeks run of streptozotocin-induced diabetes mellitus and accumulate throughout next periods of experiment. Angiopathy is a trigger mechanism for diabetic development of testicle structural changes. The findings is a basis for further morphologist and clinicist surveys for the purpose of new diabetic testicle pathology diagnostics, prevention and treatment techniques elaboration.

Key words: *testicle, hemomicrocircular channel, diabetes mellitus.*

Lascaratos G., Chau K.Y., Zhu H., Gkotsi D., King R., Gout I., Kamal D., Luthert P.J., Schapira A.H., Garway-Heath D.F.

Resistance to the most common optic neuropathy is associated with systemic mitochondrial efficiency

Neurobiol Dis. 2015 Jun 6;82:78-85. doi: 10.1016/j.nbd.2015.05.012.

Glaucomatous optic neuropathy, an important neurodegenerative condition and the commonest optic neuropathy in humans, is the leading cause of irreversible blindness worldwide. Its prevalence and incidence increase exponentially with ageing and raised intraocular pressure (IOP). Using glaucomatous optic neuropathy as an exemplar for neurodegeneration, this study investigates putative factors imparting resistance to neurodegeneration. Systemic mitochondrial function, oxidative stress and vascular parameters were compared from isolated lymphocytes, whole blood and urine samples between 30 patients who have not developed the neuropathy despite being exposed for many years to very high IOP ('resistant'), 30 fast deteriorating glaucoma patients despite having low IOP ('susceptible'), and 30 age-similar controls. We found that 'resistant' individuals showed significantly higher rates of ADP phosphorylation by mitochondrial respiratory complexes I, II and IV, hyperpolarised mitochondrial membrane potential, higher levels of mitochondrial DNA, and enhanced capacity to deal with cytosolic calcium overload and exogenous oxidative stress, as compared to both controls and glaucoma patients. While it has been known for some years that mitochondrial dysfunction is implicated in neurodegeneration, this study provides a fresh perspective to the field of neurodegeneration by providing, for the first time, evidence that systemic mitochondrial efficiency above normal healthy levels is associated with an enhanced ability to withstand optic nerve injury. These results demonstrate the importance of cellular bioenergetics in glaucomatous disease progression, with potential relevance for other neurodegenerative disorders, and raise the possibility for new therapeutic targets in the field of neurodegeneration.

Key words: *Glaucoma, Intraocular pressure, Mitochondria, Neurodegeneration, Normal tension glaucoma, Ocular hypertension.*

Martinez D.L., Tsuchiya Y., Gout I.

Coenzyme A biosynthetic machinery in mammalian cells

Biochem Soc Trans. 2014 Aug;42(4):1112-7. doi: 10.1042/BST20140124.

CoA (coenzyme A) is an essential cofactor in all living organisms. CoA and its thioester derivatives [acetyl-CoA, malonyl-CoA, HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) etc.] participate in diverse anabolic and catabolic pathways, allosteric regulatory interactions and the regulation of gene expression. The biosynthesis of CoA requires pantothenic acid, cysteine and ATP, and involves five enzymatic steps that are highly conserved from prokaryotes to eukaryotes. The intracellular levels of CoA and its derivatives change in response to extracellular stimuli, stresses

and metabolites, and in human pathologies, such as cancer, metabolic disorders and neurodegeneration. In the present mini-review, we describe the current understanding of the CoA biosynthetic pathway, provide a detailed overview on expression and subcellular localization of enzymes implicated in CoA biosynthesis, their regulation and the potential to form multi-enzyme complexes for efficient and highly coordinated biosynthetic process.

Tsuchiya Y., Pham U., Gout I.

Methods for measuring CoA and CoA derivatives in biological samples

Biochem Soc Trans. 2014 Aug;42(4):1107-11. doi: 10.1042/BST20140123.

