Suprun U[1], Dubey L[2] [et al.]

Vilnius Declaration on chronic respiratory diseases: multisectoral care pathways embedding guided self-management, mHealth and air pollution in chronic respiratory diseases

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(2-year IF=3.539)

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KEYWORDS: *Air pollution; Asthma; Chronic respiratory diseases; Guidelines; Integrated care pathways; Rhinitis; Vilnius Declaration; mHealth*

BACKGROUND:
Over 1 billion people suffer from chronic respiratory diseases such as asthma, COPD, rhinitis and rhinosinusitis. They cause an enormous burden and are considered as major non-communicable diseases. Many patients are still uncontrolled and the cost of inaction is unacceptable. A meeting was held in Vilnius, Lithuania (March 23, 2018) under the patronage of the Ministry of Health and several scientific societies to propose multisectoral care pathways embedding guided self-management, mHealth and air pollution in selected chronic respiratory diseases (rhinitis, chronic rhinosinusitis, asthma and COPD). The meeting resulted in the Vilnius Declaration that was developed by the participants of the EU Summit on chronic respiratory diseases under the leadership of Euforea.

CONCLUSION:
The Vilnius Declaration represents an important step for the fight against air pollution in chronic respiratory diseases globally and has a clear strategic relevance with regard to the EU Health Strategy as it will bring added value to the existing public health knowledge.

Makar O[1], Siabrenko G[1]

Influence of physical activity on cardiovascular system and prevention of cardiovascular diseases (review)

Georgian Med News. 2018 Dec; (285):69-74.

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Regular physical activity causes many positive effects on the cardiovascular system and improves cardiorespiratory fitness. Long term exercise leads to physiologic remodeling of the heart, including adaptive molecular and cellular reprogramming, that have cardioprotective effect. Aerobic physical activity, the most studied modality with beneficial dose-response effect on prognosis, is recommended for all healthy adults, subjects with coronary risk factors and patients with chronic cardiac diseases. To check cardiorespiratory fitness is recommended to carry out cardiopulmonary exercise testing with measuring VO2max for risk assessment, exercise prescription, physical activity counseling and improving patient management.

Holota S[1], Kryshchyshyn A[2], Trufin Y[2], Demchuk I[2], Lesyk R[3][et al.]

Synthesis of 5-enamine-4-thiazolidinone derivatives with trypanocidal and anticancer activity

Bioorg Chem. 2019 Jan 22;86:126-136. doi: 10.1016/j.bioorg.2019.01.045. [Epub ahead of print], (2017 IF= 3.929)

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KEYWORDS: *5-ene-4-thiazolidinones; Anticancer activity; Antitrypanosomal activity; X-ray*

A series of novel 2-(5-aminomethylene-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropionic acid ethyl esters has been synthesized. Target compounds were evaluated for their trypanocidal activity towards Trypanosoma brucei brucei and Trypanosoma brucei gambiense. Several hit-compounds (8, 10, 12) inhibited growth of the parasites at sub-micromolar concentrations (IC50 0.027-1.936 μM) and showed significant selectivity indices (SI = 108-1396.2) being non-toxic towards the human primary fibroblasts. The screening of anticancer activity in vitro within NCI DTP protocol allowed to identify active 2-(5-{[5-(2,4-dichlorobenzyl)-thiazol-2-ylamino]-methylene}-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropionic acid ethyl ester 14 that demonstrated inhibition against all 59 human tumor cell lines with the average GI50 value of 2.57 μM. It was established that the activity type (antitrypanosomal or anticancer) as well as its level depends on the character of enamine fragment in the C5 position of thiazolidinone core.

Strilchuk L[1], Besh D[2]

Estimation of cardiosurgical intervention risk according to EuroSCORE in patients with acute coronary syndrome and different gallbladder conditions before coronary artery bypass grafting

Kardiochir Torakochirurgia Pol. 2018 Dec;15(4):238-240. doi: 10.5114/kitp.2018.80920. Epub 2018 Dec 3

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KEYWORDS*: EuroSCORE; cardiosurgical intervention risk; gallbladder*

Abstract in English, Polish

INTRODUCTION:
Estimation of cardiosurgical intervention risk according to EuroSCORE is an important aspect of cardiosurgery. EuroSCORE allows prediction of the probability of a post-operational fatal outcome.

AIM:
To estimate the influence of gallbladder condition on the prognosis after coronary artery bypass grafting (CABG) and and the interactions between metabolic background and cardiosurgical intervention risk.

MATERIAL AND METHODS:
We investigated data of 98 patients with unstable angina pectoris or acute myocardial infarction before planned CABG. These patients were divided into the following groups according to their gallbladder condition: intact bladder; bile sludge or cholesterosis; bent gallbladder body; gallbladder neck deformations or cholecystitis; cholelithiasis; history of cholecystectomy.

RESULTS:
The mean cardiosurgical intervention risk score according to the EuroSCORE system in our patients was 6.03 ±0.62%. It was significantly higher in patients with low serum bilirubin levels. There were direct correlations between the risk score result and presence of left ventricular dilatation ($r = 0.31$, $p < 0.05$) and fasting glucose level ($r = 0.82$, $p < 0.01$), as well as with means of other parameters, i.e., left atrial dimension, right ventricular size, grade of stenosis of anterior interventricular branch of left coronary artery, serum levels of total cholesterol, β-lipoproteins, bilirubin and potassium.

CONCLUSIONS:
These correlations suggest that the EuroSCORE results estimated before surgery may be used as a simple informative prognostic criterion of intra-operational cardiac mortality and also as a marker of structural and functional heart condition and metabolic background. However, these correlations were different in patients with different gallbladder conditions.

Nehuliaieva L[1][et al.]

Hemihyperplasia/hemihypertrophy in adolescents: prospective international study

Int J Adolesc Med Health. 2019 Jan 12. pii: /j/ijamh.ahead-of-print/ijamh-2018-0066/ijamh-2018-0066.xml. doi: 10.1515/ijamh-2018-0066. [Epub ahead of print]

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KEYWORDS: *adolescents; asymmetric regional; body asymmetry; body overgrowth; hemihyperplasia; hemihypertrophy*

Aim The reported incidence of isolated hemihyperplasia (IH) has a very wide range (from 1:13,000 to 1:86,000 live births) and further clarification is needed. We hypothesized that a survey of the birth prevalence of IH among newborn infants may underestimate the incidence of IH by overlooking late-onset cases. Methods The prospective international multicenter study utilized the two-steps selection tool for an anonymous survey of volunteers of 15-18 years old. The initial step was «three measurements-three questions» screening, or «face-palms-calves survey». The subsequent step was an in-depth assessment of selected cases to exclude localized, lesional and syndrome-related cases as well as body asymmetry within normative range and to

select suspected cases of IH. This step included measurements of various anatomical regions and a subsequent questionnaire. The participants that were selected in a risk group were advised to refer to medical institutions for clinical, genetic and instrumental investigation. Results Out of 6000 of selected participants (male, M 3452, female, F 2548), 229 (3.82%) were selected for detailed investigation and 57 (0.95%) were assigned to the risk group. Only 36 of them were actually referred to medical institutions and in two cases the diagnosis of IH was confirmed. Conclusion Our survey indicated the prevalence of IH at the age of adolescence as approximately 1:3000. While IH is a hereditary genetic disorder, it may not be detected in newborns and infants and the true prevalence of the disease can be estimated if older age children are screened.

Bilyy R[1], Dumych T[1] [et al.]

To NET or not to NET: current opinions and state of the science regarding the formation of neutrophil extracellular traps

Cell Death Differ. *2019 Jan 8. doi: 10.1038/s41418-018-0261-x. [Epub ahead of print], (2017/2018 IF= 8)*

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Since the discovery and definition of neutrophil extracellular traps (NETs) 14 years ago, numerous characteristics and physiological functions of NETs have been uncovered. Nowadays, the field continues to expand and novel mechanisms that orchestrate formation of NETs, their previously unknown properties, and novel implications in disease continue to emerge. The abundance of available data has also led to some confusion in the NET research community due to contradictory results and divergent scientific concepts, such as pro- and anti-inflammatory roles in pathologic conditions, demarcation from other forms of cell death, or the origin of the DNA that forms the NET scaffold. Here, we present prevailing concepts and state of the science in NET-related research and elaborate on open questions and areas of dispute.

Kobylinska L[1][et al.]

