

1. *Sergiev P.V., Osterman I.A., Golovina A.Ya., Laptev I.G., Pletnev P.I., Evratov S.A., Marusich E.I., Leonov S.V., Ivanenkov Ya.A., Bogdanov A.A., Dontsova O.A.*

Application of reporter strains for new antibiotic screening.

Screening for new antibiotics remains an important area of biology and medical science. Indispensable for this type of research is early identification of antibiotic mechanism of action. Preferentially, it should be studied quickly and cost-effectively, on the stage of primary screening. In this review we describe an application of reporter strains for rapid classification of antibiotics by its target, without prior purification of an active compound and determination of chemical structure

DOI: 10.18097/PBMC20166202117

2. *Roslavtceva V.V., Salmina A.B., Prokopenko S.V., Pozhilenkova E.A., Kobanenko I.V., Rezvitskaya G.G.*

The role of vascular endothelial growth factor in the regulation of development and functioning of the brain: new target molecules for pharmacotherapy.

Vascular endothelial growth factors (VEGFs) have been shown to participate in atherosclerosis, arteriogenesis, cerebral edema, neuroprotection, neurogenesis, angiogenesis, postischemic brain and vessel repair. Most of these actions involve VEGF-A and the VEGFR-2 receptor. VEGF signaling pathways represent an important potential for treatment of neurological diseases affecting the brain

DOI: 10.18097/PBMC20166202124

3. *Smirnova A.V., Sukhorukov V.N., Karagodin V.P., Orekhov A.N.*

Epigenetic factors in atherogenesis: microRNA.

MicroRNAs (miRNAs) are small (~22 nucleotides in length) noncoding RNA sequences regulating gene expression at posttranscriptional level. MicroRNAs bind complementarily to certain mRNA and cause gene silencing. The involvement of miRNAs in the regulation of lipid metabolism, inflammatory response, cell cycle progression and proliferation, oxidative stress, platelet activation, endothelial and vascular smooth muscle cells (VSMC) function, angiogenesis and plaque formation and rupture indicates important roles in the initiation and progression of atherosclerosis. The key role of microRNAs in pathophysiology of cardiovascular diseases (CVDs), including atherosclerosis, was demonstrated in recent studies. Creating antisense oligonucleotides is a novel technique for selective changes in gene expression both in vitro and in vivo. In this review, we draw attention to the role of miRNAs in atherosclerosis progression, using miRNA as the potential biomarkers and targets in the CVDs, as well as possible application of antisense oligonucleotides

DOI: 10.18097/PBMC20166202134

4. *Timofeev A.V.*

Basic carboxypeptidases of blood: significance for coagulology.

This review considers the basic metallo-carboxypeptidases of human blood and their role in coagulologic disorders. It includes information on the history of the discovery and biological characteristics of potential enzymes-regulators of the fibrinolytic process: carboxypeptidase U and carboxypeptidase N. Certain attention is paid to the biochemical mechanisms and the main modern concepts of the antifibrinolytic effects of these enzymes

DOI: 10.18097/PBMC20166202141

5. *Sanzhakov M.A., Ignatov D.V., Kostryukova L.V., Druzhilovskaya O.S., Medvedeva N.V., Prozorovskiy V.N., Ipatova O.M.*

The in vivo study of the medicinal composition property of doxorubicin as a part of colloidal nanoparticles with the address fragment.

The use of targeted transport systems for drug delivery is a promising approach to improve pharmacokinetics of drug substances, accumulation in the lesion. In this study we have obtained and characterized the pharmaceutical composition of doxorubicin in colloidal nanoparticles equipped with targeted conjugates based on folic acid and biotin with dodecylamine. The inclusion of the address fragments into colloidal nanoparticle was carried out without surface and drug substance modification. The accumulation of anthracycline antibiotic doxorubicin in tumor tissue was compared in Lewis lung carcinoma mouse models after intravenous administration of the composition of colloidal nanoparticles with targeted conjugates biotin-dodecylamine and folic acid-dodecylamine or free doxorubicin. It was shown that the doxorubicin accumulation in tumor tissue when administered in drug compositions with targeted fragments are 2 times higher for the folic acid-dodecylamine conjugate and 1.4 times higher for the biotin-dodecylamine conjugate

DOI: 10.18097/PBMC20166202150

6. *Gulyaeva L.F., Chanyshv M.D., Kolmykov S.K., Ushakov D.S., Nechkin S.S.*

Effect of xenobiotics on microRNA expression in rat liver.