CoA (coenzyme A) is a ubiquitous and essential cofactor that acts as an acyl group carrier in biochemical reactions. Apart from participating in numerous metabolic pathways as substrates and intermediates, CoA and a number of its thioester derivatives, such as acetyl-CoA, can also directly regulate the activity of proteins by allosteric mechanisms and by affecting protein acetylation reactions. Cellular levels of CoA and CoA thioesters change under various physiological and pathological conditions. Defective CoA biosynthesis is implicated in NBIA (neurodegeneration with brain iron accumulation). However, the exact role of CoA in the pathogenesis of NBIA is not well understood. Accurate and reliable assays for measuring CoA species in biological samples are essential for studying the roles of CoA and CoA derivatives in health and disease. The present mini-review discusses methods that are commonly used to measure CoA species in biological samples.

Dusi S., Valletta L., Haack T.B., Tsuchiya Y., Venco P., Pasqualato S., Goffrini P., Tigano M., Demchenko N., Wieland T., Schwarzmayr T., Strom T.M., Invernizzi F., Garavaglia B., Gregory A., Sanford L., Hamada J., Bettencourt C., Houlden H., Chiapparini L., Zorzi G., Kurian M.A., Nardocci N., Prokisch H., Hayflick S.,Gout I., Tiranti V.

Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation

Am J Hum Genet. 2014 Jan 2;94(1):11-22. doi: 10.1016/j.ajhg.2013.11.008.

Neurodegeneration with brain iron accumulation (NBIA) comprises a clinically and genetically heterogeneous group of disorders with progressive extrapyramidal signs and neurological deterioration, characterized by iron accumulation in the basal ganglia. Exome sequencing revealed the presence of recessive missense mutations in COASY, encoding coenzyme A (CoA) synthase in one NBIA-affected subject. A second unrelated individual carrying mutations in COASY was identified by Sanger sequence analysis. CoA synthase is a bifunctional enzyme catalyzing the final steps of CoA biosynthesis by coupling phosphopantetheine with ATP to form dephospho-CoA and its subsequent phosphorylation to generate CoA. We demonstrate alterations in RNA and protein

expression levels of CoA synthase, as well as CoA amount, in fibroblasts derived from the two clinical cases and in yeast. This is the second inborn error of coenzyme A biosynthesis to be implicated in NBIA.

Oliynyk Y.

Comparative survival analysis of patients with stomach cancer after combined surgery

Canadian Scientific Journal 2 (2014)
http://csjournal.ca/wp-content/uploads/2014/12/2_Oliynyk.pdf

Study included 1114 patients (804 men and 310 women) after combined surgery due to stomach cancer. It was investigated sex and age features and their influence of survival with Kaplan-Meier methods, including Log-rank and Breslow tests and $\chi 2$-statistics. It was determined the prevalence of male patients over women (ratio 2.6:1), total gastrectomy (TG) over distal and proximal subtotal gastrectomy (SG) (ratio 4.6:1.5:1). Significant differences between the average life expectancy of men and women after combined TG were not found ($p>0,1$). Instead, there is a difference between life expectancy of men and women after combined TG and SG ($p<0,001$). 3- and 5-year survival rate after combined TG was respectively 16.7% and 10.1%, and after combined SG subtotal – 29.6% and 24.2%. The difference between the 3- and 5-year survival rates of patients of both sexes after completed combined SG was statistically significant ($\chi 2=4,692$, $p=0,032$). Our results on average life expectancy, 3- and 5-year survival rates indicate the feasibility of the implementation of combined surgery as current trend to expand the possibilities of surgical radical treatment of patients with gastric cancer, and indications for their conduct.

Key words: *Locally advanced stomach cancer, Combined operations, Survival rate*

Souchelnytskyi S.

Implementation Science – "new kid on the block" and what to expect from it

ResearchGate, comment, 2014, doi: 10.13140/2.1.4768.8969

In the last years, the term "Implementation Science" has entered the medical vocabulary. As a newcomer, implementation science attracts a number of questions. What is the subject of implementation science? How does it differ from already established fields of medicine? What to expect from implementation science? In this letter, I would like to raise discussion about place of implementation science in the process of introduction of fundamental research into clinical practice. Recent publications tend to limit implementation science to observations and making recommendations. I believe that implementation science should be also pro-active and identify and promote practices of the future health care, and not only observe existing practices.