Comb-like PEG-containing polymeric composition as low toxic drug nanocarrier

Cancer Nanotechnol. 2018;9(1):11. doi: 10.1186/s12645-018-0045-5. Epub 2018 Dec 20

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KEYWORDS: *Drug delivery system; Mice; Polyethylene glycol; Polymeric nanocarrier; Rats; Toxicity*

BACKGROUND:
Development of biocompatible multifunctional polymeric drug carriers is crucial in modern pharmaceutics aimed to create "smart" drugs. The high potential of the PEGylated comb-like polymeric nanocarrier (PNC) in delivering both traditional and experimental drugs to tumor cells in vitro and in vivo has been demonstrated previously. In the present study, we investigated the general toxicity of polyethylene glycol (PEG) processed with both covalent and non-covalent

attachments of PEG to compose a comb-like polymer that behaves like a simple chain of n monomers decorated with swollen side chains. The PNC possesses properties of a water-soluble surfactant containing methyl-terminated PEG side branches in some monomer units attached covalently to the carbon chain backbone.

RESULTS:
We have demonstrated that the synthesized PNC possesses weak toxic effects toward human leukemia cells (HL-60 and Jurkat lines), as well as toward hepatocellular (HepG2), colon (HCT116) and breast (MCF-7) tumor cell lines. Additionally, after a long period (20 days) of intraperitoneal administration, the PNC had no significant toxic effects in laboratory white mice (470 mg/kg body mass in 1 ml) and Wistar rats (440 mg/kg body mass in 10 ml).

CONCLUSION:
The developed PNC we studied can be qualified as a compound of grade 4 toxicity (low toxicity substance). The reduced toxicity of this PNC in combination with its improved bioavailability and previously detected capability to enhance cytotoxicity toward tumor cells in vitro and potential tumor treatment effects in vivo suggests its potential as a safe drug delivery platform for treating various diseases, especially cancer.

Yevtushok L[1,2], [et al.]

Patterns of Prenatal Alcohol Use That Predict Infant Growth and Development

Pediatrics. 2019 Jan 4. pii: e20182399. doi: 10.1542/peds.2018-2399. [Epub ahead of print], (IF =5.297)

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BACKGROUND:
Previous studies have had inconsistent findings regarding the quantity and frequency of prenatal alcohol exposure (PAE) that lead to deficits in growth and neurodevelopment. This may be due to imprecise methods of exposure classification. Our objective in this study was to employ longitudinal trajectory modeling of maternal drinking patterns associated with infant growth or neurodevelopmental deficits to a homogenous sample of mothers and infants.

METHODS:
From a sample of 471 pregnant women prospectively enrolled in a longitudinal study in the Ukraine, we performed a longitudinal cluster analysis of drinking patterns across gestation. We employed multivariable regression analyses to determine if each trajectory group was associated with infant weight, length, or head circumference at birth or psychomotor or mental deficits in infancy.

RESULTS:
We identified 5 distinct PAE trajectory groups: minimal or no PAE throughout gestation, low-to-moderate PAE with discontinuation early in gestation, low-to-moderate PAE sustained across gestation, moderate-to-high PAE with reduction early in gestation, and high PAE sustained across gestation. The highest-trajectory group was associated with deficits in infant weight and length at birth and deficits in psychomotor and mental performance at 6 to 12 months of age. Although

confidence intervals overlapped, low-to-moderate sustained use was more strongly associated with most negative infant outcomes than moderate-to-high PAE with early reduction.

CONCLUSIONS:
With these findings, we confirm that high, sustained PAE confers the highest risk for adverse infant outcomes but demonstrate that even low-to-moderate PAE continued across gestation is associated with certain deficits. This approach may be used to help clinicians identify high-risk infants for targeted early intervention.

Ogonovsky R[1], Hrynovets V[1], Szybiński V[1], Hrynioh V[1] [et al.]

The condition of mineralized tooth tissue of the inhabitants of Szackie Lake District (Ukraine) with regard to the content of silver and chosen microelements in drinking water and the soil

Ann Agric Environ Med. 2018 Dec 20;25(4):581-586. doi: 10.5604/12321966.1235178. Epub 2017 May 11, IF (=1.116)

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KEYWORDS: *D3MFT; macro-elements; mineralized tooth tissues; rural inhabitants*

INTRODUCTION AND OBJECTIVE:
The aim of the study is to evaluate the mineralization tooth tissues in the inhabitants of Melniki village Szackie, Lake District, Ukraine, with regard to silver content and chosen macro-elements in the soil, tap water, and the water in Pisoczno Lake located in the vicinity of village.

MATERIAL AND METHODS:
The macro-elements, silver ions contained in the lake, tap water and soil were examined. 125 people aged 12-73, indigenous inhabitants of Melniki village, were qualified for dental examinations. The research took into account the distance between the place of residence and Pisoczno Lake as a source of silver ions, dividing the examined patients into 2 groups: A) living at a distance less than 2,500 m from the lake, and B) living at a distance more than 2.500 m from the lake.

RESULTS:
In area A, significantly higher contents of phosphorus and potassium were detected, while in the soil of area B there was more Ca and Mg with 3 times higher number of Mg ions. A high concentration of Ag ions was observed in both Pisoczno Lake and tap water. The severity of caries expressed by D3MFT number was 4.18 in the group aged 12-16 living in area A, and 4.24 for the inhabitants of area B. The mean value of D3MFT for the group aged 32- 45 living in area A equalled 21.58, while for area B it was 21.19. The severity of caries expressed by the mean D3MFT value in the examined group of 46-73-year-olds was 24.60 for area A, and 23.80 for area B. The observed differences were not statistically significant.

CONCLUSIONS:
The high value of D3MFT recorded in the inhabitants of Melniki village indicates the poor condition of mineralized tooth tissues. The fact that the contents of macro-elements in the soil and drinking water increased, together with the distance from the Pisoczno Lake shoreline, did not affect the oral health of the indigenous inhabitants. No impact of silver ions contained in the lake and tap water on the condition of mineralized tooth tissue was detected in the examined group of inhabitants of Szackie Lake District.

Gerasimov S[1], Guta N[2], Bobyk V[3], Kaprus V[4] [et al.]

Role of Lactobacillus rhamnosus (FloraActive™) 19070-2 and Lactobacillus reuteri (FloraActive™) 12246 in Infant Colic: A Randomized Dietary Study.

Nutrients. 2018 Dec 13;10(12). pii: E1975. doi: 10.3390/nu10121975. IF (=4.196)

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KEYWORDS: *colic; infant; lactobacilli*

Infant colic is a common condition of unknown pathogenesis that brings frustration to families seeking for effective management. Accumulating evidence suggests that some single strains of lactobacilli may play a positive dietary role in attenuation of colic in exclusively breastfed infants. The objective of this study was to evaluate a mixture of two Lactobacillus strains in decreasing infant cry and fuss in this population. Infants aged 4□12 weeks received L. rhamnosus 19070-2 and L. reuteri 12246 in a daily dose of 250 × 10□ CFU, 3.33 mg of fructooligosaccharide, and 200 IU of vitamin D□ (84 infants, probiotic group) or just vitamin D□ (84 infants, control group) for 28 days. Cry and fuss time were measured with validated Baby's Day Diary on days 0 and 28. At baseline, mean (SD) duration of cry and fuss time was comparable in the probiotic and control groups: 305 (81) vs. 315 (90) min., respectively ($p = 0.450$). On day 28, mean cry and fuss time became statistically different: 142 (89) vs. 199 (72), respectively ($p < 0.05$). Mean change in cry and fuss time from day 0 through day 28 was -163 (99) minutes in the probiotic and -116 (94) minutes in the control group ($p = 0.019$). Our findings confirm that lactobacilli decrease cry and fuss time and provide a dietary support in exclusively breastfed infants with colic.

Senkiv J[1,2] [et al.]

Lysosomal Sequestration Impairs the Activity of the Preclinical FGFR Inhibitor PD173074

Cells. 2018 Dec 8;7(12). pii: E259. doi: 10.3390/cells7120259, IF (=4.829)

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KEYWORDS: *TKI; cancer; drug sequestration; fibroblast growth factor receptor; fluorescence; lysosomes*

Knowledge of intracellular pharmacokinetics of anticancer agents is imperative for understanding drug efficacy as well as intrinsic and acquired cellular resistance mechanisms. However, the factors driving subcellular drug distribution are complex and poorly understood. Here, we describe for the first time the intrinsic fluorescence properties of the fibroblast growth factor receptor inhibitor PD1703074 as well as utilization of this physicochemical feature to investigate intracellular accumulation and compartmentalization of this compound in human lung cancer cells. Cell-free PD173074 fluorescence, intracellular accumulation and distribution were investigated using analytical chemistry and molecular biology approaches. Analyses on a subcellular scale revealed selective drug accumulation in lysosomes. Coincubation with inhibitors of lysosomal acidification strongly enhanced PD173074-mediated fibroblast growth factor receptor (FGFR) inhibition and cytotoxicity. In conclusion, intrinsic fluorescence enables analysis of molecular factors influencing intracellular pharmacokinetics of PD173074. Lysosome-alkalinizing agents might represent candidates for rational combination treatment, preventing cancer cell-intrinsic PD173074 resistance based on lysosomal trapping.

