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*1. Severina I.S., Fedchenko V.I., Veselovsky A.V., Medvedev A.E.*

**The history of renalase from amine oxidase to alpha-NAD(P)H-oxidase/anomerase.**

Renalase is a recently discovered secretory protein, which plays a certain (still poorly understood) role in regulation of blood pressure. The review summarizes own and literature data accumulated since the first publication on relanase (2005). Initial reports on FAD-dependent amine oxidase activity of this protein were not confirmed in independent experiments performed in different laboratories. In addition, proposed amine oxidase activity of circulating extracellular renalase requires the presence of FAD, which has not been detected either in blood or urinary renalase. Moreover, renalase excreted into urine lacks its N-terminal peptide, which is ultimately needed for accommodation of the FAD cofactor. Results of the Alivertiâ€™s group on NAD(P)H binding by renalase and weak diaphorase activity of this protein stimulated further studies of renalase as NAD(P)H oxidase catalyzing reaction of catecholamine co-oxidation. However, physiological importance of such extracellular catecholamine-metabolizing activity (demonstrated in one laboratory and not detected in another laboratory) remains unclear due to existence of much more active enzymatic systems (e.g. neutrophil NAD(P)H oxidase, xanthine oxidase/xanthine) in circulation, which can perform such co-oxidation reactions. Recently a-NAD(P)H oxidase/anomerase activity of renalase, which also pomotes oxidative conversion of b-NADH isomers inhibiting activity of NAD-dependent dehydrogenases, has been described. However, itspossible contribution tothe antihypertensive effect ofrenalase remains unclear. Thus, theantihypertensive effect of renalase still remains a phenomenon with unclear biochemical mechanim(s) and functions of intracellular and extracellular (circulating) renalases obviously differ.

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*2. Solovyeva N.I., Timoshenko O.S., Gureeva T.A., Kugaevskaya E.V.*

**Matrix metalloproteinases and their endogenous regulators in squamous cervical carcinoma (review of the own data).**

Expression of matrix metalloproteinases (MMPs) and their endogenous regulators has been investigated in squamous cervical carcinoma (SCC). The study included (i) immortalized fibroblasts (IF) and three clones of fibroblasts transformed by oncogene E7 HPV-16 (TF); (ii) cell lines associated with HPV-16 and HPV-18; (iii) tumor tissue samples from patients with SCC, associated with gene E7 HPV-16. Transfection of fibroblasts with the E7 HPV16 oncogen was accompanied by induction of collagenase (MMP-1, MMP-14) and gelatinase (MMP-9) gene expression and the increase in catalytic activity of these MMP, while gelatinase MMP-2 expression remained unchanged. Expression of MMP-9 was found only inTF. MMP-9 may serve as a TF marker. In TF expression mRNA TIMP-1 was decreased. The level of free endogenous inhibitors in TF was significantly lower then the level in IF. Expression MMP correlated with the tumorigenic potential of TF. Invasive potential of cell lines associated with HPV18 (HeLa and S4-1) was more pronounced than that of cell lines associated with HPV16 (SiHa and Caski). The cell lines differed substantially in the level of expression of MMPI and their endogenous regulators. In most cell lines mRNA levels of collagenases MMP-1 and MMP-14 and the activator (uPA) increased, while gelatinase MMP-2 mRNA and tissue inhibitors mRNAs changed insignificantly. MMP-9 expression in cell lines was not detected. Results of studies on these cell lines suggest existence of an imbalance in the system enzyme / inhibitor / activator, that increases destructive potential of these cells. The study of expression of MMP and their endogenous regulators performed using SCC tumor samples associated with HPV16 has shown that the invasive and metastatic potentials of tumor tissue in SCC is obviously determined by the increase of expression of collagenases MMP-1, MT1-MMP and gelatinase MMP-9, decreased expression of inhibitors (TIMP-1 and TIMP-2), and to a lesser extent to increased expression of MMP-2. MMP-1 and MMP-9 can serve as markers of invasive and metastatic potential of the SCC tumor. In adjacent to the tumor normal tissue revealed a significant expression of MMP-1,-2,-9.