Key word: *Implementation Science*

Mäbert K., Cojoc M., Peitzsch C., Kurth I., Souchelnytskyi S., Dubrovska A.

Cancer biomarker discovery: current status and future perspectives

Int. J. Radiation Biology, 2014, 12, 1-19.

Cancer is a multigene disease which arises as a result of mutational and epigenetic changes coupled with activation of complex signaling networks. The use of biomarkers for early cancer detection, staging and individualization of therapy might improve patient care. A few fundamental issues such as tumor heterogeneity, a highly dynamic nature of the intrinsic and extrinsic determinants of radio- and chemoresistance, along with the plasticity and diversity of cancer stem cells (CSC) make biomarker development a challenging task. In this review we outline the preclinical strategies of cancer biomarker discovery including genomic, proteomic, metabolomic and microRNomic profiling, comparative genome hybridization (CGH), single nucleotide polymorphism (SNP) analysis, high throughput screening (HTS) and next generation sequencing (NGS). Other promising approaches such as assessment of circulating tumor cells (CTC), analysis of CSC-specific markers and cell-free circulating tumor DNA (ctDNA) are also discussed.

CONCLUSIONS: The emergence of powerful proteomic and genomic technologies in conjunction with advanced bioinformatic tools allows the simultaneous analysis of thousands of biological molecules. These techniques yield the discovery of new tumor signatures, which are sensitive and specific enough for early cancer detection, for monitoring disease progression and for proper treatment selection, paving the way to individualized cancer treatment.

Key words: *cancer, markers.*

Saini R.K., Attarha S., da Silva Santos C., Kolakowska J., Funa K., Souchelnytskyi S.

Proteomics of dedifferentiation of SK-N-BE2 neuroblastoma cells

Biochemical and Biophysical Research Communications, 2014, 454, 202-209, doi: 10.1016/j.bbrc.2014.10.065.

Neuroblastoma develops through processes which include cellular dedifferentiation. Ability of tumors to form spheroids is one of the manifestations of dedifferentiation and carcinogenic transformation. To study mechanisms of dedifferentiation of neuroblastoma cells, we generated spheroids and performed a proteomics study to compare the spheroids with parental SK-N-BE2 cells. We observed that dedifferentiation induced extensive changes in the proteome profiles of the cells, which affected more than 30% of detected cellular proteins. Using mass spectrometry, we identified 239 proteins affected by dedifferentiation into spheroids as compared to the parental cells. These proteins represented such regulatory processes as transcription, cell cycle regulation, apoptosis, cell adhesion, metabolism, intracellular transport, stress response, and angiogenesis. A number of potent regulators of stemness, differentiation and cancer were detected as subnetworks formed by the identified proteins. Our validation tissue microarray study of 30 neuroblastoma cases confirmed that two of the identified proteins, DISC1 and DNA-PKcs, had their expression increased in advanced malignancies. Thus, our report unveiled

extensive changes of the cellular proteome upon dedifferentiation of neuroblastoma cells, indicated top subnetworks and clusters of molecular mechanisms involved in dedifferentiation, and provided candidate biomarkers for clinical studies.

Key words: *neuroblastoma, proteomics, systems biology, markers.*

Souchelnytskyi S.

Functional Molecular Diagnostic for anti-cancer treatment

ResearchGate, 2014. doi:10.13140/2.1.1704.0645.

More than 100 anti-cancer drugs are used in the clinic today, and new drugs are under development for use tomorrow. The challenge is to match a patient with the right drugs. The clinicians face this challenge with practically every patient, because of the limitations of diagnostics. Information obtained with current diagnostics is still far from predicting securely how the tumor and patient would respond to a treatment. The recent developments of cancer research have opened for the qualitative improvement of diagnostics. In this document is described Functional Molecular Diagnostics (FMDx) which is for the clinical use. FMDx tests responsiveness of individual patient's tumors to different drugs by testing responsiveness of the living tumor samples in organ culture (Organ Culture FMDx), testing targets and modulators of the drugs' action (Functional Biochemical Assays), and by unbiased testing of the tumor's proteome profile (Proteomics FMDx).