Using bioinformatics analysis we selected microRNAs which could bind 3'-UTR-region of cytochrome P450 (CYP) genes. Three microRNA miR-21, -221, -222, their potential targets might be mRNA for CYP1A1, and two microRNA miR-143, miR-152 for CYP2B1 accordingly were selected for experimental verification. Expression level of these microRNAs in rat liver upon benzo(a)pyrene (BP), phenobarbital (PB), and DDT induction was

determined using RT-qPCR method. In rats treated by both BP, and DDT the hepatic content of miR-21, -221, -222 significantly demonstrated a 2-3-fold decrease. The decrease in miR expression was accompanied by a considerable (5.5-8.7-fold) increase in the CYP1A1-mediated EROD activity. The expression of miR-143 remained unchanged after the PB treatment, while the expression of miR-152 increased by 2 times, however, the (10.5-fold) increase in PROD activity of CYP2B was much higher. In the DDT-treated liver PROD activity increased by 20 times, the expression of miR-152 didn't change, and the expression of miR-143 increased by 2 times. The bioinformatics analysis of interactions between microRNAs and targets showed that the studied miRs can potentially bind 3'-end of AhR, ESR1, GR, CCND1, PTEN mRNA. Thus, the expression profile of miR-21, -221, -222, -143, -152 might change under the xenobiotics exposure. In silico analysis confirmed, that microRNAs target not only cytochrome P450 mRNA but also other genes, including those involved in hormonal carcinogenesis, they also can be regulated with studied miRs

DOI: 10.18097/PBMC20166202154

7. *Buneeva O.A., Gnedenko O.V., Medvedeva M.V., Ivanov A.S., Medvedev A.E.*

Oxidative modification of glyceraldehyde-3-phosphate dehydrogenase influences its interaction with endogenous neuroprotector isatin.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a classical glycolytic redox sensitive enzyme, exhibits various non-glycolytic functions, which are considered to be especially important for progression of various neurodegenerative diseases. GAPDH binds isatin (indole-dione-2,3), an endogenous indole often used as a parent component in numerous derivatives demonstrating diverse pharmacological (including neuroprotector) activities. In this study we have investigated binding of intact and mildly oxidized GAPDH to immobilized isatin, using an optical biosensor technique, employing surface plasmon resonance (SPR), and the effect of isatin as a probe for this binding. Mild GAPDH oxidation by 70 mM H₂O₂ increased enzyme dissociation from immobilized isatin. Since GAPDH is considered as a putative target for various neuroprotector agents, this suggests that its redox state determines sensitivity to neuroprotective agents, and oxidative stress typical for various neurodegenerative disorders may significantly reduce pharmacological effectiveness of such compounds

DOI: 10.18097/PBMC20166202160

8. *Chesnokova N.B., Beznos O.V., Lozinskaya N.A., Beyshenova G.A., Nesterova T.V.*

Effect of melatonin instillations on the clinical course of experimental uveitis and biochemical processes in tears and aqueous humor.

Acute immunogenic uveitis was modeled in rabbits via the subcutaneous and intravitreal injections of normal horse serum. We studied the effect of instillations of 0.1% melatonin solution on the clinical course of uveitis and biochemical parameters of tear fluid and aqueous humor: antioxidant activity, protein concentration and α 2-macroglobulin level. Melatonin instillations decreased clinical manifestations of uveitis. We found that the antioxidant activity in tears of the rabbits treated with melatonin was substantially higher and the α 2-macroglobulin level lower than in untreated animals. Antioxidant activity in aqueous humor taken on day 10 of uveitis was also twice higher while protein and α 2-macroglobulin levels were 1.5-2 times lower than in untreated animals. These data indicate that instillations of melatonin increase the local antioxidant activity and decrease the acuity of inflammation and permeability of hematoophthalmic barrier in uveitis

DOI: 10.18097/PBMC20166202164

9. *Voloshchuk O.N., Kopylchuk G.P.*

Activity of liver mitochondrial NAD⁺-dependent dehydrogenases of the krebs cycle in rats with acetaminophen-induced hepatitis developed under conditions of alimentary protein deficiency.