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*3. Moskaleva E.Yu., Perevozchikova V.G., Zhirnik A.S., Severin S.E.*

**Molecular mechanisms of niclosamide antitumor activity.**

In this review the recent data regarding the antitumor activity of niclosamide and the molecular mechanisms of its antitumor activity are presented. Niclosamide has been used in the clinic for the treatment of intestinal parasite infections. In recent years in several screening investigations of various drugs and chemical compounds niclosamide was identified as a potential anticancer agent. Niclosamide not only inhibits the Wnt/b-catenin, mTORC1, STAT3, NF-kB and Notch signaling pathways, but also targets mitochondria in cancer cells to induce growth inhibition and apoptosis. A number of studies have established the anticancer activity of niclosamide in both in vitro and in vivo in xenotransplantation models using human tumors and immunodeficient mice. It is important that niclosamide is active not only against tumor cells but also cancer stem cells. Normal cells are resistant to niclosamide. The accumulated experimental data suggest niclosamide is a promising drug for the treatment of various types of cancer.

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*4. Severina I.S., Pyatakova N.V., Shchegolev A.Yu., Rozhkov V.Yu., Batog L.V., Makhova N.N.*

**Potentiation of activation of soluble guanylate cyclase by YC-1, NO-donors and increase of the synergistic effect of YC-1 on NO-dependent activation of the enzyme by 1,2,3-triazolyl-1,2,5-oxadiazole derivatives.**

The influence of (1H-1,2,3-triazol-1-yl)-1,2,5-oxadiazole derivatives: 4-amino-3-(5-methyl-4- ethoxycarbonyl-(1H-1,2,3-triazol-1-yl)-1,2,5-oxadiazole (TF 4 CH 3 ) and 4,4â€™-bis(5-methel-4-ethoxycarbonyl-1H- 1,2,3-triazol-1-yl)-3,3â€™-azo-1,2,5-oxadiazole (2TF 4 CH 3 ) on stimulation of human platelet soluble guanylate cyclase by YC-1, NO-donors (sodium nitroprusside, SNP, and spermine NONO ) and on a synergistic increase of NO-dependent

enzyme activation in the presence of YC-1 has been investigated. Both compounds increased guanylate cyclase activation by YC-1, potentiated guanylate cyclase stimulation by NO-donors and increased the synergistic effect of YC-1 on NO-dependent activation of soluble guanylate cyclase. The similarity in the properties of the examined TF 4 CH 3 and 2TF 4 CH 3 with that of YC-1 and the possible mechanism underlying the revealed properties of compounds used are discussed.
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*5. Ivanov S.Yu., Bonartsev A.P., Gazhva Yu.V., Zharkova I.I., Mukhametshin R.F., Mahina T.K., Myshkina V.L., Bonartseva G.A., Voinova V.V., Andreeva N.V., Akulina E.A., Kharitonova E.S., Shaitan K.V., Muraev A.A.*

**Development and preclinical studies of insulating membranes based on poly-3-hydroxybutyrate-co-3-hydroxyvalerate for guided bone regeneration.**

Bone tissue damages are one of the dominant causes of temporary disability and developmental disability. Currently, there are some methods of guided bone regeneration employing different osteoplastic materials and insulation membranes used in surgery. In this study, we have developed a method of preparation of porous membranes from the biopolymer poly-3-hydroxybutyrate-co-3-hydroxyvalerate (PHBV), produced by a strain of Azotobacter chroococcum 7B. The biocompatibility of the porous membranes was investigated in vitro using mesenchymal stem cells (MSCs) and in vivo on laboratory animals. The cytotoxicity test showed the possibility of cell attachment on membrane and histological studies confirmed good insulating properties the material. The data obtained demonstrate the high biocompatibility and the potential application of insulating membranes based on PHBV in bone tissue engineering.
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*6. Oferkin I.V., Sulimov A.V., Katkova E.V., Kutov D.K., Grigoriev F.V., Kondakova O.A., Sulimov V.B.*