Sehin Y[1], Koshla O[1], Fedorenko V[1], Ostash B[1] [et al.]

Gene ssfg_01967 (miaB) for tRNA modification influences morphogenesis and moenomycin biosynthesis in Streptomyces ghanaensis ATCC14672

Microbiology. 2019 Feb;165(2):233-245. doi: 10.1099/mic.0.000747. Epub 2018 Dec 13., (2-year IF=1.9)

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KEYWORDS: *MiaB; moenomycin; morphogenesis; streptomyces; tRNA modification*

Streptomyces ghanaensis ATCC14672 is remarkable for its production of phosphoglycolipid compounds, moenomycins, which serve as a blueprint for the development of a novel class of antibiotics based on inhibition of peptidoglycan glycosyltransferases. Here we employed mariner transposon (Tn) mutagenesis to find new regulatory genes essential for moenomycin production. We generated a library of 3000 mutants which were screened for altered antibiotic activity. Our focus centred on a single mutant, HIM5, which accumulated lower amounts of moenomycin and was impaired in morphogenesis as compared to the parental strain. HIM5 carried the Tn insertion within gene ssfg_01967 for putative tRNA (N6-isopentenyl adenosine(37)-C2)-methylthiotransferase, or MiaB, and led to a reduced level of thiomethylation at position 37 in the anticodon of S. ghanaensis transfer ribonucleic acid (tRNA). It is likely that the mutant phenotype of HIM5 stems from the way in which ssfg_01967::Tn influences translation of the rare leucine codon UUA in several genes for moenomycin production and life cycle progression in S. ghanaensis. This is the first report showing that quantitative changes in tRNA modification status in Streptomyces have physiological consequences.

Djiambou-Nganjeu H[1]

Hepatic Encephalopathy in Patients in Lviv (Ukraine)

J Transl Int Med. 2018 Oct 9;6(3):146-151. doi: 10.2478/jtim-2018-0021. eCollection 2018 Sep., (2-year IF=4.197)

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KEYWORDS: *Child-Pugh score; Halstead-Reitan; alcoholic and viral liver cirrhosis; coagulopathy; hepatic encephalopathy*

BACKGROUND AND OBJECTIVES:
Hepatic encephalopathy (HE) research has long been impeded by the vague definition of this disabling complication of liver failure. This article provides an overview of the etiology and impact of HE on neuromuscular functions as well as its role in the development of infections and anemia.

MATERIALS AND METHODS:
This was a descriptive study conducted in 36 patients with HE. Close monitoring of these patients was done by checking on several parameters.

RESULTS:
The etiological distribution: alcohol (67%), hepatitis C virus (HCV; 17%), HCV and alcohol (8%), hepatitis B virus (HBV; 3%), HBV and alcohol (3%), HBV and HCV (6%), and cryptogenic (3%). The laboratory results indicated an elevation of De Ritis level in 69% of cases and in 92% of total bilirubin values. The Halstead-Reitan (H-R) test score with regards to gender indicated that more than half of the patients had a score of 2, while only few cases received the scores 3 and 4. The frequency of H-R score with regards to Child-Pugh score showed the significant preponderance of Child-Pugh score of 7-9 (B): 58.3% compared to others groups of results, and these results indicated patients' poor prognosis.

CONCLUSION:
Findings showed the preponderance of female patients towards developing HE and the poor survival rate of patients older than 65 years. Alcohol and hepatitis C were the main causes associated with the development of HE. The neurological assessment marked the preponderance of Child-Pugh grades B and C and also the prevalence in female patients with neuropsychological disabilities through the assessment of H-R test.

Lysiuk R[1] [et al.]

Targeting Cancer with Phytochemicals via Their Fine Tuning of the Cell Survival Signaling Pathways

Int J Mol Sci. 2018 Nov 12;19(11). pii: E3568. doi: 10.3390/ijms19113568. (IF=3.687)

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KEYWORDS: *apoptosis; cancer; flavonoids; mitochondria; phytochemicals*

The role of phytochemicals as potential prodrugs or therapeutic substances against tumors has come in the spotlight in the very recent years, thanks to the huge mass of encouraging and promising results of the in vitro activity of many phenolic compounds from plant raw extracts against many cancer cell lines. Little but important evidence can be retrieved from the clinical and nutritional scientific literature, where flavonoids are investigated as major pro-apoptotic and anti-metastatic compounds. However, the actual role of these compounds in cancer is still far to be fully elucidated. Many of these phytochemicals act in a pleiotropic and poorly specific manner, but, more importantly, they are able to tune the reactive oxygen species (ROS) signaling to activate a survival or a pro-autophagic and pro-apoptosis mechanism, depending on the oxidative stress-responsive endowment of the targeted cell. This review will try to focus on this issue.

Mytsyk Y[1], Borys Y[1], Diychuk Y[2], Kucher A[1], Kowalskyy V[1],
Pasichnyk S[1], Mytsyk O[3], Manyuk L[4] [et al.]

Potential clinical applications of microRNAs as biomarkers for renal cell carcinoma

Cent European J Urol. 2018;71(3):295-303. doi: 10.5173/ceju.2018.1618. Epub 2018 Jul 2

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KEYWORDS: *biomarker; diagnostics; microRNA; prediction; prognosis; renal cell carcinoma*

INTRODUCTION:
Renal cell carcinoma (RCC) accounts for 3% of adult malignancies and more than 90% of kidney neoplasms. High rates of undiagnostic percutaneous kidney biopsies and difficulties in reliable pre-operative differentiation between malignant and benign renal tumors using contemporary imaging techniques result in large numbers of redundant surgeries. Absence of specific biomarkers for early detection and monitoring complicates on-time diagnosis of the disease and relapse. For the patients followed up after having a nephrectomy, a noninvasive and sensitive biomarker enabling early detection of disease relapse would be extremely useful.

MATERIAL AND METHODS:
The study is a review of recent knowledge regarding potential clinical applications of microRNAs (miRNAs) as biomarkers of RCC.

RESULTS:
MicroRNAs are essential regulators of various processes such as cell proliferation, differentiation, development and death; they have been implicated in diverse biological and pathological processes in RCC. There is a class of miRNAs that promote RCC development (oncomirs) and a class of miRNAs that negatively regulate oncogenes, suppress tumor growth and invasion, and thus could be considered treatment agents (anti-oncomirs). Separate miRNAs and specific miRNAs expression profiles have been identified, enabling early detection of the disease, prediction of response to systemic therapy, or prognostication of biological behavior of the disease.

CONCLUSIONS:
The miRNA network analysis and gene profiling may help to identify the most sensible molecular signatures of RCC that can be used for diagnostic purposes, as well as poor prognosis signatures and poor therapeutic response signatures in patients who undergo systemic therapy.

Bilyy R[1], Dumych T[1], Paryzhak S[1], Vovk V[1] [et al.]

Reduced Graphene-Oxide-Embedded Polymeric Nanofiber Mats: An "On-Demand" Photothermally Triggered Antibiotic Release Platform

ACS Appl Mater Interfaces. 2018 Nov 19. doi: 10.1021/acsami.8b14784. [Epub ahead of print], (IF=8.097)

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KEYWORDS: *antibiotic release; electrospinning; nanofibers; photothermal effect; reduced graphene oxide*

The steady increase of antimicrobial resistance of different pathogens requires the development of alternative treatment strategies next to the oral delivery of antibiotics. A photothermally activated platform based on reduced graphene oxide (rGO)-embedded polymeric nanofiber mats for on-demand release of antibiotics upon irradiation in the near-infrared is fabricated. Cross-linked hydrophilic nanofibers, obtained by electrospinning a mixture of poly(acrylic acid) (PAA) and rGO, show excellent stability in aqueous media. Importantly, these PAA@ rGO nanofiber mats exhibit controlled photothermal heating upon irradiation at 980 nm. Nanofiber mats are efficiently loaded with antibiotics through simple immersion into corresponding antibiotics solutions. Whereas passive diffusion based release at room temperature is extremely low, photothermal activation results in increased release within few minutes, with release rates tunable through power density of the applied irradiation. The large difference over passive and active release, as well as the controlled turn-on of release allow regulation of the dosage of the antibiotics, as evidenced by the inhibition of planktonic bacteria growth. Treatment of superficial skin infections with the antibiotic-loaded nanofiber mats shows efficient wound healing of the infected site. Facile fabrication and implementation of these photothermally active nanofiber mats makes this novel platform adaptable for on-demand delivery of various therapeutic agents.

Dumych T[1], Paryzhak S[2], Bilyy R[3] [et al.]