Activity of isocitrate dehydrogenase, α -ketoglutarate dehydrogenase, malate dehydrogenase, and the NAD⁺/NAD⁺ ratio were studied in the liver mitochondrial fraction of rats with toxic hepatitis induced by acetaminophen under conditions of alimentary protein deprivation. Acetaminophen-induced hepatitis was characterized by a decrease of isocitrate dehydrogenase, α -ketoglutarate dehydrogenase and malate dehydrogenase activities, while the mitochondrial NAD⁺/NAD⁺ ratio remained at the control level. Modeling of acetaminophen-induced hepatitis in rats with alimentary protein caused a more pronounced decrease in the activity of NAD⁺-dependent dehydrogenases studied and a 2.2-fold increase of the mitochondrial NAD⁺/NAD⁺ ratio. This suggests that alimentary protein deprivation potentiated drug-induced liver damage

DOI: 10.18097/PBMC20166202169

10. *Grigorev V.Yu., Solodova S.L., Polianczyk D.E., Raevsky O.A.*

Classification models of structure - P-glycoprotein activity of drugs.

Thirty three classification models of substrate specificity of 177 drugs to P-glycoprotein have been created using of the linear discriminant analysis, random forest and support vector machine methods. QSAR modeling was carried out using 2 strategies. The first strategy consisted in search of all possible combinations from 1 \hat{A} ,5 descriptors on the basis of 7 most significant molecular descriptors with clear physico-chemical interpretation. In the second case forward selection procedure up to 5 descriptors, starting from the best single descriptor was used. This strategy was applied to a set of 387 DRAGON descriptors. It was found that only one of 33 models has necessary statistical parameters. This model was designed by means of the linear discriminant analysis on the basis of a single descriptor of H-bond (SCad). The model has good statistical characteristics as evidenced by results to both internal cross-validation, and external validation with application of 44 new chemicals. This confirms an important role of hydrogen bond in the processes connected with penetration of chemical compounds through a blood-brain barrier

DOI: 10.18097/PBMC20166202173

11. *Yurova K.A., Sokhnevich N.A., Khaziakhmatova O.G., Litvinova L.S.*

Cytokine-mediated regulation of expression of Gfi1 and U2afll4 genes activated by T-cells with different differentiation status in vitro.

The dose-dependent effects of cytokines (IL-2, IL-7, and IL-15), which have a common g-chain, on mRNA expression of U2afll4 and GFi1 genes involved in regulation of alternative splicing of the Ptpcr gene, have been investigated in vitro using T-lymphocyte cultures with different degrees of differentiation. IL-2, IL-7, and IL-15 caused a similar unidirectional inhibitory effect of various severity on restimulated CD45RO⁺ T-cells exposed to an

antigen-independent activation; they caused a dose-dependent decrease of the U2af114 gene expression, and an increase of Gfi1 gene expression. This may suggest formation of active forms of the CD45 receptor, and also limitation of the formation of low-molecular short splice variants of the CD45RO receptor. Under conditions of antigen-independent stimulation of naive CD45RA⁺-cells rIL-7 and IL-15 exhibited opposite effects on U2af114 and Gfi1 gene expression. The increase of IL-7 concentrations in the incubation medium of naive cells was accompanied by a decrease in expression of both genes. IL-15 IL-7 exhibited opposite effects. Cytokines possessing a common g-chain (IL-2, IL-7, and IL-15) prevented antigen-independent differentiation of naive T-cells, by preventing the formation of polyclonal surrogate cells. In general, the study of the molecular mechanisms of genetic control determining homeostatic processes of T-cells in response to exposure to antigenic or non-antigenic treatments may be important for construction of a general model of self-maintenance and differentiation of immune cells

DOI: 10.18097/PBMC20166202180

12. *Surikova E.I., Goroshinskaja I.A., Nerodo G.A., Frantsiyants E.M., Malejko M.L., Shalashnaja E.V., Kachesova P.S., Nemashkalova L.A., Leonova A.V.*

The activity of redox-regulatory systems in the tumor and its surrounding tissues in various histological types of tumor.

According to modern concepts cancer is a complex dynamic system having multiple relationships with both the immediate environment and with remote nonmalignant tissues and organs. Changes in the redox balance in them can result in disruption of the normal tissue control. Understanding of the biology of redox processes in a particular tumor and its surroundings, and of their functioning mechanisms is necessary for the development of new anti-cancer strategies based on the effects on the redox state of the tumor and surrounding tissue. Thus the aim of this work was to investigate activity of enzymatic systems influencing the redox state in the tumor tissue, peritumoral area and nonmalignant tissue (taken along the line of resection) for different histological types of tumors. The data obtained showed a similar level of reduced glutathione (GSH) in tumor tissues of gastric adenocarcinoma and vulvar squamous cell carcinoma, but its dynamics in the tissues surrounding the tumor was different. In contrast to the gastric adenocarcinoma the carcinoma of the vulva had a significant level of GSH and higher activity of glutathione dependent enzymes in the tumor tissue and its peritumoral area compared with the surrounding nonmalignant tissue. The results indicate that there are differences in the functioning of the redox regulatory systems in the tumor tissue and its surrounding tissues of various histological origin and localization, possibly due to different mechanisms involved in maintenance of the redox balance in the originally nonmalignant tissue

DOI: 10.18097/PBMC20166202187

13. *Makletsova M.G., Rikhireva G.T., Poleshuk V.V., Grjakalov K.V., Timerbaeva S.L., Fedorova T.N.*

The effect of antioxidants on in vivo and in vitro methemoglobin formation in erythrocytes of patients with Parkinson`s disease.