**Supercomputer investigation of the protein-ligand system low-energy minima.**

The accuracy ofthe protein-ligand binding energy calculations andligand positioning isstrongly influenced by the choice of the docking target function. This work demonstrates the evaluation of the five different target functions used in docking: functions based on MMFF94 force field and functions based on PM7 quantum-chemical method accounting orwithout accounting the implicit solvent model (PCM, COSMO or SGB). For these purposes the ligand positions corresponding to the minima of the target function and the experimentally known ligand positions in the protein active site (crystal ligand positions) were compared. Each function was examined on the same test-set of 16 protein-ligand complexes. The new parallelized docking program FLM based on Monte Carlo search algorithm was developed to perform the comprehensive low-energy minima search and to calculate the protein-ligand binding energy. This study demonstrates that the docking target function based on the MMFF94 force field can be used to detect the crystal or near crystal positions of the ligand by the finding the low-energy local minima spectrum of the target function. The importance of solvent accounting in the docking process for the accurate ligand positioning is also shown. The accuracy of the ligand positioning as well as the correlation between the calculated and experimentally determined protein-ligand binding energies are improved when the MMFF94 force field is substituted by the new PM7 method with implicit solvent accounting.
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*7. Tapbergenov S.O., Sovetov B.S., Bekbosynova R.B., Bolysbekova S.M.*

**Glutathione redox system, immune status, antioxidant enzymes and metabolism of purine nucleotides in hypothyroidism.**

The immune status, components of the glutathione redox system, the activity of antioxidant enzymes and metabolism of purine nucleotides have been investigated in animals with experimental hypothyroidism. On day 8 after an increase in the number of leukocytes, lymphocytes, T-helpers and T-suppressors as well as increased number of B-lymphocytes was found in blood of thyroidectomized rats. This was accompanied by decreased activity of adenosine deaminase (AD), AMP-deaminase (AMPD), and 5'-nucleotidase (5'N) in blood, but the ratio of enzyme activity AD/AMPD increased. These changes in the activity of enzymes, involved in purine catabolism can beregarded as increased functional relationships between T and B lymphocytes in hypothyroidism. The functional changes of immune system cells were accompanied by increased activity of glutathione peroxidase (GPx), a decrease in the activity of superoxide dismutase (SOD), glutathione reductase (GR) and the ratio GH/GPx. Thyroidectomized rats had increased amounts of total, oxidized (GSSG) and reduced glutathione (GSH), but the ratio GSH/GSSG decerased as compared with control animals. In the liver, hypothyroidism resulted in activation of SOD, GPx, decreased activity of GR and decreased ratio GR/GPx. At the same time, the levels of total, oxidized, and reduced glutathione increased, but the ratio GSH/GSSG as well as activities of enzymes involved in purine nucleotide metabolism ratio (and their ratio 5'N/AD + AMPD) decreased. All these data suggest a functional relationship of the glutathione redox system not only with antioxidant enzymes, but also activity of enzymes involved purine nucleotide metabolism and immune status.
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*8. Eschenko N.D., Putilina F.E., Galkina O.V., Vilkova V.A., Zacharova L.I., Fidarov A.F., Morozkina S.N., Shavva A.G.*

**Study of osteoprotective and hypolipidemic effects of estrogen 8a a-analogues.**

The aim of this work was to study the ability of some estrogen 8a-analogues, that have CH 3 -group in the C-3 position, exhibit osteoprotective and cholesterolemic effects. The properties of these analogues was comparisoned with effects of native estradiol and 17a-ethynylestradiol (EE). We showed that compounds 3 ((d,l)-17b-acethoxy-3-methoxy-8a-estra-1,3,5(10)-triene) and 4 ((d,l)-3-methoxy-8a-estra-1,3,5(10)-triene-17-one) had the same osteoprotective and cholesterolemic effects as EE. The utherotropic effects of compound 3 and EE were the same, while the utherotropic activity of 17-keto derivative (compound 4) was higher than effect of EE. The osteoprotective and cholesterolemic effects of compounds 5 and 6 (d- or l-17b-acethoxy-3-methoxy- 13-ethyl-8a-gone-1,3,5(10)-triene) were approximately the same, however the utherotropic action of these compounds was different: the compound 5 had significantly lower activity, but the compound 6 had the same effect in comparison with EE. Thus, all studied estrogen 8a-analogues may be used as basic constructions for structural modifications which is necessary as medications with while spectrum of biological properties.