A Novel Integrated Way for Deciphering the Glycan Code for the FimH Lectin

Molecules. 2018 Oct 28;23(11). pii: E2794. doi: 10.3390/molecules23112794.
(IF=3.098)

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KEYWORDS: *Enzyme-Linked LectinoSorbent assay; FimH; Manα1,2Man; Manα1,3Man; binding mode; entropy; high-mannose N-glycan; microcalorimetry; molecular dynamics; thermodynamics*

The fimbrial lectin FimH from uro- and enteropathogenic Escherichia coli binds with nanomolar affinity to oligomannose glycans exposing Manα1,3Man dimannosides at their non-reducing end, but only with micromolar affinities to Manα1,2Man dimannosides. These two dimannoses play a significantly distinct role in infection by E. coli. Manα1,2Man has been described early on as shielding the (Manα1,3Man) glycan that is more relevant to strong bacterial adhesion and invasion. We quantified the binding of the two dimannoses (Manα1,2Man and Manα1,3Man to FimH using ELLSA and isothermal microcalorimetry and calculated probabilities of binding modes using molecular dynamics simulations. Our experimentally and computationally determined binding energies confirm a higher affinity of FimH towards the dimannose Manα1,3Man. Manα1,2Man displays a much lower binding enthalpy combined with a high entropic gain. Most remarkably, our molecular dynamics simulations indicate that Manα1,2Man cannot easily take its major conformer from water into the FimH binding site and that FimH is interacting with two very different conformers of Manα1,2Man that occupy 42% and 28% respectively of conformational space. The finding that Manα1,2Man binding to FimH is unstable agrees with the earlier suggestion that E. coli may use the Manα1,2Man epitope for transient tethering along cell surfaces in order to enhance dispersion of the infection.

Bilyy R[1,2], Vovk V[2] [et al.]

Active NET formation in Libman-Sacks endocarditis without antiphospholipid antibodies: A dramatic onset of systemic lupus erythematosus

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KEYWORDS: *Anti-dsDNA antibodies; Libman–Sacks endocarditis; NET remnants; elastase activity; neuropsychiatric lupus; neutrophil extracellular traps; systemic lupus erythematosus*

Although neutrophil extracellular traps (NETs) have been highlighted in several systemic inflammatory diseases, their clinical correlates and potential pathological role remain obscure. Herein, we describe a dramatic onset of systemic lupus erythematosus (SLE) with clear-cut pathogenic implications for neutrophils and NET formation in a young woman with cardiac (Libman-Sacks endocarditis) and central nervous system (psychosis and seizures) involvement. Despite extensive search, circulating antiphospholipid autoantibodies, a hallmark of Libman-Sacks endocarditis, could not be detected. Instead, we observed active NET formation in the tissue of the mitral valve, as well as in the circulation. Levels of NET remnants were significantly higher in serially obtained sera from the patient compared with sex-matched blood donors ($p = .0011$), and showed a non-significant but substantial correlation with blood neutrophil counts ($r = 0.65$, $p = .16$). The specific neutrophil elastase activity measured in serum seemed to be modulated by the provided immunosuppressive treatment. In addition, we found anti-Ro60/SSA antibodies in the cerebrospinal fluid of the patient but not NET remnants or

increased elastase activity. This case illustrates that different disease mechanisms mediated via autoantibodies can occur simultaneously in SLE. NET formation with release of cytotoxic NET remnants is a candidate player in the pathogenesis of this non-canonical form of Libman-Sacks endocarditis occurring in the absence of traditional antiphospholipid autoantibodies. The case description includes longitudinal results with clinical follow-up data and a discussion of the potential roles of NETs in SLE.

Paryzhak S[1], Dumych T[1], Boichuk M[1], Bila G[1], Peshkova S[1], Nehrych T[1], Bilyy R[1] [et al.]

Neutrophil-released enzymes can influence composition of circulating immune complexes in multiple sclerosis

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KEYWORDS: *Multiple sclerosis; glycosylation; immunoglobulin; interferon; lectins; treatment*

During NET formation, the content of neutrophils granules is released into the intercellular milieu. Consisting of many proteases and ROS species, formed NETs were shown to degrade cytokines (Schauer, Nat Med, 2014); while the content of neutrophil's azurophilic granules proved to contain glycosidases, secreted upon activation (Thaysen-Andersen, JBC, 2015), and formation of autoantibodies to neutrophil beta-glucoronidase was connected with the level of anti-MPO antibodies (Ab) (Martensson, Autoimmunity, 1992). Taking into account these facts, we aimed to investigate the possibility of NET-related changes in glycan composition on circulating IgG molecules and IgG-IgM immune complexes in multiple sclerosis (MS). This autoimmune disorder still has no reliable detection markers or established ways of treatment, besides widely accepted interferon therapy, making it a particularly interesting clinical condition. By applying capture lectin-ELISA, we analysed binding of α2,6 sialyl-specific lectins SNA, PSqL, and core α1,6-fucose specific lectin AAL to circulating IgG and related complexes in five groups of MS patients: untreated (17 persons); undergoing therapy with interferon (IFN) β-1 b (15 persons), corticosteroids (methylprednisolone) (12 persons) and anti-B-cell monoclonal Ab (12 persons: Ocrelizumab, 6 persons and alemtuzumab, 6 persons). A group of 23 healthy donors served as control. Significant increase in neutrophil elastase activity, observed in the group of patients under corticosteroid treatment was also accompanied by sialyl-specific PSqL and SNA lectin binding to captured IgG molecules. Subsequent analysis demonstrated that sialic acid residues were exposed on free IgG and on circulating IgG-IgM immune complexes. Increased lectin binding was not observed for anti-myelin basic protein (one of the major autoAb in MS) Ab compared to total serum Ab. IFN therapy was accompanied by low neutrophil elastase activity and low amount of circulating immune complexes. Incubation of in vitro generated NETs with human serum revealed the digestion of high-molecular weight immune complexes with subsequent exposure of hidden glycoepitops. Obtained data indicate the potential of neutrophil-derived proteases to modify (partially degrade) circulating immune complexes leading to exposure of internal glycoepitops.

Bilyy R[1][et al.]

Autoimmune, rheumatic, chronic inflammatory diseases: Neutrophil extracellular traps on parade

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KEYWORDS: *Neutrophil extracellular traps; antiphospholipid syndrome; rheumatic diseases; rheumatoid arthritis; systemic lupus erythematosus*

Rheumatic diseases are a group of inflammatory conditions that affect joints and connective tissues and are often accompanied by pain and restriction of motility. In many of these diseases, autoantibodies develop that react with molecules/structures commonly found hidden in neutrophils. Neutrophil extracellular trap (NET) formation and release is considered a defense mechanism against pathogens or endogenous danger signals and it has been associated with initial inflammatory responses. NETs are also endowed with an important resolution potential based on its intrinsic enzymatic activity, but in the case they are not timely removed from the crime scene they might modulate subsequent immune responses and contribute to the pathogenesis of chronic inflammatory diseases. In this review, we will summarize the actual knowledge about the multifaceted roles of NETs in the etiology and pathogenesis of rheumatic autoimmune diseases.

Nadashkevich O[1] [et al.]

Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial

Lancet. 2018 Dec 1;392(10162):2378-2387. doi: 10.1016/S0140-6736(18)32463-2. Epub 2018 Oct 22

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BACKGROUND:
At present, biological disease-modifying anti-rheumatic drugs (DMARDs) are the only treatment recommended for patients with ankylosing spondylitis who have not responded to first-line treatment with non-steroidal anti-inflammatory drugs (NSAIDs). The TORTUGA trial investigated the efficacy and safety of filgotinib, an oral selective Janus kinase 1 (JAK1) inhibitor, for the treatment of patients with active ankylosing spondylitis.

METHODS:
In this completed, randomised, double-blind, placebo-controlled, phase 2 trial, we enrolled adult patients from 30 sites in seven countries (Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine). Eligible patients had active ankylosing spondylitis and an inadequate response or intolerance to two or more NSAIDs. Patients were randomly assigned (1:1) with an interactive web-based response system to receive filgotinib 200 mg or placebo orally once daily for 12 weeks. Randomisation was stratified by current use of conventional synthetic DMARDs

and previous receipt of anti-tumour necrosis factor therapy. The patients, study team, and study sponsor were masked to treatment assignment. The primary endpoint was the change from baseline in ankylosing spondylitis disease activity score (ASDAS) at week 12, which was assessed in the full analysis set (ie, all randomised patients who received at least one dose of study drug). Safety was assessed according to actual treatment received. This trial is registered with ClinicalTrials.gov, number NCT03117270.