Key words: *cancer, diagnostics, proteomics, systems biology, circulating tumor cells, organ culture.*

Dubrovska A., Souchelnytskyi S.

Low-density microarray analysis of TGFbeta1-dependent cell cycle regulation in human breast adenocarcinoma MCF7 cell line

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Transforming growth factor β1 (TGFβ1) is a growth regulator that has antiproliferative effects on a range of epithelial cells at the early stages and promoting tumorigenesis at the later stages of cancer progression. The molecular mechanisms of a duel role of TFGβ1 in tumor growth regulation remain poorly understood. Recent development of proteomic and genomic technologies allowing to analyze hundreds or thousands biological molecules simultaneously, has begun to uncover the TGFβ1 signaling network in a comprehensive way. Our present study was designed to examine the regulatory effect of TFGβ1 on the expression of a panel of 96 genes which are known to be critically involved in cell cycle regulation. GEArray Q series Human Cell Cycle Gene Array was applied to profile the gene expression changes in MCF-7 human breast adenocarcinoma cell line treated with TFGβ1. The gene expression array data enabled us to reveal the genes that might connect the TFGβ1 signaling to the promoting of the tumor growth. Finding of these key TFGβ1signaling modules might provide an insight into the mechanisms of TGFβ1-dependent cell cycle control and can be applied for the development of novel therapeutic approaches.

Key words: *TGFbeta, cell cycle, microarray.*

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Proteome profiling of biopsies from Human Cutaneous Leishmaniasis patients showed up-regulation of proteins related to the pathogenesis of the lesions

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In this study, we used proteomics and biological network analysis to evaluate the potential biological processes and components present in the identified proteins of biopsies from cutaneous leishmaniasis (CL) patients infected by Leishmania braziliensis in comparison with normal skin. We identified 59 proteins differently expressed in samples from infected and normal skin. Biological network analysis employing identified proteins showed the presence of networks that may be involved in the cell death mediated by cytotoxic T lymphocytes. After immunohistochemical analyses, the expression of caspase-9, caspase-3, and granzyme B was validated in the tissue and positively correlated with the lesion size in CL patients. In conclusion, this work identified differentially expressed proteins in the inflammatory site of CL, revealed enhanced expression of caspase-9, and highlighted mechanisms associated with the progression of tissue damage observed in lesions.

Key words: *Leishmaniasis, proteomics, markers.*

Mints M., Souchelnytskyi S.

Proliferation Response of Human Breast Cancer Cells to Combinatorial Treatments with EGF, TGFbeta, 17alpha-oestradiol, Iressa, SB431542 and Tamoxifen

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AIM: The impact of combinations of anti-cancer drugs and growth factors on tumour cells may differ from the assumed sum of the effects of each factor separately. Therefore it is important to study the effects of different combinations of various drugs and treatments. Our aim was to study the effects on breast cancer cell proliferation of EGF, TGFβ and 17β-oestradiol, three important regulators of breast tumourigenesis, and their respective inhibitors in different combinations.

MATERIALS AND METHODS: We screened the effects on proliferation of MCF7 and MDA-MB-231 cells of ninety different combinations of EGF, TGFβ and 17β-oestradiol, Iressa, SB431542 and Tamoxifen. Meta-data analysis of available clinical data was performed to validate observed proliferation data.