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*9. Zavodnik I.B.*

**Mitochondrial dysfunction and compensatory mechanisms in liver cells during acute carbon tetrachloride-induced rat intoxication.**

Electron-transport chain and redox-balance of mitochondria are important targets that are damaged during intoxication. The aim of the present work was to estimate the role of impairments in cellular bioenergetic function in the development of liver damage during acute carbon tetrachloride intoxication in rats and to elucidate possible compensatory mechanisms. Acute CCl 4 â€“induced rat intoxication (0.8 g/kg or 4 g/kg) resulted in considerable impairments of respiratory and synthetic mitochondrial functions; their manifestations depended on the dose of the toxic agent and the duration of the intoxication increased and accompanied by complete uncoupling of oxidation and phosphorylation processes in liver mitochondria. The intoxication induced considerable liver damage and accumulation of NO in blood plasma and liver tissue. The changes of some parameters of liver mitochondrial functional activity demonstrate an oscillative pattern, reflecting compensatory mechanisms during intoxication that involved increased reduced glutathione level and enhanced succinate dehydrogenase activity.

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*10. Dubinkina V.B., Tyakht A.V., Ilina E.N., Ischenko D.S., Kovarsky B.A., Yarygin K.S., Pavlenko A.V., Popenko A.S., Alexeev D.G., Taraskina A.E., Nasyrova R.F., Krupitski E.M., Skorodumova L.O., Larin A.K., Kostryukova E.S., Govorun V.M.*

**Metagenomic analysis of taxonomic and functional changes in gut microbiota of patients with alcoholic dependence syndrome.**

Here we present the first metagenomic study of gut microbiota in patients with alcohol dependence syndrome (ADS) performed in the whole-genome (â€œshotgunâ€•) format. Taxonomic analysis highlighted changes in community â€œdriversâ€• abundance previously associated with inflammatory processes (including increase in Ruminococcus gnavus and torques, as well as decrease in Faecalibacterium and Akkermansia). Microbiota of alcoholics manifested presence of specific opportunistic pathogens rarely detected in healthy control subjects of the world. Differential analysis of metabolic potential basing on changes in KEGG Orthology groups abundance revealed increase in pathways associated with response to oxidative stress. Analysis of two specific gene groups â€“ alcohol metabolism and virulence factors â€“ also showed increase in comparison with the control groups. We suggest that gut microbiota distinct in alcoholics by both taxonomic and functional composition plays role in modulating the effect of alcohol on host organism.

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*11. Sagaradze G.D., Grigorieva O.A., Efimenko A.Yu., Chaplenko A.A., Suslina S.N., Sysoeva V.Yu., Kalinina N.I., Akopyan Zh.A., Tkachuk V.A.*