FINDINGS:
Between March 7, 2017, and July 2, 2018, 263 patients were screened and 116 randomly assigned to filgotinib (n=58) or placebo (n=58). 55 (95%) patients in the filgotinib group and 52 (90%) in the placebo group completed the study; three (5%) patients in the filgotinib group and six (10%) in the placebo group discontinued treatment. The mean ASDAS change from baseline to week 12 was -1·47 (SD 1·04) in the filgotinib group and -0·57 (0·82) in the placebo group, with a least squares mean difference between groups of -0·85 (95% CI -1·17 to -0·53; p<0·0001). Treatment-emergent adverse events were reported in 18 patients in each group, the most common being nasopharyngitis (in two patients in the filgotinib group and in four patients in the placebo group). Treatment-emergent adverse events led to permanent treatment discontinuation in two patients (a case of grade 3 pneumonia in the filgotinib group and of high creatine kinase in the placebo group). No deaths were reported during the study.

INTERPRETATION:
Filgotinib is efficacious and safe for the treatment of patients with active ankylosing spondylitis who have not responded to first-line pharmacological therapy with NSAIDs. Further investigation of filgotinib for ankylosing spondylitis is warranted.

FUNDING:
Galapagos and Gilead Sciences.

Panas M[1], Kyryk K[1], Dzhalilova E[1], Kaminsky R[1], Kefeli-Ianovska L[1], Sokurenko L[1]

The effect of combined action of antibacterial drugs with low-intensive laser radiation on clinical strains s. Aureus and s. Salivarius in the oral cavity

Georgian Med News. 2018 Sep;(282):116-120

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The oral mucosa is constantly contaminated by a large number of microorganisms that may cause diseases such as periodontitis and caries. The present paper aims to study the effectiveness of the antimicrobial effect of combined use of antibacterial drugs (AD) and low-intensity laser radiation (LLR) on S. aureus S. salivarius isolated from the oral cavity. The study included 20 individuals with dental caries, 20 individuals with periodontitis and 10 without any signs of dental disease. The material for the microbacterial study was collected from surfaces of the teeth, oral cavity with dental caries and periodontal pockets. The intensity of bacterial isolation was estimated by two factors: the frequency of isolation and percentage of other aerobic microorganisms. The obtained data demonstrated that the use of several antibacterial drugs had a different impact on the strains of S. salivarius and S. aureus, depending on the source of their collection. The collected isolates were used to determine the effect of a 5 minute laser radiation combined with antibacterial drugs. The

simultaneous use of antibacterial therapy and laser radiation showed an increase in the therapeutic effect of all investigated antibiotics followed by the inhibition of the growth presentations in S. aureus and S. salivarius. The application of photodynamic therapy, e.g. LLR, combined with antibacterial drugs allowed to achieve a complete inhibition of the microbial growth.

Karalashvili L[1], Kakabadze A[2], Uhryn M[2], Vyshnevska H[2], Ediberidze K[2], Kakabadze Z[2]

Bone grafts for reconstruction of bone defects (review)

Georgian Med News. 2018 Sep;(282):44-49.

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Reconstruction of large size defects of bone is a challenging task. To this date, discussions and controversies on selection of auto-, allo-, xeno- or synthetic grafts continue to take place. Vascularized autologous bone graft is considered as gold standard in reconstruction of large size defects of bone; however an additional surgery is required for obtaining it. Allografts and xenografts possess osteoconductive features, but osteogenesis is less expressed and risk of various infection transmissions is high and may have probability of developing immunological conflict. Main advantages of grafts created from synthetic materials through bioengineering methods are biocompatibility and good bioreabsorption. Despite these features, studies related to the creation of an ideal bone graft continue to take place that should have biomechanical stability, be able to degrade within an appropriate period, exhibit osteoconductive, osteogenic and osteoinductive properties. Nowadays, there is an attempt of creating grafts that contain platelet-rich plasma, growth factors or stem cells for strengthening osteoconduction and osteoinduction of bone grafts. In 2016, we created bioactive bone from decellularized bovine femoral bone and freeze-dried bone marrow stem cell paracrine factors. We hypothesized that freeze-dried BMSC paracrine factors would have ability to strengthen osteoinduction, osteoconduction and osteointegration. Experimental and preliminary clinical investigations indicated that bioactive bone grafts containing freeze-dried BMSC paracrine factors may be used for reconstruction of large size bone defects. Despite acquired positive results, it requires multiple experimental and clinical studies for further improvement of graft.

Kryshchyshyn A[1], Kaminskyy D[2], Nektegayev I[3], Lesyk R[4] [et al.]

Isothiochromenothiazoles-A Class of Fused Thiazolidinone Derivatives with Established Anticancer Activity That Inhibits Growth of Trypanosoma brucei brucei

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KEYWORDS: *SAR analysis; Trypanosoma brucei; antitrypanosomal activity; isothiochromenothiazoles; thiazolidinones*

Recently, thiazolidinone derivatives have been widely studied as antiparasitic agents. Previous investigations showed that fused 4-thiazolidinone derivatives (especially thiopyranothiazoles) retain pharmacological activity of their synthetic precursors-simple 5-ene-4-thiazolidinones. A series of isothiochromeno[4a,4-d][1,3] thiazoles was investigated in an in vitro assay towards bloodstream forms of Trypanosoma brucei brucei. All compounds inhibited parasite growth at concentrations in the micromolar range. The established low acute toxicity of this class of compounds along with a good trypanocidal profile indicates that isothiochromenothiazole derivatives may be promising for designing new antitrypanosomal drugs.

Kozak Y[1], Panchuk R[1], Kobylinska L[2] [et al.]

Cytotoxicity of doxorubicin-conjugated poly[N-(2-hydroxypropyl)methacrylamide]-modified γ-Fe2O3 nanoparticles towards human tumor cells

Beilstein J Nanotechnol. 2018 Sep 25;9:2533-2545. doi: 10.3762/bjnano.9.236. eCollection 2018, (2017 IF=2.97)

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KEYWORDS: *cytotoxicity; doxorubicin; magnetic; nanoparticles; poly[N-(2-hydroxypropyl) methacrylamide]*

Doxorubicin-conjugated magnetic nanoparticles containing hydrolyzable hydrazone bonds were developed using a non-toxic poly[N-(2-hydroxypropyl)methacrylamide] (PHPMA) coating, which ensured good colloidal stability in aqueous media and limited internalization by the cells, however, enabled adhesion to the cell surface. While the neat PHPMA-coated particles proved to be non-toxic, doxorubicin-conjugated particles exhibited enhanced cytotoxicity in both drug-sensitive and drug-resistant tumor cells compared to free doxorubicin. The newly developed doxorubicin-conjugated PHPMA-coated magnetic particles seem to be a promising magnetically targeted vehicle for anticancer drug delivery.

Zubach O[1], Telegina T[1], Semenyshyn O[2], Vasiunets L[2], Zinchuk A[1]

Leptospirosis in Ukraine (Lviv Oblast): Clinical and Epidemiological Features

Vector Borne Zoonotic Dis. 2018 Oct 18. doi: 10.1089/vbz.2018.2375. [Epub ahead of print], (2017 IF=2.171)

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KEYWORDS: *Leptospira icterohaemorrhagiae; epidemiology; leptospirosis; microagglutination test*

The article describes the results of a retrospective analysis of medical records of 395 patients with a clinical diagnosis of leptospirosis treated at the Lviv Oblast Infectious Disease Clinical Hospital (Ukraine) between 2002 and 2016. The main risk factors for leptospirosis were contact with rodents or their excrements (26.84%) and bathing in ponds, small lakes, and reservoirs (10.63%). Among 276 patients in whom the anti-leptospira antibodies were detected by the microscopic agglutination test (MAT), the most common serotypes were Leptospira icterohaemorrhagiae (33.33%) and Leptospira grippotyphosa (25.0%). The mortality rate was significantly higher in patients where leptospirosis diagnosis was established based on clinical symptoms without confirmation by MAT (15.13% vs. 5.43%, $p < 0.01$).

Bilyy R[1], Dumych T[1], Paryzhak S[1], Vovk V[1][et al.]

Inert Coats of Magnetic Nanoparticles Prevent Formation of Occlusive Intravascular Co-aggregates With Neutrophil Extracellular Traps

Front Immunol. 2018 Oct 2;9:2266. doi: 10.3389/fimmu.2018.02266. eCollection 2018, (IF=5.511)

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KEYWORDS: *biocompatibility; clearance; nanoparticle aggregation; neutrophil extracellular traps (NETs); superparamagnetic iron oxide nanoparticles (SPIONs); vascular occlusion*

If foreign particles enter the human body, the immune system offers several mechanisms of response. Neutrophils forming the first line of the immune defense either remove pathogens by phagocytosis, inactivate them by degranulation or release of reactive oxygen species or immobilize them by the release of chromatin decorated with the granular proteins from cytoplasm as neutrophil extracellular traps (NETs). Besides viable microbes like fungi, bacteria or viruses, also several sterile inorganic particles including nanoparticles reportedly activate NET formation. The physicochemical nanoparticle characteristics fostering NET formation are still elusive. Here we show that agglomerations of non-stabilized superparamagnetic iron oxide nanoparticles (SPIONs) induce NET formation by isolated human neutrophils, in whole blood experiments under static and dynamic conditions as well as in vivo. Stabilization of nanoparticles with biocompatible layers of either human serum albumin or dextran reduced agglomeration and NET formation by neutrophils. Importantly, this passivation of the SPIONs prevented vascular occlusions in vivo even when magnetically accumulated. We conclude that higher order structures formed during nanoparticle agglomeration primarily trigger NET formation and the formation of SPION-aggregated NET-co-aggregates, whereas colloid-disperse nanoparticles behave inert and are alternatively cleared by phagocytosis.