RESULTS: In MDA-MB-231 cells, TGFβ1 was found inhibitory when cells were simultaneously treated with EGF and 17β-oestradiol, with the effect potentiated by addition of all inhibitors combined. In the same cells, Iressa when combined with EGF was paradoxically stimulatory. Tamoxifen inhibited MCF7 cells co-treated with EGF or oestrogen, and enhanced the inhibitory effect of TGFβ in MDA-MB-231 cells. Meta-analysis of clinical gene expression studies confirmed several of these points, showing

enhanced TGFβ and EGF expression in Tamoxifen-treated patients to correlate with decreased tumour size and grade respectively, and combined TGFβ-EGF expression to decrease the risk of metastasis.

CONCLUSION: Our study shows significant differences in proliferation response to drugs and growth factors between MCF7 cells which do not have propensity to form metastases in animal models and MDA-MB-231 cells which may form metastases upon inoculation into animals. Several of these differences are unexpected and confirmed by clinical observations.

Key words: *TGFbeta, EGF, tamoxifen, SB431542, iressa, cell proliferation.*

Attarha S., Andersson S., Mints M., Souchelnytskyi S.

Mammalian Sterile-like 1 kinase (MST1) inhibits TGFbeta and EGF–dependent regulation of migration and proliferation of HEC-1-A endometrial cancer cells

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Transforming growth factor-β (TGFβ) and epidermal growth factor (EGF) are two potent regulators of tumorigenesis. Signaling cross-talk of TGFβ and EGF employs a number of regulators which define the impact on cell physiology. MST1 has recently been reported as a regulator of tumorigenesis and differentiation. To investigate the role of mammalian sterile-like 1 (MST1) in TGFβ and EGF signaling, we established transiently MST1-transfected HEC-1-A endometrial cancer cells, and subjected the cells to treatment with TGFβ1, EGF and their combination. We report MST1 as a negative regulator of combined TGFβ and EGF signaling. We observed that enhanced expression of MST1 inhibited the combined action of TGFβ1 and EGF on cell invasiveness, migration and proliferation. Monitoring of the intracellular regulatory proteins showed that MST1 contribution to the TGFβ-EGF cross-talk may involve focal adhesion kinase and E-cadherin, but not activation of Smad2. Our data unveiled the role of MST1 as a negative feedback for TGFβ1- and EGF-regulated cell invasiveness, migration and proliferation.

Key words: *MST1, endometrial cancer, proliferation, cell death.*

Attarha S., Andersson S., Mints M., Souchelnytskyi S.

PKN1 modulates TGFbeta and EGF signaling in HEC-1-A endometrial cancer cell line

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BACKGROUND: The response of cells to TGFβ and EGF is mediated by a network of various intracellular regulators. The signaling crosstalk between different regulators is of key importance for tumorigenesis. The crosstalk may explain the modulation of cellular

responses to the same regulator by another signaling molecule. As PKN1 - a serine/threonine kinase implicated in tumorigenesis - was identified as potential crosstalk node for TGFβ and EGF signaling, the cellular functions that may be affected by PKN1 in a crosstalk of TGFβ and EGF were explored.

METHODS: To investigate the contribution of PKN1 to TGFβ and EGF signaling, transiently PKN1-transfected HEC-1-A endometrial cancer cells were generated and subjected to treatment with TGFβ1, EGF, and their combination. Proliferation, apoptosis, invasion, wound healing, and migration assays were performed. The impact of PKN1 on the expression and phosphorylation of intracellular proteins was monitored by immunoblotting.

RESULTS: It was demonstrated that PKN1 modulated the responses of HEC-A-1 endometrial cancer cells to TGFβ1 and EGF. PKN1 had an inhibitory effect on the stimulation of cell migration, and PKN1 kinase activity was required for the inhibitory effect of TGFβ and EGF on cell proliferation and invasiveness. It was observed that phosphorylation of Smad2, FAK, and Erk1/2 correlated with responses of the cells to TGFβ1 and EGF.

CONCLUSION: PKN1 modulates TGFβ- and EGF-dependent regulation of cell proliferation, migration, and invasiveness, and therefore is a component of the network signaling downstream of TGFβ and EGF.

Key words: *PKN1, endometrial cancer, TGFbeta, EGF, proliferation, cell death.*

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