**Therapeutic potential of human mesenchymal stromal cells secreted components: a problem with standartization.**

Regenerative medicine approaches, such as replacement of damaged tissue by ex vivo manufactured constructions or stimulation of endogenous reparative and regenerative processes to treat different diseases, are actively developing. One of the major tools for regenerative medicine are stem and progenitor cells, including multipotent mesenchymal stem/stromal cells (MSC). Because the paracrine action of bioactive factors secreted by MSC is considered as a main mechanism underlying MSC regenerative effects, application of MSC extracellular secreted products could be a promising approach to stimulate tissue regeneration; it also has some advantages compared to the injection of the cells themselves. However, because of the complexity of composition and multiplicity of mechanisms of action distinguished the medicinal products based on bioactive factors secreted by human MSC from the most of pharmaceuticals, it is important to develop the approaches to their standardization and quality control. In the current study, based on the literature data and guidelines as well as on our own experimental results, we provided rationalization for nomenclature and methods of quality control for the complex of extracellular products secreted by human adipose-derived MSC on key indicators, such as â€œIdentificationâ€•, â€œSpecific activityâ€• and â€œBiological safetyâ€•. Developed approaches were tested on the samples of conditioned media contained products secreted by MSC isolated from subcutaneous adipose tissue of 30 donors. This strategy for the standardization of innovative medicinal products and biomaterials based on the bioactive extracellular factors secreted by human MSC could be applicable for a wide range of bioactive complex products, produced using the different types of stem and progenitor cells.

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*12. Mikaelyan N.P., Terentev A.A., Nguen K.H., Mikaelyan A.V., Novikova S.A.*

**Changes of blood fatty acid in women with obesity and type 2 diabetes mellitus.**

Obesity and type 2 diabetes (DM2) in women are accompanied by atherogenic dyslipidemia, with the activation of lipid peroxidation (LPO), as well as disturbances in the antioxidant defense system (ADS). DM2 due to imbalance in LPO-ADS is accompanied by a high concentration of LPO products, decreased parameters of antioxidant systems and timpaired utilization of glucose by cells. The results obtained in this study suggest an important role of fatty acids and their metabolites in the pathogenesis of obesity and DM2, which should be taken into consideration during design and selection of appropriate preventive and therapeutic measures aimed at prevention or elimination of the violations.

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*13. Gimadieva A.R., Khazimullina Yu.Z., Belaya E.A., Zimin Yu.S., Abdrakhmanov I.B., Mustafin A.G.*

**Express evaluation of antioxidant activity of uracil derivatives.**

Using photometric methods the antioxidant activity of 19 uracil derivatives has been analyzed. The test using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals can be applied for the rapid assessment ofantioxidant activity ofuracils. Among uracil derivatives studied thecompounds possesing a proton-donor group in C-5 position â€“ free or alkylated amino group, as well as hydroxyl group were the most active: 5-aminouracil (IC 50 3 mg/ml), 5-amino-6-methyluracil (IC 50 of 5 mg/ml), 5-hydroxy-6-methyluracil (IC 50 of 15 mg/ml), 5-hydroxy-1,3,6-trimethyluracil (IC 50 of 15 mg/ml), 5-ethylamino-6-methyluracil (IC 50 of 20 mg/ml), 5-methylamino-6-methyluracil (IC 50 of 20 mg/ml), 5-allylaminouracil (IC 50 of 20 mg/ml), 5-amino-1,3,6- trimethyluracil (IC 50 of 25 mg/ml). These uracil derivatives were more active than the reference compounds ionol (IC 50 of 30 mg/ml)

and a-naphthylamine (IC 50 of 45 mg/ml), but less active than ascorbic acid (IC 50 0.8 mg/ml). There was a correlation between the results of DPPH test (IC 50 ) and coupling constants of uracil derivatives with peroxide radicals of 1,4-dioxane (fk 7 ). Uracil with proton-donor group at C-5 also showed high ferrum-reducing activity as determined by FRAP.
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*14. Skvortsov V.S., Alekseychuk N.N., Khudyakov D.V., Mikurova A.V., Rybina A.V., Novikova S.E., Tikhonova O.V.*