Shparyk Y[1] [et al.]

Bevacizumab biosimilar BEVZ92 versus reference bevacizumab in combination with FOLFOX or FOLFIRI as first-line treatment for metastatic colorectal cancer: a multicentre, open-label, randomised controlled trial

Lancet Gastroenterol Hepatol. 2018 Dec;3(12):845-855. doi: 10.1016/ S2468-1253(18)30269-3. Epub 2018 Sep 24.

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Erratum in
Correction to Lancet Gastroenterol Hepatol 2018; published online Sept 24. http://dx.doi.org/10.1016/S2468-1253(18)30269-3. [Lancet Gastroenterol Hepatol. 2018]

BACKGROUND:
BEVZ92 is a proposed biosimilar to bevacizumab. The two molecules have similar physicochemical and functional properties in in-vitro and preclinical studies. In this clinical study, we compared the pharmacokinetic profile, efficacy, safety, and immunogenicity of BEVZ92 with reference bevacizumab as a first-line treatment in patients with metastatic colorectal cancer.

METHODS:
We did a randomised, open-label trial at 15 centres in Argentina, Brazil, India, Spain, and Ukraine. Eligible patients were aged 18 years or older, had metastatic colorectal cancer with at least one measurable non-irradiated lesion for which first-line chemotherapy was indicated and Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, had not received previous treatment for advanced disease, and whose bone marrow, hepatic, renal, and coagulation markers were all within normal ranges. Patients were randomly assigned (1:1) to either BEVZ92 or reference bevacizumab (5 mg/kg on day 1 of each cycle every 2 weeks) in combination with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or fluorouracil, leucovorin, and irinotecan (FOLFIRI). Randomisation was done via a web service based on a stochastic minimisation algorithm and was stratified by chemotherapy regimen (FOLFOX vs FOLFIRI), previous adjuvant therapy (yes vs no), ECOG performance status (0-1 vs 2), and study site. The primary endpoint was the area under the concentration-versus-time curve after a single infusion (AUC0-336h) and at steady state (AUCss)-ie, at cycle 7-in the assessable population, which comprised all treated patients for whom serum concentration measurements were available during the first seven cycles. Bioequivalence was established if the 90% CIs for the ratio of BEVZ92 to reference bevacizumab of the geometric means for AUC0-336h and AUCss were within the acceptance interval of 80-125%. Secondary endpoints included objective response, clinical benefit, and progression-free survival in the intention-to-treat population and immunogenicity and safety profiles in all treated patients. This trial is registered with ClinicalTrials.gov, number NCT02069704, and is closed to new participants, with follow-up completed.

FINDINGS:
142 patients were randomly assigned, 71 to the BEVZ92 group and 71 to the reference bevacizumab group. Two participants assigned to BEVZ92 did not receive treatment (one withdrew consent, the other had a serious intestinal obstruction before starting treatment); therefore, the treated population comprised 69 patients in the BEVZ92 group and 71 in the reference bevacizumab group. The geometric mean ratio of AUC0-336h in the BEVZ92 versus the control group was 99·4% (90% CI 90·5-109·0) and of AUCss was 100·0% (90·2-112·0). Objective response (35 [49%] of 71 vs 40 [56%] of 71), clinical benefit (62 [87%]

vs 65 [92%]), and progression-free survival (median 10·8 months [95% CI 7·4-11·5] vs 11·1 months [95% CI 8·0-12·8]) were similar in the BEVZ92 and reference bevacizumab groups. No relevant differences were noted between the safety profiles of the two study treatments. Neutropenia was the most common grade 3 or 4 adverse event reported in the BEVZ92 (14 [20%] of 69 patients) and reference bevacizumab (19 [27%] of 71 patients) groups. Serious adverse events occurred in 19 (28%) patients in the BEVZ92 group and 21 (30%) in the reference bevacizumab group. Two patients died because of bevacizumab-related serious adverse events: a sudden death in the BEVZ92 group and a serious large intestinal perforation in the reference bevacizumab group. The occurrence of anti-drug antibodies was low and similar in both treatment groups (two patients in the BEVZ92 group and one in the reference bevacizumab group).

INTERPRETATION:
Our results suggest that BEVZ92 and reference bevacizumab are pharmacokinetically bioequivalent and have no appreciable differences in efficacy, immunogenicity, and safety profiles as first-line treatment in combination with FOLFOX or FOLFIRI in patients with metastatic colorectal cancer.

FUNDING: mAbxience Research SL.

Sharikadze O[1], Zubchenko S[1], Maruniak S[1], Yuriev S[1]

Investigation of protective effects of synbiotics on allergopathy formation

Georgian Med News. 2018 Jul-Aug;(280-281):90-94.

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A strategic direction of modern medicine in combating allergy is the search for new methods of primary prophylaxis, among which a key role may belong to normalization of the human body microflora. The aim of the research was to study the influence of synbiotics on bacteriological and immune indices in premature infants evaluating their preventive role in allergopathy formation. During prospective cohort investigation, 88 babies from one to four months of age, born on the 27th to 37th week of gestation to healthy mothers and women with allergopathy, were examined. Routine laboratory, bacteriological and instrumental investigations were performed. Measuring total serum IgE, cytokines IL-5, IL-10 and TNF-alpha in coprofiltrates was performed by means of immunoenzymatic assay. The activity of histaminase was detected by means of "Histamine 50-Skin-Prick Test". All examined patients were divided into four groups, depend on parents's atopic disease and prescribing synbiotics. For month, children from the first and the third groups were administered a commercial synbiotic - nutritional supplement with probiotics and fructooligosaccharides in the dose: one billion viable microencapsulated bacteria Lactobacillus rhamnosus GG in combination with fructooligosaccharides. Children from the second and the fourth groups were not administered synbiotic. Control of indices was conducted after 4 weeks. On bacteriological analysis of feces, the number of lacto- and bifidobacteria increased by 30% in children from the first and the third groups. Indices of total serum IgE were within age norm both before intake of synbiotic (1-2 groups) and after treatment. A reliable ($p \leq 0.01$) reduction of TNF-alpha and increase in IL-10 was revealed in coprofiltrates of children, who received synbiotic Preema sachet. Inclusion of synbiotic, which contains one billion viable microencapsulated

bacteria Lactobacillus rhamnosus GG in combination with fructooligosaccharides to complex therapy of premature children results in regulation of cytokine balance with the tendency to reduction of an inflammatory process and has a preventive effect concerning allergopathy formation.

Karalashvili L[1], Mardaleishvili K[1], Uhryn M[1], Chakhunashvili D[1], Kakabadze Z[1]

CURRENT CONDITION AND CHALLENGES IN TREATMENT OF NON-HEALING WOUND AFTER RADIATION THERAPY (REVIEW)

Georgian Med News. 2018 Jul-Aug;(280-281):23-28.

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Radiotherapy is a common cancer treatment, but often together with tumor cells, the surrounding normal tissues are damaged as well, which leads to the complications such as skin atrophy, soft tissue fibrosis, desquamation, epithelial ulceration which leads to poor healing of wounds. In this review, our main attention will be paid to the treatment of non-healing wound after radiation therapy. Irradiated wounds are often resistant to conventional treatment modalities and may often require surgical reconstructive intervention. The reconstructive options usually include skin grafts, local and regional flaps. Local flaps may be unreliable, since in some of the cases they are affected by irradiation. However, the complication rate with regional flaps is just as high as that with local flaps, and is not significantly different when analyzed according to the type of reconstructive procedure performed. In addition, such wounds affect not only the physical, but also the mental health of patients and their productivity. Therefore, non-healing wounds represent a significant problem for patients and remain a major challenge in modern medicine. Recently, for the healing of non-healing wound, several novel approaches have been proposed such as using the bone marrow stem cells (BMSC), biologically active dressings, bioengineered skin equivalents and others. Of special interest are bioactive membrane consisting of decellularized human amniotic membrane and BMSC paracrine factors, which may be effectively used for the treatment of non-healing wounds that have developed following the radiotherapy. Despite the positive results achieved in a number of cases, it is early to state that the all of the above methods is an ideal for the treatment of non-healing wounds, since it requires additional experimental and clinical studies for ascertaining positive and negative features.