Methemoglobin formation was examined in erythrocytes of 16 patients with Parkinson`s disease (PD) (stage 3-4 by the Hoehn and Yahr scale). The patients receiving levodopa-containing drugs (madopar, nakom) were also treated with intramuscular injections of mexidol (daily dose 100 mg/day) for 14 days. Control group included 12 clinically healthy persons. The erythrocyte methemoglobin content was determined by electronic paramagnetic resonance (EPR) using the EPR signal intensity with g-factor 6.0. The methemoglobin content was significantly higher in erythrocytes of PD patients than in healthy donors. The complex therapy with mexidol normalized the methemoglobin content in erythrocytes of PD patients. Incubation in vitro of erythrocytes of donors and PD patients with acrolein increased the methemoglobin content, while incubation with carnosine normalized the methemoglobin content in erythrocytes of PD patients. Prophylactic (i.e. before acrolein addition) and therapeutic administration of carnosine to the incubation system with acrolein decreased the methemoglobin content to its initial level. Results of this study suggest that inclusion of the antioxidants mexidol and carnosine in the scheme of basic therapy of PD may reduce side effects associated with methemoglobinemia

DOI: 10.18097/PBMC20166202193

14. *Zhloba A.A., Subbotina T.F., Alekseevskaya E.S., Moiseeva O.M., Gavrilyuk N.D., Irtyuga O.B.*

The level of circulating PGC1a in cardiovascular disease.

The level of peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC1a) in human blood plasma was investigated. Samples of healthy individuals (n=34) and patients with cardiovascular diseases (n=110), including aortic aneurysm (n=69), aortic stenosis (n=25) and patients without aortic pathologies were analyzed. In patients the PGC1a concentration was higher than that in healthy persons, and tended to decrease with age. Elevated concentrations of lactic acid, total homocysteine and asymmetric dimethylarginine in the blood of patients suggested a parallel development of endothelial and secondary mitochondrial dysfunction. However, concentrations of lactic and pyruvic acids exceeding reference limit were associated with the decrease in the PGC1a level

DOI: 10.18097/PBMC20166202198

15. *Akmurzina V.A., Petryairina E.E., Saveliev S.V., Selishcheva A.A.*

The profile of plasma non-esterified fatty acids in children with different terms of type 1 diabetes mellitus.

Composition and quantitative content of non-esterified fatty acids (NEFA) were investigated in plasma samples of healthy children (12) and children with type 1 diabetes mellitus (DM1) (31) by gas chromatography (GC) after preliminary NEFA solid-phase extraction from plasma lipids. There was a significant (p<0.001) 1.6-fold increase in the total level of NEFA regardless of the disease duration. In the group of DM1 children with the disease period less than 1 year there was an increase in the arachidonic acid (20:4) content (30%) and the oleic acid trans-isomer (18:1) content (82%), and also a decrease in the docosahexaenoic acid (22:6 n3) content (26%) and the docosapentaenoic acids (22:5 n-6) content (60%). In the group of DM1 children with prolonged course of this disease the altered NEFA levels returned to the normal level

DOI: 10.18097/PBMC20166202206

16. *Soloveva A.G., Peretyagin S.P.*

The effect of subchronic inhalations of nitric oxide on metabolic processes in blood of experimental animals.

Metabolic processes were investigated in plasma and erythrocytes of Wistar rats exposed to daily 10-min sessions of NO inhalation for 30 days. These included determination of glucose and lactate, catalase activity, and activities of aldehyde dehydrogenase (ALDH), lactate dehydrogenase (LDH), and catalase. NO inhalation in a concentration of 20 ppm, 50 ppm and 100 ppm caused an increase in glucose and lactate. Inhalation of 100 ppm NO also increased catalase activity. Inhalation of all NO concentrations resulted in a decrease of ALDH activity, while the decrease in LDH activity was observed at NO concentrations of 50-100 ppm

DOI: 10.18097/PBMC20166202212