**ProteoCat: a tool for planning of proteomic experiments.**

ProteoCat is a computer program has been designed to help researchers in the planning of large-scale proteomic experiments. The central part of this program is the subprogram of hydrolysis simulation that supports 4 proteases (trypsin, lysine C, endoproteinases AspN and GluC). For the peptides obtained after virtual hydrolysis or loaded from data file a number of properties important in mass-spectrometric experiments can be calculated or predicted. The data can be analyzed or filtered to reduce a set of peptides. The program is using new and improved modification of our methods developed to predict pI and probability of peptide detection; pI can also be predicted for a number of popular pKa's scales, proposed by other investigators. The algorithm for prediction of peptide retention time was realized similar to the algorithm used in the program SSRCalc. ProteoCat can estimate the coverage of amino acid sequences of proteins under defined limitation on peptides detection, as well as the possibility of assembly of peptide fragments with user-defined size of â€œstickyâ€• ends. The program has a graphical user interface, written on JAVA and available at http://www.ibmc.msk.ru/LPCIT/ProteoCat.
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*15. Kononikhin A.S., Fedorchenko K.Yu., Ryabokon A.M., Starodubtseva N.L., Popov I.A., Zavialova M.G., Anaev E.C., Chuchalin A.G., Varfolomeev S.D., Nikolaev E.N.*

**Proteomic analysis of exhaled breath condensate for diagnosis of pathologies of the respiratory system.**

Study of the proteomic composition of exhaled breath condensate (EBC), is a promising non-invasive method for the diagnosis of the respiratory tract diseases in patients. In this study the EBC proteomic composition of the 79 donors, including patients with different pathologies of the respiratory system has been investigated. Cytoskeletal keratins type II (1, 2, 3, 4, 5, 6) and cytoskeletal keratins the type I (9, 10, 14, 15, 16) were invariant for all samples. Analyzing the frequency of occurrence of proteins in different groups of examined patients, several categories of protein have been recognized: found in all pathologies (Dermcidin, Alpha-1-microglobulin, SHROOM3), found in several pathologies (CSTA, LCN1, JUP, PIP, TXN), and specific for a single pathology (PRDX1, Annexin A1/A2). The EBC analysis by HPLC-MS/MS can be used to identify potential protein markers characteristic for pathologies such as chronic obstructive pulmonary disease (PRDX1) and pneumonia (Annexin A1/A2).
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*16. Nikitina A.S., Babenko V.V., Babalyan K.A., Vasiliev A.O., Govorov A.V., Prilepskaya E.A., Danilenko S.A., Selezneva O.V., Sharova E.I.*

**Primary candidate RNA biomarker screening by RNA-seq for prostate cancer diagnostics.**

The RNA-seq approach for prostate cancer candidate RNA biomarkers screening in plasma and urine obtained by minimally invasive or noninvasive methods is proved to be feasible. Significant amount of RNA biomarkers associated with prostate cancer according to the literature were found in plasma and urine samples obtained from patients with benign prostatic hyperplasia (BPH). The number of detected markers was shown to vary in accordance with method of library preparation used for transcriptome profiling. The detection of known RNA biomarkers for prostate cancer in urine and plasma samples shows the feasibility of such method for minimally invasive diagnostics. The fact of presence of the same RNA biomarkers in samples from patients with BPH suggests their possible lack of specificity and confirms the need for further research in this area.
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*17. Veselov M.S., Sergiev P.V., Osterman I.A., Skvortsov D.A., Golovina A.Ya., Andreyanova E.S., Laptev I.G., Pletnev P.I., Evfratov S.A., Marusich E.I., Leonov S.V., Ivanenkov Ya.A., Bogdanov A.A., Dontsova O.A.*

**Common features of antibacterial compounds: an analysis of 10000 compounds library.**

Antibacterial compounds are one of the essential classes of clinically important drugs. High throughput screening allowed revealing potential antibiotics active towards any molecular target in bacterial cell. We used a library of 9820 organic compounds with highly diversified structures to screen for antibacterial activity. As the result of automated screening, 103 compounds were found to possess antibacterial activity against Escherichia coli. The properties of these compounds were compared with those of initial library. Non-linear Kohonen mapping was used to analyze the differences between non-active molecules from initial library, identified antibacterial hits and compounds with reported antibacterial activity. It was found that identified antibacterial compounds are located in the separated area of chemical space. It can be therefore suggested that these molecules belong to novel classes of antibacterial compounds and could be studied further.
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