Cherkas A[1] [et al.]

4-Hydroxynonenal in Redox Homeostasis of Gastrointestinal Mucosa: Implications for the Stomach in Health and Diseases

Antioxidants (Basel). 2018 Sep 3;7(9). pii: E118. doi: 10.3390/antiox7090118, (IF=3.56)

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KEYWORDS: *4-hydroxynonenal; Helicobacter pylori; gastric cancer; gastritis; lipid peroxidation; non-steroid anti-inflammatory drugs-induced gastropathy; oxidative stress; peptic ulcer; redox balance; stomach*

Maintenance of integrity and function of the gastric mucosa (GM) requires a high regeneration rate of epithelial cells during the whole life span. The health of the gastric epithelium highly depends on redox homeostasis, antioxidant defense, and activity of detoxifying systems within the cells, as well as robustness of blood supply. Bioactive products of lipid peroxidation, in particular, second messengers of free radicals, the bellwether of which is 4-hydroxynonenal (HNE), are important mediators in physiological adaptive reactions and signaling, but they are also thought to be implicated in the pathogenesis of numerous gastric diseases. Molecular mechanisms and consequences of increased production of HNE, and its protein adducts, in response to stressors during acute and chronic gastric injury, are well studied. However, several important issues related to the role of HNE in gastric carcinogenesis, tumor growth and progression, the condition of GM after eradication of Helicobacter pylori, or the relevance of antioxidants for HNE-related redox homeostasis in GM, still need more studies and new comprehensive approaches. In this regard, preclinical studies and clinical intervention trials are required, which should also include the use of state-of-the-art analytical techniques, such as HNE determination by immunohistochemistry and enzyme-linked immunosorbent assay (ELISA), as well as modern mass-spectroscopy methods.

Yarema R[1], Fetsych T[1], Volodko N[1], Ohorchak M[2] [et al.]

Complete cytoreduction for ovarian cancer: Is it enough for long-term survival?

J Surg Oncol. 2018 Sep;118(3):593-594. doi: 10.1002/jso.25141. Epub 2018 Aug 24, (IF=2.886)

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No abstract is available for this article.

Turkevych M[1], Turkevych A[2,3] [et al.]

Pathomorphological criteria of use efficiency of resorbable and permanent implants in aesthetic medicine and cosmetic dermatology

J Cosmet Dermatol. 2018 Oct;17(5):731-735. doi: 10.1111/jocd.12737. Epub 2018 Aug 19, (IF=1.529)

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KEYWORDS: *collagen; collagenogenesis; permanent implants; resorbing implants*

BACKGROUND:
The use of threads in aesthetic medicine is based on its ability to stimulate collagen production, which is claimed by the manufacturers, but this information has no basis at all, as no research has been carried out that would confirm the claimed information.

AIMS:
To determine effectiveness of collagenogenesis as a result of setting of resorbing and permanent implants on the basis of study pathomorphological changes in the skin.

METHODS:
The studies were performed on 30 mature white male rats which were divided into two groups depending on the type of implanted threads.

RESULTS:
Dependence between type of implantation thread (structure) and stimulation of collagenogenesis has been established.

CONCLUSIONS:
While studying morphological changes in the peri-implant zone, it was found that in all groups of experimental rats, collagen with different term of biodegradation and in different quantities on various chronological stages is formed. It was established that collagenogenesis is stimulated unevenly, depending on the type of implantation thread (chemical composition and structure). On the 90th day of the experiment, the resorbing thread did not completely degrade, which does not contradict the information provided by the manufacturer about the period of disintegration (365 days), and the expediency of using these cosmetic threads in aesthetic dermatology for the purpose of prolonged lifting skin correction. The specificity of the structure of implant threads, namely, the form of a spring (AS), as a provocative factor for long-term alteration, causes long-term inflammatory response in tissues (90th day of the experiment).

Senkiv J[1][et al.]

Nanoformulations of anticancer FGFR inhibitors with improved therapeutic index

Nanomedicine. 2018 Nov;14(8):2632-2643. doi: 10.1016/j.nano.2018.08.001. Epub 2018 Aug 16, (IF=6.500)

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KEYWORDS: *Drug delivery; FGFR inhibitors; Liposomes; Nanoencapsulation; Nintedanib; Ponatinib*

Fibroblast growth factor receptor (FGFR) inhibitors like ponatinib and nintedanib are clinically approved for defined cancer patient cohorts but often exert dose-limiting adverse effects. Hence, we encapsulated the FGFR inhibitors ponatinib, PD173074, and nintedanib into polylactic acid nanoparticles and liposomes to enable increased tumor accumulation/specificity and reduce side effects. Different methods of drug loading were tested and the resulting formulations compared regarding average size distribution as well as encapsulation efficiency. Appropriate encapsulation levels were achieved for liposomal preparations only. Nanoencapsulation resulted in significantly decelerated uptake kinetics in vitro with clearly decreased short-term (up to 72 h) cytotoxicity at

higher concentrations. However, in long-term clonogenic assays liposomal formations were equally or even more active as compared to the free drugs. Accordingly, in an FGFR inhibitor-sensitive murine osteosarcoma transplantation model (K7M2), only liposomal but not free ponatinib resulted in significant tumor growth inhibition (by 60.4%) at markedly reduced side effects.

Paryzhak S[1], Dumych T[1], Bilyy R[1] [et al.]

ROS-Responsive N-Alkylaminoferrocenes for Cancer-Cell-Specific Targeting of Mitochondria

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KEYWORDS: *aminoferrocene; anticancer prodrugs; cancer; mitochondria targeting; reactive oxygen species*

Mitochondrial membrane potential is more negative in cancer cells than in normal cells, allowing cancer targeting by delocalized lipophilic cations (DLCs). However, as the difference is rather small, these drugs affect also normal cells. Now a concept of pro-DLCs is proposed based on an N-alkylaminoferrocene structure. These prodrugs are activated by the reaction with reactive oxygen species (ROS) forming ferrocenium-based DLCs. Since ROS are overproduced in cancer, the high-efficiency cancer-cell-specific targeting of mitochondria could be achieved as demonstrated by fluorescence microscopy in combination with two fluorogenic pro-DLCs in vitro and in vivo. We prepared a conjugate of another pro-DLC with a clinically approved drug carboplatin and confirmed that its accumulation in mitochondria was higher than that of the free drug. This was reflected in the substantially higher anticancer effect of the conjugate.

Masliak Z[1]; EMMOS Investigators [et al.]

Multiple Myeloma Treatment in Real-world Clinical Practice: Results of a Prospective, Multinational, Noninterventional Study

Clin Lymphoma Myeloma Leuk. 2018 Oct;18(10):e401-e419. doi: 10.1016/j.clml.2018.06.018. Epub 2018 Jun 25, (2017 IF=2.308)

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KEYWORDS: *Bortezomib; Global; Observational study; Routine practice; Stem cell transplantation*

BACKGROUND:
The present prospective, multinational, noninterventional study aimed to document and describe real-world treatment regimens and disease progression in multiple myeloma (MM) patients.

PATIENTS AND METHODS:
Adult patients initiating any new MM therapy from October 2010 to October 2012 were eligible. A multistage patient/site recruitment model was applied to minimize the selection bias; enrollment

was stratified by country, region, and practice type. The patient medical and disease features, treatment history, and remission status were recorded at baseline, and prospective data on treatment, efficacy, and safety were collected electronically every 3 months.

RESULTS:
A total of 2358 patients were enrolled. Of these patients, 775 and 1583 did and did not undergo stem cell transplantation (SCT) at any time during treatment, respectively. Of the patients in the SCT and non-SCT groups, 49%, 21%, 14%, and 15% and 57%, 20%, 12% and 10% were enrolled at treatment line 1, 2, 3, and ≥ 4, respectively. In the SCT and non-SCT groups, 45% and 54% of the patients had received bortezomib-based therapy without thalidomide/lenalidomide, 12% and 18% had received thalidomide/lenalidomide-based therapy without bortezomib, and 30% and 4% had received bortezomib plus thalidomide/lenalidomide-based therapy as frontline treatment, respectively. The corresponding proportions of SCT and non-SCT patients in lines 2, 3, and ≥ 4 were 45% and 37%, 30% and 37%, and 12% and 3%, 33% and 27%, 35% and 32%, and 8% and 2%, and 27% and 27%, 27% and 23%, and 6% and 4%, respectively. In the SCT and non-SCT patients, the overall response rate was 86% to 97% and 64% to 85% in line 1, 74% to 78% and 59% to 68% in line 2, 55% to 83% and 48% to 60% in line 3, and 49% to 65% and 36% and 45% in line 4, respectively, for regimens that included bortezomib and/or thalidomide/lenalidomide.

CONCLUSION:
The results of our prospective study have revealed great diversity in the treatment regimens used to manage MM in real-life practice. This diversity was linked to factors such as novel agent accessibility and evolving treatment recommendations. Our results provide insight into associated clinical benefits.

Magorivska I[1],Bilyy R[2], Hychka K[2] [et al.]

Low amounts of bisecting glycans characterize cerebrospinal fluid-borne IgG

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Immunoglobulin G (IgG) harbors a conserved N-glycosylation site which is important for its effector functions. Changes in glycosylation of IgG occur in many autoimmune diseases but also in physiological conditions. Therefore, the glycosylation pattern of serum IgG is well characterized. However, limited data is available on the glycosylation pattern of IgG in cerebrospinal fluid (CSF) compared to serum. Here, we report significantly reduced levels of bisected glycans in CSF IgG. Galactosylation and sialylation of IgG4 also differed significantly. Therefore, we propose a common mechanism mediating glycosylation changes of IgG at the transition from serum to CSF in steady state conditions.

Lozynskyy Y1 [et al.]

Budesonide Suppositories Are Effective and Safe for Treating Acute Ulcerative Proctitis

Clin Gastroenterol Hepatol. 2019 Jan;17(1):98-106.e4. doi: 10.1016/j.cgh.2018.04.027. Epub 2018 Apr 24, (IF=7.680)

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KEYWORDS: *Inflammatory Bowel Disease; Mesalazine; RCT; Ulcerative Colitis*

BACKGROUND & AIMS:
Although proctitis is the most limited form of ulcerative colitis, it causes unpleasant symptoms. Topical mesalamine, the standard treatment, is not always effective. We conducted a randomized phase 2 trial to determine the efficacy and safety of 2 doses of a budesonide suppository vs mesalamine suppositories vs combined budesonide and mesalamine suppositories for proctitis.

METHODS:
We performed a prospective, double-blind, double-dummy, multicenter trial in 337 patients with active proctitis to compare the efficacies of 4 different suppository treatments. Patients were randomly assigned to groups given 2 mg budesonide suppositories (2 mg BUS; n = 89 patients), 4 mg BUS (n = 79), 1 g mesalamine suppositories (1 g MES; n = 81), or the combination of 2 mg BUS and 1 g MES (n = 88). The study was performed from November 2013 through July 2015 at 36 study sites in Europe and Russia. The primary end point was the time to resolution of clinical symptoms, defined as the first of 3 consecutive days with a score of 0 for rectal bleeding and stool frequency.

RESULTS:
The mean time to resolution of symptoms in the 4 mg BUS (29.8 days) and combination of 2 mg BUS and 1 g MES (29.3 days) groups resembled that of the standard 1 g MES treatment (29.2 days), but was significantly longer in the 2 mg BUS group (35.5 days). Furthermore, proportions of patients with deep, clinical, and endoscopic remission, as well as mucosal healing, were similar among the 1 g MES, 4 mg BUS, and combination therapy groups, but significantly lower in the group that received 2 mg BUS. No safety signals were observed, and the patients' treatment acceptance was high (67%-85% of patients).

CONCLUSIONS:
In a multicenter randomized trial, we found that the efficacy and safety of 4 mg BUS in treatment of active proctitis did not differ significantly from those of 1 g MES. Budesonide suppositories offer an alternative therapy to mesalamine for topical treatment of proctitis. Clinicaltrialsregister.eu no: 2012-003362-41.

Lysiuk R[1][et al.]

Selenium, selenoprotein P, and Alzheimer's disease: is there a link?

Free Radic Biol Med. 2018 Nov 1;127:124-133. doi: 10.1016/j.freeradbiomed.2018.02.030. Epub 2018 Mar 2, (IF= 6.020)

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KEYWORDS: *Alzheimer's disease; Amyloid-beta; Brain; Human studies; Model studies; Neurodegeneration; Oxidative stress; Redox regulation; Selenium; Selenoprotein P; Supplementation; Trace elements*

The essential trace element, selenium (Se), is crucial to the brain but it may be potentially neurotoxic, depending on dosage and speciation; Se has been discussed for decades in relation to Alzheimer's disease (AD). Selenoprotein P (SELENOP) is a secreted heparin-binding glycoprotein which serves as the main Se transport protein in mammals. In vivo studies showed that this protein might have additional functions such as a contribution to redox regulation. The current review focuses on recent research on the possible role of SELENOP in AD pathology, based on model and human studies. The review also briefly summarizes results of epidemiological studies on Se supplementation in relation to brain diseases, including PREADViSE, EVA, and AIBL. Although mainly positive effects of Se are assessed in this review, possible detrimental effects of Se supplementation or exposure, including potential neurotoxicity, are also mentioned. In relation to AD, various roles of SELENOP are discussed, i.e. as the means of Se delivery to neurons, as an antioxidant, in cytoskeleton assembly, in interaction with redox-active metals (copper, iron, and mercury) and with misfolded proteins (amyloid-beta and hyperphosphorylated tau-protein).

Cherkas A[1,2], Golota S[3], Abrahamovych O[1], Krupak V[4],
Bugiichyk V[1,5], Yatskevych O[1], Pliatsko M[1] [et al.]

A Helicobacter pylori-associated insulin resistance in asymptomatic sedentary young men does not correlate with inflammatory markers and urine levels of 8-iso-PGF2-α or 1,4-dihydroxynonane mercapturic acid

Arch Physiol Biochem. 2018 Jul;124(3):275-285. doi: 10.1080/13813455.2017.1396346. Epub 2017 Nov 6, (2017 IF=1.806)

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KEYWORDS: *Helicobacter pylori; inflammation; insulin resistance; oxidative stress; sedentary lifestyle*

A potential contribution of H. pylori contamination to low-grade inflammation, oxidative stress (OS) and insulin resistance as well as correlations between these parameters in asymptomatic sedentary males was analysed. We enrolled 30 apparently healthy asymptomatic young subjects (18 H. pylori negative and 12 positive) and measured whole blood glucose, glycated haemoglobin, insulin, C-peptide, cortisol, aldosterone, testosterone, thyroid stimulating hormone, C-reactive protein, interleukins 6 and 10, TNF-alpha and comet assay. As markers of OS, we used urine levels of iso-PGF2-α and 1,4-dihydroxynonane mercapturic acid (DHN-MA). Twofold elevation of fasting insulin level and HOMA index in H. pylori-positive subjects ($p < .05$) was shown. Inflammatory parameters and monocyte DNA damage, urine levels of DHN-MA and iso-PGF2-α did not show significant differences between the groups. The early stage of H. pylori-triggered

metabolic derangements in sedentary subjects include development of insulin resistance in H. pylori-positive subjects; however, there is no evidence of systemic inflammatory and OS-related changes.

Akopyan H[1,2], Kitsera N[1] [et al.]

Targeted massively parallel sequencing characterises the mutation spectrum of PALB2 in breast and ovarian cancer cases from Poland and Ukraine

Fam Cancer. 2018 Jul;17(3):345-349. doi: 10.1007/s10689-017-0050-6. (IF=1.943)

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KEYWORDS: *Breast cancer; Genetic susceptibility; Massively parallel sequencing; Ovarian cancer; PALB2*

Loss-of-function germline mutations in the PALB2 gene are associated with an increase of breast cancer risk. The purpose of this study was to characterise the spectrum of PALB2 mutations in women affected with breast or ovarian cancer from South-West Poland and West Ukraine. We applied Hi-Plex, an amplicon-based enrichment method for targeted massively parallel sequencing, to screen the coding exons and proximal intron-exon junctions of PALB2 in germline DNA from unrelated women affected with breast cancer (n = 338) and ovarian cancer (n = 89) from Poland (n = 304) and Ukraine (n = 123). These women were at high-risk of carrying a genetic predisposition to breast and/or ovarian cancer due to a family history and/or early-onset disease. Targeted-sequencing identified two frameshift deletions: PALB2:c.509_510del; p.R170Ifs in three women affected with breast cancer and PALB2:c.172_175del;p.Q60Rfs in one woman affected with ovarian cancer. A number of other previously described missense (some predicted to be damaging by PolyPhen-2 and CADD) and synonymous mutations were also identified in this population. This study is consistent with previous reports that PALB2:c.509_510del and PALB2:c.172_175del are recurrent mutations associated with breast cancer predisposition in Polish women with a family history of the disease. Our study contributes to the accumulating evidence indicating that PALB2 should be included in genetic testing for breast cancer susceptibility in these populations to enhance risk assessment and management of women at high-risk of developing breast cancer. This data could also contribute to ongoing work that is assessing the possible association between ovarian cancer risk and PALB2 mutations for which there is currently no evidence.

Матеріал підготувала
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